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RELAPSED/REFRACTORY MULTIPLE MYELOMA

BLENREP (BELANTAMAB MAFODOTIN)

SPONSOR BRIEFING DOCUMENT
(VERSION 2.0)

ONCOLOGIC DRUGS ADVISORY COMMITTEE

MEETING DATE: 17 JULY 2025

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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List of Abbreviations

Abbreviation	Definition
1L	First line
2L+	Two lines or more
3L+	Three lines or more
4L+	Four lines or more
ADC	Antibody-drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	Adverse event
AESI	Adverse event of special interest
AutoSCT	Autologous stem cell transplantation
B	BLENREP
BCMA	B-cell maturation antigen
BCVA	Best-corrected visual acuity
BLA	Biologics License Application
BPd	BLENREP in combination with Pomalyst® (pomalidomide) and dexamethasone
BVd	BLENREP in combination with Velcade® (bortezomib) and dexamethasone
CBR	Clinical benefit rate
CD38	Cluster of differentiation 38
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CR	Complete response
CRR	Complete response rate
CTCAE	Common Terminology Criteria for Adverse Events
cys-mcMMAF	Cysteine maleimidocaproyl monomethyl auristatin F
DoR	Duration of response
DVd	Darzalex® (daratumumab), Velcade® (bortezomib), and dexamethasone
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMD	Extramedullary disease
EORTC IL52	European Organisation for Research and Treatment of Cancer Item Library 52
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma Module
EoS	End of Study
ETASU	Elements to assure safe use
FDA	United States Food and Drug Administration
FLC	Serum free light chain

List of Abbreviations

GHS	Global Health Status
GSK	GlaxoSmithKline
$H_{1\text{-}4}$	Hypothesis 1-4
HR	Hazard ratio
IA1-4	Interim analysis 1-4
IgG	Immunoglobulin G
IMiD	Immunomodulatory agent
IMWG	International Myeloma Working Group
IRC	Independent Review Committee
ISS	International staging system
ITT	Intent-to-Treat
IV	Intravenous
KVA	Keratopathy Visual Acuity
mAb	Monoclonal antibody
max	Maximum
min	Minimum
MM	Multiple myeloma
MRD	Minimal residual disease
NCCN	National Comprehensive Cancer Network
NCT	ClinicalTrials.gov identifier
NE	Not evaluable
NR	Not reached
ORR	Overall response rate
OS	Overall survival
OSDI	Ocular Symptom Disease Index
Pd	Pomalidomide and dexamethasone
PD	Progressive disease
PFS	Progression-free survival
PFS2	Progression-free survival on subsequent line of therapy
PI	Proteasome inhibitor
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient-reported outcome
PVd	Pomalidomide in combination with bortezomib and dexamethasone
Q1	First quartile
Q12W	Once every 12 weeks
Q3	Third quartile
Q3W/q3w	Once every 3 weeks

List of Abbreviations

Q4W/q4w	Once every 4 weeks
Q6W	Once every 6 weeks
Q8W	Once every 8 weeks
QoL	Quality of life
RDI	Relative Dose Intensity
REMS	Risk evaluation and mitigation strategy
R-ISS	Revised international staging system
RP2D	Recommended Phase 2 dose
RRMM	Relapsed or refractory multiple myeloma
SAP	Statistical analysis plan
sBCMA	Soluble BCMA
sCR	Stringent complete response
SD	Standard deviation
SoC	Standard of care
TTP	Time to progression
TTR	Time to response
US	United States
Vd	Bortezomib and dexamethasone
VGPR	Very good partial response

1 EXECUTIVE SUMMARY

Summary

The application for BLENREP for the treatment of relapsed or refractory multiple myeloma (RRMM) is supported by two independent, Phase 3 comparator-controlled clinical studies. Results from these two studies, which consistently demonstrated meaningful benefit across endpoints and supported the positive benefit-risk of BLENREP, will be discussed at the Oncologic Drugs Advisory Committee on 17 July 2025. This briefing document outlines the applicant's position on topics being brought forward by the Food and Drug Administration (FDA).

Unmet Need	Efficacy	Safety
▪ MM is incurable ▪ Disease will ultimately relapse, despite treatment options ▪ Only one BCMA-targeted treatment with improved OS ▪ Need for effective, accessible therapies with novel MOA to extend survival	▪ Consistent benefit across all endpoints in two positive Ph 3 studies ▪ ~2-year improvement in mPFS ▪ 42% reduction in risk of death (DREAMM-7); positive trend in OS (DREAMM-8) ▪ Doubling of CR/sCR and DoR ▪ MRD negativity 2.5-5x ▪ Benefit across all subgroups	▪ Safety consistent with known and well-characterized profile ▪ Ocular events reversible with time; effectively managed with dose modifications ▪ Allows administration in out-patient setting ▪ Proposed risk management enables patients to access treatment while mitigating frequency and nature of ocular events

1.1 Background and Unmet Medical Need

1.1.1 Multiple Myeloma

Multiple myeloma (MM) is an incurable malignant clonal plasma cell disorder that accounts for 10% of all hematologic malignancies globally (Bobin 2020, Rajkumar 2016) and is the second most prevalent hematologic malignancy in the United States (US) (Durer 2020). In the US, patients with MM are diagnosed at a median age of 69 years and have a 5-year relative survival of 62.4% (data from 2015-2021) (SEER 2025). Despite recent advances in the treatment of MM, most patients will experience relapse and die from their disease. Thus, the goal of therapy is to prolong each remission as long as possible to preserve patient quality of life and to extend survival.

1.1.2 Current Treatment Regimens for Refractory and Relapsed Multiple Myeloma

The treatment of RRMM following the first relapse must be individualized based on factors that predict long-term outcomes including comorbidities, prior treatments received, and disease characteristics as described in Section 2.1. The key classes of approved agents used in the treatment of frontline MM and subsequent RRMM include proteasome

inhibitors (PI), immunomodulatory (IMiD) agents, monoclonal antibodies (mAbs), chemotherapy agents, steroids, B-cell maturation antigen (BCMA)-directed CAR-T cell therapies, and bi-specific antibodies, described in Table 8. The National Comprehensive Cancer Network (NCCN) preferred regimens for the treatment of RRMM include triplet combinations (e.g. PI, IMiD agents and/or anti-Cluster of differentiation 38 (CD38) mAbs) as described in Table 9. Chimeric antigen receptor (CAR)-T cell therapies targeting BCMA are recommended after at least one prior line of therapy including an IMiD and a PI, where the patient is refractory to lenalidomide.

1.1.3 Unmet Medical Need

Though the use of triplet and even quadruplet regimens incorporating PIs, IMiDs, and mAbs in frontline therapy for newly diagnosed MM is increasing, the early use of these drugs leads to relapsed disease that is exposed or refractory to the three main classes of MM therapy earlier in the disease course. BCMA-targeting CAR-T therapies are approved in the early relapse/refractory setting for patients with RRMM with access to a specialized treatment center and able to tolerate the bridging therapy and CAR-T treatment. CAR-T therapy has a reported overall response rate (ORR) of 85% to 94% (ABECMA PI, CARVYKTI PI); however, these therapies are not available to or appropriate for all patients (Gajra 2022, Kourelis 2023, Haslam 2024). There are safety concerns with CAR-T therapies that include cytokine release syndrome (CRS), neurotoxicity including immune effector cell-associated neurotoxicity syndrome (ICANS), prolonged/recurrent cytopenias, severe or life-threatening infections, and hypogammaglobinemia (Afrough 2024). Neurotoxicities found in real-world use include cranial nerve palsies, Parkinson's disease and parkinsonism, acute and chronic polyneuropathies, confusion, disorientation, seizures, balance disturbances, and tremors (Ellithi 2025). These limitations are described further in Section 2.3.2.

Thus, there remains a high unmet need for effective and accessible therapies with a novel mechanism of action that offer deep, durable responses leading to long-term remission and improved survival. BLENREP, administered in combination with bortezomib and dexamethasone (Vd) or pomalidomide and dexamethasone (Pd), provides a novel, highly effective, off-the-shelf, anti-BCMA option that is accessible in an outpatient setting without the need for hospitalization or specialized care.

1.2 Product Description

1.2.1 Proposed Indication and Dosing Regimens

The proposed BLENREP indications align with the enrolled populations from the two pivotal Phase 3 studies, DREAMM-7 and DREAMM-8, that demonstrated substantial benefit over standard of care (SoC) triplet therapies (efficacy results shown in Section 1.4 and Section 6).

Indication	Starting Dose for BLENREP*
Treatment of MM in combination with bortezomib and dexamethasone in adult patients who have received at least 1 prior line of therapy.	BLENREP in combination with bortezomib and dexamethasone: 2.5 mg/kg of actual body weight every 3 weeks in combination for the first 8 cycles, and then continued as a single agent
Treatment of MM in combination with pomalidomide and dexamethasone in adult patients who have received at least 1 prior line of therapy including lenalidomide.	BLENREP in combination with pomalidomide and dexamethasone: 2.5 mg/kg of actual body weight on Cycle 1 followed by 1.9 mg/kg every 4 weeks starting on Cycle 2.

Note: BLENREP administered as an IV infusion over approximately 30 minutes

The recommended dose is based on comprehensive dose exploration and exposure-response analyses showing that the 2.5 mg/kg starting dose is necessary to maximize clinically meaningful responses. Subsequent dose and schedule modifications enable adverse events (AEs) to resolve while enabling patients to remain on BLENREP to maintain effective disease control (optimized dosing discussed in Sections 1.3 and 5.2).

Dose modification (delays and/or reductions) to manage adverse events are recommended based on safety and tolerability as described in Section 1.5.3.3 and Table 7.

1.2.2 BLENREP (Belantamab Mafodotin)

BLENREP is an antibody-drug conjugate comprised of an afucosylated humanized IgG1 conjugated via a protease-resistant maleimidocaproyl (mc) linker to monomethyl auristatin F (MMAF). Upon binding to BCMA, a protein expressed on MM cells, BLENREP is internalized followed by proteolytic cleavage and intracellular release of cys-mcMMAF. BLENREP provides immediate and sustained effects by binding to BCMA and killing BCMA-expressing MM cells via the delivery of the active cytotoxic drug cys-mcMMAF, enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) / antibody-dependent cellular phagocytosis (ADCP) killing of MM cells, and adaptive immune response (discussed in Section 3.2.2).

1.2.3 Regulatory History and Clinical Development Program in 2L+ Relapsed or Refractory Multiple Myeloma

1.2.3.1 Regulatory History

GSK submitted a Biologic License Application (BLA) for BLENREP as part of two triplet combinations (with Vd [BVd] and Pd [BPd]) for the treatment of RRMM in adults who have received at least 1 prior therapy (i.e., 2L+). BLENREP was recently approved for this indication in the United Kingdom (April 2025) and Japan (May 2025). BLENREP received a positive Committee for Medicinal Products for Human Use (CHMP, European Medicines Agency's) opinion for these indications in May 2025, with European Commission approval expected in July 2025.

A separate BLA, in a different population and with a different data package supported the approval of BLENREP in the US in 2020 as monotherapy in 5L+ RRMM under an accelerated approval. That approval was voluntarily withdrawn in early 2023 after the

monotherapy confirmatory study failed to demonstrate superiority over SoC doublet therapy on the primary endpoint of PFS. The regulatory history of BLENREP is discussed in Section 4.1.

1.2.3.2 Registrational Studies DREAMM-7, DREAMM-8 – 2L+Relapsed or Refractory Multiple Myeloma Triplet Combinations

Two randomized global, multicenter, active controlled Phase 3 studies (DREAMM-7 and DREAMM-8) demonstrate a positive benefit-risk for BLENREP in combination with SoC therapies, vs. SoC combinations, one of which includes daratumumab (Darzalex®), considered a gold standard treatment in MM. Interim data analyses support the BLA.

The key protocol characteristics are summarized in Table 1. Study designs are further described in Sections 6.2.1 (DREAMM-7) and 6.3.1 (DREAMM-8).

Table 1 DREAMM-7 and DREAMM-8: Key Protocol Characteristics

	DREAMM-7 (BVd)	DREAMM-8 (BPd)
BLENREP Regimen	BLENREP administered at **2.5 mg/kg Day 1, Q3W** for 8 cycles in combination with **bortezomib (Velcade®)** and dexamethasone (BVd), then administered as monotherapy	BLENREP, **pomalidomide (Pomalyst®)**, dexamethasone (BPd). BLENREP administered at: • 2.5 mg/kg Cycle 1, Day 1 • **1.9 mg/kg Cycle 2+ Day 1, Q4W**
Comparator Combination	**Daratumumab** administered for 8 cycles in combination with bortezomib and dexamethasone (DVd), then as monotherapy	**Pomalidomide**, bortezomib, dexamethasone (PVd)
Key Enrollment Criteria	• Adults with RRMM • ≥ 1 prior line • No prior anti-BCMA therapy • **Not intolerant or refractory to anti-CD38 (e.g., daratumumab)** • Not intolerant or refractory to bortezomib	• Adults with RRMM • ≥ 1 prior line (**including lenalidomide (**Revlimid®)[a]) • No prior anti-BCMA therapy • No prior pomalidomide • Not intolerant or refractory to bortezomib
Endpoints [b]	• Primary: Progression free survival • Key Secondary: overall survival, duration of response, minimal residual disease • Others: complete response rate, overall response rate, clinical benefit rate time to response, time to progression, progression free survival 2, quality of life	

BCMA = B-cell maturation antigen; BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib, dexamethasone; KVA = keratopathy visual acuity scale; RRMM = relapse and refractory multiple myeloma

a At least two cycles

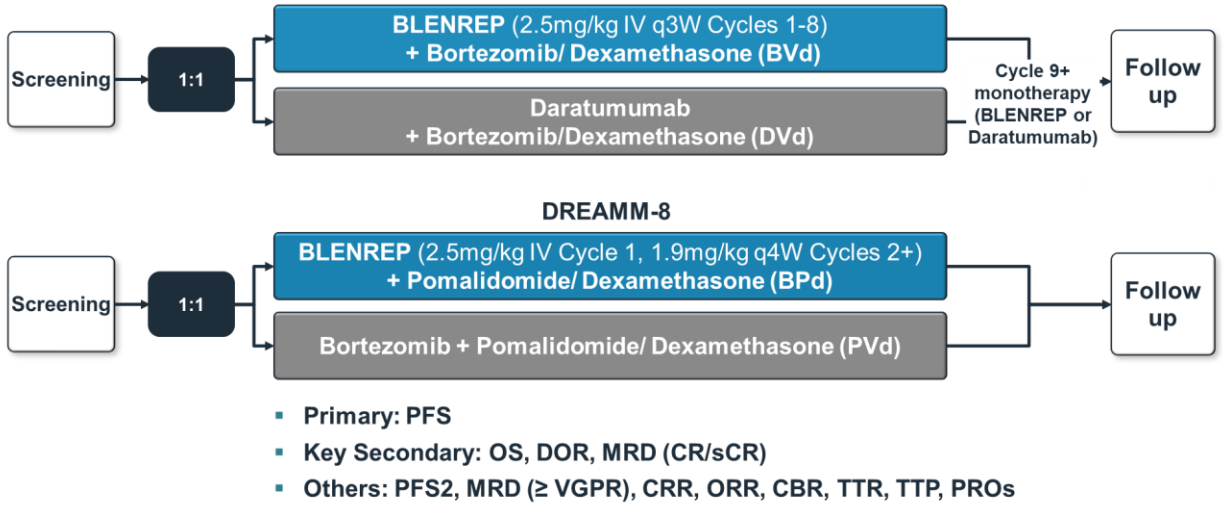
b Endpoints not listed in order for DREAMM-8. Endpoints are summarized by study in Section 11.3.1.

Note: **bold text** indicates a difference between studies

Note: Starting dose schedules in DREAMM-7 (Q3W) and DREAMM-8 (Q4W) are based on the dosing intervals for the bortezomib and pomalidomide, respectively.

The study designs for the registrational studies were similar and are summarized in Figure 1.

Figure 1 DREAMM-7 and DREAMM-8 Study Designs



BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib, dexamethasone; CBR = clinical benefit rate; CR = complete response; CRR = complete response rate; DoR = duration of response; DVd = daratumumab, bortezomib, dexamethasone; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PFS2 = progression free survival 2; PRO = patient reported outcomes; PVd = pomalidomide, bortezomib, dexamethasone; sCR = stringent complete response; TTP = time to progression, TTR = time to relapse; VGPR = very good partial response

In both studies, dosing was initiated with 2.5 mg/kg BLENREP, administered in 3-week (Q3W) (DREAMM-7) or 4-week (Q4W) (DREAMM-8) cycles based on the dosing schedule of the combination partners (bortezomib or pomalidomide). In DREAMM-8, the BLENREP dose stepped down to 1.9 mg/kg after the first cycle and further extending to 1.9 mg/kg every 8 weeks (Q8W) if a Grade 2 or higher ocular event was observed. In both studies, pre-specified dose modifications, including dose reductions to a lower dose or longer dose interval could be implemented based on a participant's AEs as summarized in Table 7.

The different dose and schedule in DREAMM-8 from DREAMM-7 was implemented to test if the proactive step down to 1.9 mg/kg and an extended dose to every 8 weeks (Q8W) upon Grade 2+ Keratopathy Visual Acuity (KVA) findings would improve the ocular safety profile while maintaining efficacy.

1.2.3.3 Supportive Studies

Several studies of BLENREP as monotherapy and in combination contributed to the dose selection and the evaluation of dose and exposure-response.

- Phase 1/2 combination-therapy dose and schedule exploration studies: DREAMM-6 (BVd, Arm B) and ALGONQUIN (BPd)
- Monotherapy dose optimization study that contributes to the evaluation of pharmacokinetics (PK) and dose selection: DREAMM-14.

A summary of clinical studies included in the BLA are provided in Appendix Table 1.

1.3 BLENREP Clinical Pharmacology and Dose Justification

1.3.1 Introduction

The starting dosing regimens for DREAMM-7 and DREAMM-8 were selected based on established PK and extensive dose and dose schedule exploration.

- A comprehensive evaluation of BLENREP in combination and monotherapy was conducted that included nearly 400 participants and a range of doses from 1.9 mg/kg to 3.4 mg/kg and a range of schedules from Q3/Q4W to extended schedules of every 6 weeks (Q6W), every 8 weeks (Q8W), and every 12 weeks (Q12W).
- Across all studies, a higher/more frequent starting dose and schedule followed by subsequent AE-guided dose modification was associated with deeper response and clinically meaningfully longer PFS.
- Though lower starting doses or less frequent schedules were associated with a modest improvement in safety:
    - Ocular events were observed across all doses and schedules studied. There was not a meaningful difference in the incidence of Grade 2+ keratopathy or AEs leading to discontinuation, although lower doses and extended schedule allows for faster recovery.
    - Ocular events were effectively managed through dose modifications, allowing participants to remain on treatment and benefit from BLENREP therapy.
- The extent of dose modification was high and variable across all doses and schedules studied, resulting in a median relative dose intensity (RDI–which measures the proportion of per protocol planned dose participants received) typically between 40% and 60%. The median dose intensity is driven by the fact that ocular events happen across the range of all clinically efficacious doses evaluated. Once a Grade 2+ ocular event occurs, a dose hold is required until event resolution before treatment is re-initiated. There is variability in resolution times of ocular events between participants that inevitably results in variable dosing frequencies.
- Based on the dosing exploration and optimization conducted to date, there has not been a dose and schedule that offers a robust efficacy benefit while avoiding ocular events. Therefore, the starting dose and schedule and subsequent dose modification based on tolerability are an integral part of the BLENREP dosing recommendation.

Integrated exposure-response analyses confirmed the clinical findings demonstrating that higher Cycle 1 exposure was positively associated with deeper response (very good partial response or better [VGPR+]), and though there was a numerical increase in ocular safety parameters, the slope of the exposure-efficacy curve was much steeper than for the exposure-safety curve.

1.3.2 Pharmacokinetics

BLENREP has dose-proportional PK, with a time-dependent decrease in clearance. Maximum concentrations of BLENREP were observed at or shortly after the end of infusion with limited accumulation (less than 2-fold) of BLENREP during subsequent cycles. BLENREP had an elimination half-life of 13 days after the first dose. Over the first 6 months after the start of combination treatment, as disease burden decreases, the elimination half-life was 19 days. There is moderate to large between participant variability in PK. Pharmacokinetics is described further in Section 5.1.

1.3.3 Dose Rationale

In DREAMM-7, the dose interval of Q3W aligns with the treatment schedule for the combination partner, bortezomib. In DREAMM-8, the dose interval of Q4W aligns with the treatment schedule for the combination partner, pomalidomide. The starting dose of 2.5 mg/kg with subsequent dose modifications is supported by dose exploration and optimization studies performed in almost 400 participants in monotherapy (DREAMM-14) and combination settings (BVd in DREAMM-6 and BPd in ALGONQUIN) as summarized in Table 2 and detailed in Section 5.2. In these studies, ORR/VGPR rates trended lower in the cohorts with a 1.9 mg/kg starting dose and/or extended starting schedule (Q6W or greater) with marginal improvement in safety, as summarized in Figure 2, Figure 3, and Table 13.

Table 2 Summary of BLENREP Doses and Schedules Evaluated

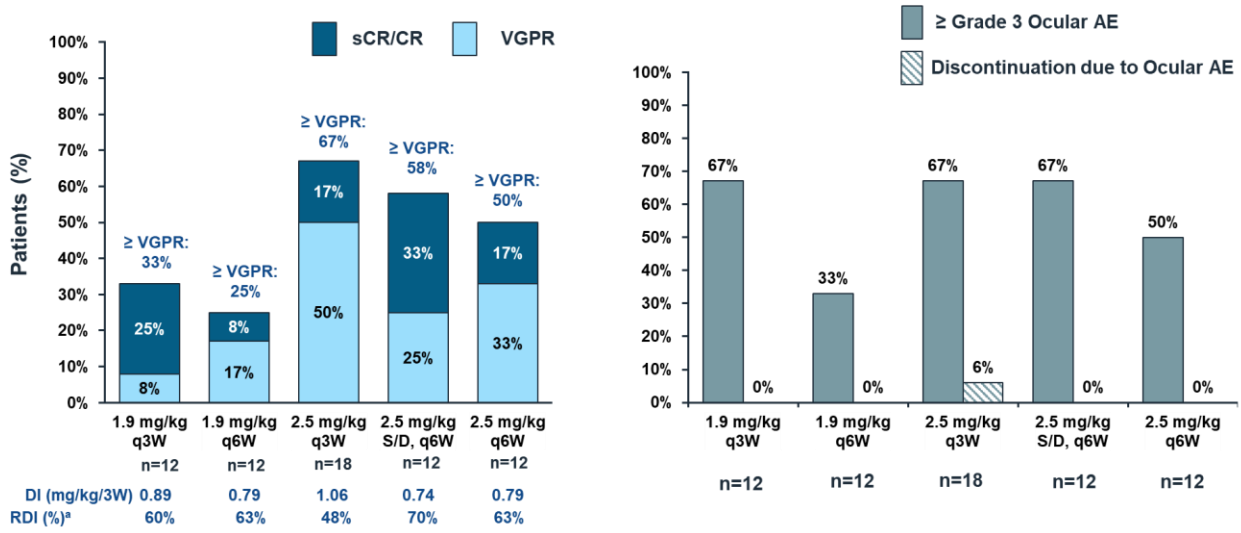
Exploration	Tested	Conclusions	Recommendation
Different starting doses	• 1.9 mg/kg • 2.5 mg/kg • 3.4 mg/kg	1.9 mg/kg dose lowered efficacy without significantly improving safety/tolerability. The 3.4 mg/kg dose had worse safety.	2.5 mg/kg starting dose
Different starting dosing schedules	• D1/D8, Q3/4W • Q3/4W • Q6/8W • Q12W	Less frequent starting schedules were associated with limited improvement in safety across dosing schedules with loss of efficacy.	Q3/4W starting schedule selected. Aligns with combination therapy partner schedules.
Proactive step down	Drop to 1.9 mg/kg after Cycle 1	Similar efficacy and safety profile	2.5 mg/kg with or without proactive step down are viable options

D1 = Day 1; D8 = Day 8; Q3/4W = every 3 or 4 weeks ; Q6/8W = every 6 or 8 weeks
Table 13 provides additional details on the studies exploring the BLENREP dose regimen

DREAMM-6 (BVd) and ALGONQUIN (BPd) are studies evaluating BLENREP in combination with the relevant regimens in a similar line of therapy and key safety and efficacy results by dose and schedule combinations are provided in Figure 2 and Figure 3. Note that the individual participant data needed to calculate the dose intensity (DI) for ALGONQUIN is not available to the applicant. Key safety and efficacy results by

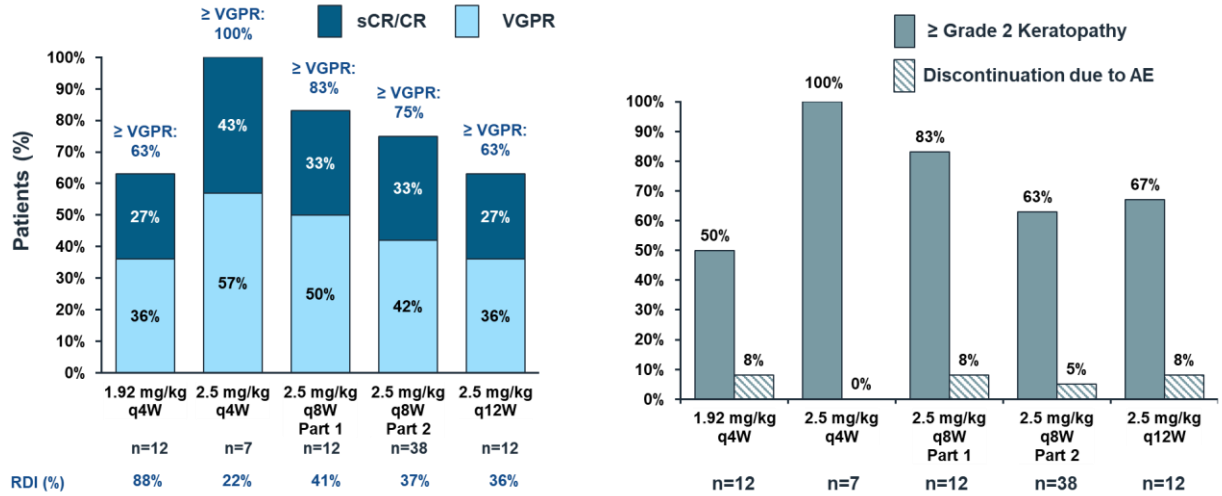
dose and schedule combinations for DREAMM-14, a dose optimization study of monotherapy in a later line of therapy, are provided in Appendix Figure 1.

Figure 2 DREAMM-6: Efficacy vs. Tolerability Across Dose and Dose Schedules



AE = adverse event; CR = complete response; q#W = every # of weeks; sCR = stringent complete response; S/D = step down to 1.9 mg/kg Cycle 3+; VGPR = very good partial response
a Cycle 2 onwards

Figure 3 ALGONQUIN: Efficacy vs. Tolerability Across Dose and Dose Schedules



AE = adverse event; CR = complete response; q#W = every # of weeks; sCR = stringent complete response; VGPR = very good partial response

Dose intensity (DI) for the DREAMM-6 study was evaluated at 6-month intervals and overall; results are provided in Table 3. This analysis showed that median DI was generally higher in the first 6 months across all dose cohorts. The arms with a higher

starting dose (2.5 mg/kg) and shorter dosing intervals (i.e., more frequent BLENREP administration) showed deeper responses and had higher median DIs relative to the 1.9 mg/kg starting dose or longer dosing intervals in the first 6 months. The trend was similar after 6 months, but median DI was generally lower across all dose cohorts (Table 3). These results suggest doses associated with deeper responses have a higher median DI within the first 6 months, and higher overall median DI.

Table 3 DREAMM-6: Dose Intensity Over Time (mg/kg/3-week interval)

Median mg/kg/3 weeks	1.9 Q3W (N=12)	1.9 Q6W (N=12)	2.5 Q3W (N=18)	2.5 Step-down Q6W (N=12)	2.5 Q6W (N=12)
Overall	0.89	0.79	1.06	0.74	0.79
0 to 6 months	0.87	0.44	1.01	0.69	0.57
6 to 12 months	0.78	0.42	0.72	0.51	0.54

D1 = Day 1; D8 = Day 8; Q3W = every 3 weeks; Q6W = every 6 weeks; Step-down = 1.9 mg/kg Cycles 3+

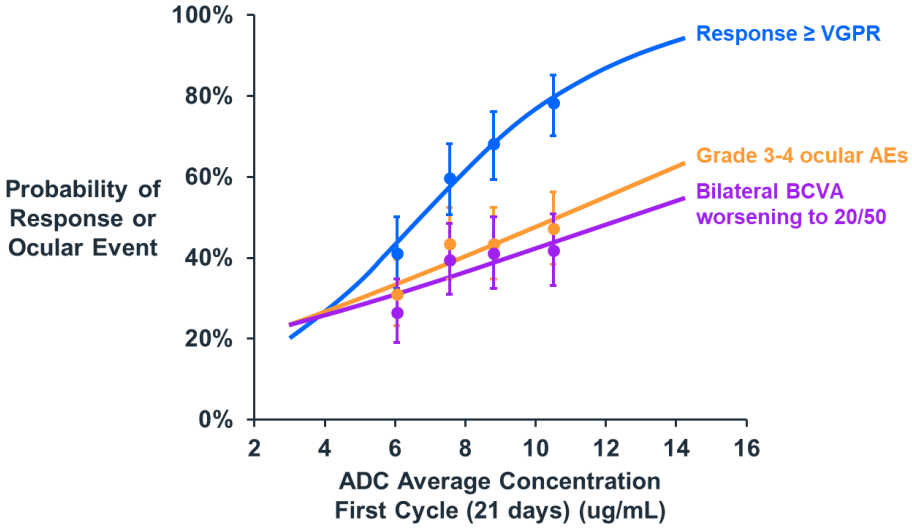
This observation was confirmed in the two pivotal trials, DREAMM-7 and DREAMM-8 where the DI was highest in the first 6 months and tapered off thereafter (Figure 5). This initial period of higher dosing is critical to elicit deeper responses which subsequently translates into long-term clinical benefit in progression free survival (PFS) and overall survival (OS).

The selected dose regimens are further supported by comprehensive and integrated exposure-response analyses. Prior clinical data supported exclusion of the 3.4 mg/kg dose from further investigation in the Phase 3 MM studies. Therefore, this dose was not included in the exposure-response analyses.

Multivariate exposure-response model prediction (Table 14) demonstrated that the BLENREP starting dose of 2.5 mg/kg with subsequent dose modifications is key to drive deeper and faster clinical response with no meaningful increase of key safety risks such as ocular symptoms (i.e., Common Terminology Criteria for Adverse Events [CTCAE], best corrected visual acuity [BCVA] changes to 20/50 or worse) compared to a starting dose of 1.9 mg/kg.

Results for a combined analysis of DREAMM-6, DREAMM-7 and DREAMM-8 are provided in Figure 4 for an overall representation. Analyses show that for most of the range of Cycle 1 BLENREP average concentration (C_{avg}), the probability of response (VGPR or better) was higher than the probability of ocular symptoms measured by Grade ≥3 ocular AEs (CTCAE) or BCVA worsening to 20/50. Overall, the starting dose of 2.5 mg/kg BLENREP in combination with Vd and Pd, with subsequent dose modification, is predicted to have a relatively higher benefit with little additional risk compared to a starting dose of 1.9 mg/kg. Integrated exposure-response figures for the individual studies and for DREAMM-14 are provided in Appendix Section 11.2.

Figure 4 DREAMM-6, DREAMM-7, DREAMM-8: Integrated Exposure-Response Relationship



ADC = antibody-drug conjugate; AE = adverse event; BCVA = best corrected visual acuity; VGPR = very good partial response
Note: Prior clinical data supported exclusion of the 3.4 mg/kg dose from further investigation in the Phase 3 MM studies. Therefore, this dose was not included in the exposure-response analyses.
Note: The independent variable was divided into quartiles. Points and error bars represent the observed proportions and 95% CIs (confidence intervals) for each quartile (plotted at the median exposure within each quartile), respectively. The curves represent the prediction of the univariate logistic regression model.
Note: Individual exposure-response analyses are provided for DREAMM-6 in Appendix Figure 2, for DREAMM-7 in Appendix Figure 3, and for DREAMM-8 in Appendix Figure 4.

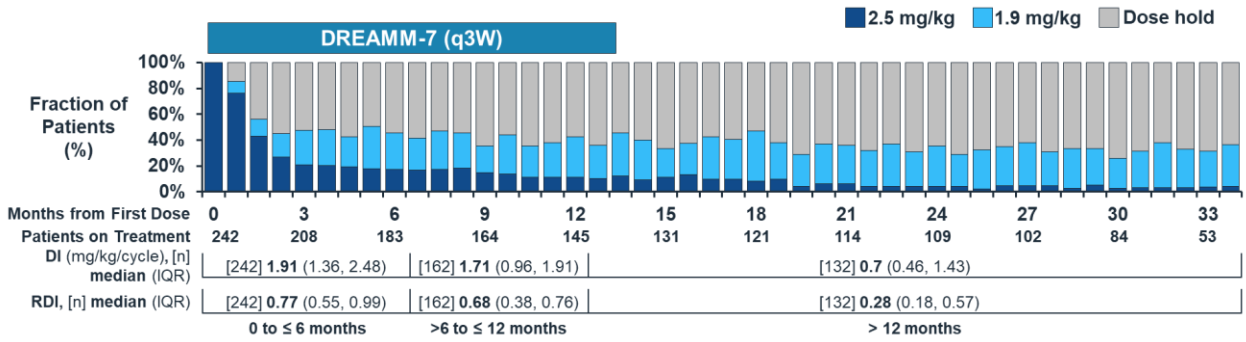
The proposed starting dosing regimens for BLENREP in combination with Vd and Pd is supported by the exposure-response modeling of a broad range of exposure levels aligned with Project Optimus guideline and by the total weight of clinical evidence. Importantly, none of the alternative regimens, including those with the different dosing frequencies, further improved the benefit: risk profile.

While there were subtle differences in dose modification guidance between the two registrational studies, physicians effectively managed ocular events in very similar ways across the two studies. The drug exposure, measured by DI and RDI, was similar between the two studies (Figure 5).

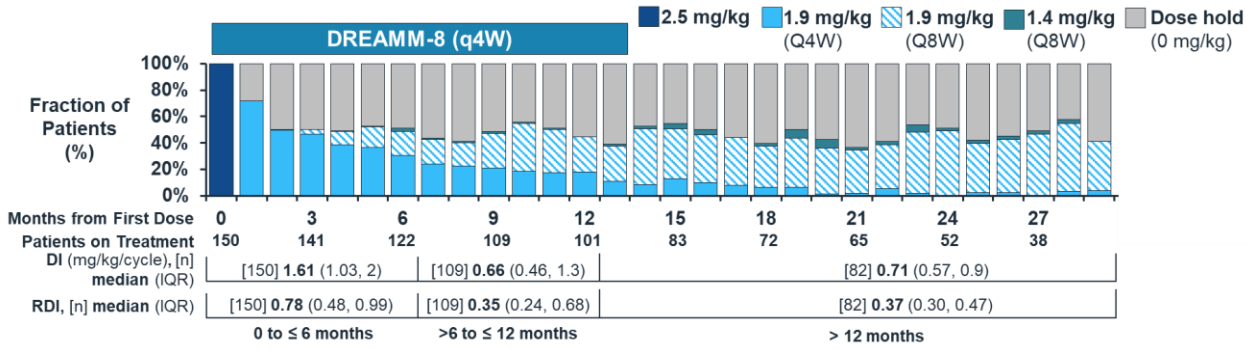
Dose intensity and RDI was higher in the first six months indicating participants received treatment more closely aligned with the protocol recommended dose and schedule. Participants also went into deeper responses whereby subsequent doses could be held to effectively manage ocular events without compromising on efficacy. Figure 5 also shows the proportion of participants receiving BLENREP at the starting schedules of Q3W (DREAMM-7) or Q4W (DREAMM-8) and subsequent dosing at reduced dose levels. Despite dose modifications after Cycle 1, a large proportion of participants in both studies received BLENREP per the protocol-specified schedule in the first six months.

Figure 5 DREAMM-7 and DREAMM-8: Dose Administration over Time

DREAMM-7:



DREAMM-8:



DI = dose intensity; IQR = interquartile range; Q#W = every # of weeks; RDI = relative dose intensity

In summary, the starting dose of 2.5 mg/kg (Q3W in DREAMM-7; Cycle 1 then step down to 1.9 mg/kg every 4 weeks Cycle 2+ in DREAMM-8) with subsequent dose modifications led to deeper and durable responses which translated into long term PFS and OS improvement across two Phase 3 trials with a consistent and manageable tolerability profile. Dose modifications, including dose delays and reductions, based on participant tolerability were effective and allowed participants to remain on treatment and derive therapeutic benefit. Further details on the dose rationale are discussed in Section 5.2.

1.4 Key Efficacy Findings

In DREAMM-7 (BVd vs. DVd, Section 6.2) and DREAMM-8 (BPd vs. PVd, Section 6.3), there was a statistically significant and clinically meaningful benefit for the BLENREP-containing triplets over SoC triplet combinations. Efficacy analyses presented in this briefing document are based on the primary analyses data cut offs (DCOs) for both studies unless otherwise noted.

The key demographic and disease characteristics of the study populations were broadly similar between the two studies (DREAMM-7: Table 15, Table 16; DREAMM-8: Table 18, Table 19) and aligned with other recent MM registration studies. In DREAMM-7, approximately half of the study population had prior lenalidomide exposure, with a third

of participants refractory to lenalidomide. In DREAMM-8, all participants (100%) had prior exposure to lenalidomide and approximately 80% were refractory to lenalidomide.

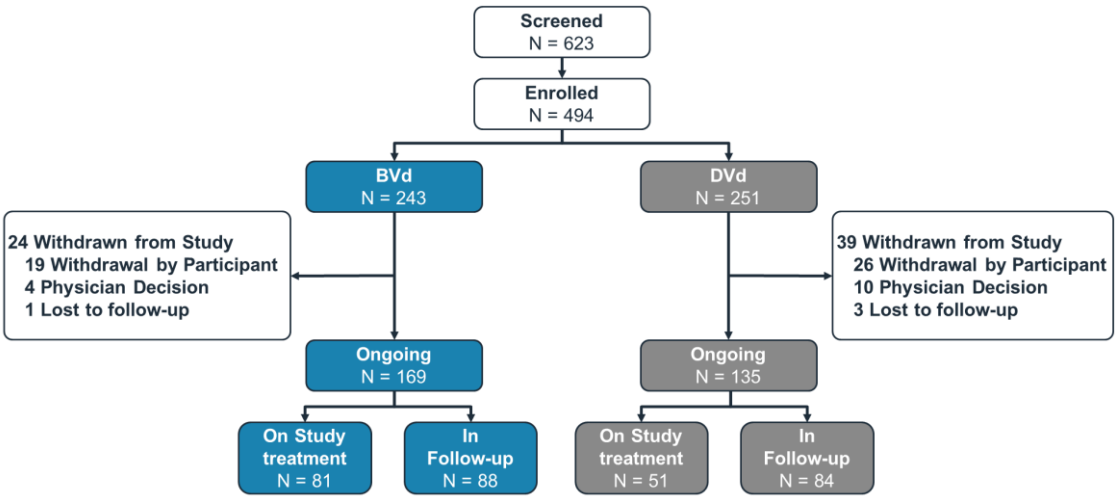
Overall, participants in both studies were representative of the RRMM population. Participants received a median of 1 prior line of therapy in both treatment groups. The types of prior anti-myeloma therapies participants received and the percentage of participants refractory to different types of prior anti-myeloma therapies were similar between treatment groups in each study. In DREAMM-8, anti-CD38 antibodies (primarily daratumumab) were previously received by 25% of participants.

In DREAMM-7, the median duration of follow up at the time of the primary analysis was 29 months in the BVd arm and 27.6 months in the DVd arm. The median duration of follow-up at the time of the most recent preplanned interim OS analysis in DREAMM-7 was 40.2 months in the BVd arm and 38.2 months in the DVd arm. In DREAMM-8, the median duration of follow-up was similar in the BPd vs. PVd groups, (22.4 months vs. 20.5 months). The median follow-up at the time of the update PFS analysis was 28.8 months in the BPd arm and 27.5 months in the PVd arm.

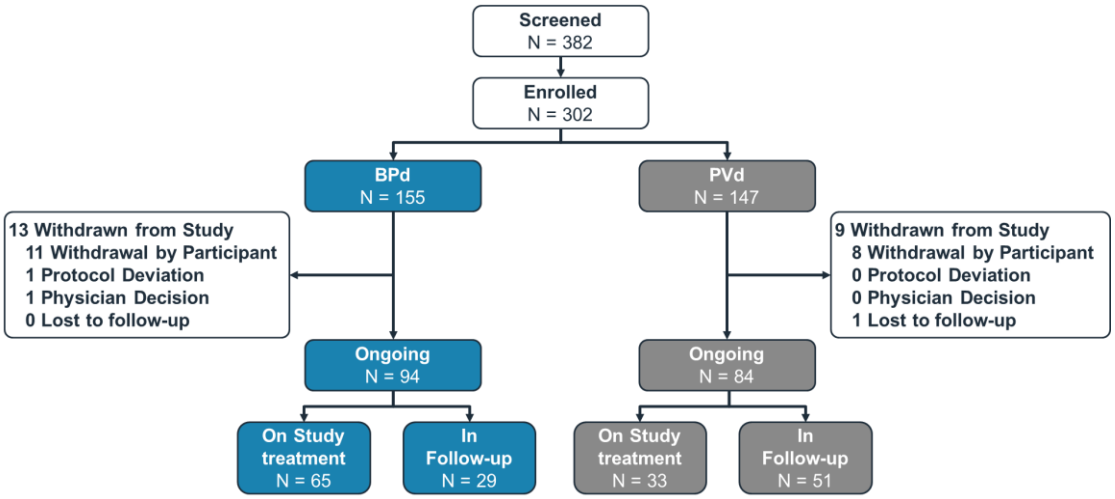
Disposition is summarized in Figure 6 and treatment status is summarized in Table 4. Almost double the proportion of participants in the comparator arms discontinued treatment due to progressive disease (PD) vs. the BLENREP combinations, which aligns with the improved PFS observed with BLENREP therapy. The proportion of participants who discontinued treatment due to an AE in the BLENREP arm was about twice that of the comparator arm in DREAMM-7 (19% vs. 9%) and was the same between arms in DREAMM-8 (16% vs. 16%). To account for participant exposure time in quantifying the risk of an AE or event of interest, exposure-adjusted event incidence rates (EAIRs) were calculated for key AE parameters.

Figure 6 DREAMM-7 and DREAMM-8: Participant Disposition

DREAMM-7:



DREAMM-8:



BVd = BLENREP, bortezomib, dexamethasone; BPd = BLENREP, pomalidomide, dexamethasone; DVd = daratumumab, bortezomib, dexamethasone; PVd = pomalidomide, bortezomib, dexamethasone

Table 4 DREAMM-7 and DREAMM-8: Participant Treatment Status

Analysis Value, n (%)	DREAMM-7		DREAMM-8	
	BVd (N=243)	DVd (N=251)	BPd (N=155)	PVd (N=147)
Treatment status				
Ongoing	81 (33%)	51 (20%)	56 (36%)	31 (21%)
Discontinued [a,b]	161 (66%)	195 (78%)	99 (64%)	116 (79%)
Primary reasons for treatment discontinuation [b,c]				
Progressive disease	59 (24%)	148 (59%)	44 (28%)	71 (48%)
Adverse event	45 (19%)	22 (9%)	25 (16%)	23 (16%)

a Includes participants who have discontinued treatment or died prior to End of Treatment Visit.
b Participants may have only 1 primary reason for discontinuation.
c Percentages for subreasons may sum to more or less than 100%. Participants may have more than one subreason underneath a single primary reason. Participants are not required to indicate subreasons.
Note: A full presentation of disposition is provided in Appendix Table 8.
Note: Treatment status for daratumumab is reported for the DREAMM-7 comparator arm and bortezomib for the DREAMM-8 comparator arm.

1.4.1 Efficacy Results in the Registrational Studies (DREAMM-7, DREAMM-8)

Across endpoints and studies, there was a consistent statistically significant and clinically meaningful benefit for the BLENREP-containing triplets over the comparator triplets. Of note, in the DREAMM-7 study, the BLENREP-containing triplet arm significantly outperformed the triplet arm that included the key early line RRMM treatment product, daratumumab, across endpoints.

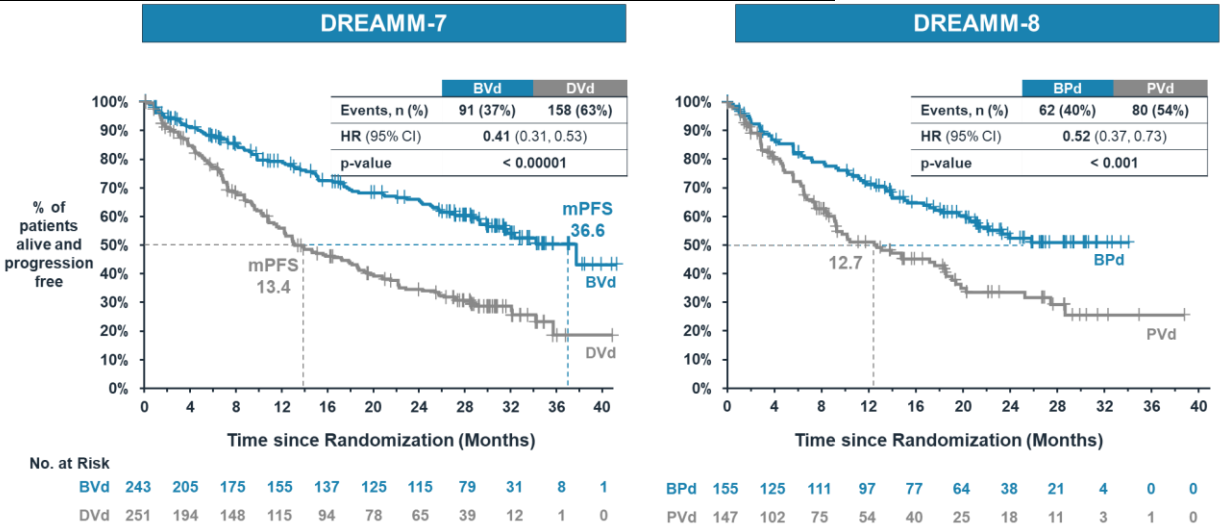
- Progression free survival (PFS): DREAMM-7 (BVd) and DREAMM-8 (BPd) met their PFS primary endpoints, demonstrating statistically significant and clinically meaningful improvements for the BLENREP arms vs. the SoC arms.

- DREAMM-7 demonstrated a 59% reduction in the risk of progression or death in DREAMM-7 (hazard ratio [HR], 95% CI: 0.41 [0.31, 0.53], p<0.00001) and an approximately 2-year improvement in mPFS (36.6 months for BVd vs. 13.4 for DVd).
- DREAMM-8 demonstrated a 48% reduction in the risk of progression or death (HR, 95% CI: 0.52 [0.37, 0.73], p<0.001). At the time of primary analysis, the median PFS was not reached in the BLENREP arm vs. 12.7 months in the comparator (Figure 7, Panel A). In an updated analysis, the mPFS was 32.6 months in the BLENREP arm vs. 12.5 months in the comparator arm. In both studies a consistently strong PFS benefit favoring the BLENREP arms was observed across subgroups, including those that are associated with worse outcomes, such as lenalidomide refractory, high-risk cytogenetics, and extramedullary disease (Figure 7, Panel B).

- Overall Survival (OS): DREAMM-7 (BVd) demonstrated a robust improvement in OS with a statistically significant 42% reduction in the risk of death (HR, 95% CI: 0.58 [0.43, 0.79], p=0.00023). At the time of this analysis there were 35 (corresponding to 13%) more deaths in the comparator arm. In DREAMM-8 (BPd), where the OS follow-up time remained low (median follow-up 21.8 months at first interim analysis), there is a positive trend in OS (Figure 8) and follow-up is ongoing.
- Response Rate and Durability: DREAMM-7 (BVd) and DREAMM-8 (BPd) demonstrate deeper and more durable responses in the BLENREP arms vs. the comparator arms. In both studies, BLENREP triplet therapy resulted in deeper responses with at least doubling of complete response (CR)/stringent CR (sCR) (Figure 9, Panel A) and two-fold increases in median durations of response (DOR) (Figure 9, Panel B).
- Minimal residual disease (MRD) negativity: DREAMM-7 and DREAMM-8 demonstrated a 2.5 to 5 times improvement in MRD negativity rate for the BLENREP arms vs. the comparator arms (Figure 10).

Figure 7 DREAMM-7 and DREAMM-8: Progression Free Survival

A Progression Free Survival: Primary Endpoint (ITT population)



B Progression Free Survival: Subgroup Analyses

DREAMM-7:

Category	BVd n/N	DVd n/N	DREAMM-7 Hazard Ratio (95% CI)
Overall*	91 / 243	158 / 251	0.41 (0.31, 0.53)
Prior LOT – 1	46 / 125	76 / 125	0.52 (0.36, 0.76)
Prior LOT – > 1	45 / 118	82 / 126	0.36 (0.25, 0.52)
Prior Bortezomib – Yes	79 / 210	132 / 211	0.45 (0.34, 0.59)
Prior Bortezomib – No	12 / 33	26 / 40	0.42 (0.21, 0.84)
Prior Lenalidomide – Yes	44 / 127	88 / 130	0.33 (0.23, 0.48)
Prior Lenalidomide – No	47 / 116	70 / 121	0.57 (0.39, 0.83)
Refractory to Lenalidomide – Yes	33 / 79	64 / 87	0.37 (0.24, 0.56)
Refractory to Lenalidomide – No	58 / 164	94 / 164	0.48 (0.34, 0.67)
Refractory to Anti-CD38 – Yes	NA	NA	NA
Refractory to Anti-CD38 – No	NA	NA	NA
R-ISS Staging at Screening – I	37 / 102	64 / 103	0.42 (0.28, 0.64)
R-ISS Staging at Screening – II / III	53 / 139	94 / 146	0.45 (0.32, 0.64)
Age < 65 years	42 / 121	84 / 126	0.39 (0.27, 0.56)
Age 65 - < 75 years	37 / 85	61 / 95	0.48 (0.32, 0.73)
Age ≥ 75 years	12 / 37	13 / 30	0.62 (0.28, 1.38)
Female	48 / 115	59 / 107	0.59 (0.40, 0.87)
Male	43 / 128	99 / 144	0.35 (0.25, 0.50)
Time to Relapse After Initiation of 1L Treatment – ≤ 12 months**	23 / 49	31 / 50	0.46 (0.26, 0.79)
Time to Relapse After Initiation of 1L Treatment – > 12 months**	68 / 194	127 / 201	0.43 (0.32, 0.58)
Cytogenetics Risk – High Risk	26 / 67	48 / 69	0.36 (0.22, 0.58)
Cytogenetics Risk – Standard Risk	65 / 175	106 / 175	0.48 (0.35, 0.65)
Extramedullary Disease at Baseline – Yes	8 / 13	18 / 25	0.57 (0.24, 1.34)
Extramedullary Disease at Baseline – No	83 / 230	140 / 226	0.44 (0.34, 0.58)

DREAMM-8:

Category	BPd n/N	PVd n/N	DREAMM-8 Hazard Ratio (95% CI)
Overall*	62 / 155	80 / 147	0.52 (0.37, 0.73)
Prior LOT – 1	25 / 82	34 / 77	0.52 (0.31, 0.88)
Prior LOT – > 1	37 / 73	46 / 70	0.52 (0.33, 0.80)
Prior Bortezomib – Yes	54 / 134	70 / 130	0.55 (0.38, 0.78)
Prior Bortezomib – No	8 / 21	10 / 17	NA
Prior Lenalidomide – Yes	62 / 155	80 / 147	0.52 (0.37, 0.73)
Prior Lenalidomide – No	NA	NA	NA
Refractory to Lenalidomide – Yes	54 / 125	70 / 111	0.45 (0.31, 0.65)
Refractory to Lenalidomide – No	8 / 30	10 / 36	NA
Refractory to Anti-CD38 – Yes	20 / 35	25 / 36	0.65 (0.36, 1.18)
Refractory to Anti-CD38 – No	42 / 120	55 / 111	0.49 (0.33, 0.75)
ISS Staging at Screening – I	33 / 93	46 / 85	0.48 (0.30, 0.75)
ISS Staging at Screening – II / III	29 / 61	34 / 62	0.62 (0.38, 1.02)
Age < 65 years	28 / 64	27 / 53	0.64 (0.37, 1.09)
Age 65 - < 75 years	29 / 72	34 / 59	0.48 (0.29, 0.79)
Age ≥ 75 years	5 / 19	19 / 35	0.40 (0.15, 1.07)
Female	17 / 56	33 / 65	0.44 (0.25, 0.80)
Male	45 / 99	47 / 82	0.58 (0.39, 0.88)
Time to Relapse After Initiation of 1L Treatment – ≤ 12 months	8 / 22	12 / 20	0.26 (0.10, 0.68)
Time to Relapse After Initiation of 1L Treatment – > 12 months	54 / 133	68 / 127	0.58 (0.40, 0.83)
Cytogenetics Risk – High Risk	29 / 52	31 / 47	0.57 (0.34, 0.95)
Cytogenetics Risk – Standard Risk	24 / 72	35 / 75	0.51 (0.30, 0.86)
Extramedullary Disease at Baseline – Yes	13 / 20	9 / 11	0.67 (0.28, 1.59)
Extramedullary Disease at Baseline – No	49 / 135	71 / 136	0.48 (0.33, 0.70)

1L = first line; BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib, dexamethasone; CI = confidence interval; DVd: daratumumab, bortezomib, dexamethasone; ITT = intent to treat; LOT = lines of therapy; mPFS = median progression free survival; PVd = pomalidomide, bortezomib, dexamethasone; R-ISS = revised International Staging System

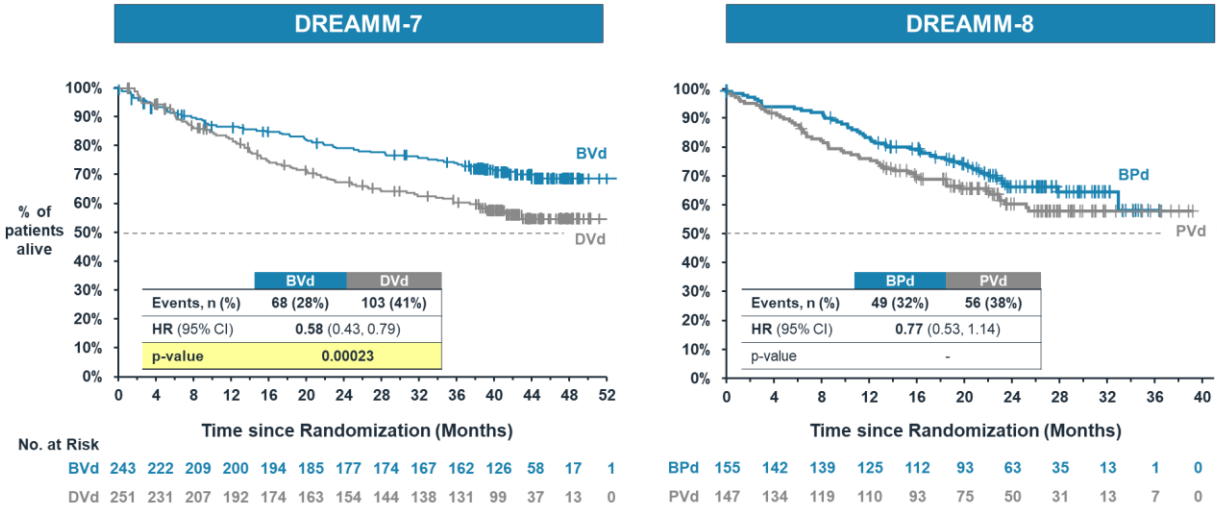
* stratified

** Post-hoc analysis for DREAMM-7

Note: 1.R-ISS staging was used for DREAMM-7; ISS Staging was used for DREAMM-8; Time to relapse is after completion of treatment for DREAMM-7 and after initiation of 1L treatment for DREAMM-8

More detailed results for PFS are provided in Table 17 (DREAMM-7) and Table 20 (DREAMM-8).

Figure 8 DREAMM-7 and DREAMM-8: Overall Survival (ITT Population)



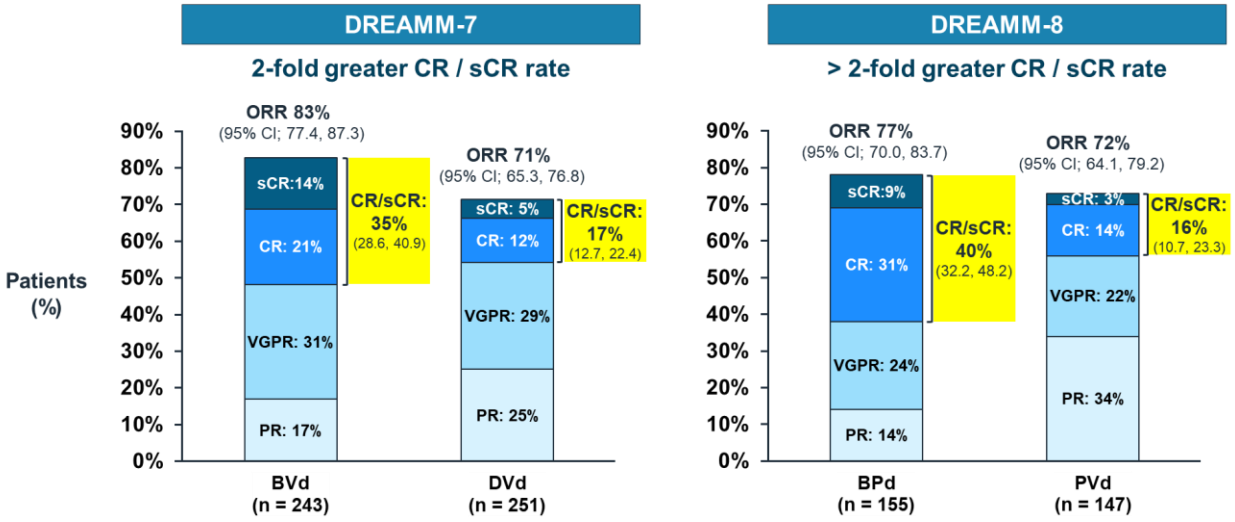
BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib, dexamethasone; DVd: daratumumab, bortezomib, dexamethasone; ITT = intent to treat; OS = overall survival; PVd = pomalidomide, bortezomib, dexamethasone.

More detailed results for OS are provided in Table 17 (DREAMM-7) and Table 20 (DREAMM-8).

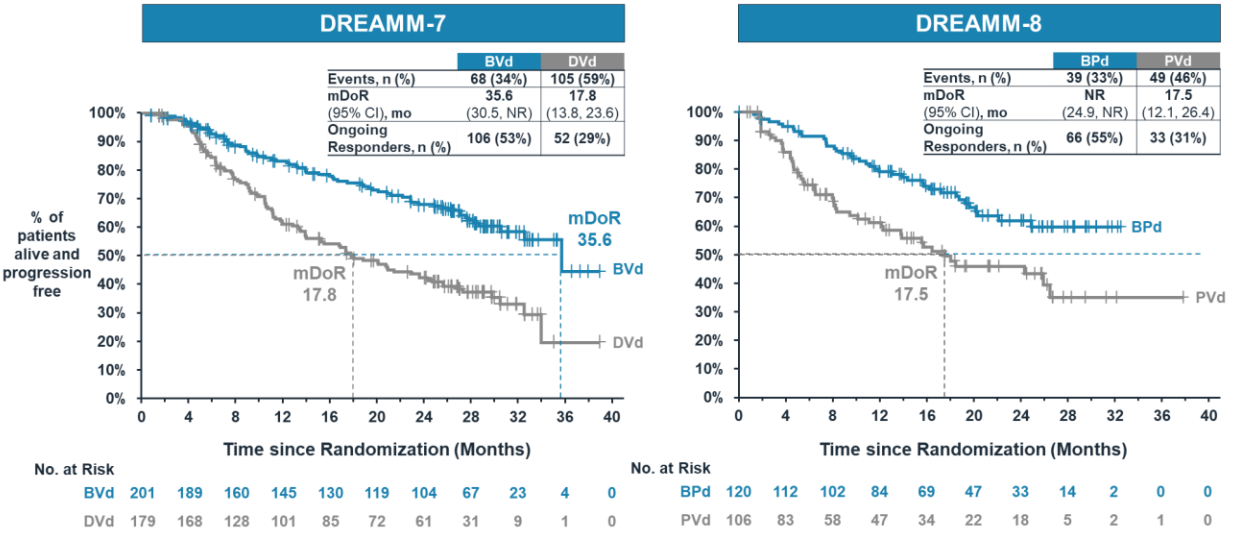
Note: DREAMM-7 OS from the October 2024 prespecified updated interim analysis.

Figure 9 DREAMM-7 and DREAMM-8: Independent Reviewer-Assessed Confirmed Response and Duration of Response (IMWG Criteria) (ITT Population)

A Overall Response Rate

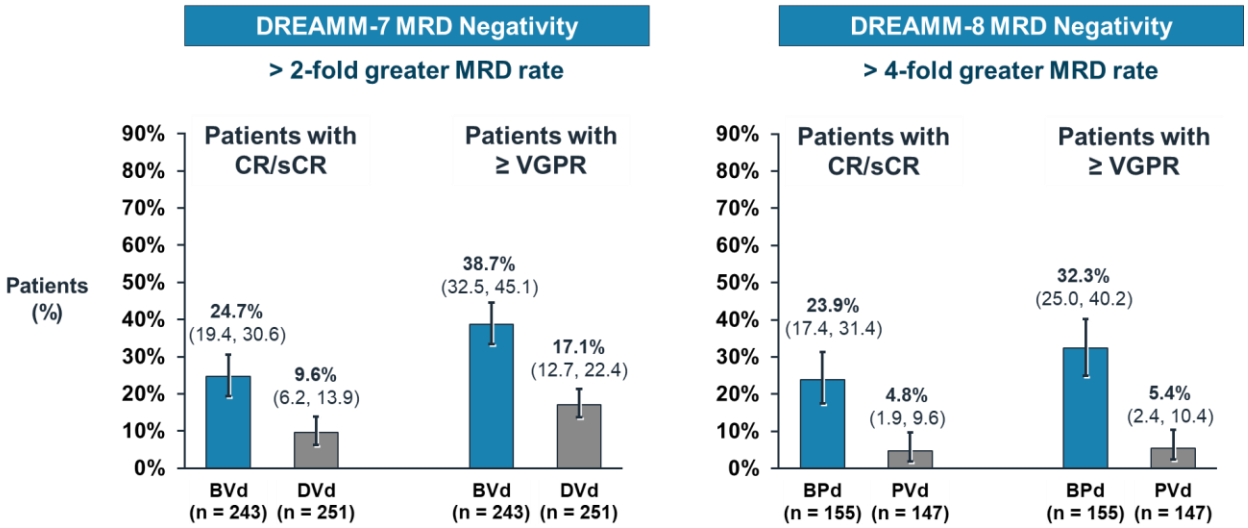


B Duration of Response



BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib, dexamethasone; CR = complete response; DOR = duration of response; DVd: daratumumab, bortezomib, dexamethasone; IMWG = International Myeloma Working Group; ITT = intent to treat; NR = not reached; ORR = overall response rate; PR = partial response; PVd = pomalidomide, bortezomib, dexamethasone; sCR = stringent complete response; VGPR = very good partial response.
More detailed results are provided in Table 17 (DREAMM-7) and Table 20 (DREAMM-8).

Figure 10 DREAMM-7 and DREAMM-8: Independent Reviewer-Assessed Minimal Residual Disease Negativity (ITT Population)



BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib, dexamethasone; CR = complete response; DVd: daratumumab, bortezomib, dexamethasone; ITT = intent to treat; MRD = minimum residual disease; PVd = pomalidomide, bortezomib, dexamethasone; sCR = stringent complete response; VGPR = very good partial response.
More detailed results are provided in Table 17 (DREAMM-7) and Table 20 (DREAMM-8).

1.4.2 Efficacy Conclusions

Two independent, randomized Phase 3 studies consistently demonstrated clinically meaningful benefits of BLENREP arms over SoC arms across all endpoints, including statistically significant improvement in overall survival from the DREAMM-7 study. In both registrational studies, the primary efficacy results are consistently supported by the subgroup analyses and prespecified secondary endpoints. BLENREP demonstrated compelling efficacy against the gold standard MM therapy of daratumumab in DREAMM-7, and in participants refractory to lenalidomide and anti-CD38 antibody in DREAMM-8. Further, BLENREP was effective in participants with high-risk cytogenetics or extramedullary disease. Overall, the efficacy data demonstrate the promise of BLENREP as an effective therapy in the evolving MM treatment landscape.

1.5 Key Safety Findings

The overall safety of BLENREP in DREAMM-7 and DREAMM-8 is consistent with its well-characterized and previously established safety profile in participants with RRMM. Ocular events are the predominant adverse event associated with BLENREP.

1.5.1 Extent of Exposure

Participants in the BLENREP arms of DREAMM-7 and DREAMM-8 had a longer duration of exposure to study treatment vs. those in the comparator arms by 3 to 8 months (15.9 vs. 12.9 months and 16.5 vs. 8.5 months, respectively). The overall relative dose intensity of BLENREP throughout treatment was about 50% for each study (Table 5). As

noted in Section 5.2, both the DI and RDI was highest in the first 6 months of treatment and tapered off thereafter indicating participants received treatment more closely aligned to the protocol recommended dose and schedule initially after which there was more dose modification.

Table 5 DREAMM-7 and DREAMM-8: Dose Intensity and Relative Dose Intensity Over Time

	DREAMM-7	DREAMM-8
Median (IQR)	**BVd (N=242)**	**BPd (N=150)**
Dose intensity (mg/kg/Q3W or Q4W)		
Overall	(n=242) 1.27 (0.72, 2.22)	(n=150) 1.04 (1.03, 2)
0-≤6 months	(n=242) 1.91 (1.36, 2.48)	(n=150) 1.61 (0.4, 2.5)
>6-≤12 months	(n=162) 1.71 (0.96, 1.91)	(n=109) 0.66 (0.21, 1.93)
>12 months	(n=132) 0.7 (0.46, 1.43)	(n=82) 0.71 (0.33, 1.97)
Relative dose intensity (%)		
Overall	(n=242) 50.1 (29, 89)	(n=150) 52.5 (18.6, 100.4)
0-≤6 months	(n=242) 77 (55, 99)	(n=150) 78 (16, 102)
>6-≤12 months	(n=155) 68 (38, 76)	(n=109) 35 (11, 102)
>12 months	(n=130) 28 (18, 57)	(n=82) 37 (17, 103)

BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib, dexamethasone; DVd = daratumumab, bortezomib, dexamethasone; IQR = interquartile range; PVd = pomalidomide, bortezomib, dexamethasone

Most participants reduced to a BLENREP dose of 1.9 mg/kg during the study (due to dose reduction in DREAMM-7 [69%], or per the step-down regimen at Cycle 2 in DREAMM-8 [100%]). Exposure is further discussed in Section 7.2.

1.5.2 Adverse Events

Table 6 provides an overview of AEs in the two registrational studies. All reported AEs are treatment emergent. Serious adverse events and events leading to a dose modification occurred in more participants receiving BLENREP (Table 6). The fatal events were balanced across treatment arms and studies. Adverse events are discussed further in Section 7.4.

Given the longer time on treatment with BLENREP combinations relative to the SoC, the sponsor also computed the EAIRs to evaluate the incidence of safety events when accounting for a longer time on treatment in the BLENREP arms. Given the likelihood of

experiencing certain toxicities (e.g., thrombocytopenia, infections) increases the longer participants remain on-treatment, the EAIRs also provide a view on the incidence of adverse events when adjusting for time on treatment.

Table 6 DREAMM-7 and DREAMM-8: Overview of Adverse Events and Exposure-Adjusted Adverse Events

	DREAMM-7 n (%)		DREAMM-7 EAIR [c]		DREAMM-8 n (%)		DREAMM-8 EAIR	
Parameter	**BVd N=242**	**DVd N=246**	**BVd N=242**	**DVd N=246**	**BPd N=150**	**PVd N=145**	**BPd N=150**	**PVd N=145**
Any adverse event, (n%)	242 (100%)	246 (100%)	60.2	71.7	149 (>99%)	140 (97%)	59.8	91.3
Adverse events related to any study treatment	242 (100%)	234 (95%)	-	-	143 (95%)	120 (83%)	-	-
Maximum Grade 3 or 4 adverse events [a]	205 (85%)	176 (72%)	51.0	51.3	123 (82%)	95 (66%)	49.4	61.9
Adverse events leading to permanent discontinuation of any study treatment	77 (32%)	47 (19%)	19.1	13.7	28 (19%)	21 (14%)	11.2	13.7
Adverse events leading to dose reduction	181 (75%)	146 (59%)	44.99	42.58	94 (63%)	88 (61%)	37.72	57.38
Adverse events leading to dose interruption/delay	229 (95%)	186 (76%)	56.92	54.25	137 (91%)	110 (76%)	54.97	71.72
Any serious adverse event, n (%)	129 (53%)	94 (38%)	32.07	27.42	101 (67%)	68 (47%)	40.53	44.34
Fatal serious adverse events [b]	26 (11%)	20 (8%)	6.5	5.8	19 (13%)	18 (12%)	7.6	11.7

BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib, dexamethasone; DVd: daratumumab, bortezomib, dexamethasone; EAIR = exposure-adjusted incidence rate; PVd: bortezomib, pomalidomide, dexamethasone

a Includes participants reporting any Grade 3 or Grade 4 event at any time during the study.

b If a fatal SAE occurred but no active decision to discontinue study treatment before death occurred, then the fatal SAE was not reported as leading to study treatment discontinuation. If an AE led to decision to discontinue treatment prior to a fatal outcome, then the AE was reported as leading to study treatment discontinuation.

c The exposure-adjusted incidence rate (EAIR) is defined as the [number of participants with the event(s)/total person-years]×100 where the total person-years is the sum of person-years for all participants within the treatment arm, which is calculated as last dose - first dose + 1) / 365.25.

Nearly all (≥ 97%) participants in the registrational studies experienced an AE, and AEs reported with greatest frequency in participants receiving BLENREP were ocular events (Section 1.5.3). Other common AEs reported ≥20% in at least one of the two registrational studies included thrombocytopenia, diarrhea, infections (e.g., COVID-19, pneumonia, upper respiratory infection), fatigue, neuropathy, neutropenia, and anemia. Common AEs (≥20%) are summarized in Appendix Table 9.

The proportion of participants receiving BLENREP reporting Grade 3 and 4 AEs (maximum grade, by CTCAE) was comparable between DREAMM-7 (85%) and

DREAMM-8 (82%) (Table 21). Events in the SOC Blood and lymphatic disorders were the most common of Grade 3/4 events, and PTs included thrombocytopenia, neutropenia, anaemia, and lymphopenia. Consistent with the known safety profile of BLENREP, ocular AEs (by CTCAE) were more prevalent in the BLENREP arms (38% and 49%). Grade 3 and higher events are discussed further in Section 7.5.

A greater proportion of participants treated with BLENREP combinations experienced SAEs. The EAIRs were similar between the BLENREP and comparator arms in each study (Table 22), suggesting that when adjusting for longer exposure, the incidence of SAEs was similar to the SoC comparators. The most frequently reported SAEs (≥3%) were pneumonia, COVID-19 or COVID-19 pneumonia, pyrexia, neutropenia, febrile neutropenia, and thrombocytopenia. There were no ocular events reported as an SAE. SAEs are discussed in Section 7.8.

Adverse events leading to dose modifications (of any agent of the triplet regimen) were more frequent in the BLENREP arms than in the comparator arms of DREAMM-7 (98% vs. 89%) and DREAMM-8 (91% vs. 86%). An overview of dose modifications (any treatment component) is provided in Table 23 and discussed in Section 7.8.1.

A larger proportion of participants in the BLENREP arms experienced AEs leading to permanent discontinuation of study treatment vs. the comparator arms - 32% vs. 19% in DREAMM-7 and 19% vs.14% in DREAMM-8 (discussed in Section 7.8.2). Events in DREAMM-7 leading to permanent discontinuation of study drug in ≥1% of participants included peripheral sensory neuropathy, neuropathy peripheral, polyneuropathy, pneumonia, Covid-19, Covid-19 pneumonia, thrombocytopenia, sepsis, and vision blurred (Table 24). In DREAMM-8, events leading to permanent discontinuation of study drug included fatigue, keratopathy, muscular weakness, and neuralgia (Table 25).

1.5.3 Ocular Events

1.5.3.1 Introduction

BLENREP has a stable, well-characterized safety profile that includes ocular events. Overall, the ocular safety profile was comparable between the BLENREP treatment arms in the two registrational studies. Most participants treated with BLENREP experienced one or more ocular adverse events or had ophthalmic examination findings, as summarized in this section and discussed in detail in Section 7.10.

- Ocular findings on ophthalmic examination are confined to the corneal epithelium and are primarily superficial punctate keratopathy (SPK), microcyst-like deposits, and sub-epithelial haze. Such corneal changes have been seen with other approved ADC products and are not unique to BLENREP.
- BLENREP can enter some cells through macropinocytosis, releasing cys-mcMMAF, which accumulates within the cells, leading to apoptosis. Because events occur in the corneal epithelium (Figure 25), which is continuously renewed, events are transient, manageable with dose modifications (dose holds and reductions), and generally resolve with adequate follow-up.

- Most participants (65%) did not experience a clinically meaningful change in vision of bilateral 20/50 or worse. For the about 35% of participants who did experience a clinically meaningful change at some point on treatment, the majority of these changes in vision (87% to 91%) resolved with follow-up. These participants experienced such worsening in vision for a mean of 11-14% of their time on-treatment.
- Severe ocular events were infrequent or rare and resolved with follow-up.
    - Bilateral 20/200 or worse occurred in 1-2% (5 participants in DREAMM-7; 2 participants in DREAMM-8), the majority (4 in DREAMM-7; 1 in DREAMM-8) of which had resolved at the time of data cutoff with remaining 2 participants being lost to follow-up.
    - There were 3 (< 0.1%) cases of infected ocular ulcers in >7500 patients treated globally based on both the clinical trial and real-world experience. The infection resolved in all three cases, and in 1 case the patient was lost to follow-up prior to vision resolving.
- Discontinuations attributed to ocular events occurred in 10% and 11% of participants receiving BLENREP in DREAMM-7 and DREAMM-8, respectively, with a majority (85-90%) of these participants achieving benefit from BLENREP before treatment discontinuation.

1.5.3.2 Assessment of Ocular Events

A comprehensive assessment of ocular events, described in Figure 11 and Section 7.10, was based on:

1. Ocular AEs/symptoms defined by the CTCAE (v5) library; and
2. Ophthalmic visits that included corneal examination findings identified by slit-lamp and an assessment of best corrected visual acuity (BCVA) using Snellen equivalent.

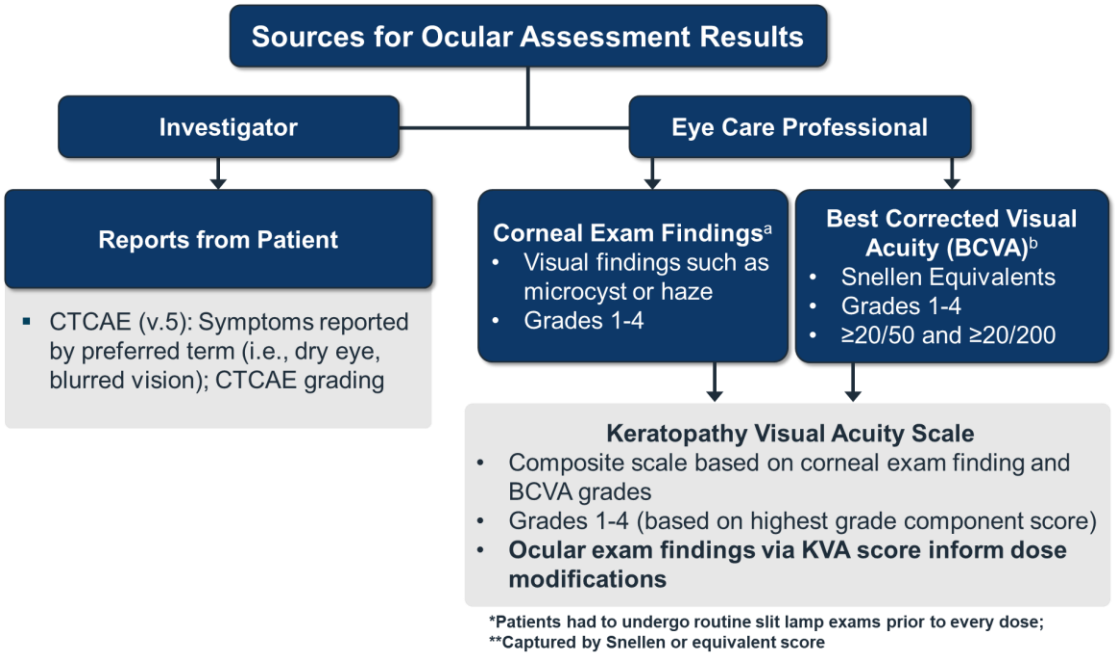
Corneal findings were graded using the KVA scale, a composite scale of corneal and BCVA findings developed by the applicant to guide BLENREP dose modifications in clinical studies.

Ophthalmic exams were performed at each cycle before BLENREP dosing. The eye care professional's findings were communicated to the oncologist, and the oncologist determined the appropriate dose modification based on protocol specifications. The protocol specified that if there were no ocular findings by the sixth dose of BLENREP, visits were reduced to once every three months. Additional ophthalmic visits occurred as clinically indicated based on the occurrence of ocular events. Assessments occurred before dosing and the severity of findings on the KVA scale (i.e., Grade ≥2) determined decisions on dose modifications.

Patient-reported outcome measures (PROs) relevant to ocular safety were collected, including the Ocular Surface Disease Index (OSDI) and a two-item unvalidated questionnaire assessing the ability of participants to read and drive, collected by the eye

care professional prior to each ocular examination. Results are discussed in Section 1.5.6.

Figure 11 Comprehensive Assessment of Ocular Events



CTCAE = Common Toxicity Criteria for Adverse Events; KVA = Keratopathy Visual Acuity scale
*Participants had routine slit lamp exams prior to every dose; **Captured by Snellen or equivalent score

Assessment of ocular events was also conducted for the comparator arms (discussed in Section 7.10.1.) but occurred at a much lower frequency compared to the BLENREP arms, limiting direct comparisons between groups. However, the assessment of ocular events in the comparator arms demonstrated a 'background' event rate in the generally older patient population in the absence of exposure to BLENREP. The incidence of ocular events by CTCAE was 31% (DVd) and 32% (PVd), with vision blurred being most common, and the incidence of sponsor-assessed corneal events by KVA was 54% (DVd) and 43% (PVd), predominately Grade 1 and Grade 2 severity.

1.5.3.3 Use of Dose Modifications to Manage Ocular Events

The use of dose modifications (i.e., dose reductions and dose delays) based on the occurrence of ocular events is the most effective and practical approach to managing ocular events. BLENREP dose modification allowed the cornea to heal and ocular events to resolve. DREAMM-7 and DREAMM-8 had protocol-defined dose modifications as summarized in Table 7.

Table 7 DREAMM-7 and DREAMM-8: Protocol-defined Dose Modifications

	DREAMM-7 (BVd) (Cycle Length = 3 Weeks)	DREAMM-8 (BPd) (Cycle Length = 4 Weeks)
Recommended Starting Dose Schedule	2.5 mg/kg Q3W	2.5 mg/kg once on Cycle 1, followed by 1.9 mg/kg Q4W starting on Cycle 2
Reduced Dose Level 1	1.9 mg/kg Q3W	1.9 mg/kg Q8W
Reduced Dose Level 2	Not Applicable	1.4 mg/kg Q8W

Q#W = every # weeks

In both studies, the need for dose modification for an ocular event was determined by the occurrence of a KVA Grade 2+ event. Dose modifications of BLENREP occurred frequently - most study participants (83% to 95%) required a dose modification to a lower dose or dose frequency.

- In DREAMM-7, 75% of participants had a reduction from 2.5 mg/kg to 1.9 mg/kg. In DREAMM-8, dose reduction from 2.5 mg/kg to 1.9 mg/kg occurred following Cycle 1 per protocol; thereafter, 58% of participants reduced to a Q8W schedule. Very few participants reduced to 1.4 mg/kg.
- Dose delays due to ocular events occurred in 78% and 83% of participants in DREAMM-7 and DREAMM-8, respectively. The duration of delay extended over time with a median duration of delay of ~8 weeks. Nearly all responders (97% for DREAMM-7 and 99% for DREAMM-8) had at least one dose delay with a majority (74% and 73%) requiring ≥ 3 dose delays indicating nearly all participants who benefited from treatment went through multiple dose modifications.

Dose modifications specific to ocular events are further discussed in Section 7.10.7. and the interaction between the eyecare professionals and the treating oncologists is illustrated in Figure 27.

The totality of the ocular safety data from DREAMM-7 and DREAMM-8 demonstrate that the implementation of the protocol-specified dose modifications (dose reduction and/or dose delay) allow participants to remain on BLENREP and gain benefit. Importantly, the strong efficacy observed in both pivotal studies was in the context of these dose modifications, including extended dose intervals after the starting schedule of every 3 to 4 weeks.

1.5.3.4 Best Corrected Visual Acuity (BCVA)

A worsening of BCVA to 20/50 or greater on the Snellen scale is considered clinically impactful to participants. Reduction in BCVA to 20/50 in participants with normal vision at baseline means participants see less clearly and having at least 20/50 vision is a cut-off for driving in many US states. Images simulating real-life vision a participant would experience are provided in Figure 26. Bilateral BCVA of 20/200 defines severe visual impairment.

Table 28 presents the onset, duration, outcome, and occurrence of BCVA events of worsening to 20/50 or worse and to 20/200 or worse.

- There were no discernable differences in the impact on BCVA between the BVd and BPd arms of the registrational studies; 34 to 35% of participants receiving BLENREP had worsening of BCVA to 20/50 or worse with median time to onset of first occurrence of 79 to 112 days. The worsening was transient with 93% of first occurrences resolved in DREAMM-7 and 88% in DREAMM-8 at the time of the DCO, with a median time to resolution of 63.5 and 57 days. Remaining participants were either still in follow-up or lost to follow-up at the time of the DCO. Overall, these events were generally reversible with time and effectively managed with dose modifications allowing participants to remain on treatment and benefit from BLENREP.
- Declines in BCVA to a bilateral worsening to 20/200 or worse were infrequent (1-2%, 5 participants in DREAMM-7 and 2 participants in DREAMM-8) and resolved in 5 of 7 cases at the time of each study's DCO. For two participants the event was not resolved when follow-up was discontinued. From the clinical program and post-marketing data, there were no cases of permanent bilateral vision loss of 20/200 or worse observed in over 7500 patients treated to date with BLENREP.

1.5.3.5 Corneal Examination Findings Identified by Slit Lamp Exam

Besides BCVA changes, corneal examination findings identified by slit lamp exam were frequent and primarily included SPK, microcyst-like deposits, and sub-epithelial haze. The clinical significance of these findings is often unclear given that events may be asymptomatic. In many cases changes were not accompanied by clinically meaningful vision loss. In DREAMM-7 and DREAMM-8, about 90% of participants had a corneal exam finding (~83% ≥Grade 2) but only about 35% experienced a BCVA worsening of 20/50 or worse. Most corneal examination findings resolved with adequate follow-up (90% and 91% in DREAMM-7 and DREAMM-8, respectively), after which the participants could resume BLENREP. Corneal examination findings identified by slit-lamp examination are summarized in Table 29 and discussed further in Section 7.10.3.

1.5.3.6 Keratopathy and Visual Acuity (KVA) Scale

A sponsor-assessment of ophthalmic examination findings was conducted using the GSK KVA scale. Ophthalmic examination findings by sponsor-assessed KVA scale occurred in most participants receiving BLENREP (93% in DREAMM-7, 95% in DREAMM-8) with 13% to 15% being Grade 1 or 2 (Table 29). Events were managed with dose modifications until events resolved to baseline or Grade 1.

Ocular events by KVA grade also occurred in the comparator arms – 54% in the DVd arm (25% ≥ Grade 2); 43% of participants in the PVd arm (24% ≥ Grade 2).

In the BLENREP arms, the majority of first occurrences resolved (80% and 85% for DREAMM-7 and DREAMM-8); 20% and 15% of first occurrence events were ongoing e at the time of the DCO. The majority of participants in both studies continued treatment with BLENREP on (in the case of Grade 1) or after resolution (in the case of Grade 2 or

3) of their first KVA event. KVA-graded events could recur multiple times; however, they were predictable including both the time to resolution and the management of events through dose modification. The KVA Scale events are described in more detail in Section 7.10.4

1.5.3.7 Ocular Adverse Events (By CTCAE)

Ocular adverse events were reported by 80% and 89% of participants in the DREAMM-7 and DREAMM-8 BLENREP arms, respectively, vs. 31% and 32%, respectively, of participants in the comparator arms. The most frequently reported ocular AEs were vision blurred, dry eye, photophobia, and foreign body sensation in eye (Table 30). Most participants required dose modification to manage ocular AEs. The majority of occurrences had resolved at the time of the latest DCO (84% in DREAMM-7 and 84% in DREAMM-8). Adverse events by CTCAE grade are discussed in Section 7.10.5.

1.5.4 Non-Ocular Adverse Events of Special Interest and Adverse Events of Clinical Interest

Thrombocytopenia and infusion related reactions (IRRs) were non-ocular adverse events of special interest (AESIs). Hepatobiliary disorders and infections were identified as key AEs of clinical interest. Events of thrombocytopenia reported in the BLENREP arms of DREAMM-7 and DREAMM-8 were characterized by low SAE rates (5% and 2%, respectively), low rates of Grade 3/4 decreased platelet counts associated with Grade ≥2 bleeding events, and high resolution rates (71% and 79%, respectively). Treatment discontinuation rates due to thrombocytopenia were low in both studies (DREAMM-7 [3% BVD, 1% DVD], DREAMM-8 [0% both arms]) (Section 7.12.1). No Grade 3 or higher infusion-related reactions were reported in the BVd arm in DREAMM-7. In the BPd arm in DREAMM-8, Grade 3 IRRs were reported in 2 (1%) participants; no Grade 4 or Grade 5 events were reported. In the majority of participants for both studies, IRRs were managed by dose interruption and resolution was documented.

Regarding events of clinical interest, the incidence of hepatobiliary disorders in the BLENREP arms of DREAMM-7 and DREAMM-8 was low (Section 7.13.2). Changes in ALT (ALT ≥5xULN) and other biochemical parameters of liver function were seen in a higher proportion of participants in the BLENREP arm in DREAMM-7, and in DREAMM-8 in similar proportions vs. the comparator arms. Infections were characterized by high resolution rates, low treatment discontinuation rates, and low rates of fatal SAEs (Section 7.12.2). Upper respiratory tract infection, pneumonia, and COVID-19 were the most frequently reported preferred terms (PTs) in the Infections and infestations SOC. The EAIRs for all grade infections were higher in the SOC arms in both studies, but Grade 3 or higher events occurred more frequently in the BLENREP arms (Table 36).

1.5.5 Deaths

In both registrational studies, there were more deaths in the comparator arms than the BLENREP arms: 37% (DVd) and 39% (PVd) compared to 26% (BVd) and 36% (BPd)

(Table 26). The disease under study (RRMM) was the most common cause of death. Deaths are discussed in Section 7.9.

The rates of fatal SAEs in the BLENREP arms were relatively low (10% to 13%) and similar to the comparator arms (8% to 12%) in the registrational studies. A summary of fatal SAEs is provided in Appendix Table 11. Overall, pneumonia and COVID-19 related illness were the most frequently reported fatal SAEs.

1.5.6 Patient Reported Outcomes Related to Ocular Safety

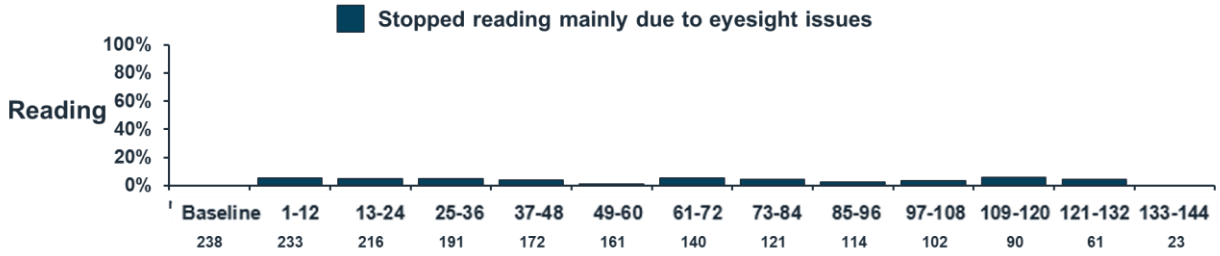
Despite the incidence of ocular events in participants receiving BLENREP, overall patient-reported quality of life (QoL) as measured by EORTC-QLQ-C30, which includes functional scales assessing physical, role, cognitive, emotional, and social functioning and symptom scales was maintained over time in both studies and there was no differences between the BLENREP and comparator groups (Figure 17, Figure 21).

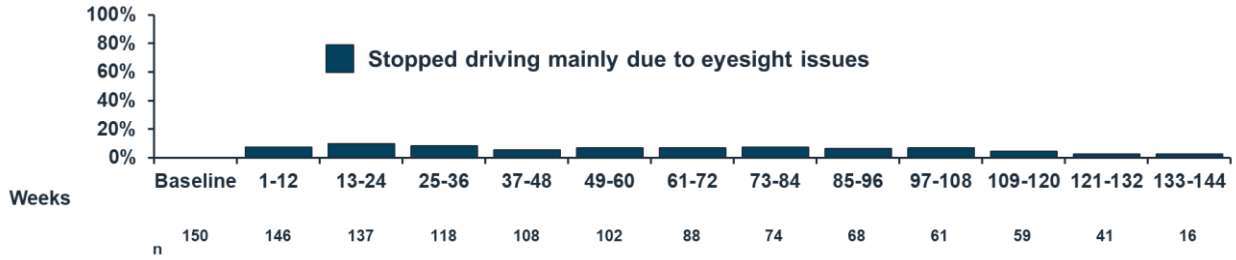
The OSDI was designed to assess the frequency of dry eye symptoms and their impact on vision-related functioning. Minimally important deterioration is the smallest change in a participants OSDI score that reflects a meaningful worsening of their vision-related function, as perceived by the participant or clinician.

In the registrational studies, participants who experienced minimally important deteriorations in vision-related functioning of the OSDI, typically saw improvement or resolution within 6 to 8 weeks in both the BVd and BPd arms. Symptomatic worsening of visual function was reversible in the majority of participants in both the BVd and BPd arms. The median time to improvement in visual related function from the first minimally important deterioration was 44.0 days and 57.0 days in BVd arm and BPd arm, respectively.

The results from the two-item unvalidated reading and driving questionnaire showed, at any given visit, that less than 10% of participants reported that they had stopped driving and less than 6% of participants reported that they had stopped reading due to eyesight issues (Figure 12). Over the full duration of treatment with BLENREP combinations, 24% of participants stopped reading and 33% stopped driving at some point. Follow-up for this questionnaire was every 3 or 4 weeks based on the protocol-specified visit schedule; participants stopped reading or driving for a median of approximately 1 month and more than 90% of participants had data to demonstrate a return to baseline.

Figure 12 DREAMM-7 and DREAMM-8: Pooled Summary of Results – Proportion of Participants Who Stopped Reading or Driving





1.5.7 Safety Conclusions

The overall safety of BLENREP in triplet combinations from DREAMM-7 and DREAMM-8 is broadly consistent with the previously well-characterized and stable safety profile of BLENREP and/or Vd or Pd. The ocular events that occur with BLENREP are reversible with time and effectively managed with dose modifications or delays, allowing participants to remain on treatment and derive benefit in the longer term. The most commonly reported ocular AEs (CTCAE) were vision blurred and dry eye, and the majority of events resolved with a median resolution time of about 3 months. Worsening of BCVA to 20/50 was transient with most participants returning to baseline with a median time to resolution of about 2 months. Worsening to 20/200 or greater was infrequent and resolved in almost all cases during follow-up. For participants with unresolved 20/50 or 20/200 events, follow-up was either ongoing or ended primarily due to disease progression or death. Importantly, there was no meaningful difference between treatment groups in the ocular PROs for participants experiencing ocular events.

Thrombocytopenia, IRRs, hepatobiliary disorders, and infections were characterized by low SAE rates and high rates of event resolution.

1.6 Benefit-Risk Summary

1.6.1 Risk Mitigation Plan

The risk management plan includes a REMS, the prescribing information, and an enhanced pharmacovigilance plan.

As part of a comprehensive approach to ocular risk management, GSK has proposed a robust Risk Evaluation and Mitigation Strategy (REMS) with Elements to Ensure Safety Use (ETASU) to facilitate appropriate management of ocular events. Ocular risk management plans are discussed further in Section 8.

1.6.2 Benefit-Risk Conclusions

In two independent, controlled Phase 3 studies, the benefit-risk profile of BLENREP was favorable:

- The studies demonstrated clinically meaningful improvements of PFS and OS with BLENREP vs. SoC comparators (DREAMM-7: statistically significant 59% reduction in the risk of progression and 42% reduction in the risk of death; DREAMM-8: statistically significant 48% reduction in risk of progression and a positive trend with a

23% reduction in the risk of death) with highly supportive secondary endpoints (ORR, MRD negativity, and DoR) corroborating the benefit.

- In the DREAMM-7 study, BLENREP demonstrated superior efficacy head-to-head against daratumumab, the “gold” SoC in newly diagnosed MM and RRMM. BLENREP was effective in participants exposed or refractory to prior lenalidomide and prior anti-CD38, and participants with poor prognostic factors, including high-risk cytogenetics and extramedullary disease (EMD). BLENREP is easily administered via infusion in the community setting and is not associated with CRS, ICANS or other neurotoxicities, hypogammaglobulinemia or severe, prolonged infections that are safety limitations of other approved BCMA therapies, like CAR-T cell therapies or T-cell engagers. Further, BLENREP has been shown not to impact the levels of soluble BCMA (sBCMA) at the time of progression or the binding of the BCMA target. In addition, treatment with BLENREP is not associated with loss of BCMA antigen at the time of progression or with T cell exhaustion supporting the potential for utilizing BLENREP ahead of other anti-BCMA therapies in MM without loss of efficacy.
- Nearly all patients will experience ocular events with BLENREP; however, these events are transient and manageable through dose modifications (dose reduction and dose delay). Ocular events are not a novel risk; other FDA-approved ADC therapies are associated with ocular events. Oncologists are acquainted with the need to collaborate with eyecare professionals for the use of such ADC products.

Considering the robust efficacy with BLENREP in the registrational DREAMM-7 and DREAMM-8 studies and the safety data in participants in those studies, GSK considers BLENREP in combination with Vd and Pd to have a favorable benefit-risk profile for patients with RRMM, a population for which there continues to be a high unmet medical need, particularly in 2L+ treatment.

2 BACKGROUND ON RELAPSED OR REFRACTORY MULTIPLE MYELOMA

Summary

- Multiple myeloma has a heterogeneous progression pathway, whereby several MM cell subclones coexist at baseline and compete for dominance over time, leading to the emergence of drug-resistant clones.
- Patients commonly receive the most effective agents, IMiD, PI, anti-CD38, in front-line, resulting in limited options after first relapse.
- CAR-T cell therapy, approved as a 2+ and 3+ line (L) treatment, is not available to a significant proportion of RRMM patients due to access and/or safety concerns.
- There is a high unmet need for accessible and effective therapies, with novel mechanisms of action, which offer deep durable responses and long-term remission, ultimately extending survival.

2.1 Overview of Relapsed Refractory Multiple Myeloma

Multiple myeloma is an incurable malignant clonal plasma cell disorder, which accounts for 10% of all hematologic malignancies globally (Bobin 2020; Rajkumar 2016). From 2017 to 2021, the age-adjusted incidence rate of MM in the US was 7.2 per 100,000 person-years (SEER Explorer 2024) and an estimated 35,730 new cases of MM and 12,590 deaths from MM are anticipated to occur in 2024 (Siegel 2024).

Diagnosis and response are based on the well-established International Myeloma Working Group (IMWG) criteria (IMWG 2003; Rajkumar 2014). Staging follows the International Staging System (ISS), a three-stage classification where; Stage III is associated with the poorest outcome (Greipp 2005). Minimal residual disease (MRD) negativity is an important prognostic factor for progression and survival. A large meta-analysis of patients with MM, including RRMM, confirmed the utility of MRD as a relevant endpoint for PFS and OS in MM (Munshi 2020). The analysis demonstrated the strong prognostic value of MRD negativity and its association with favorable outcomes for progression free survival (PFS) and overall survival (OS).

In the US, patients with MM are diagnosed at a median age of 69 years and have a 5-year relative survival of 62.4% (2015-2021) (SEER Cancer 2025). Despite the availability of treatment options and the improved survival outcomes over the last decade, most patients eventually become refractory to existing therapies (Verelst 2018), and prognosis worsens with each subsequent relapse. Refractory and relapsed MM is defined by IMWG (Rajkumar 2014) as disease that is nonresponsive to the chosen line of therapy in patients who had achieved a minimal response or better at some point previously in their disease - refractory MM is non-responsive to therapy or progresses within 60 days of the last line

of therapy and relapsed MM progresses ≥ 60 days after prior therapy and requires new therapy.

2.2 Current Treatment Options for Relapsed or Refractory Multiple Myeloma

Treatment of RRMM is individualized based on several factors such as Eastern Cooperative Oncology Group (ECOG) performance, prior treatments received, age, comorbidities, and disease characteristics such as the presence of EMD and high-risk genetics (Durer 2020, Raab 2023). The key classes of approved agents for the treatment of RRMM and examples of each are summarized in Table 8. Therapies from multiple classes can be combined in doublet, triplet, or quadruplet regimens and used with or without high-dose chemotherapy, rescued by autologous stem cell transplant (autoSCT) (Moreau 2021). Agents targeting BCMA (i.e., CAR-T and bispecific antibodies) have become an important and effective class of therapies for RRMM; however, these therapies carry significant safety or availability concerns, as discussed in Section 2.3.2.

Table 8 Key Approved Classes of Drugs for Refractory and Relapsed Multiple Myeloma

Product Class	Approved Product Examples
Proteasome inhibitors (PI)	ixazozomib, carfilzomib, bortezomib
Immunomodulatory (IMiD) agents	pomalidomide, lenalidomide, thalidomide
Monoclonal antibodies (mAbs)	daratumumab, isatuximab [CD38-directed)
Anti-BCMA targeted cell-based therapies	CAR-T therapies [a]: ciltacabtagene autoleucel [cilta-cel][a], idecabtagene vicleucel [ide-cel] [b] Bispecific antibodies (bsAbs): elranatamab[c] teclistamab [c]
Chemotherapy agents	Melphalan, cyclophosphamide, bendamustine
Steroids	dexamethasone

Nuclear transport inhibitors; BCMA = B-cell maturation antigen; CAR-T = Chimeric antigen receptor T-cell; CD38 = cluster of differentiation 38; citla-cel = ciltacabtagene autoleucel; ide-cel = idecabtagene vicleucel
a approved for the treatment of adult patients who have received at least one prior line of therapy (2+L)
b approved for the treatment of adult patients who have received at least two prior lines of therapy (3+L)
c approved for the treatment of adult patients who have received at least four prior lines of therapy (4+L)

The National Comprehensive Cancer Network (NCCN) publishes guidelines for the management of RRMM, summarized in Table 9.

Preferred regimens for the treatment of RRMM after 1 (1L) to 3 prior lines (3L+) of therapy include triplet combinations (e.g.,. PI, IMiD, anti-CD38 mAb) and CAR-T cell therapies (2L+, 3L+). Addition of chemotherapy agents such as cyclophosphamide may be useful in certain circumstances.

Table 9 National Comprehensive Cancer Network Treatment Guidelines for Relapsed/Refractory Multiple Myeloma (Preferred Regimens)

<table>
<tr><th colspan="3">Relapsed/Refractory Disease After 1-3 Prior Therapies (Preferred Regimens)</th></tr>
<tr><th>Anti-CD-38 Refractory</th><th>Bortezomib-Refractory</th><th>Lenalidomide Refractory</th></tr>
<tr>
<td>• Carfilzomib/lenalidomide/dexamethasone [a]
• Carfilzomib/pomalidomide/dexamethasone [a]
After two prior therapies including lenalidomide and a PI: •
• Elotuzumab/pomalidomide/dexamethasone
After two prior therapies including an IMiD and a PI and with disease progression on or within 60 days of completion of last therapy:
• Ixazomib/pomalidomide/dexamethasone</td>
<td>• Carfilzomib/lenalidomide/dexamethasone [a]
• Daratumumab/carfilzomib/dexamethasone [a]
• Daratumumab/lenalidomide/dexamethasone [a]
• Isatuximab-irfc/carfilzomib/dexamethasone [a]
• Carfilzomib/pomalidomide/dexamethasone
After one prior therapy including lenalidomide and a PI:
• Daratumumab/pomalidomide/dexamethasone [a]
After two prior therapies including lenalidomide and a PI:
• Isatuximab-irfc/pomalidomide/dexamethasone [a]
• Elotuzumab/pomalidomide/dexamethasone</td>
<td>• Daratumumab/bortezomib/dexamethasone [a, b]
• Daratumumab/carfilzomib/dexamethasone [a]
• Isatuximab-irfc/carfilzomib/dexamethasone [a]
• Pomalidomide/bortezomib/dexamethasone [a, b]
• Carfilzomib/pomalidomide/dexamethasone
After one prior therapy including lenalidomide and a PI
• Daratumumab/pomalidomide/dexamethasone [a]
After two prior therapies including lenalidomide and a PI
• Isatuximab-irfc/pomalidomide/dexamethasone [a]
• Elotuzumab/pomalidomide/dexamethasone
After two prior therapies including an IMiD and a PI and with disease progression on or within 60 days of completion of last therapy:
Ixazomib/pomalidomide/dexamethasone</td>
</tr>
<tr>
<td colspan="2">CAR T Therapy
After one prior line of therapy including IMiD and a PI, and refractory to lenalidomide:
• Ciltacabtagene autoleucel [a]</td>
<td>After two prior lines of therapies including an IMiD, and anti-CD38 monoclonal antibody and am PI:
• Idecabtagene vicleucel [a]</td>
</tr>
<tr><th colspan="3">Relapsed/Refractory Disease After 3 Prior Therapies (Preferred Regimens)</th></tr>
<tr><td colspan="3">CAR T Therapy
• Ciltacabtagene autoleucel, Idecabtagene vicleucel</td></tr>
<tr><td colspan="3">After at least four prior therapies and refractory to at least two PIs, at least two immunomodulatory agents, and an antiCD38 monoclonal antibody
Bi-specific antibodies:
• Elranatamab-bcmm, Talquetamab-tgvs, Teclistamab-cqyv</td></tr>
</table>

CAR-T = Chimeric antigen receptor T-cell; HCT = hematopoietic cell transplant; IMiD = Immunomodulatory; mAbs = monoclonal antibodies; NCCN = National Comprehensive Cancer Network; PI = Proteasome inhibitors

a Category 1: Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.

b Comparator regimen in the DREAMM-7 or DREAMM-8 study

NCCN Guidelines Version 2.2025 Multiple Myeloma

2.3 Patient Unmet Medical Need

2.3.1 Consideration of Treatment-Resistant Disease

The widespread use of triple and even quadruple combinations (including lenalidomide, anti-CD38 antibodies such as daratumumab, and a PI), in frontline treatment lines leads to disease that is refractory to the main frontline classes of therapy earlier in treatment (Kumar 2023, Mateos 2022). Observational studies in patients receiving three or more lines of prior therapy or refractory to CD38-targeting antibodies indicate an overall response rate of about 30%, PFS of 3.4 to 4.6 months, and OS of between 5 and 12 months, depending on the number and classes of agents to which a patient is refractory (Mateos 2022, Gandhi 2019).

Patients who become refractory to the major classes of available therapies have limited therapeutic options (Kumar 2017, Costa 2022).There is need for additional treatment options in the early RRMM setting and therapies with a multi-modal mechanism of action that target MM cells and elicit an immunogenic response, expected to reduce development of drug resistance in MM.

2.3.2 Limitations of Available Therapies Meriting Need for Off the Shelf Option

CAR-T therapies are approved in the early relapse/refractory setting for more vigorous patients who can tolerate the bridging therapy and CAR-T treatment. Clinical studies showed overall response rates of 84.6% to 94% (ABECMA PI, CARVYKTI PI). Despite their promise for the treatment of early RRMM, there are limitations for CAR-T (2L+) in the real-world setting and not all patients are eligible for treatment (Gajra 2022, Kourelis 2023, Haslam 2024). Patients must live in a reasonable proximity to (or be able to travel to) a certified tertiary cancer center; and there are significant safety concerns related to CAR-T therapies. Adverse reactions include cytokine release syndrome (CRS), neurotoxicity including immune effector cell-associated neurotoxicity syndrome (ICANS), prolonged and recurrent cytopenias, severe or life-threatening infections, and hypogammaglobulinemia (Afrough 2024). In the CARTITUDE-1 study, neurotoxicities including cognitive impairment and personality change were experienced by 5% of patients with one fatality (Cohen 2022). A recent analysis of FDA AE Reporting System (FAERS) data for cilta-cel and ide-cel from January 2021 to December 2023 also found neurotoxicities in real-world use, including cranial nerve palsies, Parkinson's disease and parkinsonism, acute and chronic polyneuropathies, confusion, disorientation, seizures, balance disturbances, and tremors (Ellithi 2025). Additional safety concerns are emerging, such as immune effector cell (IEC)-associated enterocolitis, a rare but distinct potential complication of CAR-T therapy, the outcomes from which have included bowl perforation, sepsis, and death (Fortuna 2024).

BLENREP administered as the combinations BVd and BPd provides a novel, highly effective off-the-shelf anti-BCMA option that does not require access to specialized cancer centers, does not require a wait time for manufacturing, does not have risk of severe IEC-related events, and may be particularly valuable for patients unable to tolerate

the adverse effects of CAR-T therapy or those patients who cannot wait for or access CAR-T therapy.

2.3.3 Summary of Unmet Need

Despite the availability of treatment options and improved survival outcomes over the last few years, most patients still experience relapse and develop resistance to existing therapies (Verelst 2018). The duration of remission declines dramatically with each line of treatment, and patients who become refractory to the major classes of available therapies have a very poor prognosis and limited therapeutic options (Kumar 2017, Costa 2022). CAR-T therapies are not universally available to these refractory patients, thus there remains an unmet need for a therapy with a novel, multi-modal mechanism of action that targets MM cells and elicits an immunogenic response, that is accessible to most RRMM patients. BLENREP is expected to fill the current need for an additional effective BCMA-targeting therapy for RRMM that will reduce development of drug resistance in MM and prolong the therapeutic benefit to patients with RRMM.

3 PRODUCT DESCRIPTION

Summary

- BLENREP is a first-in-class antibody drug conjugate (ADC) comprising an afucosylated humanized anti-BCMA (immunoglobulin G) IgG1 conjugated via a protease-resistant maleimidocaproyl (mc) linker to maleimidocaproyl monomethyl auristatin F (mcMMAF).
- BLENREP binds to and kills MM cells via a multi-modal mechanism, inducing apoptosis via delivery of cys-mcMMAF, enhancing antibody-dependent cellular cytotoxicity, inducing antibody dependent cellular phagocytosis, and inducing release of markers characteristic of immunogenic cell death (ICD)
- BLENREP is the only anti-BCMA therapy not requiring systemic premedication or post-infusion monitoring for cytokine release syndrome.
- BLENREP is administered as a short 30-minute outpatient infusion with a convenient dosing schedule, allowing patients to maintain their quality of life and daily activities

3.1 Proposed Indication and Dosing Regimens

The proposed indications for BLENREP are:

- Treatment of MM in combination with bortezomib and dexamethasone in adult patients who have received at least 1 prior therapy.
- Treatment of MM in combination with pomalidomide and dexamethasone in adult patients who have received at least 1 prior therapy including lenalidomide.

BLENREP is administered as an intravenous (IV) infusion over approximately 30 minutes with treatment continuing until disease progression or unacceptable toxicity. The dosing regimens for BVd and BPd are summarized in in Table 12 and are based on the specific triplet combination. Dose modifications (i.e., dose delays and/or reductions) of BLENREP to manage adverse events were prespecified in the DREAMM-7 and DREAMM-8 protocols and based on participant safety and tolerability as described in Table 7. The development of the dosing regimens for BLENREP in triplet combination is discussed in detail in Section 5.2.

3.2 Product Overview

3.2.1 BCMA as a Therapeutic Target in Multiple Myeloma

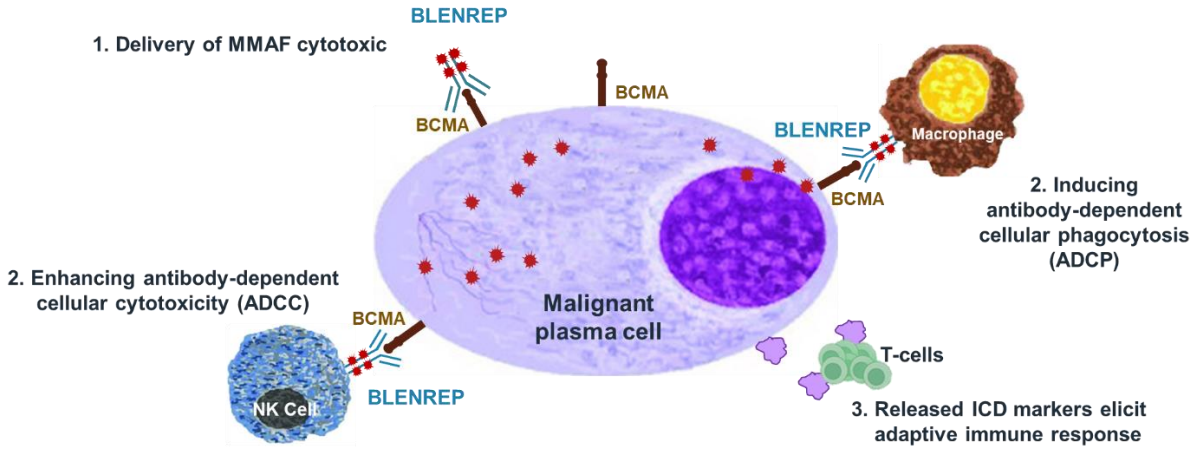
B-cell maturation antigen is a cell-surface receptor widely expressed on malignant plasma cells in MM (and to a lesser degree in other B-cell malignancies) with limited expression on normal late-stage B cells. BCMA plays a key role in the upregulation of survival molecules by MM cells, as well as upregulation of drug resistance (Tai 2015). The

restricted expression profile of BCMA makes it an ideal therapeutic target with limited potential for off-target effects. BCMA has been validated as a therapeutic target in preclinical MM studies and in clinical studies with novel immunotherapeutic approaches, including chimeric antigen receptor T-cell therapies and bi-specific antibodies (Cho 2018).

3.2.2 Multi-Model Mechanisms of Action of BLENREP

BLENREP is comprised of an afucosylated humanized IgG1 conjugated via a protease-resistant maleimidocaproyl (mc) linker to maleimidocaproyl monomethyl auristatin F (mcMMAF). Upon binding to BCMA, a protein expressed on MM cells, BLENREP is internalized followed by release of cys-mcMMAF via proteolytic cleavage. BLENREP provides immediate and sustained effects by binding to BCMA and killing BCMA-expressing MM cells via (1) the delivery of the active cytotoxic drug cys-mcMMAF, (2) enhanced ADCC/ADCP killing of MM cells, and (3) adaptive immune response (Figure 13).

Figure 13 BLENREP Mechanisms of Action Targeting Myeloma



ADC = antibody drug conjugate; ADCC = antibody-dependent cellular cytotoxicity; ADCP = antibody-dependent cellular phagocytosis; ICD = immunogenic cell death; NK = natural killer
Note: red dots indicate cytotoxic MMAF released into the cell

3.2.3 Antibody-Drug Conjugates with Microtubule Inhibitors

There are a number of FDA-approved antibody-drug conjugate (ADC) products that include microtubule-inhibiting payloads such as auristatins (monomethyl auristatin E [MMAE], MMAF) and maytansinoid derivatives (DM2, DM4). Three of these ADCs, approved since 2019, are associated with ocular events (Table 10).

Table 10 FDA-Approved Antibody-Drug Conjugates Including Microtubule-Inhibiting Payloads with Ocular Toxicity

ADC Product Name	Approval Year	Payload Compound	Indication(s)	Reported Ocular Events
Padcev (enfortumab vedotin)	2019	MMAE	Locally advanced or metastatic urothelial cancer.	dry eye, blurred vision
Tivdak (tisotumab-vedotin)	2021	MMAE	Recurrent or metastatic cervical cancer	conjunctivitis, dry eye, keratopathy, and blepharitis
Elahere (mirvetuximab soravtansine)	2022	maytansinoid DM4	Platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer	vision impairment, keratopathy, dry eye, cataract, photophobia, eye pain

ADC = antibody-drug conjugate; DM4 = maytansinoid derivative; MMAE = monomethyl auristatin E; MMAF = monomethyl auristatin F

Because ADCs such as those summarized in Table 10 have ocular adverse events as a frequent side effect, ocular events are no longer considered novel, and oncologists are becoming increasingly familiar with the management of ocular events according to label guidance and the need to collaborate with an eye care professional.

3.2.4 B-Cell Maturation Antigen Therapy Sequencing

Various drug classes target BCMA, including CAR-T therapies, bsAbs, and antibody-drug conjugates (ADCs). Outcomes with CAR-T and bsAb therapies in MM have been affected by T-cell exhaustion, a state where T cells lose their ability to function properly often due to prolonged exposure to antigens (Da Via 2021, Xia 2023). Abrogated expression or mutation of the BCMA target has been observed with anti-BCMA therapies (Lee 2023, Lee 2024). Optimal anti-BCMA sequencing strategies are needed to improve long-term clinical outcomes.

The impact of BLENREP as monotherapy and combination regimens on BCMA levels and binding (using electrochemiluminescence methodology) and T-cell/natural killer (NK) cell fitness (including cell counts, expression of functional markers) was evaluated to determine whether BLENREP could be sequenced ahead of other BCMA-targeting therapies for MM. Levels of free sBCMA were measured at the best-confirmed response (BCR) and at progression, which demonstrated that sBCMA dropped at BCR but returned to near baseline at time of disease progression (unpublished data). There was no apparent impact on the binding epitope of BCMA, as indicated by the retention of BLENREP binding to sBCMA. No significant changes in cell counts or expression of T-cell exhaustion markers (PD-1, TIGIT, TIM-3 [except NK cells], or CTLA-4) and co-stimulatory markers (ICOS [except CD4+ T-cells], OX40, 4-1BB) were observed at relevant timepoints (up to 4 or 21+ months depending on the marker). No negative impact was observed on expression of proliferation (Ki67) and antitumor activity (granzyme B, CD107a) markers. These results support the potential for utilizing BLENREP ahead of other anti-BCMA therapies in MM without loss of efficacy.

4 REGULATORY AND CLINICAL DEVELOPMENT HISTORY OF BLENREP FOR 2L+ RELAPSED/REFRACTORY MULTIPLE MYELOMA

Summary

- BLENREP is recently approved in triplet combination (BVd or BPd) in the United Kingdom and Japan and has received a positive CHMP opinion for the treatment of adults with RRMM who have received at least one prior therapy with approval by the European Commission expected in July 2025.
- The BLENREP development program for the treatment of RRMM as combination therapies includes two independent Phase 3 randomized registrational studies of BLENREP administered in a triplet combination, compared to current SoC triplet combinations: DREAMM-7 (BVd vs. DVd), DREAMM-8 (BPd vs. PVd).
- A supportive Phase 1/2 open-label dose and schedule exploration/expansion study supports each combination: DREAMM-6 (BVd) and Algonquin (BPd).

4.1 Regulatory History

GSK has submitted an application for BLENREP as part of a triplet combination for the treatment of RRMM in adults who have received at least one prior therapy, with the results of the primary analyses from the two randomized controlled Phase 3 registrational studies DREAMM-7 and DREAMM-8. BLENREP was recently approved for this indication in the United Kingdom (April 2025) and Japan (May 2025). BLENREP received a positive Committee for Medicinal Products for Human Use (CHMP, European Medicines Agency's) opinion for these indications in May 2025, with European Commission approval expected in July 2025.

A separate BLA, in a different population and with a different data package, supported the approval of BLENREP in the US in 2020 as monotherapy in 5L+ RRMM under an accelerated approval. That approval was voluntarily withdrawn in early 2023 after the monotherapy confirmatory study failed to demonstrate superiority over SoC doublet therapy on the primary endpoint of PFS.

A summary of regulatory interactions relevant to the development of BLENREP as part of combination therapy are summarized in Table 11.

Table 11 Relevant Regulatory Interactions for BLENREP Development in Combination with Other Drugs

Date	Meeting / Interaction Description
31 January 2014	IND 119333 was opened in the US.
23 June 2017	Orphan Drug Designation approval for “treatment of multiple myeloma”.
27 December 2019	Protocol for DREAMM-7 submitted to IND 119333.
26 May 2020	Protocol for DREAMM-8 submitted to IND 119333.

Date	Meeting / Interaction Description
05 August 2020	BLENREP granted accelerated approval on as a monotherapy for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 mAb, a PI, and an IMiD.
06 February 2023	Voluntary revocation of the BLENREP BLA approval
10 May 2023	Type D Meeting for DREAMM-7 and DREAMM-8: to discuss the OS analysis and SAP.
25 May 2023	Type C Meeting for DREAMM-7 and DREAMM-8: to discuss the safety pooling strategy, clinical pharmacology strategy, and BLA content and format
03 April 2024	Type B Pre-BLA meeting to discuss the planned joint filing for the proposed DREAMM-7 and DREAMM-8 indications.
10 July 2024	Type D Meeting for DREAMM-7 to discuss descriptive OS analysis at the time of submission (Preliminary comments/additional clarification were adequate, meeting cancelled).

BLA=Biologic License Application; BTD=Breakthrough Therapy Designation; FDA=Food and Drug Administration; GSK=GlaxoSmithKline; IND=Investigational New Drug; OS = overall survival; SAP = statistical analysis plan

4.2 Clinical Development Program in 2L+ Line Relapsed/Refractory Multiple Myeloma

To date, approximately 7500 patients with multiple myeloma have been treated with BLENREP in the clinical development program and in clinical practice.

The overall clinical development program for BLENREP in combination with Vd and with Pd for the treatment of participants with at least 1 prior line of MM therapy includes:

- Two registrational studies: DREAMM-7 (BVd) and DREAMM-8 (BPd)
- Supportive BLENREP dose and schedule exploration combination-therapy studies: DREAMM-6 (BVd, Arm B) and ALGONQUIN (BPd)
- Monotherapy studies that contribute to the evaluation of PK, dose and regimen selection, and safety including the dose optimization study DREAMM-14.

The clinical program supporting the BLA for BLENREP is summarized in Appendix Table 1

4.2.1 Registrational Studies

The registrational study, DREAMM-7 (NCT 04246047), is an ongoing Phase 3, open-label, randomized, clinical study to evaluate the efficacy and safety of BVd compared with DVd in participants with RRMM previously treated with at least 1 prior line of therapy.

The registrational study, DREAMM-8 (NCT 04484623), is an ongoing Phase 3, open-label, randomized, clinical study to evaluate the efficacy and safety of BPd compared with PVd in participants with RRMM previously treated with at least 1 prior line of therapy including lenalidomide. The registrational study designs are summarized in Figure 15 (DREAMM-7) and Figure 18 (DREAMM-8). The two registrational studies, DREAMM-7

and DREAMM-8, were very similar in design but with several important differences, summarized below:

DREAMM-7	DREAMM-8
• 494 participants with RRMM were randomized to either BLENREP, bortezomib, and dexamethasone (BVd), or daratumumab, bortezomib, and dexamethasone (DVd) • Participants were mostly anti-CD38 naive • There was no specific requirement on prior lenalidomide exposure • The visit schedule for dosing and assessment was Q3W to align with the bortezomib dosing schedule • The combination partner Vd was administered for a maximum total of 8 cycles, after which BLENREP or daratumumab was continued as monotherapy	• 302 participants with RRMM were randomized to either BLENREP, pomalidomide, and dexamethasone (BPd) or pomalidomide, bortezomib, and dexamethasone (PVd) • Participants were allowed to have received prior anti-CD38 therapy • Participants were required to have had a prior lenalidomide-containing regimen • The visit schedule for dosing and assessment was Q4W to align with the pomalidomide dosing schedule • The combination partner Pd was administered continuously with BLENREP, if tolerated, until disease progression, death, toxicity, or withdrawal from the study

4.2.2 Supportive Studies – Efficacy and Safety

DREAMM-6 is a completed Phase 1/2, open-label, dose escalation and expansion clinical study to assess different BLENREP doses (1.9 mg/kg, 2.5 mg/kg, and 3.4 mg/kg) and dosing schedules given in combination with lenalidomide and dexamethasone (Rd) or Vd. The combination in the DREAMM-6 study, BVd, aligns with the combination evaluated in DREAMM-7. ALGONQUIN is an ongoing Phase 1/2, open-label, dose-escalation and expansion study evaluating the efficacy and safety of BPd vs. PVd, aligning with the combination evaluated in DREAMM-8 (Trudel 2024).

Both studies evaluated BLENREP in participants with RRMM receiving at least one prior therapy and documented disease progression during or after their most recent therapy. For ALGONQUIN, participants had to be lenalidomide refractory and PI exposed (in separate regimens or in combination) and participants could not have previously received pomalidomide or a prior BCMA-targeted therapy. The primary efficacy endpoint for DREAMM-6 and ALGONQUIN was ORR based on response assessments by the investigator. Secondary endpoints for DREAMM-6 included PFS and DoR. Safety, PK, and immunogenicity were also assessed.

5 CLINICAL PHARMACOLOGY

Summary

- The BLENREP program included a thorough characterization of clinical pharmacology as a triplet combination therapy with bortezomib and dexamethasone (BVd) or with pomalidomide and dexamethasone (BPd), and also as monotherapy.
- Exposure-response analyses consistently showed that higher exposures were associated with higher probability of response (and deep response).
- Higher exposures were associated with occurrence of a corneal event but not significantly associated with ocular symptoms (CTCAE and bilateral BCVA worsening to 20/50).
- Extensive dose and schedule exploration and optimization did not identify an alternate dosing regimen with significantly improved safety with no impact on efficacy.
- BLENREP has low incidence of immunogenicity (1-3%), with no evidence immunogenicity impacts PK, safety, or efficacy.
- Overall, the comprehensive results of pharmacokinetic (PK), integrated exposure-response analyses, and the factors influencing the PK, efficacy, and safety responses, support a favorable benefit:risk profile of BLENREP in triplet combination for 2+ line RRMM.

5.1 Pharmacokinetics

BLENREP exhibited linear, dose-proportional PK when administered as an IV infusion over approximately 30 minutes. The PK were well described by a linear 2-compartment population PK model with a time-varying decrease in clearance for ADC and a time-varying drug-antibody ratio for cys-mcMMAF in a population PK analysis. BLENREP clearance (0.901 L/day initially and 0.605 L/day at steady state) and steady-state volume of distribution values (10.8 L) were low, and half-life values were long (13.2 days initially and 19 days at steady state), as seen with other mAb-based therapeutics. The average time to 50% change in clearance was 66 days. Moderate to large variability was observed between participant in the extent of the change as well as the time to 50% change in clearance, respectively. Accumulation of BLENREP was minimal to moderate with the proposed dosing regimens. The PK of BLENREP is variable (between-patient coefficient of variation% ranging from 22% for C_{max} to 63% for trough concentration in Cycle 1) and associated with baseline characteristics including body weight and disease burden related factors. Lower clearance, longer half-life, and higher drug exposure were observed in participants with lower disease burden (i.e., lower IgG, sBCMA, beta-2 microglobulin, and higher albumin).

Cys-mcMMAF has poor membrane permeability and exposure to free cys-mcMMAF is very low (less than 1% of ADC exposure) with no accumulation observed in clinical

studies under the tested dosing regimens. Renal clearance is a minor elimination pathway. Cys-mcMMAF has low plasma protein binding and limited metabolic clearance. Cys-mcMMAF is a substrate of several transporters (e.g. organic anion transporter peptide 1B1 and 1B3) and not an inhibitor, an inducer, or a sensitive substrate of cytochrome P450 enzymes based on in vitro data.

Co-administered combination agents (dexamethasone, bortezomib, pomalidomide, and lenalidomide) did not have an impact on BLENREP or cys-mcMMAF PK profiles. Moreover, BLENREP did not impact on the PK profiles of bortezomib, pomalidomide, or lenalidomide.

5.2 Dose Rationale – BLENREP in a Triplet Combination Regimen

The proposed dose regimen for the two combinations are described in Table 12.

Table 12 Proposed Dosage and Administration of BLENREP

Combination Regimen	Recommended Starting Dose Schedule for BLENREP
With bortezomib and dexamethasone	2.5 mg/kg of actual body weight once every 3 weeks in combination for the first 8 cycles, and then continued as a single agent
With pomalidomide and dexamethasone	2.5 mg/kg of actual body weight on Cycle 1 followed by 1.9 mg/kg every 4 weeks starting on Cycle 2

Extensive dose exploration and optimization studies (summarized in Table 13) and exposure-response analyses, support the 2.5 mg/kg starting dose and schedule as the key driver to the deep and durable responses observed with BLENREP. Dose modifications to manage ocular and other adverse (AEs) are an intrinsic part of the BLENREP dose regimen that maintain a positive benefit:risk profile. In regard to the exposure-response analyses, prior clinical data supported exclusion of 3.4 mg/kg dose from further investigation in the Phase 3 MM studies. Therefore, this dose was not included in the exposure-response analyses.

5.2.1 Dose Selection of Recommended Clinical Dose

The dosing regimens used in DREAMM-7 and DREAMM-8 were selected and further supported based on clinical data from Phase 1 and Phase 2 dose escalation and dose optimization studies of BLENREP monotherapy and combination therapies. For DREAMM-7, the selection of the 2.5 mg/kg starting dose administered on a Q3W schedule with allowance for dose modifications for ocular and other events, is supported by results from the early monotherapy studies, the DREAMM-14 monotherapy study, and the DREAMM-6 combination study. In DREAMM-8 (BPd), the starting dose of 2.5 mg/kg with 1.9 mg/kg in subsequent cycles at a dosing interval of Q4W is supported by data from the ALGONQUIN study.

A summary of the three key studies supporting the DREAMM-7 and DREAMM-8 dose regimens including the dose regimens evaluated, the number of participants administered BLENREP under each regimen, the RDIs, key efficacy data, and key ocular safety data are summarized in Table 13.

Table 13 Dose Exploration/Optimization Studies of BLENREP Administered as Monotherapy or in Combination – Summary of Results

Starting Dose/Schedule	Number of Participants	Relative Dose Intensity (%) Median	Efficacy Results		Safety		
			VGPR+ (%)	mPFS, months (95% CI)	KVA Grade 2+ (%)	Serious AE (%)	Discontinued BLENREP Treatment due to an AE (%)
DREAMM-6 Arm B (BVd in 2L+) [a]							
1.9 mg/kg							
Q3W	12	60.2	33	13.2 (1.4, -)	10 (84)	8 (67)	1 (8)
Q6W	12	62.9	25	6.3 (0.7, 12.1)	7 (58)	8 (67)	1 (8)
2.5 mg/kg							
Q3W	18	47.6	67	10.8 (8.3, -)	14 (79)	13 (72)	3 (17)
Q6W	12	63.2	50	9.2 (2.1, 16.8)	12 (100)	6 (50)	3 (25)
2.5 mg/kg Step Down to 1.9 mg/kg Cycle 3+							
Q6W	12	70.0	58	16.0 (5.6, -)	12 (100)	6 (50)	2 (17)
ALGONQUIN (BPd in 2L+) [b]							
1.9 mg/kg							
Q4W	12	88	63.7	16.9 (5.3-19.7)	50	75	8.3
2.5 mg/kg							
Q4W	7	22	100	25.3 (11.8, NR)	100	71.4	0
Q8W (Part 1) Q8W (Part 2)	12 38	41 37	83.3 75.7	18.3 (10.8, NR) NR (13.7-NR)	83 63	83.3 61	8.3 5.2
Q12W	12	36	63.7	22.5 (10.7, NR)	67	58.3	8.3
2.5 mg/kg Step Down to 1.9 mg/kg Cycle 2+							
Q4W	5	29	80.0	9.0 (5.3, NR)	60	100	
DREAMM-14 (B in 4L+) [b,c]							
1.9 mg/kg							
Q3W	40	99.5	18	2.1 (1.0, 3.6)	40	43	8
Q6W	40	100	15	2.7 (1.9, 4.2)	38	40	5

Starting Dose/Schedule	Number of Participants	Relative Dose Intensity (%) Median	Efficacy Results		Safety		
			VGPR+ (%)	mPFS, months (95% CI)	KVA Grade 2+ (%)	Serious AE (%)	Discontinued BLENREP Treatment due to an AE (%)
2.5 mg/kg							
Q3W	40	80.4	25	5.7 (2.8, 9.0)	64	44	10
Q6W	40	100	8	2.8 (1.4, 3.5)	44	54	10

2L+ = two lines or more; 4L+ = four lines or more; B = BLENREP; L = line; Pd = pomalidomide, dexamethasone; Q#W = every # weeks; Rd = lenalidomide, dexamethasone; Vd = bortezomib, dexamethasone

a Relative dose intensity (post-Dose 1) was calculated as a percent and was defined as 100*(mean overall dose intensity post-Dose 1 divided by planned dose intensity post Dose 1)

b Relative dose intensity was calculated as a percent and was defined as 100*(median overall dose intensity divided by planned dose intensity).

c Due to the short treatment exposure period, the RDIs in this study treating participants with advanced RRMM with BLENREP monotherapy is higher compared to the RDI values from the studies conducted in participants with 2L+ RRMM using BLENREP in combination with SoC. In the Note: Q3W arms, participants received a median of 4.0 treatment cycles in the 2.5 mg/kg cohort and 3.0 treatment cycles in the 1.9 mg/kg cohort. Note: In the Q6W arms, participants received a median of 2.0 treatment cycles.

There were some common observations across all three studies.

1. The dose regimens with the higher starting doses and more frequent starting schedules consistently resulted in deeper responses, as evidenced by the proportion of participants attaining a VGPR or better and median PFS. Both efficacy measures are meaningfully different where the starting dose was 2.5 mg/kg, compared to a starting dose of 1.9 mg/kg.
2. Dose regimens with a lower dose or less frequent starting schedule were associated with only a modest improvement in safety. However, ocular events were common regardless of the dose and schedule studied and were managed through dose modifications.
3. Dose modifications due to ocular events were common, and high interpatient variability in the time to resolution of ocular events often results in variability in dosing frequency. Together, dose modifications and variable dosing frequency lead to achieving a modest RDI across most doses and schedules evaluated.

Interim data from DREAMM-6 Arm B found 2.5 mg/kg Q3W induced deep and durable responses with a manageable safety profile (Figure 2). Additional dosing regimens were explored in DREAMM-6 with the BVd combination – a lower starting dose (1.9 mg/kg), split dosing (between Day 1 and Day 8, to lower peak concentration) and less frequent dosing (i.e., Q6W, to lower the average concentration and reduce drug accumulation). There was a trend towards more favorable safety profiles in cohorts with lower doses, but deeper responses were observed for the dose cohorts with a higher starting dose.

The ALGONQUIN study tested doses ranging from 1.9 mg/kg to 3.4 mg/kg with different schedules including Q4W, Q8W, and Q12W. Regardless of the dosing schedule, the RDI ranged between 22-88% (Figure 3). This indicates that dose modifications are likely to be required even when lower doses and stretched dosing schedules are used. The PFS and depth of response was lower for 1.9 mg/kg Q4W compared to the 2.5 mg/kg regimens, underscoring the importance of higher starting dose.

The DREAMM-14 dose optimization study tested 2.5 mg/kg and 1.9 mg/kg doses in Q3W and Q6W schedules. Higher efficacy (VGPR+ and PFS) was observed with 2.5 mg/kg Q3W with similar safety across the different doses and schedules (Appendix Figure 1). Regardless of the dosing schedule, the relative dose intensity (RDI) was high and ranged between 80-100%, Notably, this study enrolled a late-line population who received fewer doses before progressing, which resulted in higher RDI as participants do not have the opportunity for dose modification

Overall, the extensive dose exploration over a dose range of 1.9 mg/kg to 3.4 mg/kg and across different schedules for BVd or BPd combination and as monotherapy showed modest differences in safety but meaningful impact on efficacy with lower starting dose or dosing frequency in the indicated participant population and further supported the

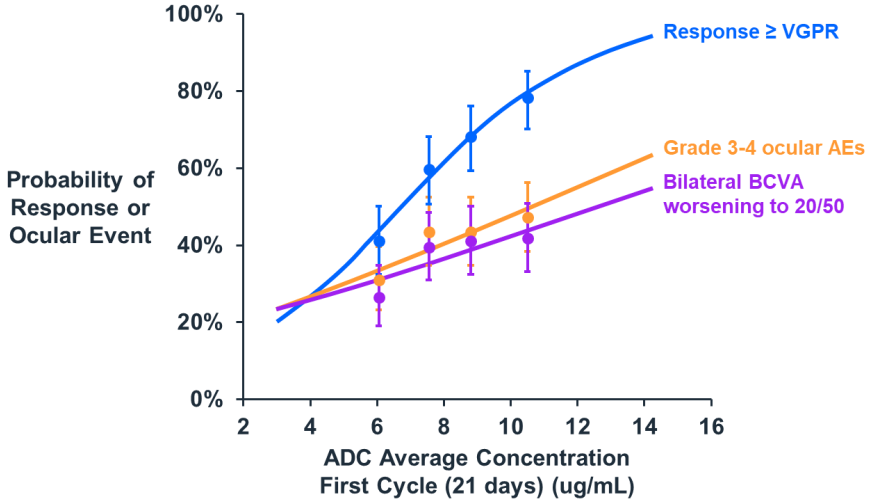
selection of the starting dose of 2.5 mg/kg and schedule in DREAMM-7 and DREAMM-8 studies.

5.2.2 Dose Confirmation Based on Favorable Clinical Benefit: Risk Profiles

The DREAMM-7 and DREAMM-8 studies demonstrated a significant benefit of the selected dosing regimens over SoC comparators in the indicated participant population (Section 6.4) with a manageable safety profile utilizing dose modifications for ocular toxicity (Section 7.14). Dose intensity and dosing interval were variable among participants because dose modifications were implemented as needed to mitigate safety events and enable participants to remain on treatment for a prolonged period without compromising efficacy (Section 1.5.3.3).

An integrated exposure-response analyses including DREAMM-6, DREAMM-7, and DREAMM-8 were performed using different first cycle exposure metrics (i.e. peak concentration, average concentration over first 21 days, and concentration at 21 days), selected for evaluation due to the rapid onset of efficacy (median time to response of 1.1 to 1.4 months in DREAMM-8 and DREAMM-7) and ocular events (median time to first Grade 2+ corneal events of about 2 months for DREAMM-7 and DREAMM-8). Figure 14 shows the integrated exposure-response analysis plot with probability of VGPR or better overlaid with exposure-response curves of safety with probability of Grade ≥3 ocular AESIs (CTCAE) and probability of BCVA bilateral worsening to 20/50 or worse against average BLENREP concentration, the exposure metric most associated with efficacy. The probability of achieving VGPR or better response was positively associated with higher BLENREP exposure across the three studies while key safety parameters of interest such as probability of occurrence of BCVA bilateral worsening to 20/50 or worse and Grade ≥3 ocular AESIs (CTCAEs) remained relatively flat. In addition, for most of the range of Cycle 1 BLENREP C_{avg}, the probability of response (VGPR or better) was higher than the probability of ocular symptoms (e.g. Grade ≥3 ocular AEs (CTCAE) and BCVA bilateral worsening to 20/50 or worse). Individual analyses per study are provided in Section 11.2.

Figure 14 DREAMM-6, DREAMM-7, DREAMM-8: Integrated Exposure-Response Relationship



ADC = antibody-drug conjugate; AE = adverse event; BCVA = best corrected visual acuity; Gr = grade; VGPR = very good partial response
Note: Exposure-response analyses do not include the 3.4 mg/kg dose from DREAMM-6 Arm B.
Note: The independent variable was divided into quartiles. Points and error bars represent the observed proportions and 95% CIs for each quartile (plotted at the median exposure within each quartile), respectively. The curves represent the prediction of the univariate logistic regression model.
Note: Individual exposure-response analyses are provided for DREAMM-6 in Appendix Figure 2, for DREAMM-7 in Appendix Figure 3, and for DREAMM-8 in Appendix Figure 4.

The starting dose of 2.5 mg/kg was further supported by multivariate exposure-response model prediction (Table 14). Based on the multivariate exposure-response modeling, probability of achieving VGPR or better response was 70.4% with 2.5 mg/kg vs. 54.3% with 1.9 mg/kg BLENREP dose. The probability of BCVA bilateral worsening to 20/50 or worse occurrence and Grade ≥3 ocular AEs (CTCAEs) was the same or similar for 2.5 mg/kg vs. 1.9 mg/kg.

The individual exposure-response analyses for DREAMM-6 and DREAMM-14 (Section 11.2) showed a positive association between exposures and probability of response (and deep response); while there was an association between exposure and ocular symptoms (Grade ≥2 or 3 CTCAE scale), there was a flat relationship with probability of bilateral BCVA worsening to 20/50 or worse. Split dosing and less frequent dosing were not found to be significant on efficacy or safety endpoints in these analyses.

Table 14 Multivariate Exposure-Response Model Prediction for Combination

	BVd / BPd	
Probability (%) for initial dose	**1.9 mg/kg**	**2.5 mg/kg**
VGPR+	54.3 (46.4 – 61.9)	70.4 (65.3 – 75.0)
Grade ≥3 Ocular AESI (CTCAE)	52.2 (45.8 – 58.6)	52.2 (45.8 – 58.6)
BCVA Bilateral Worsening to 20/50 or worse	27.5 (21.9 – 34.0)	33.3 (29.0 – 37.9)

BCVA = best corrected visual acuity; CR+ = complete response or better; CTCAE = Common Terminology Criteria for Adverse Events; KVA = Keratopathy and Visual Acuity Scale; VGPR = very good partial response

Note: Prediction with 95% confidence interval generated from final models resulting from the combined DREAMM-6 (excluding 3.4 mg/kg cohorts), DREAMM-7, and DREAMM-8 efficacy and safety analyses. Cycle 1 ADC C_{avg} for the 2.5 mg/kg dose (C_{avg}: 7.83 ug/mL) was derived from *post hoc* simulation using the final population PK model. Cycle 1 ADC C_{avg} for the 1.9 mg/kg dose (C_{avg}: 5.95 ug/mL) was calculated using a linear proportion assumption. Participants were assumed to have no extramedullary disease, no prior anti-CD38 treatment, and normal baseline BCVA.

The registrational studies DREAMM-7 and DREAMM-8 have dosing regimens with an initial dose of 2.5 mg/kg and initial dose intervals that align with the bortezomib and pomalidomide treatments. A different dose schedule was used in DREAMM-8 to assess whether proactively reducing the dose after the first cycle would impact the rate or severity of ocular events. The change in dosing schedule didn't significantly impact safety or efficacy compared to DREAMM-7, where similar dose modifications were implemented reactively in response to ocular events or other AEs.

Importantly, while there were subtle differences in dose modification guidance between the studies, regardless of the protocol, physicians effectively managed ocular events in very similar ways across the two studies. Indeed, the actual drug exposure in participants was similar between the two studies (Figure 5). In both studies, the RDI was higher in the first six months indicating participants received treatment more closely aligned with the protocol recommended dose and schedule. Participants also went into deeper responses whereby subsequent doses could be held to effectively manage ocular events without compromising on efficacy. It is this higher starting dose/more frequent schedule followed by subsequent dose modifications to manage tolerability that has translated to long term favorable clinical outcomes while having a manageable tolerability profile.

In conclusion, the proposed dosing regimen for BLENREP in combination with Vd or Pd in the treatment of participants with RRMM with at least 1 prior line of therapy is supported by the exposure-response modeling of a broad range of exposure levels aligned with Project Optimus guideline and the total weight of clinical evidence. These include the favorable clinical benefit:risk profiles from the registrational Phase 3 studies, DREAMM-7 and DREAMM-8, and supportive studies (DREAMM-6, ALGONQUIN, DREAMM-14), as well as PK and integrated E-R analyses for efficacy and safety endpoints.

5.3 Immunogenicity

BLENREP has a low risk for immunogenicity. During clinical development, immunogenicity was assessed using an appropriate risk-based bioanalytical assay strategy. To date, treatment-emergent anti-BLENREP antibody incidence in monotherapy (DREAMM-1, DREAMM-2, and DREAMM-3) and combination studies (DREAMM-7, DREAMM-8 and DREAMM-6) has been low (1% and 3%, respectively) with no impact on PK, safety, or efficacy.

5.4 Conclusion

Based on extensive evaluation, the data demonstrate the 2.5 mg/kg starting dose drives the efficacy outcomes. Though dose modifications to manage ocular events, such as ocular symptoms by CTCAE and BCVA worsening to 20/50 or worse, are an intrinsic part of the dosing of BLENREP, the exposure-response analyses support that the starting dose cannot be reduced below 2.5 mg/kg without sacrificing efficacy results as measured by VGPR+.

6 CLINICAL EFFICACY

Summary

- Two independent randomized, active controlled Phase 3 studies consistently demonstrated meaningful benefits over SoC across all endpoints, including significant improvement in overall survival from the DREAMM-7 study.
  - The BLENREP combination in DREAMM-7 demonstrated statistically significant 59% reduction in the risk of progression, equating to an ~ 2-year improvement in median PFS. There was also a 42% reduction in the risk of death and projected 3-year benefit in median OS compared to the daratumumab-containing comparator (DVd).
  - In ongoing study DREAMM-8, statistically significant PFS 48% reduction in the risk of progression was observed with a median PFS not reached (BPd) vs. 12.7 months (95% CI 9.1, 18.5) (PVd) along with a positive trend in OS. In an updated analysis, a > 20 months improvement in median PFS was observed.
  - More participants derived longer benefit with deeper response in arms containing BLENREP. DREAMM-7 and DREAMM-8 show at least a doubling in CR/sCR rates and duration of response, and a 2.5 to 5 fold increase in MRD negativity versus the SOC comparator arms.
  - Progression free survival 2, an important endpoint, as it provides an intermediate efficacy measure between PFS and OS, indicated a continued benefit for BVd (HR: 0.56; 95%CI: 0.41,0.76) or BPd (HR: 0.61; 95%CI: 0.43,0.86) beyond initial progression.
  - The recommended starting dose of 2.5 mg/kg dose with subsequent pre-specified dose modification (dose delays/reductions) based on individual participant tolerability helped maximizes benefit including greater depth and durability of response and long term clinical endpoints including PFS and OS.

6.1 Introduction

Interim analyses from two randomized, open-label, comparator controlled registrational studies of BLENREP in triplet combinations provide the key efficacy data. The efficacy data presented in this briefing document are derived from the primary analysis DCOs, unless otherwise specified:

- DREAMM-7 (BVd): N=494, Primary analysis (IA1) data cut-off (DCO) date: 02 October 2023. The median (range) duration of follow up at the time of the primary analysis was 29 (0.16, 40) months in the BVd arm and 27.6 (0.10, 39.7) months in the DVd arm. Prespecified survival analysis OS update (IA2) DCO for: 07 October 2024 (Section 6.2). Median (range) of follow up was 40.2 (0.16 to 52.3) months for the BVd vs. 38.2 (0.10 to 51.3) months for the DVd arm.

- DREAMM-8 (BPd): N=302, Primary analysis (IA2) DCO: 29 January 2024; post-hoc updated analysis of PFS (Section 6.3). In the BPd vs. PVd arms, the median (range) duration of follow-up was similar – 22.4 (0.03, 36.4) months and 20.5 (0.10, 39.2) months.

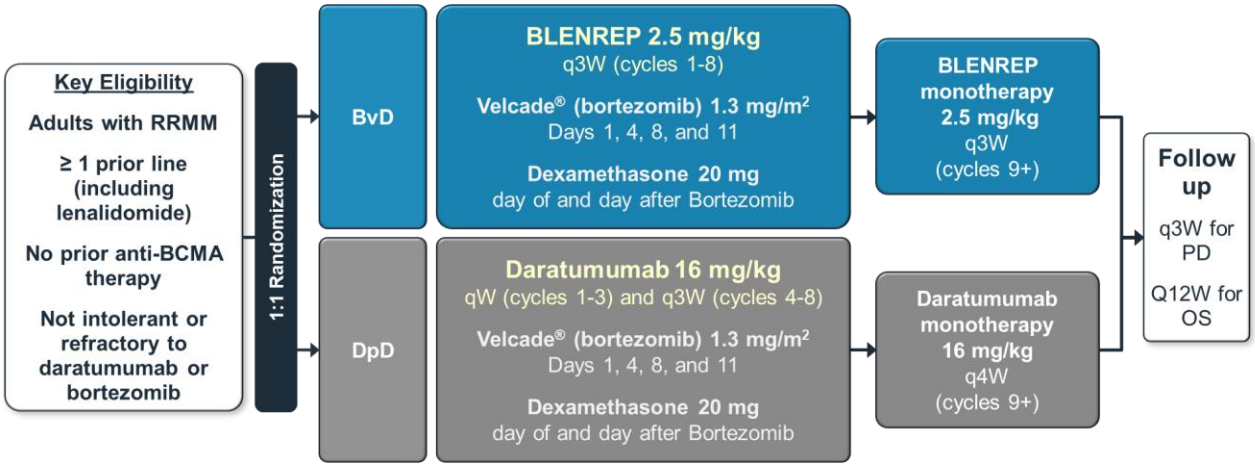
6.2 DREAMM-7 (BVd Triplet Combination, Registrational Study)

6.2.1 DREAMM-7 Overall Study Design

DREAMM-7 is an ongoing multicenter Phase 3, randomized, open-label study evaluating the efficacy and safety of the combination of BVd compared with the SoC combination of DVd in participants with RRMM. DVd was chosen as a comparator in DREAMM-7 because combination therapy with DVd is approved for the treatment of patients with RRMM and at least 1 prior line of therapy and is a SoC regimen in RRMM (Darzalex USPI 2024; Dimopoulos 2021a; NCCN 2025). A study schematic is provided in Figure 15.

BLENREP is administered IV at a dose of 2.5 mg/kg on Day 1 of every 21-day cycle in combination with Vd for the first 8 cycles. After Cycle 8, BLENREP monotherapy treatment was continued until disease progression or death. If needed, BLENREP dose modifications (dose delays and dose reductions to 1.9 mg/kg Q8W) were implemented as needed to manage ocular and other adverse events. Daratumumab was administered according to the approved label schedule in combination with Vd as shown in for a total of up to 8 cycles, followed by daratumumab monotherapy until disease progression or death.

Figure 15 DREAMM-7: Schematic of Study Design



BCMA = B-cell maturation antigen; RRMM = relapsed refractory multiple myeloma; OS = overall survival; PD = progressive disease; q = every; W = weeks

Participants were followed until confirmed, documented disease progression, death, start of a new anti-myeloma treatment, withdrawal of consent, loss to follow-up, or end of study (EoS), whichever occurred first.

- In case of progressive disease, participants were followed every 12 weeks (Q12W) to ascertain next anti-myeloma therapy, PFS2, and survival status.

- For participants who discontinued study intervention for reasons other than disease progression or death, disease evaluations were performed every 3 weeks (Q3W).

6.2.2 Endpoints

The primary endpoint for DREAMM-7 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.

Key secondary endpoints evaluated in DREAMM-7 included:

- Overall Survival (OS): defined as the time from the date of randomization until the date of death due to any cause
- Duration of Response: defined as the time from first documented evidence of PR or better until progressive disease (PD) or death due to any cause.
- Minimal Residual Disease (MRD) Negativity Rate: defined as the percentage of participants who are MRD negative by next-generation sequencing (NGS) at 10-5 threshold at least once during the time of confirmed CR or better.

All categories of disease response - used in the calculation of study endpoints were determined by an independent review committee (IRC) using IMWG 2016 criteria.

A full list of secondary endpoints is provided in Appendix Section 11.3.1.

6.2.3 Post Hoc Analyses

Several post hoc analyses were conducted to assess the impact of dose modification on ORR, PFS, and MRD rates.

6.2.4 Selection of Study Population

Key entry criteria included:

- Participants must have documented disease progression during or after their most recent therapy and could not be refractory or intolerant to anti-CD38 therapy (e.g., daratumumab).
- Participants must have at least one aspect of measurable disease per IMWG criteria
- Participants also could not be intolerant or refractory to bortezomib (1.3 mg/m^2 twice weekly, or within 60 days of completing that treatment).
- Participants with prior autologous stem cell transplant (autoSCT) were allowed (>100 days prior to the first dose of study medication with no active bacterial, viral, or fungal infections) or should have been considered transplant ineligible.
- Participants could not be refractory to anti-CD38 therapy or intolerant to daratumumab.
- Participants could not have received prior anti-BCMA therapy.

6.2.5 Statistical Analyses

Participants were stratified based on the number of prior lines of therapy (1 vs. 2-3 vs. ≥4), prior bortezomib (yes vs. no), and the revised International Staging System (R-ISS) I vs. R-ISS II/III and centrally randomized in a 1:1 ratio to either study arm. No cross-over was allowed and at least 50% of the participants must have had no more than 1 prior line of therapy.

For the primary endpoint, the distribution of PFS for each treatment arm was estimated using the Kaplan-Meier method. The median, 25th and 75th percentiles of PFS were estimated and the corresponding 95% confidence intervals (CI) were estimated using the Brookmeyer-Crowley method. The treatment difference was compared by the one-sided stratified log-rank test, using the intent to treat (ITT) Analysis set. The hazard ratio (HR) and its corresponding 95% CI was estimated from Cox proportional hazard model stratified by randomization factors with treatment arm as the sole explanatory variable.

Duration of response (DoR) was analyzed based on the restricted mean duration of response using a non-parametric approach (Huang 2022). Using this approach, non-responders are included and will have an observed DoR of 0.

The number and percentage of participants who were in CR and MRD negative at the primary PFS analysis were summarized by study arms with corresponding 2-sided 95% exact CIs for MRD negativity rate.

Progression free survival, OS, and DoR were estimated using the Kaplan-Meier method.

6.2.5.1 Interim Analyses

The DREAMM-7 protocol pre-specified 3 interim analyses:

- Interim Analysis 1 (IA1): Efficacy, ~250 PFS events (~89% PFS information fraction; actual 249 PFS events at the time of the analysis) (DCO: 03 October 2023)
- Primary PFS / Interim Analysis 2 (IA2): Efficacy, planned after~178 OS events (~50% OS information fraction) (DCO: 07 Oct 2024)
- Interim Analysis 3 (IA3): Efficacy, planned after ~266 OS events (~75% OS information fraction)

Analyses included in the BLA submission are from IA1. Based on the recommendation of the independent data monitoring committee, IA1 included the primary PFS interim analysis originally planned for IA2. IA2 comprised the OS analysis.

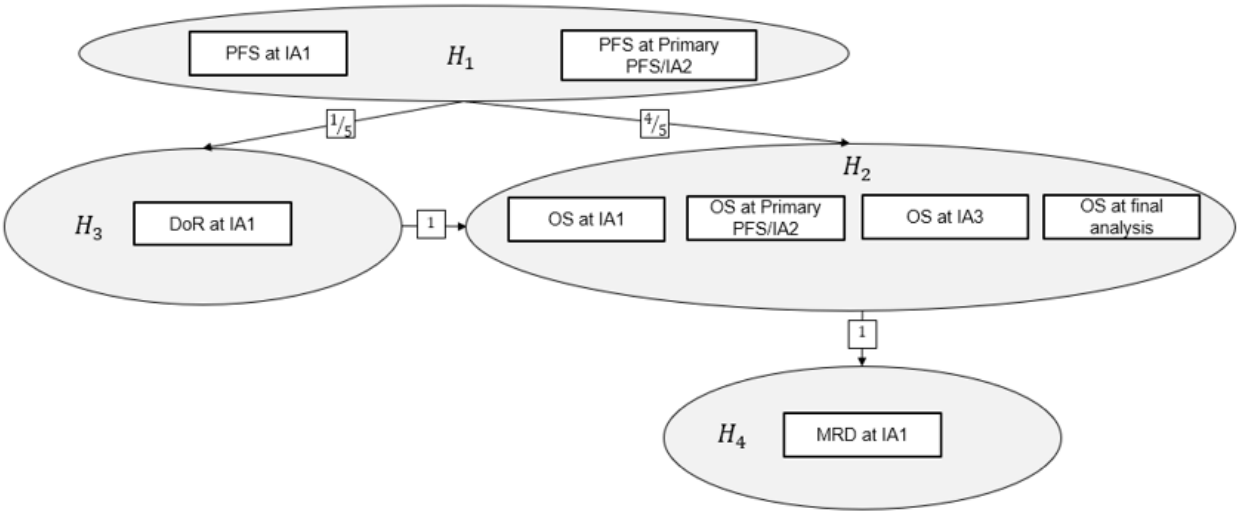
6.2.5.2 Subgroup and Sensitivity Analyses

Subgroup analyses for randomization factors and SAP-specified disease characteristics were conducted for PFS. Sensitivity analyses were conducted using alternative PFS censoring rules and using investigator-assessed responses.

6.2.5.3 *Multiple Testing Strategy*

Multiplicity adjustments were made as shown in Figure 16. Testing of the key secondary endpoints of OS, DoR, and MRD negativity was conditional on the successful rejection of the null hypothesis for the primary endpoint. A weighted Bonferroni procedure was applied across OS and DoR, where alpha was split between the endpoints, with a larger proportion assigned to OS initially. The testing of MRD was conditional on the successful rejection of the null hypothesis for OS. If the conditional testing requirements were not met, analyses of the secondary key endpoints were descriptive.

Figure 16 DREAMM-7: Multiple Testing Strategy



DoR = duration of response; IA = interim analysis; MRD = minimal residual disease; OS = overall survival; PFS = progression free survival;
Note: Arrows indicate the direction and proportion of alpha re-allocation.

6.2.6 *DREAMM-7 Study Participants*

6.2.6.1 *Demographics*

Participant demographics are summarized in Table 15. Demographic characteristics were balanced between the BLENREP treatment arm and the comparator arm. As expected for this patient population, participants were predominantly white with a median age of 65.0 years and 64.0 years in the BVd and DVd arms, respectively.

Table 15 DREAMM-7: Participant Demographics (ITT Population)

Parameter	DREAMM-7		
	BVd (N=243)	DVd (N=251)	Total (N=494)
Sex, n (%)			
Male	128 (53%)	144 (57%)	272 (55%)
Female	115 (47%)	107 (43%)	222 (45%)

Parameter	DREAMM-7		
	BVd (N=243)	DVd (N=251)	Total (N=494)
Age (years)a			
Mean (SD)	64.5 (9.47)	63.6 (10.11)	64.0 (9.80)
Median (min, max)	65.0 (34, 86)	64.0 (32, 89)	64.5 (32, 89)
Age Group (years), n (%)[a]			
18 to <65	121 (50%)	126 (50%)	247 (50%)
65 to <75	85 (35%)	95 (38%)	180 (36%)
≥75	37 (15%)	30 (12%)	67 (14%)
High level race, n (%)	N = 242	N = 249	N = 491
Asian	28 (12%)	33 (13%)	61 (12%)
Black or African American	8 (3%)	12 (5%)	20 (4%)
White	206 (85%)	203 (81%)	409 (83%)
Mixed race	0	1 (<1%)	1 (<1%)

BVd = BLENREP, bortezomib and dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone; SD = standard deviation
a Age was imputed when full date of birth was not provided.

Of note two participants who were randomized to the DVd arm, but were not treated, were re-screened and re-randomized one each to the BVd and the DVd arms within a short timeframe. They are counted as 4 unique participants in all ITT tables.

6.2.6.2 Baseline Disease Characteristics

Disease characteristics at baseline were as expected for a patient population with RRMM (Table 16). The baseline and disease characteristics were generally similar between treatment arms except for extramedullary disease (EMD), which was slightly higher in the DVd arm (10%) compared with the BVd arm (5%).

Table 16 DREAMM-7: Key Baseline Disease Characteristics (ITT Population)

	DREAMM-7		
	BVd (N=243)	DVd (N=251)	Total (N=494)
Revised International Staging System, n (%)			
I	102 (42%)	103 (41%)	205 (41%)
II	130 (53%)	132 (53%)	262 (53%)
III	9 (4%)	14 (6%)	23 (5%)
Unknown	2 (<1%)	2 (<1%)	4 (<1%)
Extra Medullary Disease, n (%)			
No	230 (95%)	226 (90%)	456 (92%)
Yes	13 (5%)	25 (10%)	38 (8%)
Lytic bone lesions, n (%)			
No	62 (26%)	66 (26%)	128 (26%)
Yes	181 (74%)	185 (74%)	366 (74%)

	DREAMM-7		
	BVd (N=243)	**DVd (N=251)**	**Total (N=494)**
Prior stem cell transplant, n (%)			
No	79 (33%)	78 (31%)	157 (32%)
Yes	164 (67%)	173 (69%)	337 (68%)
Cytogenetic risk categories, n (%)			
High risk [a]	67 (28%)	69 (27%)	136 (28%)
Double Hit Multiple Myeloma [b]	11 (5%)	13 (5%)	24 (5%)
Standard risk [c]	175 (72%)	175 (70%)	350 (71%)
Missing or NE	1 (<1%)	7 (3%)	8 (2%)
Time to relapse after initiation of first line treatment, n (%) [a]			
≤12 Months	49 (20%)	50 (20%)	99 (20%)
>12 Months	194 (80%)	201 (80%)	395 (80%)
Actual time since initial diagnosis at randomization (years)			
Median (min, max)	4.28 (0.2, 26.0)	3.94 (0.1, 23.4)	4.09 (0.1, 26.0)
Q1	2.52	2.71	2.64
Q3	6.71	6.17	6.42
Eastern Cooperative Oncology Group Performance Status [b]			
N	242	246	488
0	121 (50%)	112 (46%)	233 (48%)
1	111 (46%)	123 (50%)	234 (48%)
2	10 (4%)	11 (4%)	21 (4%)

BVd = BLENREP, bortezomib, dexamethasone; DVd = daratumumab, bortezomib, dexamethasone; Q1 = first quartile; Q3 = third quartile

a Time to relapse was defined as the time between start date of 1L of therapy to PD date on 1L treatment. If no PD date was available, start date of second line of treatment was used. If no PD date nor start date of second line of treatment was available, date of randomization into study was used.

b Analyzed in the Safety Population.

6.2.6.3 Prior and Subsequent Therapies

A summary of prior lines of therapy is provided in Appendix Table 2. Half of the participants in DREAMM-7 received 1 prior line of therapy with a mean of 2 prior lines of therapy. The types of prior anti-myeloma therapies participants received and the percentage of participants refractory to different types of prior anti-myeloma therapies were similar between treatment arms. The majority of participants in both treatment arms received steroids, PIs, IMiD agents, and chemotherapy. Less than 5% of participants received prior mAbs and only 7 participants received prior daratumumab.

More participants in the DVd arm progressed earlier and received subsequent therapy, than in the BVd arm where more participants were still receiving study treatment at the DCO. Subsequent study treatment was at the discretion of the treating physician, based on local SoC and availability. The majority of participants in both arms received standard, NCCN-recommended regimens included PIs and immunomodulators as subsequent (post-study treatment) therapy (see Appendix Table 3). Few participants received newer

therapies including bsAbs. Crossover to BLENREP in the DVd arm was not allowed on study, but 24 participants received BLENREP via local access. An OS benefit in favor of BLENREP was observed despite the use of effective, NCCN-recommended therapies in the comparator arm.

6.2.6.4 Participant Disposition

An overview of participant treatment status as of the primary analysis DCO is provided in Figure 6 and detailed with disposition in Appendix Table 8. In total, 494 participants with RRMM were randomized to either BVd (N=243) or DVd (N=251).

- A total of 63 participants (13%) withdrew from the study (24 [10%] in the BVd arm; 39 [16%] in the DVd arm). The primary reasons for withdrawal from the study included withdrawal by participant (8%, 10%) and physician decision (2%, 4%).
- BLENREP or daratumumab treatment was discontinued by 161 participants in the BVd arm (66%) compared to 195 (78%) participants in the DVd arm; the primary reasons for discontinuation included disease progression (24% vs. 59%), AEs (19% vs. 9%), and physician decision (14% vs.4%), participant withdrawal (9% vs. 5%).
- At the time of the most recent OS analysis a smaller proportion of participants in the BVd arm (68 [28%]) had died vs. the DVd arm (103 [41%]).

6.2.7 DREAMM-7 Study Efficacy Results

The key efficacy results from DREAMM-7 are summarized in Table 17. Efficacy results for the DREAMM-7 study are based on the pre-specified interim analyses

Table 17 DREAMM-7: Summary of Key Efficacy Results (ITT Population)

	BVd (N=243)	**DVd (N=251)**
Primary endpoint Progression Free Survival (Figure 7)		
Number of events, n (%)	91 (37%)	158 (63%)
Median PFS (95% CI), months	36.6 (28.4, NR)	13.4 (11.1, 17.5)
Stratified HR estimate (95% CI), p-value	0.41 (0.31, 0.53), p<0.00001	
Censored, follow-up ended	44 (18%)	41 (16%)
Censored, follow-up ongoing	108 (44%)	52 (21%)
Overall Survival (Interim Analysis 2)[a] (Figure 8)		
Number of events, n (%)	68 (28%)	103 (41%)
Median OS (95% CI), months	NR (NR, NR)	NR (41, NR)
Stratified HR estimate (95% CI), p-value	0.58 (0.43, 0.79), p=0.00023	
Censored, follow-up ended	26 (11%)	33 (13%)
Censored, follow-up ongoing	149 (61%)	115 (46%)
Overall Response Rate, % (95% CI) (Figure 9)	**82.7 (77.4, 87.3)**	**71.3 (65.3, 76.8)**
VGPR/CR/sCR, % (95% CI)	65.8 (59.5, 71.8)	46.2 (39.9, 52.6)
CR/sCR, % (95 CI)	34.6 (28.6, 40.9)	17.1 (12.7, 22.4)

	BVd (N=243)	DVd (N=251)
Minimal Residual Disease Negativity (CR/sCR)[b], % (95% CI) (Figure 10)	**24.7 (19.4, 30.6)**	**9.6 (6.2, 13.9)**
p-value	p<0.00001	
Duration of Response (Figure 9)		
Number of Responders, n	201	179
Number of events, n (%)	68 (34%)	105 (59%)
Number of ongoing responders, n (%)	106 (53%)	52 (29%)
Median DoR (95% CI), months	35.6 (30.5, -)	17.8 (13.8, 23.6)
Censored, follow-up ended	27 (13%)	22 (12%)
Censored, follow-up ongoing	106 (53%)	52 (29%)
Progression Free Survival 2		
Number of events, n (%)	70 (29%)	106 (42%)
Median PFS2 (95% CI), months	NR (NR, NR)	34.6 (27.6, NR)
Stratified HR estimate (95% CI)	0.56 (0.41, 0.76)	

BVd = BLENREP, bortezomib and dexamethasone; CI = confidence interval; CR = complete response; DVd = daratumumab, bortezomib, and dexamethasone; HR = hazard ratio; MRD = minimal residual disease; NGS = next-generation sequencing; PFS = progression free survival; PFS2 = progression free survival 2; OS = overall survival; sCR = stringent complete response; VGPR = very good partial response rate (

a DCO 07 Oct 2024

b MRD negativity rate was defined as the percentage of participants who were MRD negative by NGS based on a sensitivity of 10^{-5}

Detailed efficacy results is provided in Appendix Table 4 (PFS), Appendix Table 5 (OS), Appendix Table 6 (DoR), and Appendix Table 7 (ORR, MRD)

6.2.7.1 Primary Efficacy Result – Progression Free Survival

The DREAMM-7 study met its primary endpoint for PFS based on IRC-assessed response with a statistically significant and clinically meaningful PFS benefit for BVd compared with current daratumumab-containing SoC, DVd (Table 17).

- The median PFS was nearly 2 years longer in the BVd arm than the DVd SoC arm. The Kaplan-Meir curves for PFS showed a clear and early separation between the treatment arms in favor of BVd (Figure 7).
- The 18-month PFS rate was higher in the BVd arm than the DVd arm (69% vs. 43%) (Appendix Table 4).

6.2.7.1.1 Sensitivity Analyses and Subgroups – Progression free Survival

Progression-free survival analysis based on investigator-assessed responses was consistent with IRC results. Results of all supplementary and sensitivity analyses to assess differing intercurrent event strategies in DREAMM-7 study were consistent with the primary PFS analysis with HRs ranging from 0.40 to 0.45, demonstrating the robustness of the primary analysis.

Progression free survival was also assessed for a number of prespecified subgroups based on age, disease stage, cytogenetics, presence of extramedullary disease, relapse within 12 months of first line treatment, and prior therapy (Figure 7). Benefit favoring BVd over DVd was observed across all prespecified subgroups, including prior lines of therapy.

6.2.7.1.2 Post Hoc Analyses - Progression Free Survival

Post hoc analysis of censoring for PFS indicated that a similar number of participants were censored between 0 months and 6 months (BVd: 23 [9%]; DVd: 22 [9%]) but a slightly higher number were censored in the BVd group between 6 months and 12 months (BVd: 17 [7%]; DVd: 8 [3%]). This difference did not impact on the overall PFS results. Median follow-up for censored participants was long and similar between treatment groups, demonstrating that they contributed substantially to the analysis (BVd: 30.3 months [95% CI: 0.2, 40.0]; DVd: 28.6 months [95% CI: 0.1, 39.7]).

6.2.7.2 Secondary Efficacy Results

6.2.7.2.1 Overall Survival

At the PFS primary analysis data cut-off, a strong and clinically meaningful OS benefit favored the BVd arm versus the DVd arm with a nominal p-value of 0.00049 (HR=0.57; 95% CI: 0.40, 0.80) (Table 17) but did not meet statistical significance at this analysis. An updated pre-specified second interim analysis (IA) for OS was completed and reported at the time of the post-submission safety update report. Overall survival data have reached 34.6% (171/494 participants) overall maturity and an information fraction of 48.2% (171/355). This analysis for OS demonstrates a statistically significant improvement for the BVd arm, compared to the DVd arm (HR [95% CI] 0.58 [0.43-0.79]; p=0.00023) (Figure 8). There were 35 (13%) more deaths in the DVd arm vs. BVd at the time of the analysis.

With OS being statistically significant, the MRD negativity results at the time of the PFS primary analysis DCO (Section 6.2.7.2.3), can now also be considered statistically significant following the testing hierarchy.

6.2.7.2.2 Response Rate and Duration of Response

Overall response rate, VGPR rate, and CR rate were higher in the BVd arm compared with the DVd arm (Table 17, Figure 9 Panel A).

The median DoR was 36.5 months in the BVd arm and was 17.8 months in the DVd arm, with more participants ongoing and in response in the BVd arm (Table 17, Figure 9 Panel B). The Kaplan-Meir curves for DoR showed a clear and early separation between the treatment arms in favor of BVd.

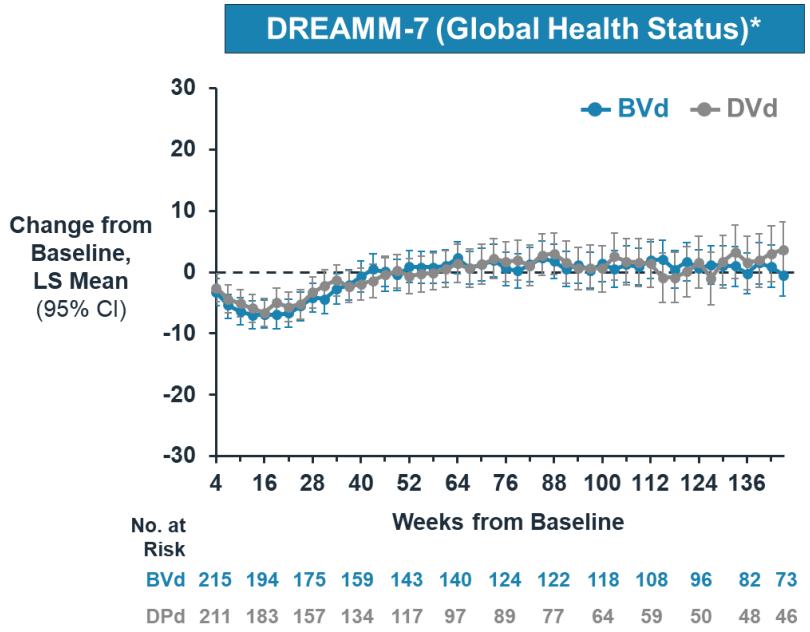
6.2.7.2.3 Minimal Residual Disease Negativity

In participants achieving CR or better, the proportion of participants who achieved MRD negativity was higher in the BVd arm compared with the DVd arm (24.7% vs. 9.6%, p<0.00001, Table 17, Figure 10).

6.2.7.2.4 Quality of Life

Patient reported outcomes designed to evaluate and compare health-related quality of life (QoL) were assessed using EORTC QLQ-C30, a 30-item questionnaire measuring five key domains (global health status, physical function, role function, fatigue, and disease symptoms), and the EORTC QLQ-MY20/IL52 a 20-item MM outcome measure. Participants receiving BVd or DVd maintained overall health-related QoL (<10-point change vs. baseline), as measured by the EORTC QLQ-C30 Global Health Score/Quality of Life (GHS/QoL) domain, and there were no differences (≥10 points) between treatment arms (Figure 17). GHS/QoL appeared to show only a small mean deterioration in both treatment arms that did not meet the meaningful change threshold. Similarly, there were no differences (≥10 points) between treatment arms for role functioning, physical functioning, fatigue, and disease symptoms.

Figure 17 DREAMM-7: Plot of Least Square Mean (95% CI) of EORTC QLQ-C30 Global Health Status Domain Score by Visit



CI = confidence interval; EORTC QLQ-C30 = 30 item European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; LS = least squares means;

6.2.7.2.5 Additional Secondary Endpoints

The BVd arm also demonstrated improvement compared to the DVd arm on the following endpoints:

- Clinical Benefit Rate: higher in the BVd arm compared with the DVd arm (86.0% vs. 75.7%).
- Time to Response (TTR): median TTR was short and similar between treatment arms (1.41 months [range: 0.7 to 8.4] vs. 0.85 months [range: 0.7 to 11.1])

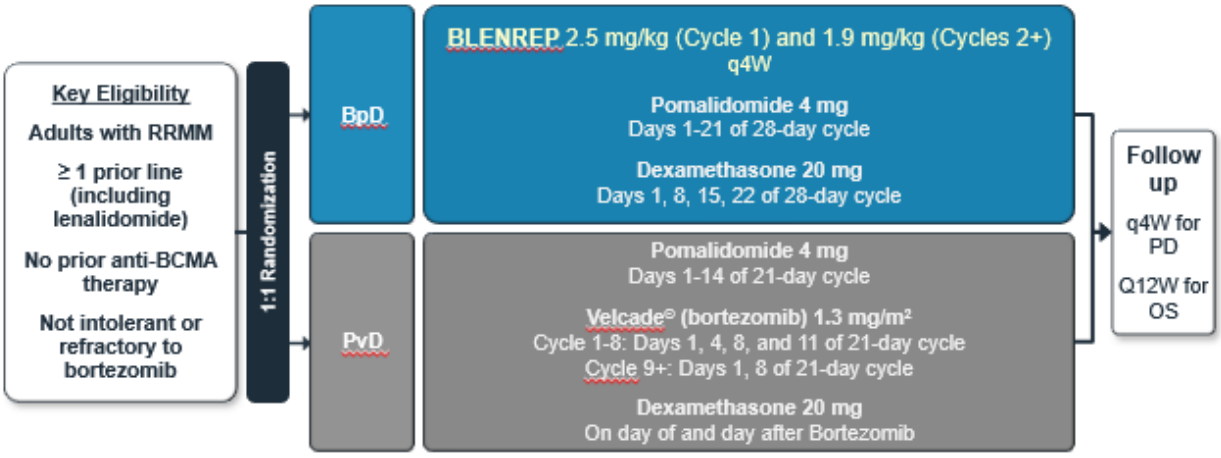
- Progression Free Survival 2: PFS2 indicated a continued benefit for BVd beyond initial progression. Median PFS2 was not reached in the BVd arm. Median PFS2 was 34.6 months in the DVd arm (HR=0.56; 95% CI: 0.41, 0.76). PFS2 was investigator assessed (Table 17).

6.3 DREAMM-8 (BPd Triplet Combination, Registrational Study)

6.3.1 DREAMM-8 Overall Study Design

DREAMM-8 is an ongoing Phase 3, open-label, randomized, clinical study to evaluate the efficacy and safety of BPd compared with PVd in participants with RRMM previously treated with at least 1 prior line of therapy including a lenalidomide-containing regimen. A schematic of the study design is provided in Figure 18.

Figure 18 DREAMM-8: Schematic of Study Design



BCMA = B-cell maturation antigen; RRMM = relapsed refractory multiple myeloma; OS = overall survival; PD = progressive disease; q = every; W = weeks

The dose for Cycle 1 is 2.5 mg/kg on Day 1 and 1.9 mg/kg for subsequent cycles. When needed, dose modifications, including dose delays and dose reductions (to 1.9 mg/kg Q8W, or 1.4 mg/kg Q8W), were implemented according to the individual tolerability of the participant to mitigate ocular effects.

Pomalidomide, bortezomib, and dexamethasone were administered as shown in Figure 18. Treatment continues in both study arms until confirmed disease progression per IMWG, death, unacceptable toxicity, start of a new anti-myeloma therapy, withdrawal of consent, or EoS, whichever occurred first.

For participants who discontinue study treatment for reasons other than disease progression, disease evaluations are performed Q4W (±3 days) until confirmed PD (documented), death, start of a new anti-myeloma therapy, withdrawal of consent, loss to follow-up, or EoS, whichever occurred first. In case of PD, participants were followed for subsequent anti-myeloma therapy, PFS2, and survival status every 12 weeks until withdrawal of consent, loss to follow up, death, or EoS.

Pomalidomide, bortezomib, and dexamethasone was chosen as the comparator because it is approved by the EMA for the treatment of patients with at least 1 prior line of therapy including lenalidomide. The global utilization of this regimen is driven by increasing use of lenalidomide and anti-CD38 antibodies in the frontline setting, raising the need for lenalidomide-sparing, non–anti-CD38 containing treatments for RRMM. Use of PVd as the comparator allowed enrollment of patients with prior anti-CD38 treatment. The NCCN recommends PVd as a preferred, Category 1 regimen for lenalidomide-refractory and anti-CD38–refractory RRMM patients following 1-3 prior therapies.

6.3.2 Endpoints

The primary endpoint for DREAMM-8 was PFS, defined as the time from randomization until the earliest date of documented disease progression based on IRC-assessment per IMWG criteria, or death due to any cause. The full endpoint list is provided in Appendix Section 11.3.1.

Key secondary endpoints included:

- Overall Survival: defined as the time from the randomization until the date of death due to any cause
- Duration of Response: defined as the time from first documented evidence of PR or better until PD or death due to any cause. Response will be based on IRC-assessment per IMWG criteria.
- Minimal Residual Disease Negativity Rate: defined as the percentage of participants who achieve MRD 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.

6.3.3 Selection of Study Population

Key entry criteria included:

- Participants had to have 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 progressed during or after their most recent therapy.
- Participants must have at least one aspect of measurable disease (Urine M-protein excretion ≥200 mg/24 h, 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 participant has no measurable urine or serum M spike.)
- Participants should have undergone autoSCT (>100 days prior to the first dose of study medication with no active bacterial, viral, or fungal infections) or should have been considered transplant ineligible.
- Participants could not be intolerant or refractory to bortezomib at a 1.3 mg/m^2 dose twice weekly dosing schedule.

- Participants could not have received a prior anti-BCMA therapy or pomalidomide.

6.3.4 Statistical Analyses

Participants were stratified based on the number of prior lines of therapy (1 vs. 2-3 vs. ≥4), prior bortezomib (yes/no). Initially ISS stage at screening (I vs. II/III) was a third stratification factor but was replaced by prior anti-CD38 treatment (yes/no) via Protocol Amendment. No cross-over was allowed, and at least 50% of the participants were required to have had no more than 1 prior line of therapy.

For the primary endpoint, the distribution of PFS for each treatment arm was estimated using the Kaplan-Meier method. The median, 25^{th} , and 75^{th} percentiles of PFS were estimated and the corresponding 95% CIs were estimated using the Brookmeyer-Crowley method. The treatment difference was compared by the one-sided stratified log-rank test, using the ITT Analysis set. The hazard ratio (HR) and its corresponding 95% CI was estimated from Cox proportional hazard model stratified by randomization factors with treatment arm as the sole explanatory variable.

The number and percentage of participants who were in CR and MRD negative at the primary PFS analysis were summarized by study groups with corresponding 2-sided 95% exact CIs for MRD negativity rate.

Overall survival was estimated using the same methodology as PFS.

6.3.4.1 Interim analyses

DREAMM-8 includes 4 pre-specified interim analyses:

- Interim Analysis for harm (IA1): Harm PFS (inferior efficacy)
- Interim Analysis 2 (IA2): Efficacy, planned after ~145 PFS events (~84% PFS information fraction; actual 142 events at the time of analysis)
- Primary PFS / Interim Analysis 3 (IA3): Efficacy, planned after ~130 OS events (~60% OS information fraction)
- Interim Analysis 4 (IA4): Efficacy, planned after ~163 OS events (~75% OS information fraction)

Analyses included in the BLA submission are from IA2. Based on the recommendation of the independent data monitoring committee, this analysis included the primary PFS interim analysis originally planned for IA3. IA3 and future analyses will comprise the OS analysis.

6.3.4.2 Subgroup and Sensitivity Analyses

Subgroup analyses for randomization factors and SAP-specified baseline demography and disease characteristics were conducted for PFS.

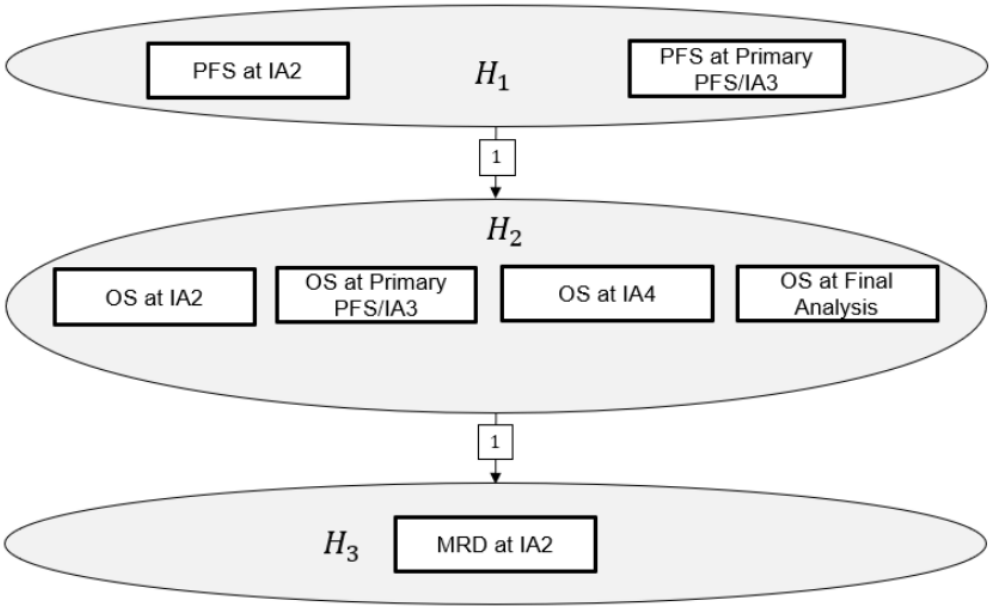
Sensitivity analyses were conducted using alternative PFS censoring rules and using investigator-assessed responses. Sensitivity analyses were also performed based on the

stratification data from clinical database (eCRF/vendor data) and using methods to account for the changes in the stratification factors (ISS and prior anti-CD38 use).

6.3.4.3 *Multiple Testing Strategy*

A multiplicity adjustment for the primary and key secondary endpoints was made as shown in Figure 19. Testing of the key secondary endpoints of OS and MRD negativity was conditional on the successful rejection of the null hypothesis for the primary endpoint. OS was tested first, and the testing of MRD was conditional on the successful rejection of the null hypothesis for OS, aligned with a step-down (or hierarchical) testing procedure (Bretz 2009, Lan 1983, Li 2017).If the conditional testing requirements were not met, analyses were descriptive.

Figure 19 DREAMM-8: Multiple Testing Strategy



IA = interim analysis; MRD = minimal residual disease; OS = overall survival; PFS = progression free survival
Note: $\boldsymbol{Hi}$ denotes the 1-sided null hypothesis for the primary and key secondary endpoints, where $\boldsymbol{i}$=**1**, **2**, **3** denotes the index indicating PFS, OS, and MRD negativity rate, respectively

6.3.5 DREAMM-8 Study Participants

6.3.5.1 *Demographics*

Participant demographics are summarized in Table 18.

Demographic characteristics were balanced between the BPd and PVd arms. The percentage of participants aged ≥75 years was slightly higher in PVd arm (12% vs. 24%).

Table 18 DREAMM-8: Participant Demographics (Intent to Treat Population)

	DREAMM-8		
	BPd (N=155)	**PVd (N=147)**	**Total (N=302)**
Sex, n (%)			
Female	56 (36%)	65 (44%)	121 (40%)
Male	99 (64%)	82 (56%)	181 (60%)
Age (years)[a]			
Mean (SD)	65.5 (8.56)	66.7 (10.03)	66.1 (9.31)
Median (min, max)	67.0 (40, 82)	68.0 (34, 86)	67.0 (34, 86)
Age Group (years), n (%)[a]			
18 to <65	64 (41%)	53 (36%)	117 (39%)
65 to <75	72 (46%)	59 (40%)	131 (43%)
≥75	19 (12%)	35 (24%)	54 (18%)
High level race, n (%)			
N	155	146	301
Asian	20 (13%)	17 (12%)	37 (12%)
Native Hawaiian or Other Pacific Islander	1 (<1%)	2 (1%)	3 (<1%)
White	133 (86%)	127 (87%)	260 (86%)
Mixed race	1 (<1%)	0	(<1%)

BPd = BLENREP, pomalidomide, dexamethasone; PVd = pomalidomide, bortezomib, dexamethasone; SD = standard deviation

a Age was imputed when full date of birth was not provided.

6.3.5.2 Key Baseline Characteristics

Disease characteristics at baseline are summarized in (Table 19). Baseline and disease characteristics were as expected for a patient population with RRMM and were generally similar between treatment arms except for EMD, which was slightly higher in the BPd arm (13%) compared with the PVd arm (7%). Most participants were ISS Stage I or II and had an ECOG performance status of either 0 or 1.

Table 19 DREAMM-8: Key Baseline Disease Characteristics (Intent to Treat Population)

	BPd (N=155)	**PVd (N=147)**	**Total (N=302)**
International Staging System at screening, n (%)			
I	93 (60%)	85 (58%)	178 (59%)
II	39 (25%)	40 (27%)	79 (26%)
III	22 (14%)	22 (15%)	44 (15%)
Unknown	1 (<1%)	0	1 (<1%)
Extra Medullary Disease, n (%)			
No	135 (87%)	136 (93%)	271 (90%)

	BPd (N=155)	PVd (N=147)	Total (N=302)
Yes	20 (13%)	11 (7%)	31 (10%)
Lytic bone lesions, n (%)			
No	37 (24%)	40 (27%)	77 (25%)
Yes	118 (76%)	107 (73%)	225 (75%)
Prior stem cell transplant, n (%)			
No	56 (36%)	65 (44%)	121 (40%)
Yes	99 (64%)	82 (56%)	181 (60%)
Cytogenetic risk categories, n (%)[a]			
High risk	52 (34%)	47 (32%)	99 (33%)
Double Hit Multiple Myeloma	9 (6%)	7 (5%)	16 (5%)
Standard risk	72 (46%)	75 (51%)	147 (49%)
Missing or NE	31 (20%)	25 (17%)	56 (19%)
Time to relapse after initiation of first line treatment, n (%)[a]			
≤12 Months	22 (14%)	20 (14%)	42 (14%)
>12 Months	133 (86%)	127 (86%)	260 (86%)
Actual time since initial diagnosis at randomization (years)			
Median (min, max)	4.04 (0.4, 16.7)	3.43 (0.4, 17.7)	3.63 (0.4, 17.7)
Q1	2.48	2.11	2.33
Q3	6.60	5.22	6.04
Eastern Cooperative Oncology Group Performance Status [b]			
N	150	145	-
0	79 (53%)	84 (58%)	-
1	67 (45%)	56 (39%)	-
2	4 (3%)	5 (3%)	-

BPd = BLENREP, pomalidomide, dexamethasone; PVd = pomalidomide, bortezomib, dexamethasone
a Time to relapse was defined as the time between start date of 1L of therapy to PD date on 1L treatment. If no PD date was available, start date of second line of treatment was used. If no PD date nor start date of second line of treatment was available, date of randomization into study was used.
b Analyzed in the Safety Population.

6.3.5.3 Prior and Subsequent Therapies

A summary of the prior lines of therapy received is provided in Appendix Table 2. Half of the participants in DREAMM-8 received 1 prior line of therapy. The types of prior anti-myeloma therapies participants received and the percentage of participants refractory to different types of prior anti-myeloma therapies were generally balanced between treatment arms. In the BPd and PVd arms, anti-CD38 antibodies (primarily daratumumab) were received by 25% and 29% of participants, respectively (21% and 23% were refractory to daratumumab). All participants received prior lenalidomide (81% and 76% in the BPd and PVd arms were refractory to lenalidomide).

More participants in the PVd arm progressed earlier and received subsequent therapy, compared to the BPd arm where more participants were still receiving study treatment at the DCO. Post-study treatment was at the discretion of the treating physician, based on

local SoC and availability. Majority of participants in both the arms received standard NCCN-recommended regimens comprising PIs and anti-CD38 antibodies as subsequent (post-study treatment) therapy (Appendix Table 3). A small proportion of participants received newer therapies including bispecific antibodies. Crossover to BLENREP in the PVd arm was not allowed on study, but 10 participants received BLENREP via local access. An OS trend favoring BLENREP was observed despite the use of effective, NCCN-recommended therapies in the comparator arm.

The first subsequent therapy is important to contextualize PFS2 (Section 6.2.7.2.5). PFS2 benefit in favor of BLENREP was observed despite the use of effective, NCCN-recommended, first subsequent therapy in the comparator arm.

6.3.5.4 Participant Disposition

Participant disposition is overviewed in and detailed with treatment status in Appendix Table 8. As of the data cut-off date for the primary analysis (29 January 2024), 302 participants with RRMM were randomized to either BPd (N = 155) or PVd (N = 147).

- A total of 22 participants (7%) withdrew from the study (13 [8%] in the BPd arm and 9 [6%] in the PVd arm). The primary reason for early withdrawal from the study was withdrawal of consent by the participant.
- At the data cut-off, the percentage of participants who discontinued BLENREP (64%) was lower compared with the percentage of participants who discontinued bortezomib (79%). The primary reasons for BLENREP or bortezomib discontinuation included disease progression (28% vs. 48%), AEs (16% vs. 16%), physician decision (12% vs. 10%), and participant withdrawal (6% vs. 5%).
- At the time of the primary analysis 49 (32%) of participants in the BPd arm had died vs. 56 (38%) in the PVd arm.
- Similar proportions of participants were ongoing in the study in the BPd arm (61%) compared with the PVd arm (57%).

In the BPd vs. PVd arms, the median (range) duration of follow-up was similar – 22.4 (0.03, 36.4) months and 20.5 (0.10, 39.2) months. .

6.3.6 DREAMM-8 Study Efficacy Results

The key efficacy results for the DREAMM-8 study are summarized in Table 20. Included are the PFS results from the prespecified IA2 and an updated PFS analysis with a DCO of 07 October 2024.

Table 20 DREAMM-8: Summary of Key Efficacy Results (ITT Population)

	BPd (N=155)	**PVd (N=147)**
Primary Endpoint Progression Free Survival [a,b] - (IA2) (Figure 7)		
Number of events, n (%)	62 (40%)	80 (54%)
Median PFS (95% CI), months	- (20.6, -)	12.7 (9.1, 18.5)

	BPd (N=155)	PVd (N=147)
Stratified HR estimate (95% CI), p-value [c]	0.52 (0.37, 0.73), p<0.001	
Censored, follow-up ended	25 (16%)	34 (23%)
Censored, follow-up ongoing	68 (44%)	33 (22%)
Progression Free Survival [a,b] - Updated		
Number of events, n (%)	68 (44%)	89 (61%)
Median PFS (95% CI), months	32.6 (21.1, -)	12.5 (9.1, 17.6)
Stratified HR estimate (95% CI)	0.49 (0.35,0.68)	
Censored, follow-up ended	28 (18%)	37 (25%)
Censored, follow-up ongoing	59 (38%)	21 (14%)
Overall Survival (Figure 8)		
Number of events, n (%)	49 (32%)	56 (38%)
Median OS (95% CI), months	NR (33.0, NR)	NR (25.2, NR)
Stratified HR estimate (95% CI)	0.77 (0.53, 1.14)	
Censored, follow-up ended	12 (8%)	7 (5%)
Censored, follow-up ongoing	94 (61%)	84 (57%)
Overall Response Rate, % (95% CI) (Figure 9)	**77 (70, 83.7)**	**72 (64.1, 79.2)**
VGPR/CR/sCR, % (95% CI)	64 (55.8, 71.4)	38 (30.2, 46.5)
CR/sCR, % (95% CI)	40 (32.2, 48.2)	16 (10.7, 23.3)
Minimal Residual Disease Negativity (CR/sCR)[a], % (95% CI) (Figure 10)	**23.9 (17.4, 31.4)**	**4.8 (1.9, 9.6)**
Duration of Response (Figure 9)		
Number of Responders, n	120	106
Number of events, n (%)	39 (33%)	49 (46%)
Number of ongoing responders, n (%)	66 (55%)	33 (31%)
Median DoR (95% CI), months	NR (24.9, -)	17.5 (12.1, 26.4)
Censored, follow-up ended	15 (13%)	24 (23%)
Censored, follow-up ongoing	66 (55%)	33 (31%)
Progression Free Survival 2		
Number of events, n (%)	56 (36%)	73 (50%)
Median PFS2 (95% CI), months	NR (33.0, -)	22.4 (13.8, NR)
Stratified HR estimate (95% CI)	0.61 (0.43, 0.86)	

BPd = BLENREP, pomalidomide, dexamethasone; CI = confidence interval; CR = complete response; DoR = duration of response; HR = hazard ratio; IA2 = interim analysis 2; MRD = minimal residual disease; OS = overall survival; PVd = pomalidomide, bortezomib, and dexamethasone; sCR = stringent complete response; VGPR = very good partial response rate

a MRD negativity rate was defined as the percentage of participants who were MRD negative by next-generation sequencing based on a sensitivity of 10^{-5}.

Updated PFS DCO = 07 Oct 2024

Detailed efficacy results are provided in Appendix Table 4 (PFS), Appendix Table 5 (OS), Appendix Table 6 (DoR), and Appendix Table 7 (ORR, MRD)

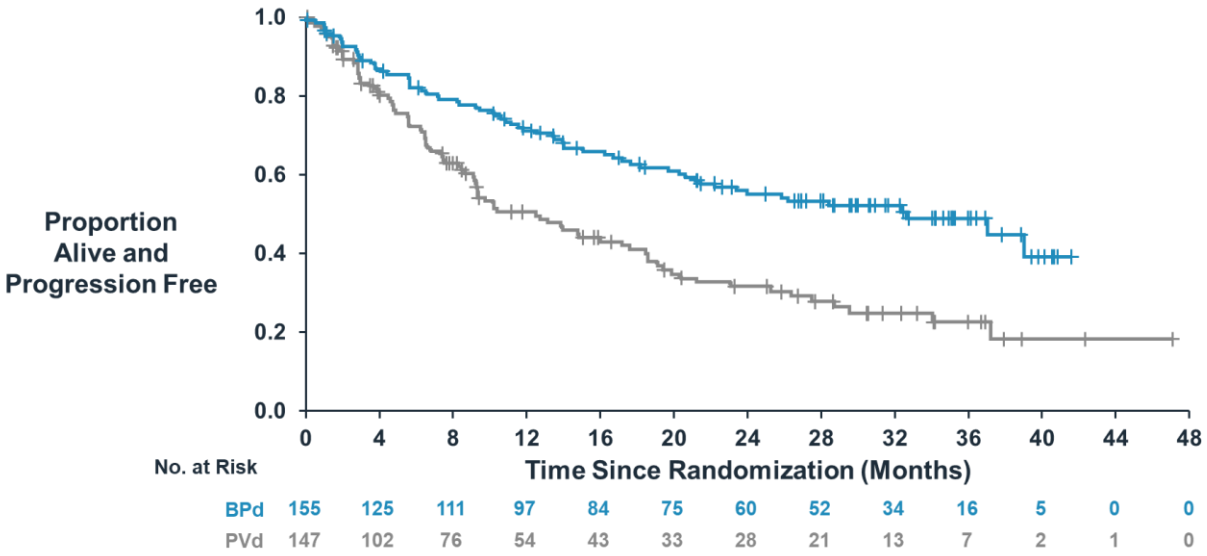
6.3.6.1 Primary Efficacy Result – Progression Free Survival

At the DCO for IA2, the DREAMM-8 study met its primary endpoint of PFS with a statistically significant and clinically meaningful PFS benefit with for BPd compared with

PVd (0.52 [0.37, 0.73], p<0.001, (Table 20). The Kaplan-Meir curves for PFS showed a clear and early separation between the treatment groups in favor of the BPd arm Figure 7.

The median PFS was reached in an updated analysis with a DCO of 07 Oct 2024; showing an almost 20-month advantage for the BLENREP arm vs. the comparator triplet combination arm (HR (95% CI) 0.49 (0.35,0.68)) (Figure 20, Table 20).

Figure 20 DREAMM-8: Kaplan Meier Curves of Progression-Free Survival Based on Independent Reviewer-Assessed Response Post Hoc Analysis (Intent to Treat Population)



BPd = BLENREP pomalidomide, dexamethasone; mPFS = median progression free survival; PVd = pomalidomide, bortezomib, dexamethasone

The most common reason for censoring were administrative censoring due to DCO (BPd 44% vs PVd 22%); Data from 25 (16%) participants in the BPd arm and 34 (23%) participants in the PVd arm were censored with follow-up ended. The most common reason for these premature censoring is starting new anti-MM therapy with adequate postbaseline assessment (BPd 5% vs PVd 12%). A summary of censoring of PFS can be seen in Appendix Table 4.

Progression free survival analysis based on investigator-assessed responses were consistent with IRC results, as were results of all supplementary and sensitivity analyses with HRs ranging from 0.48 to 0.54, demonstrating the robustness of the primary analysis.

Progression free survival was evaluated for prespecified subgroups based on age, disease stage, cytogenetics, presence of extramedullary disease, relapse within 12 months of first line treatment, and prior therapy. Benefit favoring the BLENREP group over DVd was observed across subgroups; importantly, this included prior lines of therapy (Figure 7) demonstrating a clinically meaningful benefit in participants previously exposed to or refractory to anti-CD38 antibody therapy (e.g., daratumumab) and to lenalidomide.

6.3.6.2 Key Secondary Efficacy Results

6.3.6.2.1 Overall Survival

At the PFS data cut-off, there was an OS trend in favor of the BPd arm with a HR of 0.77 (95% CI: 0.53, 1.14) (Table 20, Figure 8). Median OS was not reached in either treatment arm. Overall survival data have reached 35% (105/302 participants) overall maturity with an information fraction equal to 48% (105/217); the final OS analysis is planned at 217.The OS p-value (0.095) did not cross the pre-defined OS boundary at this analysis. Follow up for OS is ongoing.

6.3.6.2.2 Response Rate and Duration of Response

The ORR was comparable between the BPd and PVd arms (77% vs. 72%); however, the BPd arm achieved deeper responses as evidenced by CR rates more than double that of the PVd arm (Table 20, Figure 9 Panel A).

The median (range) DoR was not reached in the BPd arm (NR 24.9, NR) and was 17.5 (12.1, 26.4) months in the PVd arm with more participants ongoing and in response in the BPd arm (Table 20). The Kaplan-Meir curves for DoR showed a clear and early separation between the treatment groups in favor of BPd; 55% of participants in the BPd arm with response had not progressed or died with follow-up for PFS ongoing at the DCO compared with 31% of participants in the PVd arm (Figure 9, Panel B).

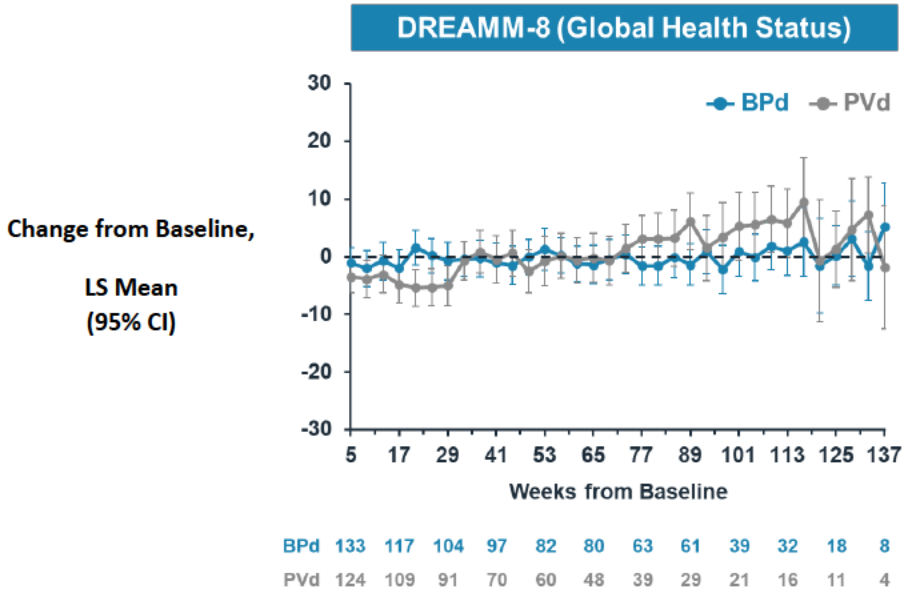
6.3.6.2.3 Minimal Residual Disease Negativity

For the key secondary endpoint of MRD negativity, the proportion of all participants who achieved MRD negativity was about 5-times higher in the BVd arm compared with the PVd arm at the time of primary PFS analysis (23.9% vs. 4.8%) (Figure 10, Table 20).

6.3.6.2.4 Quality of Life

Patient reported outcomes were assessed using EORTC QLQ-C30 and EORTC QLQ-MY20/IL52. Participants receiving BPd or PVd maintained overall QoL (<10-point change vs. baseline), as measured by the EORTC QLQ-C30 GHS/QoL domain (Figure 21), and there were no differences between treatment arms (≥10 points). Similarly, there were no differences between treatment arms for physical functioning, fatigue, role functioning, and disease symptoms (≥10 points) (except for Week 117 and Week 137 in favor of BPd for role functioning and disease symptoms, respectively).

Figure 21 DREAMM-8: Change from Baseline in EORTC QLQ-C30 Global Health Status Domain Score by Visit in Health-Related Quality of Life



BPd = BLENREP, pomalidomide, dexamethasone; PVd = pomalidomide, bortezomib, dexamethasone

6.3.6.2.5 Other Key Efficacy Results

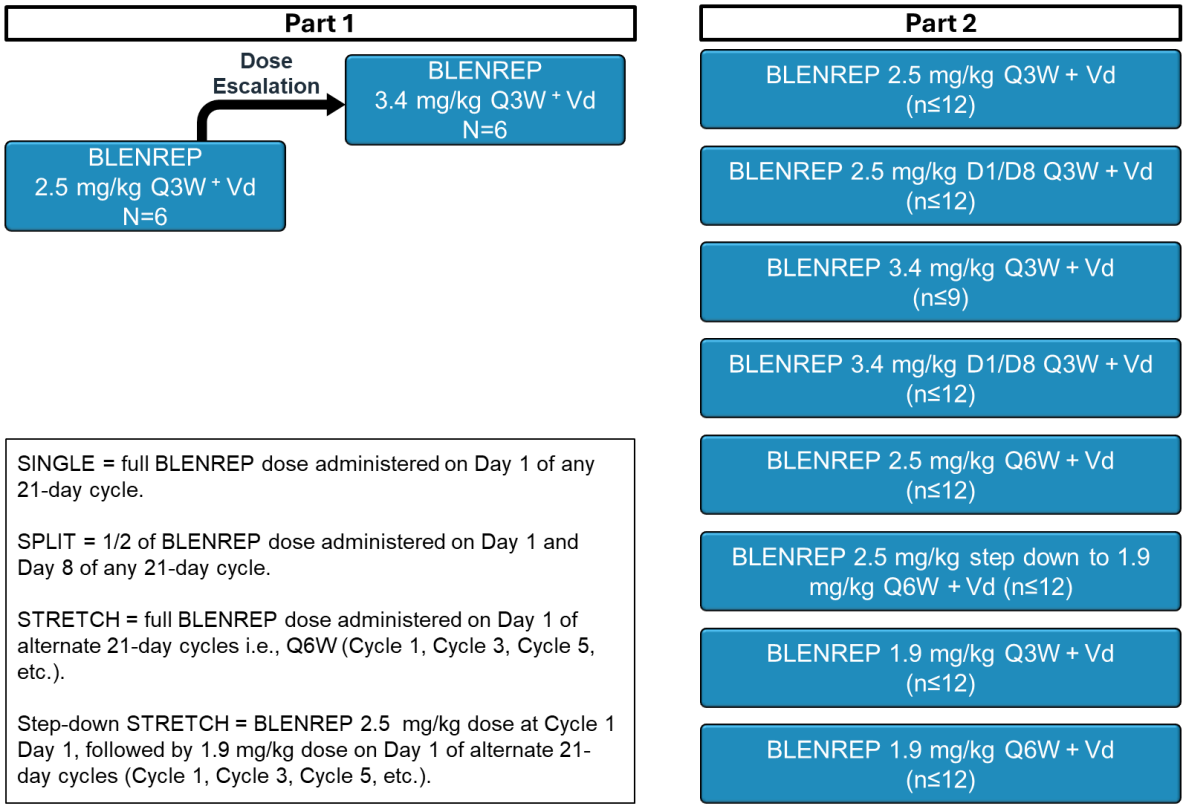
- PFS2: The treatment benefit of BPd that was observed with PFS was maintained with subsequent therapy (Table 20). Median PFS2 was not reached in the BPd arm. Median PFS2 was 22.4 months in the PVd arm (HR=0.61; 95% CI: 0.43, 0.86).
- Time to Response: The median TTR was short and similar between treatment arms (1.07 months [range: 0.9 to 9.3] vs. 1.05 months [range: 0.7 to 11.2]).

6.4 DREAMM-6 (BVd, Supportive Study)

DREAMM-6 is a completed Phase 1/2, two arm, open-label, dose escalation and expansion clinical study to assess different doses and dosing schedules of BLENREP when given in combination with lenalidomide and dexamethasone (Arm A, not discussed further) or Vd (Arm B, relevant for the efficacy and safety assessment of this application). BLENREP was administered at three different dose levels (1.9 mg/kg, 2.5 mg/kg, or 3.4 mg/kg) in combination with Vd in four different dosing schedules shown in Figure 22. Participants could receive up to eight 21-day cycles of BVd followed by BLENREP monotherapy until disease progression, withdrawal of consent, or death, whichever is earlier.

The study consisted of 2 parts. Arm B, Part 2 characterized safety, tolerability, preliminary clinical activity and PK of different doses and dosing schedules in participants with RRMM. The study design is summarized in Figure 22.

Figure 22 Schematic of Study Structure for Arm B (BVd)



dexamethasone; Q6W = every 6 weeks; Vd = bortezomib

The primary efficacy endpoint for Part 2 in DREAMM-6 was investigator-assessed ORR (VGPR or better). Secondary endpoints included PFS and DoR. Safety, PK, and immunogenicity were also assessed.

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

Demographic characteristics were generally similar across all treatment arms in Arm B (BVd). Participants were predominantly white males with a median age of 66.0 years (range: 32 to 83).

Disease characteristics at baseline were generally similar across all treatment arms in Arm B (BVd).

Participants received a median of 4 prior lines of therapies (range 1 to 13) and were previously treated with anti-myeloma therapy including regimens containing steroids, chemotherapeutic agents, PIs, immunomodulators, mAbs, histone deacetylase inhibitors, and ADCs. Prior anti-myeloma treatment with daratumumab was reported in <60% of participants.

As of the DCO date for the final analysis (28 February 2023), ≥50% of participants in Arm B (BVd) had discontinued the study. The primary reason for discontinuation of

BLENREP was PD. Seventeen participants were ongoing at the time of last visit and were offered continuation into post-analysis continued treatment.

There were differences across treatment arms in the median duration of follow-up. Overall, the median duration of follow-up across Arm B treatment arms was 17.38 months (range: 0.8 to 49.2).

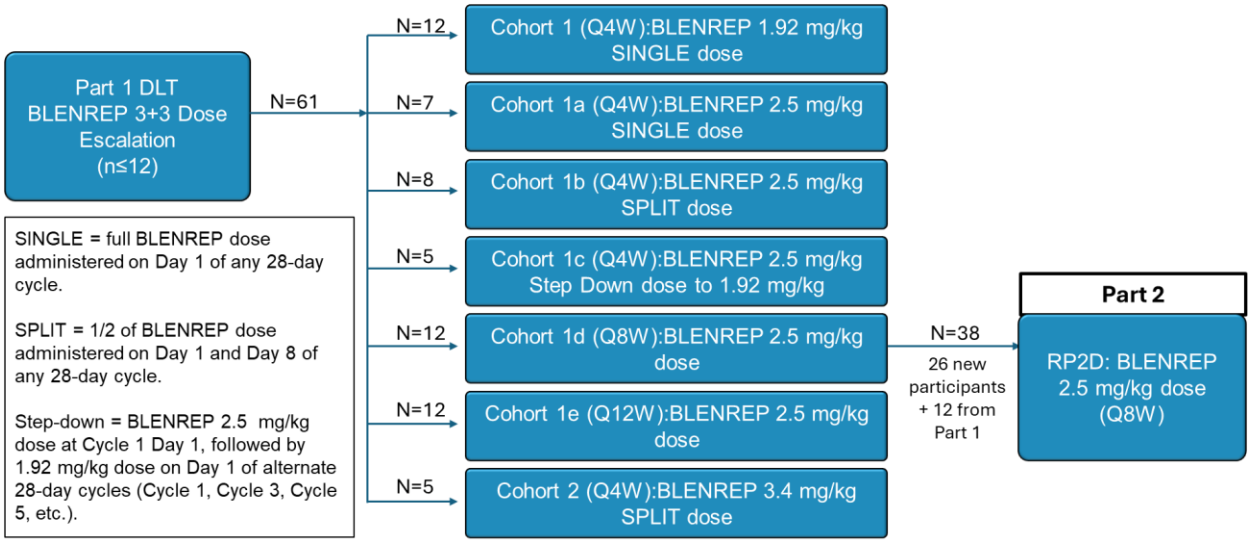
The efficacy results relevant to the exposure-response analyses are provided in Table 13.

A summary of key safety parameters is provided in Table 13, including ocular KVA events Grade ≥2, SAEs, and treatment discontinuations due to an AE.

6.5 ALGONQUIN (BPd, Supportive Study)

The ALGONQUIN study is an ongoing Phase 1/2, multicenter, single-arm, open-label, dose-escalation and expansion study evaluating the safety and efficacy of BPd in participants with RRMM (Trudel 2024). The study design is summarized in Figure 23. This study consisted of a Part 1 dose exploration phase and a Part 2 dose-expansion phase. Participants in Part 1 received doses of 1.92 mg/kg, 2.5 mg/kg, and 3.4 mg/kg BLENREP at different dosing schedules in combination with Pd (BPd). In Part 2, all participants received BPd 2.5 mg/kg Q8W on a 28-day cycle.

Figure 23 ALGONQUIN: Study Design for Part 1 and the Recommended Phase 2 Dose Parts



DLT = dose limiting toxicity; Q#W = every # weeks; RP2D = recommended Phase 2 dose

The primary endpoints of the ALGONQUIN study included evaluating dose-limiting toxicities, establishing the recommended Phase 2 dose (RP2D), and ORR for participants treated at the RP2D.

The study enrolled participants with RRMM previously treated with one or more prior lines of anti-MM therapy and must have been lenalidomide refractory and PI exposed (in

separate regimens or in combination). Participants could not have previously received pomalidomide or a prior BCMA-targeted therapy.

Across all 87 participants, the median age was 67 years. Among the 38 participants who were enrolled and treated during Part 2 (dose-expansion phase, BPd 2.5 mg/kg Q8W), the median age was 71 years.

The ALGONQUIN study included heavily pre-treated participants. Median (range) prior lines of therapy was 3 (1 to 6). All participants were lenalidomide and PI exposed, 84 (96.6%) were lenalidomide refractory, 75 (86.2%) were refractory to a PI, 58 (66.7%) had received previous anti-CD38 antibody therapy, and 48 (55.2%) were triple-class refractory.

A total of 87 participants were enrolled and treated in the ALGONQUIN study. At the time of the data cut-off (14 February 2023), 38 participants received BLENREP 2.5 mg/kg Q8W in combination with Pd (Part 1: 12 and Part 2: 26), 12 participants received 1.9 mg/kg Q4W, and 7 participants received 2.5 mg/kg Q4W. Five participants received 2.5 mg/kg in Cycle 1 followed by 1.92 mg/kg Q4W, the regimen used in DREAMM-8. Sixteen participants discontinued the study; the most common reason for discontinuation was disease progression. The median duration of follow-up for all participants was 14.5 months (range: 0.9 to 42.5).

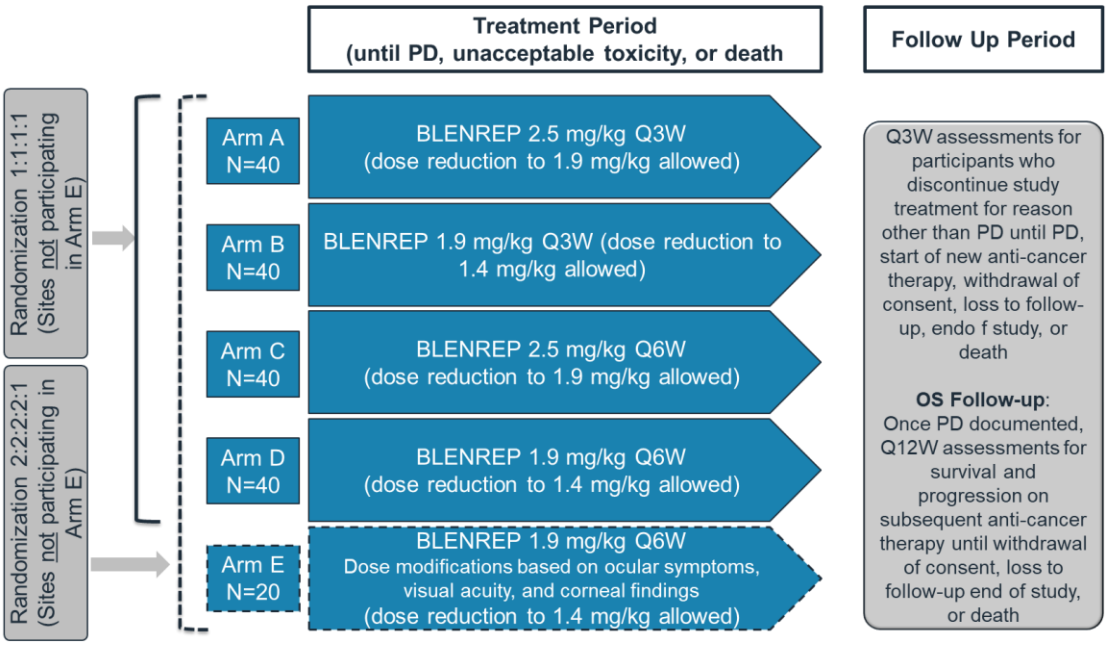
Exposure, efficacy, and safety data relevant to the exposure-response are summarized in Table 13. Data indicated that the clinical efficacy for 2.5 mg/kg Q4W was greater than for 1.92 mg/kg Q4W and 2.5 mg/kg split across Days 1 and 8. Results are discussed further in Section 5.2.1.

6.6 DREAMM-14 (Monotherapy, Supportive Study)

DREAMM-14 is a Phase 2 randomized, parallel open-label study investigating the safety, efficacy and PK of BLENREP monotherapy in participants who have had at least 3 prior lines of MM therapy. The study is examining the corneal events associated with single-agent BLENREP using alternative dosing regimens. The study design is summarized in Figure 24.

The primary endpoint is the incidence of Grade ≥2 corneal events according to the KVA scale. Other endpoints included ORR, PK, and the relationship between dose, exposure, and clinical endpoints (e.g., response, ocular toxicity).

Figure 24 DREAMM-14 Study Schema



Abbreviations: OS=overall survival; PD=progressive disease; Q12W=every 12 weeks; Q3W=every 3 weeks; Q6W=every 6 weeks
Note: All enrolling study sites participated in Arms A to D; site participation in Arm E was optional and based on site interest and ability.

As of the data cut-off date(19 August 2024), 177 participants were randomized to the five arms of the study, 84 (47%) had died, and 27 (15%) had withdrawn from the study. The most frequent reason for study withdrawal was withdrawal by the participant (11%). The study is ongoing for 66 (37%) participants; 16 (9%) are on study treatment and 50 (28%) are in follow-up. No participant withdrew from the study due to an AE or lack of efficacy.

Study treatment was permanently discontinued for 159 (90%) of participants. The most frequent reasons for treatment discontinuation were disease progression (65%), physician decision (12%), and AEs (8%). Treatment discontinuation was related to study treatment for 6 (3%) of participants.

Most participants were of non-Hispanic or Latino ethnicity (74%). The majority of the participants were White (61%) followed by Asian (28%), and Black or African American (7%). There were more male participants (53%). The median age was 66 years. Most participants had received four or more lines of therapy at screening and 16% had EMD.

Median duration of treatment exposure BLENREP ranged from 6.2 weeks in Arm B to 10.3 weeks in Arm A. The median number of cycles received ranged from 2.0 (Arms C, D, and E) to 4.0 (Arm A).

Exposure, safety, and efficacy results relevant to the exposure-response analyses are provided in Table 13 and the exposure-response analysis results are presented in Section 11.2.

6.7 Efficacy Conclusions

Two independent randomized, Phase 3 studies consistently demonstrated meaningful benefits over SoC across all endpoints, including significant improvement in overall survival from the DREAMM-7 study. The BLENREP triplet combination in DREAMM-7 demonstrated statistically significant ~ 2-year improvement in median PFS and with a statistically significant and clinically meaningful projected 3-year median OS benefit over a daratumumab combination (Hungria 2024).

DREAMM-8 also showed a statistically significant and clinically meaningful PFS benefit with BPd vs. PVd with updated PFS data showing a > 20 months improvement along with a positive trend in OS.

In both studies, PFS benefit favoring BVd over DVd and BPd over PVd was observed across all prespecified subgroups, including by prior line of therapy, those with high-risk cytogenetics, and those refractory to lenalidomide or daratumumab.

Other key secondary endpoints including MRD negativity rate, ORR, and DoR, showed clinically meaningful evidence for efficacy of the BVd and BPd combinations.

- Median DoR was twice as long in DREAMM-7 for participants in the BVd arm than in the daratumumab-containing DVd arm (median DoR for BPd is NR in DREAMM-8).
- MRD negativity rates were more than 2.5 times greater with BVd and more than 5 times greater with BPd.
- Responses with BVd and BPd were deep, with more a than double CRR compared with DVd and PVd, respectively.

DREAMM-7 and DREAMM-8 demonstrated benefit from BVd and BPd, irrespective of prior exposure or refractoriness to lenalidomide. Additionally, DREAMM-8 demonstrated benefit from BPd, irrespective of prior exposure or refractoriness to anti-CD38 treatment.

7 CLINICAL SAFETY

Summary

- Incidences of AEs and changes in laboratory parameters for the BLENREP triplet combinations (BVd/BPd) are broadly consistent with the stable, well-characterized safety profile of BLENREP and/or individual components in the triplet regimens.
- Ocular events are a known risk associated with BLENREP. These events are manageable with dose modifications, and are generally reversible with appropriate follow-up, allowing participants to continue treatment and receive benefit. In general, treatment discontinuations due to ocular events were low.
- The proposed REMS with elements ETASU is part of an appropriate risk mitigation strategy to minimize the risk of ocular events and to ensure prescribers are educated of the risk of ocular events, the need to enroll patients in the REMS and counsel them about the risk, and the need for monitoring via ophthalmic examinations. The REMS ensures that BLENREP is only dispensed to patients who are informed about the risk of ocular events and the need for monitoring via ophthalmic examinations.

7.1 Introduction

The safety profile of BLENREP was evaluated in the two registrational studies in the combination therapies BVd and BPd. Supportive safety evaluation for the triplet combinations is provided by the Phase 1/2 triplet combination studies DREAMM-6 (BVd) and ALGONQUIN (BPd). The relevant clinical trials with BLENREP are summarized in Appendix Table 1. Key safety data include:

- General safety including common AEs (Section 7.4), fatal AEs (Section 7.9), SAEs (Section 7.7), and other significant AEs (Section 7.12, 7.13).
- Ocular safety (Section 7.10)
- Non-ocular AESIs (e.g., thrombocytopenia and injection-related reactions [IRRs]) (Section 7.12).
- Safety-related Patient-reported outcome assessments (Section 7.11):

In both registrational studies, participants in the BLENREP containing groups remained on study treatment longer than participants in the respective comparator groups. Thus, AEs were collected for correspondingly longer periods in the BLENREP groups compared with the comparator groups. Exposure-adjusted AE incidence rates (EAIR) were therefore computed to enable comparison between the BLENREP and comparator groups.

7.2 Treatment Exposure

The number of participants exposed to BLENREP in triplet combination populations, by study is summarized in Table 5. Participants in the BLENREP arms of DREAMM-7 and DREAMM-8 had longer durations of exposure to study treatment compared with participants in the comparator arms (15.9 vs. 12.9 months and 16.5 vs. 8.5 months, respectively).

The median overall RDI for BLENREP was approximately 50% in both studies. The RDI by 6-month intervals is provided in Table 5, and show a reduction in RDI over time that was generally greater in DREAMM-7, compared to DREAMM-8. In DREAMM-7, the reduced RDI over time was a result of dose reductions (69% of participants) and reductions in dosing frequency (88% of participants). In DREAMM-8, the reduced RDI over time was driven primarily by reduced dosing frequency (90% of participants had a dose delay), as few participants (11, 7.3%) reduced dose to 1.4 mg/kg. Dose intensity similarly was highest in the first 6 months and reduced over time.

Dosing over time is summarized in Figure 5 and reveals that, over time, even though the initial dosing schedules are somewhat different, the implementation of dose modification to manage ocular events results in similar BLENREP exposure over time in the two registrational studies. The role of dose modification is discussed further in Section 7.10.7.

7.3 Overview of Adverse Events

The overall safety of BLENREP in DREAMM-7 and DREAMM-8 is consistent with its well-characterized and stable safety profile in participants with RRMM. Ocular events are the predominant adverse event associated with BLENREP.

An overview of AEs for the BLENREP combination is provided in Table 6. All reported AEs are treatment-emergent.

7.4 Common Adverse Events (≥20% of Participants)

Nearly all (≥ 97%) participants receiving BLENREP in all studies experienced at least one AE (Table 6). The pattern (nature, incidence and severity) of adverse events reported in DREAMM-7 (BVd) and DREAMM-8 (BPd) are broadly consistent with the known safety profile of BLENREP and/or the combination partners.

Across all studies, ocular events were the most commonly reported safety events in the BLENREP arms, as expected based on the known safety profile of BLENREP. Ocular events are discussed in detail in Section 7.10. Other commonly reported events in the registrational studies included thrombocytopenia, diarrhoea, infections (e.g., COVID-19, pneumonia, upper respiratory infection), fatigue, neuropathy, neutropenia, and anemia. The non-ocular adverse events of special interest (AESIs) included thrombocytopenia and infusion related reactions (IRRs) discussed in detail in Section 7.12.1 and Section 7.13. Events of clinical interest included infections and hepatobiliary disorders, discussed in detail in Section 7.12.2 and Section 7.13.2.

Common AEs occurring in ≥20% of participants reported in the BLENREP-containing arms in DREAMM-7 and DREAMM-8 are summarized in Appendix Table 9.

- In DREAMM-7, the most commonly reported AEs (>20% of participants) in the BVd arm by CTCAE were thrombocytopenia (87%), ocular AESI (79%), diarrhea (32%), peripheral sensory neuropathy (25%), COVID-19 (24%) and neuropathy peripheral (21%).
- In DREAMM-8, the most commonly reported AEs (>20% of participants) in the BPd arm by CTCAE were ocular AESI (89%), neutropenia/neutrophil count decreased/febrile neutropenia (63%), thrombocytopenia (55%), COVID-19 (37%), cataract (27%), fatigue (27%), upper respiratory tract infection (27%), pneumonia (24%), anemia (23%), and diarrhoea (23%).

7.5 Grade 3 and Grade 4 Adverse Events

Adverse events with a maximum Grade 3 or 4 were reported in the majority of participants treated with BLENREP, when administered in combination (85% in DREAMM-7 and -82% in DREAMM-8) (Table 6).

Table 21 summarizes events with a maximum Grade 3 or Grade 4 in DREAMM-7 and DREAMM-8, occurring in at least 5% of participants. By PT and by SOC, Grade 3 or higher AEs (by maximum grade) were generally consistent with the trends observed for the most common AEs (any grade, Appendix Table 9). The most frequently reported events by PT included thrombocytopenia (56% in DREAMM-7 and 24% in DREAMM-8) and vision blurred (24% in DREAMM-7 and 17% in DREAMM-8).

The two BLENREP-containing regimens had similar rates of Grade 3/4 events when corrected for duration of exposure. The exposure-adjusted incidence rates (EAIR) of Grade 3/4 AEs were similar between the BVd and DVd arms in DREAMM-7. In DREAMM-8, the exposure-adjusted rates of Grade 3/4 AEs were lower in the BPd arm compared with the PVd arm.

Table 21 DREAMM-7 and DREAMM-8: Grade 3 or Grade 4 (Maximum Grade) Adverse Events by Preferred Term (CTCAE) (≥5%)

System Organ Class Preferred Term	DREAMM-7		DREAMM-8	
	BVd N = 242	DVd N = 246	BPd N = 150	PVd N = 145
AE with maximum Grade 3 or 4[a]	**205 (85%)**	**176 (72%)**	**123 (82%)**	**95 (66%)**
Thrombocytopenia	135 (56%)	87 (35%)	36 (24%)	28 (19%)
Vision blurred	58 (24%)	3 (1%)	26 (17%)	0
Platelet count decreased	43 (18%)	26 (11%)	22 (15%)	18 (12%)
Neutropenia	30 (12%)	16 (7%)	65 (43%)	42 (29%)
Pneumonia	23 (10%)	8 (3%)	24 (16%)	10(7%)

System Organ Class Preferred Term	DREAMM-7		DREAMM-8	
	BVd N = 242	**DVd N = 246**	**BPd N = 150**	**PVd N = 145**
Gamma-glutamyl transferase increased	24 (10%)	4 (2%)	4 (3%)	1 (<1%)
Anaemia	21 (9%)	25 (10%)	16 (11%)	20 (14%)
Lymphopenia	13 (5%)	18 (7%)	3 (2%)	2 (1%)
Cataract	17 (7%)	9 (4%)	12 (8%)	7 (5%)
Dry eye	17 (7%)	0	13 (9%)	0
Alanine aminotransferase increased	14 (6%)	4 (2%)	3 (2%)	5 (3%)
Visual impairment	12 (5%)	1 (<1%)	15 (10%)	1 (<1%)
Eye irritation	12 (5%)	0	6 (4%)	0
Hypertension	13 (5%)	7 (3%)	1 (<1%)	2 (1%)
COVID-19	11 (5%)	6 (2%)	9 (6%)	1 (<1%)
Foreign body sensation in eyes	9 (4%)	0	9 (6%)	0
Fatigue	9 (4%)	6 (2%)	9 (6%)	7 (5%)
Neutrophil count decreased	4 (2%)	7 (3%)	31 (21%)	19 (13%)
COVID-19 pneumonia	6 (2%)	4 (2%)	11 (7%)	4 (3%)
Visual acuity reduced	3 (1%)	1 (<1%)	19 (13%)	1 (<1%)
Corneal epithelial microcysts	0	0	12 (8%)	0
Punctate keratitis	1 (<1%)	0	8 (5%)	1 (<1%)
Atrial fibrillation	4 (2%)	2 (<1%)	1 (<1%)	4 (3%)
Cardiac failure	2 (<1%)	0	0	2 (1%)
Exposure-adjusted rate (per 100 person years)	**51.0**	**51.3**	**49.4**	**61.9**

BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib and dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone; PVd = pomalidomide, bortezomib, dexamethasone;
a Events with Grade 3 or 4, maximum grade, occurring in at least one of the BLENREP-containing arms

7.6 Treatment Related Adverse Events

For DREAMM-7 and DREAMM-8, AE relatedness could be attributed to any component of the triplet regimen and the event be deemed treatment related.

Overall, the majority (83% to 100%) of participants in either arm of the two registrational studies experienced AEs that were determined by the investigator to be related to a study treatment (Table 6). These AEs were consistent with the known toxicity(ies) of BLENREP or a combination partner and included ocular toxicities and other AESIs.

In DREAMM-7, all AEs in the BVd arm (100%) were considered related to at least 1 component of the combination treatment. The most common treatment-related AEs by

PT (≥20%) for the BVd arm were thrombocytopenia (66%), vision blurred (64%), dry eye (49%), photophobia (45%) foreign body sensation in eyes (41%), eye irritation (40%), eye pain (29%), peripheral sensory neuropathy (25%), platelet count decreased (21%), and neuropathy peripheral (20%). For the DVd arm, the most common treatment-related AEs were thrombocytopenia (48%), neuropathy peripheral (22%%), and peripheral sensory neuropathy (20%).

In DREAMM-8, the majority of the AEs in the BPd arm (95%) were considered related to at least one component of the combination treatment. The most common treatment-related AEs by PT (≥20%) for the BPd arm were vision blurred (77%), foreign body sensation in eyes (59%), dry eye (59%), eye irritation (49%), photophobia (45%), neutropenia (42%), eye pain (32%), thrombocytopenia (31%), visual acuity reduced (21%), and punctate keratitis (19%). For the PVd arm, the most common treatment-related AEs were neutropenia (30%), thrombocytopenia (25%), and neuropathy peripheral (23%).

7.7 Serious Adverse Events

A summary of SAEs reported in DREAMM-7 and DREAMM-8, occurring at least 2% of the participants, is provided in Table 22.

Table 22 DREAMM-7 and DREAMM-8: Summary of Serious Adverse Events in ≥2% of Participants in Either Treatment Group by Preferred Term (Safety Population)

	DREAMM-7		DREAMM-8	
Preferred Term, n (%)	**BVd (N=242)**	**DVd (N=246)**	**BPd (N=150)**	**PVd (N=145)**
Any event	**129 (53%)**	**94 (38%)**	**95 (63%)**	**65 (45%)**
Exposure-adjusted rate (per 100 person years)	32.07	27.42	45.86	47.87
Pneumonia	29 (12%)	11 (4%)	27 (18%)	11 (8%)
COVID-19	11 (5%)	10 (4%)	10 (7%)	5 (3%)
Pyrexia	12 (5%)	10 (4%)	2 (1%)	2 (1%)
Neutropenia	1 (<1%)	1 (<1%)	10 (7%)	3 (2%)
Febrile neutropenia	1 (<1%)	1 (<1%)	6 (4%)	3 (2%)
COVID-19 pneumonia	8 (3%)	8 (3%)	17 (11%)	6 (4%)
Thrombocytopenia	8 (3%)	4 (2%)	1 (<1%)	4 (3%)
Urinary tract infection	2 (<1%)	0	5 (3%)	0
Anaemia	4 (2%)	3 (1%)	1 (<1%)	1 (<1%)
Orthostatic hypotension	4 (2%)	3 (1%)	0	0
Lower respiratory tract infection	5 (2%)	0	0	1 (<1%)
Respiratory tract infection	1 (<1%)	2 (<1%)	3 (2%)	0
Pulmonary embolism	2 (<1%)	3 (1%)	3 (2%)	4 (3%)
Respiratory failure	4 (2%)	0	2 (1%)	1 (<1%)
Acute kidney injury	3 (1%)	0	3 (2%)	4 (3%)
Pneumocystis jirovecii pneumonia	0	0	3 (2%)	0
Syncope	4 (2%)	1 (<1%)	1 (<1%)	0

	DREAMM-7		DREAMM-8	
Preferred Term, n (%)	**BVd (N=242)**	**DVd (N=246)**	**BPd (N=150)**	**PVd (N=145)**
Sepsis	4 (2%)	4 (2%)	1 (<1%)	3 (2%)
Infusion related reaction	0	4 (2%)	0	0
Atrial fibrillation	3 (1%)	2 (<1%)1 (<1%)	1 (<1%)	3 (2%)
Cardiac failure (chronic)	1 (<1%)	0	0	3 (2%)
Cardiac failure (congestive)	1 (<1%)	0	0	0
Death	0	0	0	3 (2%)

BPd = BLENREP, pomalidomide, dexamethasone; and dexamethasone; BVd = BLENREP, bortezomib, dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone; PVd = pomalidomide, bortezomib, dexamethasone

Treatment-related SAEs were reported for 21% of participants in the BVd arm (DREAMM-7) and for 33% of participants in the BPd arm (DREAMM-8). The most frequently reported treatment-related SAEs for the BLENREP-containing groups in both studies was pneumonia and thrombocytopenia (4% and 11%, respectively and discussed further in Section 7.12).

7.8 Adverse Events Leading to Dose Modifications, Dose Reductions, and Discontinuation of Study Intervention

7.8.1 Overview of Adverse Events Leading to Dose Modifications (Dose Delay or Dose Reduction)

An overview of all dose modifications (of any component of the triplet regimen), grouped by the reason for modification (any event, ocular event, or non-ocular event) is presented in Table 23.

Table 23 DREAMM-7 and DREAMM-8: Overview of Dose Modifications (Any Treatment Component)

	DREAMM-7		DREAMM-8	
	BVd (N=242)	**DVd (N=246)**	**BPd (N=150)**	**PVd (N=145)**
Any modification due to AE or KVA scale event, n (%)	**237 (98%)**	**220 (89%)**	**143 (95%)**	**125 (86%)**
Study treatment withdrawn	87 (36)	47 (19%)	36 (24%)	21 (14%)
Dose reduced	196 (81)	146 (59%)	117 (78%)	88 (61%)
Drug interrupted/delayed	231 (95)	186 (76%)	143 (95%)	110 (76%)
Any modification due to non-ocular AE, n (%)	**232 (96%)**	**219 (89%)**	**128 (85%)**	**125 (86%)**
Study treatment withdrawn	73 (30%)	47 (19%)	23 (15%)	21 (14%)
Dose reduced	169 (70%)	145 (59%)	90 (60%)	88 (61%)
Drug interrupted/delayed	217 (90%)	184 (75%)	125 (83%)	110 (76%)
Any modification due to ocular AE or KVA scale event, n (%)	**200 (83%)**	**4 (2%)**	**126 (84%)**	**2 (1%)**
Study treatment withdrawn	25 (10%)	0	16 (11%)	0
Dose reduced	104 (43%)	2 (<1%)	89 (59%)	0

	DREAMM-7		DREAMM-8	
	BVd (N=242)	DVd (N=246)	BPd (N=150)	PVd (N=145)
Drug interrupted/delayed	189 (78%)	3 (1%)	124 (83%)	2 (1%)

AE = adverse event; BPd = BLENREP, pomalidomide, dexamethasone; and dexamethasone; BVd = BLENREP, bortezomib, dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone; KVA = Keratopathy Visual Acuity; PVd = pomalidomide, bortezomib, dexamethasone

Most participants, 86% to 98% across groups, had a dose modification for a non-ocular event with treatment withdrawn due to a non-ocular event for 14% to 30 % of participants. Withdrawal of any study treatment attributed to an ocular AE or KVA scale event was 10% and 11% in the DREAMM-7 and DREAMM-8 studies, respectively. Ocular events occurred almost exclusively in the BLENREP groups. Dose modification due to ocular events is discussed in Section 7.10.7.

A summary of events from the two registrational studies leading to dose reduction is provided in Appendix Table 10. Across the studies, ocular events were a frequent cause of BLENREP dose reduction, but toxicity related to other combination components also led to dose reduction in the BLENREP groups. In DREAMM-7, the incidence of AEs leading to dose reductions and the EAIR of dose reduction in the BVd arm compared with the DVd arm were 75% and 59% and 54.657 and 48.738 per 100 person-years, respectively. The most frequently reported AEs leading to dose reductions in the BVd were thrombocytopenia (29%), peripheral sensory neuropathy (14%), vision blurred (11%), neuropathy peripheral (10%), platelet count decreased (9%), and insomnia (5%). Thrombocytopenia and peripheral neuropathy are known effects of bortezomib. In DREAMM-8, the incidence of AEs leading to dose reductions of any study treatment was similar between the BPd-arm and the PVd arm (63% and 61%); the EAIR of dose reduction was lower in the BPd arm compared with the PVd arm (44.414 and 64.812 per 100 person-years). By PT, the AEs most commonly (≥2%) leading to dose reductions in the BPd arm were neutropenia (16%), neutrophil count decreased (10%), fatigue (7%), muscular weakness (7%), and insomnia (6%).

7.8.2 Adverse Events Leading to Discontinuation of Study Intervention

The incidence of treatment withdrawal is summarized by event type in Table 23. In DREAMM-7, the incidence of AEs leading to discontinuation of any study treatment was higher in the BVd arm compared with the DVd arm (Table 24). Neuropathic AEs, a known effect of bortezomib, were the most common AEs leading to permanent treatment discontinuation reported for ≥1% of participants in the BVd arm.

Table 24 DREAMM-7 Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment in ≥1% of Participants by Preferred Term (Safety Population)

Preferred Term, n (%)	BVd (N=242)	DVd (N=246)
Any event	**77 (32)**	**47 (19)**
Peripheral sensory neuropathy	14 (6)	6 (2)
Pneumonia	9 (4)	0
Neuropathy peripheral	6 (2)	11 (4)
Polyneuropathy	7 (3)	5 (2)
COVID-19	3 (1)	4 (2)
COVID-19 pneumonia	2 (<1)	5 (2)
Thrombocytopenia	5 (2)	2 (<1)
Vision blurred	5 (2)	0
Sepsis	2 (<1)	3 (1)

BVd= BLENREP, bortezomib, dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone

In DREAMM-8, there was no overlap in the PTs leading to discontinuation of any study treatment compared to DREAMM-7. The incidence of AEs leading to discontinuation of any study treatment and the exposure-adjusted rate of discontinuation of any study treatment was similar between the BPd arm and the PVd arm (Table 25).

Table 25 DREAMM-8: Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment in ≥1% of Participants by Preferred Term (Safety Population)

Preferred Term, n (%)	BPd (N=120)	PVd (N=145)
Any event	**28 (19)**	**21 (14)**
Fatigue	2 (1)	1 (<1)
Keratopathy[a]	2 (1)	0
Muscular weakness	2 (1)	1 (<1)
Neuralgia	2 (1)	0
Neuropathy peripheral	0	3 (2)

BPd = BLENREP, pomalidomide, dexamethasone; and dexamethasone; PVd = pomalidomide, bortezomib, dexamethasone

7.9 Deaths

In both registrational studies, there were more deaths in the comparator arms than the BLENREP arms (Table 26). The disease under study (MM) was the most common cause of death.

Table 26 DREAMM-7 and DREAMM-8: Summary of Deaths in Participants Receiving BLENREP

	DREAMM-7		DREAMM-8	
	BVd (N=242)	DVd (N=246)	BPd (N=150)	PVd (N=145)
Participant status, n (%)				
Dead	64 (26)	91 (37)	54 (36)	57 (39)
Alive at last contact, follow-up ended	29 (12)	40 (16)	10 (7)	8 (6)
Death date retrieved	5 (2)	10 (4)	3 (2)	2 (1)
Alive at last contact, follow-up ongoing	149 (62)	115 (47)	86 (57)	80 (55)
Time to death from last dose, n (%)				
≤30 Days	18 (7)	23 (9)	14 (9)	18 (12)
>30 Days	50 (21)	78 (32)	43 (29)	41 (28)
Unknown	1 (<1)	0	0	0

BPd = BLENREP, pomalidomide, dexamethasone; and dexamethasone; BVd = BLENREP, bortezomib, dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone; PVd = pomalidomide, bortezomib, dexamethasone
Note 1: Time to death from last dose had been categorized as unknown for 1 participant due to a partial date of death.
Note 2: In DREAMM-8, summary of deaths includes on-study and post-study withdrawal death information, and time from last dose was considered the last dose of any study treatment component.

The rates of fatal SAEs in the BLENREP arms were low (10% to 13%) and similar to the comparator arms (8% to 12%) in the registrational studies. A summary of fatal SAEs is provided in Appendix Table 11. Overall, pneumonia and COVID-19 related illness were the most frequently reported fatal SAEs.

7.10 Ocular Safety

The small molecule portion of BLENREP is cys-mcMMAF, a microtubule inhibitor. MMAF cytotoxin is known to be associated with ocular toxicities (Donaghy 2016), including corneal events. As with other ADCs that include a microtubule inhibitor payload, discussed in Section 3.2.3, ocular events are associated with BLENREP. As discussed in Section 5.2, extensive dose exploration and exposure-response analyses were conducted to identify the dose regimen that minimizes symptomatic ocular events while allowing participants to receive the maximum benefit from BLENREP treatment. The ocular events that occur after treatment with BLENREP are well-characterized and follow a predictable pattern. These events are manageable and reversible using the prescribed dose reductions and/or dose delays utilized in the DREAMM-7 and DREAMM-8 studies (Table 7). Severe ocular events were infrequent, and overall, the impact on reading, driving, and quality of life was limited.

Effects of BLENREP are on the most superficial layer of the cornea, the epithelium, as illustrated in Figure 25. BLENREP can enter some cells through macropinocytosis, releasing cys-mcMMAF, which accumulates within the cells, leading to apoptosis. The cornea (yellow in Panel A) is the affected portion of the eye, where microcyst-like epithelial

changes (MECs) occur. These changes are observable on slit-lamp examination of the eye as shown in Panel B. The MECs start in the periphery of the cornea (Panel C, top) where they are generally asymptomatic, and move towards the center of the cornea (Panel C, center) where they affect vision. Because the cornea naturally renews epithelial cells continuously, the MECs resolve over time when administration of BLENREP is held (Panel C, bottom) and new epithelial cells replace the affected ones.

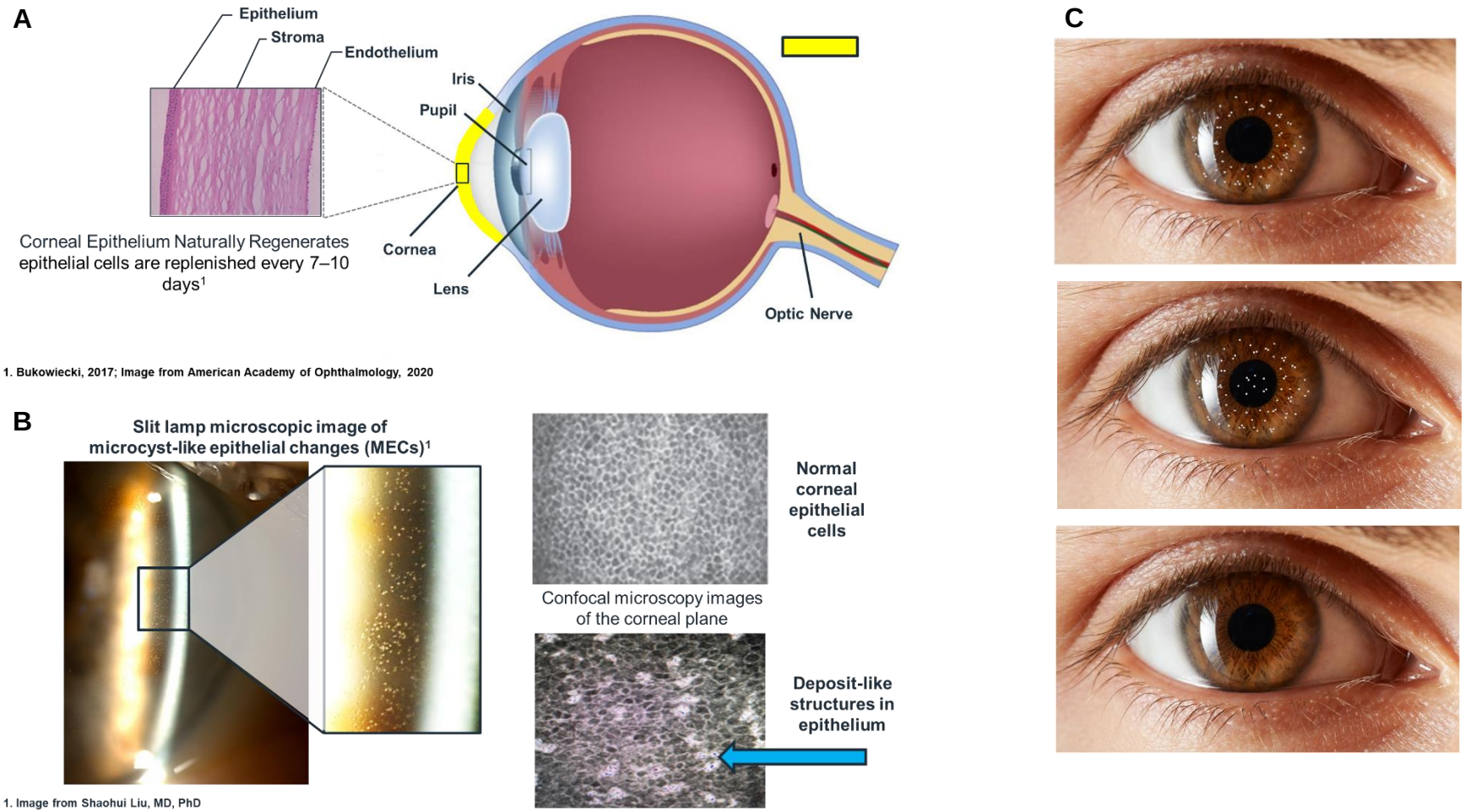
The evaluation of ocular safety included several approaches to allow a holistic and objective review of the impact of BLENREP on the cornea. The approach is summarized in Figure 11.

Corneal Events by KVA Scale is a composite assessment of:

1) Best corrected visual acuity (BCVA) measured by Snellen equivalent. Figure 26 provides simulated images of visual acuity changes as measured using the Snellen equivalent scale, and
2) corneal exam findings such as superficial punctate keratopathy or microcysts which are identified using a slit-lamp examination (see Figure 25). (Section 7.10.4).

In the KVA scale, each component (BCVA and corneal examination finding) is graded separately, and the most severe finding drives the overall KVA grade. The overall composite score is used to guide dose modifications.

Figure 25 Corneal Examination Findings with BLENREP



A: Anatomy of the eye, showing the cornea in yellow and in cross-section (inset); B: Shows the microcyst-like epithelial changes (MECs) as visualized via slit-lamp exam and by confocal microscopy; C: MECs (shown as white dots) begin in the periphery (top) then develop towards the center of the eye (center). MECs are generally reversible when BLENREP dosing is held (bottom) and new corneal epithelium is regenerated .

Ocular AEs using CTCAE consist of ocular AEs/symptoms reported by the study participants (Section 7.10.5). Ocular AESIs included a subset of the Eye disorder SOC and were defined based on the MedDRA 'corneal disorders' SMQ combined with PTs selected on medical review which represent changes in visual acuity. Table 27 summarizes the protocol-specified ocular assessment timing and required actions for the registrational studies.

Table 27 DREAMM-7 and DREAMM-8: Overview of Ocular Assessment, Grading, and Reporting

Study	Ophthalmic Examination Schedule		Action taken for	
	Investigational Arm	Control/ Comparator Arm	GSK/KVA Grade 2	GSK/KVA Grade 3
DREAMM-7	Q3W, then Q12W if no significant ocular findings in the first 6 cycles	Every 6 months	Dose delay	Dose delay and reduction
DREAMM-8	Q4W, then Q12W if no significant ocular finding in the first 6 cycles	Every 6 months	Dose delay and dose reduction if after Cycle 2	Grade 4 led to dose delay and reduction to 1.4 Q8W

CTCAE = Common Terminology Criteria For Adverse Events; GSK = GlaxoSmithKline; KVA = Keratopathy Visual Acuity; N/A = Not applicable
Note: In DREAMM-7 and DREAMM-8, corneal exam findings were reported as AEs by CTCAE prior to Protocol Amendment 1. In DREAMM-8, dose reductions were not recommended for BLENREP original protocol. After Protocol Amendment 1, dose reductions were allowed at first Grade ≥2 corneal events (KVA scale).

Sponsor-assessed KVA grading used the reported corneal findings and was applied to all participants in all treatment arms regardless of protocol version to allow a consistent, comprehensive assessment of the effects of BLENREP and facilitate comparison of findings from the ophthalmic examinations. The assessment was based on the raw data reported by the investigators in the case report forms. The sponsor-assessed findings are the focus for the ocular safety assessment and are largely consistent with the investigator-assessed findings.

7.10.1 Analysis of Ocular Safety In the DREAMM-7 and DREAMM-8 Control Arms

Despite being conducted at a much lower frequency, the assessment of ocular events in the comparator arms demonstrate a 'background' event rate in the primarily older patient population not exposed to BLENREP. The fact that ocular events are not absent in the comparator arms should be considered when evaluating the ocular events in the BLENREP-containing arms. Results are similar between the two comparator arms and are briefly summarized as follows:

- Incidence of ocular events by CTCAE was 31% (DVd) and 32% (PVd), with vision blurred being most common
- Incidence of worsening of BCVA to bilateral 20/50 was 2% (DVd) and 3% (PVd)
- Incidence of sponsor-assessed corneal events by KVA was 54% (DVd) and 43%, (PVd), predominately Grade 1 and Grade 2.

- Dose modification due to any ocular events (CTCAE or KVA) were minimal at 2% (DVd) and 1% (PVd). No treatment discontinuations due to ocular events were reported.

7.10.2 Best Corrected Visual Acuity (Ophthalmic Examinations)

Changes in best corrected visual acuity (BCVA) can impact ability to perform daily activities and worsening of vision to 20/50 or greater is considered clinically meaningful. At 20/50, images may appear slightly blurry and vision better than 20/50 reflects the accepted standard required to drive in most states. Images simulating real-life vision are provided in Figure 26. A BCVA of 20/200 is the considered severe visual impairment.

Figure 26 Simulated Vision Conditions of Normal and Clinically Meaningful Best Corrected Visual Acuity (Snellen Scale)

Considered to be normal vision.	Images appear slightly blurry	Considered severe visual impairment in the US.

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Table 28 summarizes the characteristics of bilateral worsening of Snellen scores to 20/50 or worse and to 20/200 or worse for the registrational studies in participants who had normal (20/25 or better at least in one eye) visual acuity at baseline. In DREAMM-7, there were 31 (13%) participants in the BLENREP arm and 41 (17%) in the comparator arm who did not have normal visual acuity at baseline; in DREAMM-8, it was 13 (9%) and 24 (17%) for the BLENREP and comparator arms, respectively.

In the two registrational studies, about one third of participants experienced a clinically meaningful reduction in BCVA as measured by Snellen score. There were no discernable differences between the BLENREP arms, indicating the BCVA findings are independent of the dosing schedules and combination partners. In both registrational studies, a finding of BCVA of 20/50 or worse did not occur at most ocular assessments (95% and 93% in BVd and BPd arms) and the mean time on treatment with a BCVA worsening to 20/50 or worse was 11% and 14%, further highlighting the transient nature of the events.

- BCVA change to 20/50 or worse was reported for 35% of participants in the BVd arm with a median time to onset of first occurrence of 79.0 days, and for 34% participants in the BPd arm with a median time to onset of first occurrence of 112.0 days.

- The median duration was about 2 months in both studies. First events resolved by the DCO in 93% of participants in DREAMM-7 and 88% of participants in DREAMM-8.
- Bilateral worsening of Snellen scores to 20/200 or worse was infrequent (1-2% of participants) and resolved to baseline in 5 of 7 participants with the remaining two participant lost to follow up. 79% in both studies

Across more than 7500 participants treated to date in the BLENREP clinical program and in clinical practice, there have been no confirmed reports of permanent bilateral vision loss of 20/200 or worse.

Table 28 DREAMM-7 and DREAMM-8: Onset, Duration, Outcome, and Occurrence of Bilateral Worsening of BCVA Score (Snellen Score) to 20/50 or 20/200 (or Worse) in the BLENREP Arms in Participants with Normal Baseline (Safety Population)

Characteristics, n (%)	DREAMM-7 (BVd) (N=242)	DREAMM-8 (BPd) (N=150)
Worsening to 20/50 or Worse		
Participants with Event, n	84 (35%)	51 (34%)
Time to onset of first occurrence (days), n	84	51
Median (range)	79.0 (16, 1320)	112.0 (28, 761)
Outcome of first occurrence, n	84	51
Resolved prior to the end of treatment exposure	72 (86%)	40 (78%)
Resolved post end of treatment exposure	6 (7%)	5 (10%)
Not resolved, ongoing at last follow-up	6 (7%)	6 (12%)
Not discontinued	1 (1%)	1 (2%)
Discontinued, follow-up ongoing	0	1 (2%)
Discontinued, follow-up ended	5 (6%)	4 (8%)
Duration of first occurrence (days)[a, b], n	78	45
Median (range)	63.5 (8, 908)	57.0 (14, 451)
Number of Snellen assessments (total duration), n	5237	2254
Number of assessments with bilateral 20/50 or worse	259 (5%)	149 (7%)
Total Number of Occurrences	173	87
Number of Occurrences per Participant, Median (range)	2 (1, 9)	1 (1, 5)
Resolved	158 (91%)	76 (87%)
Ongoing	15 (9%)	11 (13%)
Treatment ongoing	6 (3%)	3 (3%)
Discontinued, follow-up ongoing	2 (1%)	2 (2%)
Discontinued, follow-up ended	7 (4%)	6 (7%)
Worsening to 20/200 or Worse		
Participants with event, n	5 (2%)	2 (1%)
Time to onset of first occurrence (days), n	5	2

Characteristics, n (%)	DREAMM-7 (BVd) (N=242)	DREAMM-8 (BPd) (N=150)
Median (range)	105.0 (47, 304)	351.0 (29, 673)
Outcome of first occurrence, n [a]	5	2
Resolved prior to the end of treatment exposure	3 (60%)	1 (50%)
Resolved post end of treatment exposure [c]	1 (20%)	0
Not resolved, ongoing at last follow-up	1 (20%)	1 (50%)
Not discontinued	0	0
Discontinued, follow-up ongoing	0	0
Discontinued, follow-up ended	1 (20%)	1 (50%)
Duration of first occurrence (days) [a, b], n	4	1
Median (range)	86.5 (22, 194)	57.0 (57, 57)

BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib and dexamethasone;
a. Duration is the time from onset of any worsening of BCVA Score to 20/50 or 20/200 until the event is resolved to 20/25 or better in at least one eye.
b. Snellen acuity response of 'no equivalent value' is considered a worsening event.
c. The end of treatment exposure is defined as last dose date of BLENREP +20 days (DREAMM-7), +27 days (DREAMM-8)

7.10.3 Corneal Events Identified by Slit Lamp Exam

Abnormal corneal findings identified by slit lamp exam were frequent and primarily included SPK, microcyst-like deposits, and sub-epithelial haze. The clinical significance of these findings on their own is often unclear as events could be asymptomatic and without meaningful vision loss. Importantly, observed slit lamp findings are often non-specific with events occurring in both the BLENREP and comparator arms, as ocular changes are expected to occur in aging patients as those in the registrational studies.

Table 29 includes a summary of corneal exam findings Grade 2 or higher for DREAMM-7 and DREAMM-8. Corneal events (GSK/KVA) occur in most participants but are managed with dose modifications and with sufficient follow-up, most events resolve. There were no meaningful differences in the incidence and characteristics of the sponsor-assessed corneal events (GSK/KVA scale) between the 2 registrational studies. A majority of participants with a corneal exam finding experienced more than one event. First occurrence events resolved in 86% and 90% of participants in the BVd and BPd arms at the time of the data cutoff.

7.10.4 Corneal Events by Keratopathy Visual Acuity Scale

A summary of the sponsor-assessment of corneal events conducted using the KVA scale and the individual components (i.e., slit lamp corneal exam findings and Snellen BCVA score) is provided in Table 29. The sponsor-assessed KVA scale was developed by GSK to ensure robust assessment of ocular events reported in clinical studies. Corneal events (KVA) occurred in most participants but were managed with dose modifications, and with sufficient follow-up most events resolved. Most participants (69% to 73%) had multiple separate occurrences of KVA events.

Overall, the incidence and characteristics of the sponsor-assessed corneal events (KVA scale) were similar between the BLENREP arms in the two registrational studies. Overall, 93% and 95% of participants in the BLENREP arms in DREAMM-7 and DREAMM-8 experienced KVA events vs 54% and 43% in the comparator arms. The proportion of participants who reported a Grade 3 or Grade 4 event was much higher in the BLENREP arms (79% in both studies) vs. the comparator arms (10% and 8% in DREAMM-7 and DREAMM-8, respectively).

Based on the primary analysis, the majority of participants (91 to 92%) in the BLENREP arms in both studies continued treatment with BLENREP on or after the onset of their first Grade 2+ event. In DREAMM-7, participants received a median of 8 additional doses (range: 1 to 52), with 177/190 participants (93%) achieving a PR or better. In DREAMM-8, participants received a median of 5 additional doses (range: 1 to 21), with 106/120 participants (88%) achieving PR or better.

Table 29 DREAMM-7 and DREAMM-8: Summary of Characteristics of Sponsor-Assessed Keratopathy Visual Acuity Scale (Individual Components and Overall KVA)

	Overall KVA		Corneal Exam		BCVA	
	DREAMM-7 BVd N=242	**DREAMM-8 BPd N=150**	**DREAMM-7 BVd N=242**	**DREAMM-8 BPd N=150**	**DREAMM-7 BVd N=242**	**DREAMM-8 BPd N=150**
Events n (%) based on all participants%)	**224 (93%)**	**142 (95%)**	**218 (90%)**	**134 (89%)**	**217 (90%)**	**137 (91%)**
Grade 1	12/242 (5%)	9/150 (6%)	9/242 (4%)	9/150 (6%)	21/242 (9%)	12/150 (8%)
Grade 2	20/242 (8%)	14/150 (9%)	21/242 (9%)	26/150 (17%)	53/242 (22%)	34/150 (23%)
Grade 3	136/242 (56%)	99/150 (66%)	139/242 (57%)	84/150 (56%)	129/242 (53%)	85/150 (57%)
Grade 4	56/242 (23%)	20/150 (13%)	49/242 (20%)	15/150 (10%)	14/242 (6%)	6/150 (4%)
Time to first event onset Grade ≥2[a], days, n	212	133	209	125	196	125
Median (range%)	43.0 (15, 589)	29.0 (18, 983)	43.0 (15, 967)	29 (18, 983)	52.5 (16, 627)	58.0 (21, 704)
Outcome of first occurrence, n	212	133	209	125	196	125
Resolved prior to end of treatment exposure	146 (69%)	100 (75%)	146 (70%)	99 (79%)	155 (79%)	101 (81%)
Resolved post end of treatment exposure [c]	23 (11%)	13 (10%)	34 (16%)	14 (11%)	19 (10%)	11 (9%)
Ongoing as of last follow-up	43 (20%)	20 (15%)	29 (14%)	12 (10%)	22 (11%)	13 (10%)
Not discontinued	0	0	0	0	0	0
Discontinued, follow-up ongoing	11 (5%)	7 (5%)	5 (2%)	4 (3%)	7 (4%)	3 (2%)
Discontinued, follow-up ended	32 (15%)	13 (10%)	24 (11%)	8 (6%)	15 (8%)	10 (8%)
Duration of first event[a, b], days, n	169	113	180	113	174	112
Median (range)	117.0 (8, 1072)	111 (15, 746)	106.0 (8, 1072)	88.0 (15, 746)	48.5 (4, 481)	57 (8, 548)
Number of Occurrences	212	133	209	125	196	125
One	66 (31%)	36 (27%)	64 (31%)	33 (26%)	46 (23%)	32 (26%)
Two	29 (14%)	20 (15%)	31 (15%)	22 (18%)	29 (15%)	24 (19%)
Three or more	117 (55%)	77 (58%)	114 (55%)	70 (56%)	121 (62%)	69 (55%)

	Overall KVA		Corneal Exam		BCVA	
	DREAMM-7 BVd N=242	**DREAMM-8 BPd N=150**	**DREAMM-7 BVd N=242**	**DREAMM-8 BPd N=150**	**DREAMM-7 BVd N=242**	**DREAMM-8 BPd N=150**
Total Number of Occurrences	899	529	935	490	894	424
Number of Occurrences per Participant, Median (min, max)	3 (1, 15)	3 (1, 13)	3 (1, 16)	3 (1, 13)	4 (1, 13)	3 (1, 10)
Resolved	779 (87%)	469 (89%)	843 (90%)	448 (91%)	823 (92%)	388 (92%)
Ongoing	120 (13%)	60 (11%)	92 (10%)	42 (9%)	71 (8%)	36 (8%)
Treatment ongoing	44 (5%)	23 (4%)	41 (4%)	18 (4%)	21 (2%)	9 (2%)
Discontinued, follow-up ongoing	28 (3%)	13 (2%)	16 (2%)	7 (1%)	17 (2%)	10 (2%)
Discontinued, follow-up ended	48 (5%)	24 (5%)	35 (4%)	17 (3%)	33 (4%)	17 (4%)

BCVA = best corrected visual acuity; BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib and dexamethasone; KVA = Keratopathy and Visual Accuity

a Among participants with Grade 2+ KVA.

b Duration is the time from onset of any keratopathy visual (KVA scale) event (Grade 2 or above) until the event is resolved (Grade 1 or better).

c The end of treatment exposure is defined as last dose date of BLENREP +20 days (DREAMM-7), +27 days (DREAMM-8)

Note: Lost to follow-up refers to those who were under survival follow-up but have confirmed not coming back to site for further examination.

Note: Treatment related corneal events (corneal exam findings and changes in BCVA) are graded according to the guidelines of the KVA Scale to inform dose modifications. Sponsor-assessed KVA scale events include participants enrolled under original protocol. Start date for time to onset of first occurrence is start date of any study treatment component.

7.10.5 Ocular Adverse Events (By CTCAE)

There were no meaningful differences between the BLENREP arms in the two registrational studies (BVd and BPd) with regard to the ocular AEs (CTCAE) (Table 30). The most commonly reported ocular AEs by CTCAE were vision blurred, dry eye, foreign body sensation in the eyes, photophobia, and eye irritation. There was one serious ocular AE (CTCAE; Grade 2 diplopia) reported from DREAMM-8. No new ocular safety concerns were identified.

Table 30 DREAMM-7, DREAMM-8: Summary of Grade 3/4 and Any Grade Ocular Symptoms by Preferred Term and Maximum CTCAE Grade (in ≥5% of Total Participants (Safety Population)

PT, n (%)	DREAMM-7 (BVd) (N=242)		DREAMM-8 (BPd) (N=150)	
	Grade 3+4	Total	Grade 3+4	Total
Any event	**85 (35%)**	**194 (80%)**	**66 (44%)**	**133 (89%)**
Vision blurred	58 (24%)	165 (68%)	26 (17%)	120 (80%)
Dry eye	17 (7%)	129 (53%)	13 (9%)	92 (61%)
Foreign body sensation in eyes	9 (4%)	111 (46%)	9 (6%)	91 (61%)
Photophobia	7 (3%)	120 (50%)	5 (3%)	69 (46%)
Eye irritation	12 (5%)	110 (45%)	6 (4%)	77 (51%)
Eye pain	2 (<1%)	81 (33%)	3 (2%)	49 (33%)
Keratopathy	3 (1%)	5 (2%)	4 (3%)	11 (7%)
Visual acuity reduced	3 (1%)	13 (5%)	19 (13%)	33 (22%)
Visual impairment	12 (5%)	26 (11%)	15 (10%)	23 (15%)
Punctate keratitis	1 (<1%)	2 (<1%)	8 (5%)	33 (22%)
Corneal epithelial microcysts	0	1 (<1%)	12 (8%)	34 (23%)
Lacrimation increased	2 (<1%)	24 (10%)	1 (<1%)	9 (6%)
Diplopia	0	12 (5%)	1 (<1%)	7 (5%)
Corneal opacity	0	0	2 (1%)	13 (9%)
Keratitis	5 (2%)	7 (3%)	4 (3%)	8 (5%)

AESI = adverse event of special interest; BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib and dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone; PT = preferred term; PVd = pomalidomide, bortezomib, dexamethasone

The event characteristics for ocular symptoms by CTCAE in the two registrational studies are summarized in Table 31 and Table 32. An analysis of characteristics showed that the median time to onset of 42 and 29 days for DREAMM-7 (BVd) and DREAMM-8 (BPd), respectively. The median event duration was less in the BVd arm (51 days) vs. the BPd arm (134.5 days).

Overall, 84% and 84% of occurrences had resolved at the DCO for participants in the BVd and BPd arms, respectively. For the events not resolved, 12% and 3% are still being followed-up. with the potential to have resolution documented at a later time. The proportion of resolved events may increase with longer follow-up. For the remaining

events (10% and 6% in the BVd and BPd arms), the follow-up ended before resolution of the event could be documented.

Table 31 DREAMM-7 and DREAMM-8: Summary of Characteristics of Ocular Symptoms (CTCAE) (Safety Population)

Ocular Symptoms/AESIs (by CTCAE) Characteristics, n (%)	**DREAMM-7 (BVd) (N=242)**	**DREAMM-8 (BPd) (N=150)**
Number of participants with event	194 (80%)	133 (89%)
Number of events	2295	1868
Event characteristics (% based on all participants)[a]		
Serious	0/242	1/150 (<1%)[b]
Related to study treatment	188/242 (78%)	132/150 (88%)
Number of events (% based on all participants)		
One	22/242 (9%)[g]	5/150 (3%)[g]
Two	18/242 (7%)[g]	5/150 (3%)[g]
Three or more	154/242 (64%)[g]	123/150 (82%)[g]
Maximum grade (% based on all participants)		
Grade 1	42/242 (17%)	27/150 (18%)
Grade 2	67/242 (28%)	40/150 (27%)
Grade 3	79/242 (33%)	64/150 (43%)
Grade 4	6/242 (2%)	2/150 (1%)
Action taken (% based on all participants)[a]		
Dose not changed	164/242 (68%)	133/150 (89%)
Dose interrupted/delayed or reduced	129/242 (53%)	95/150 (63%)
Dose interrupted/delayed	118/242 (49%)	94/150 (63%)
Dose reduced	49/242 (20%)	7/150 (5%)
Treatment discontinued	9/242 (4%)	7/150 (5%)
Not applicable	35/242 (14%)	28/150 (19%)
Worst outcome (% based on participants with an event)		
Recovered/resolved	104/194 (54%)	75/133 (56%)
Recovering/resolving	15/194 (8%)	14/133 (11%)
Recovered/resolved with sequalae	4/194 (2%)	1/133 (<1%)
Not recovered/not resolved	71/194 (37%)	43/133 (32%)

AESI = adverse event of special interest; BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib and dexamethasone; CTCAE = common terminology criteria for adverse events

a Participants may be included in more than 1 category for 'Event characteristics', 'Action taken'. 'Action taken' counts actions related to any of the study treatments.

b One participant on DREAMM-8 experienced an SAE of Diplopia more than 70 days after last dose, hence was therefore included in the analysis of all events in the individual studies but not in the analysis of the treatment emergent events in the combination pool

Table 32 DREAMM-7 and DREAMM-8: Occurrence of Ocular Symptoms (CTCAE) (Safety Population)

n (%)	DREAMM-7 (BVd) (N=242)	DREAMM-8 (BPd) (N=150)
Total Number of Occurrences	**569**	**376**
Number of Occurrences per Participant, Median (range)	1 (1, 14)	2 (1, 11)
Resolved	480 (84%)	317 (84%)
Ongoing	89 (16%)	59 (16%)
Treatment ongoing	39 (7%)	24 (6%)
Discontinued, follow-up ongoing	27 (5%)	12 (3%)
Discontinued, follow-up ended	23 (4%)	23 (6%)

AESI = adverse event of special interest; BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib and dexamethasone; CTCAE = Common Terminology Criteria for Adverse Events; PT = preferred term

a Lost to follow-up refers to those who were under survival follow-up but confirmed they were not coming back to site for further examination

b Duration is the time from onset of any ocular symptom (CTCAE) to the first time the participant is free of any such event. It requires at least 1 day gap between resolution of all events from first occurrence to the onset of second occurrence.

7.10.6 Other Ophthalmic Examination Findings

Corneal ulcers with confirmed stromal involvement and infection are infrequent in the BLENREP program. Three confirmed cases of corneal ulcer with stromal involvement and infection have been reported from approximately 1800 participants treated with BLENREP in clinical studies since 2014.

- In one case, the ulcer resolved, and vision returned to baseline.
- In another case, the ulcer resolved but visual acuity in the affected eye remained severely affected at the time the participant withdrew from the study (20/400 at the last visit).
- The third case of corneal ulcer with infection was reported in another study of BLENREP (1.0 mg/kg Q12W; DREAMM-9) and was resolved after 63 days with residual corneal epithelial haze. The case is confounded by evidence of dry eye syndrome preceding the event, and the use of punctal plugs. Information on visual acuity was not available.

In both DREAMM-7 and DREAMM-8, the PT of cataract was reported in more than twice as many participants in the BLENREP-containing arms compared with the comparator arms. The higher reporting of treatment-emergent cataract AEs in BLENREP arms compared with comparator arms can be attributed to several factors specific to the comparator arms:

- Less frequent (every 6 months) eye exams were required for the comparator arms;

- Not requiring re-baselining of BCVA for the comparator arms (as it did not impact any study treatment decision), and by extension, reporting of cataracts as AE;
- The comparator arms having shorter time on study treatment, thereby a shorter period for collection of cataract AEs.

In addition, systemic dexamethasone treatment has been associated with ocular cataracts (Banerjee 2024), which would not have impacted the monotherapy studies, and would be exacerbated by the longer duration on treatment in the DREAMM-7 and DREAMM-8 studies.

7.10.7 Ocular Events Leading to Dose Modifications

7.10.7.1 Dose Reduction, Interruption, Delay

An analysis of “any ocular event” leading to dose modification included corneal events (GSK/KVA scale), which were managed with dose modifications (dose reductions and dose interruptions/delays per protocol), and ocular AEs (CTCAE). Dose modification was individualized per the participants' tolerability as assessed by corneal events (KVA grade). For both studies, the majority of participants had a dose reduction as part of protocol-defined dose modifications to optimize tolerability and duration of treatment.

Overall response and depths of response in participants with at least one event of KVA Grade 2 or higher was consistent with the ITT population, demonstrating that dose modification helped mitigate corneal events without impacting the quality of the response.

- In DREAMM-7, 181 participants (75%) had a reduction from 2.5 mg/kg to 1.9 mg/kg, with 163 (67%) having 1 reduction, 16 (7%) with 2 reductions, and 2 (<1%) with ≥3 reductions. Dose delays occurred in 78% participants.
- In DREAMM-8, 80 participants (53%) reduced to dose level -1 (1.9 mg/kg Q8W), and 9 (6%) reduced to dose level -2 (1.4 mg/kg Q8W). Dose delays occurred for 83% of participants. In DREAMM-8, once a participant reduced a dose level the participant remained on this level. Therefore, in the DREAMM-8 study, a participant could only reduce once per dose level.

For DREAMM-7, the median weeks between doses is 3 to 6 weeks over the first three months, then increases over time to an interval of approximately 12 to 15 weeks. For DREAMM-8, the median weeks between doses is approximately 4 to 8 within the first 3 months then increasing over time to about 12 weeks. This is aligned with observation that the decrease in dose intensity over time in both registrational studies was a result of following the protocol-prescribed dose modification guidance for the mitigation of adverse events, including ocular events, and was driven by a progressive increase of time between dosing.

Where a dose delay was due to a Grade ≥2 KVA event:

- For DREAMM-7, the overall median time to the next dose after the occurrence of a Grade ≥ 2 KVA event is 7.1 weeks (range 0.1 – 61.6, IQR 2.4 – 12.9). For any number of recurrences, the medians range from approximately 9 to 15 weeks.
- For DREAMM-8, the overall median time to the next dose after the occurrence of a Grade ≥ 2 KVA event is 8.1 weeks (range 0.1 – 34.4, IQR 4.0 – 12.3). For any number of recurrences, the medians range from approximately 9 to 12 weeks.

Despite the differences in the planned BLENREP dose between the DREAMM-7 and DREAMM-8 studies, the protocol-specified dose modifications applied by study physicians in response to adverse events led to a very similar dose and dose schedule between the two registrational studies (Figure 5).

7.10.7.2 Dose Discontinuation

The proportion of discontinuations from BLENREP attributed to an ocular event was 10% and 11% in DREAMM-7 and DREAMM-8, respectively. At the time of the primary analyses for each study, these participants received a median of 5 infusions (range: 2 to 37) of BLENREP in DREAMM-7 and 3 infusions (range: 1 to 7) of BLENREP in DREAMM-8. The majority of participants (20/22 in DREAMM-7 and 12/14 in DREAMM-8) experienced a response prior to withdrawal. The ocular event that led to the discontinuation resolved for 15/22 participants in DREAMM-7 and for all 14 participants in DREAMM-8.

7.10.8 Ocular Event Characteristics – Subgroup by Age

There were no meaningful differences in the ocular profile in participants receiving BLENREP who were <65 years of age versus those who were 65 to <75 years, and those ≥ 75 years across the two Phase 3 studies). Corneal events identified through ophthalmic examination presented generally similar incidence and characteristics across all age groups, further suggesting that the pathophysiology of these events is not influenced by age.

7.11 Ocular Patient Reported Outcomes Related to Ocular Safety

Patient Reported Outcomes measures relevant to ocular safety were evaluated and included Ocular Surface Disease Index (OSDI), and impact on reading and driving.

7.11.1.1 Ocular Surface Disease Index

The OSDI is designed to assess the frequency of dry eye symptoms and their impact on vision-related functioning and environmental triggers. Minimally important deterioration is the smallest change in a participants OSDI score that reflects a meaningful worsening of their vision-related function, as perceived by the participant or clinician. A higher score indicates poorer vision-related functioning. The recall period is the last week.

In the registrational studies, participants who experienced minimally important deteriorations in vision-related functioning of the OSDI, typically saw improvement or

resolution within 6 to 8 weeks in both the BVd and BPd arms. Symptomatic worsening of visual function was reversible in the majority of participants in both the BVd and BPd arms. The median time to improvement in visual related function from the first minimally important deterioration was 44.0 days and 57.0 days in BVd arm and BPd arm, respectively.

7.11.1.2 Impact on Reading and Driving

During each ophthalmologist visit (Q3W for DREAMM-7, Q4W for DREAMM-8), change in a participant's ability to read or drive was assessed using a non-validated qualitative 2-item questionnaire. Over the course of treatment with BLENREP, very few participants reported they had stopped reading or driving due to eyesight issues at any visit, as shown in the pooled DREAMM-7 and DREAMM-8 results in Figure 12. Over the full duration of treatment with BLENREP combinations, 24% of participants stopped reading and 33% of participants stopped driving at some point, with a median duration of approximately 1 month. More than 90% of participants had data to demonstrate a return to baseline at the time of the DCO.

7.12 Adverse Events of Special Interest – Non-Ocular Toxicities

7.12.1 Thrombocytopenia

Thrombocytopenia is a frequently observed AE in patients with RRMM and is a known class effect of MMAF (Donaghy 2016) and is a proposed adverse reaction for BLENREP. Bortezomib (combination partner for DREAMM-7), pomalidomide and dexamethasone (combination partners in DREAMM-8) (Velcade USPI 2021, Pomalyst USPI 2025) are also associated with thrombocytopenia.

In DREAMM-7, thrombocytopenia was reported in the majority of participants in both arms (Table 33). The rate of thrombocytopenia (including Grade 3/4) and exposure-adjusted rates were higher in the BVd than the DVd arm. Thrombocytopenia and severe thrombocytopenia remained higher in the BVd arm compared with the DVd arm (any event: 52.695 vs. 46.664 per 100 PY; Grade 3/4: 43.747 vs. 32.956 per 100 PY). No Grade 5 events were reported in either treatment arm.

In DREAMM-8, the rate of thrombocytopenia (including Grade 3/4 events) was higher in the BPd arm compared with the PVd arm (Table 33); however, after adjusting for exposure, the rates of thrombocytopenia and severe thrombocytopenia were comparable in the BPd versus the PVd arm (Any event: 32.503 vs. 39.119 per 100 PY; Grade 3+4 event: 22.872 vs. 27.383 per 100 PY, respectively). No Grade 5 events were reported in either treatment arm.

Table 33 DREAMM-7, DREAMM-8: Summary of Thrombocytopenia All Events and Grade/3/4 by Preferred Term and Maximum Grade (Safety Population)

	DREAMM-7		DREAMM-8	
Thrombocytopenia AESIs/PTs, n (%)	**BVd (N=242)**	**DVd (N=246)**	**BPd (N=150)**	**PVd (N=145)**
Any event	212 (88%)	160 (65%)	81 (54%	60 (41%)
Any Grade 3/4 Event	176 (73%)	113 (46%)	57 (38%)	42 (29%)
Thrombocytopenia	169 (70) %)	122 (50%)	54 (36%)	42 (29%)
Grade 3/4 Thrombocytopenia	135 (56%)	87 (35%)	36 (24%)	28 (19%)
Platelet count decreased	51 (21%)	40 (16%)	30 (20%)	23 (16%)
Grade 3/4 Platelet count decreased	43 (18%)	26 (11%)	22 (15%)	18 (12%)

AESI = adverse event of special interest; BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib and dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone; PT = MedDRA preferred term; PVd = pomalidomide, bortezomib, dexamethasone
Note: In DREAMM-7 thrombocytopenia AESI is based on a hybrid of terms identified in the electronic case report forms, and the terms thrombocytopenia and platelet count decreased.
Note: In DREAMM-8, an AE of 'Thrombocytosis' was also flagged as a Thrombocytopenia AESI in error by the investigator. The event has been updated and is no longer flagged as an AESI in the database following interim analysis database lock.
Note: In DREAMM-8, thrombocytopenia is based on a hybrid of terms identified in the eCRF, and a list of terms identified by GSK internal review. The terms are thrombocytopenia and platelet count decreased.

In both DREAMM-7 and DREAMM-8, the majority of thrombocytopenia events reported in the BLENREP arms had resolved at the time of data cut-off (71% and 79%, respectively). The incidence of thrombocytopenia SAEs was low (5% and 2%, respectively) (Table 34).

Table 34 DREAMM-7 and DREAMM-8: Summary of Characteristics of Thrombocytopenia for (Safety Population)

	DREAMM-7		DREAMM-8	
Thrombocytopenia AESIs/ Characteristics, n (%)	**BVd (N=242)**	**DVd (N=246)**	**BPd (N=150)**	**PVd (N=145)**
Number of participants with event	212 (88%)	160 (65%)	81 (54%)	60 (41%)
Number of events	644	360	199	148
Event characteristics (% based on participants with an event) [a,b]				
Serious	11/212 (5%)	4/160 (3%)	2/81 (2%)	6/60 (10%)
Related to study treatment	204/212 (96%)	154/160 (96%)	72/81 (89%)	53/60 (88%)
Number of events (% based on participants with an event)				
One	82/212 (39%)	77/160 (48%)	42/81 (52%)	32/60 (53%)
Two	39/212 (18%)	34/160 (21%)	19/81 (23%)	7/60 (12%)
Three or more	91/212 (43%)	49/160 (31%)	20/81 (25%)	21/60 (35%)
Maximum grade (% based on participants with an event)				
Grade 1	11/212 (5%)	15/160 (9%)	8/81 (10%)	8/60 (13%)
Grade 2	25/212 (12%)	32/160 (20%)	16/81 (20%)	10/60 (17%)
Grade 3	63/212 (30%)	60/160 (38%)	39/81 (48%)	22/60 (37%)

Thrombocytopenia AESIs/ Characteristics, n (%)	DREAMM-7		DREAMM-8	
	BVd (N=242)	DVd (N=246)	BPd (N=150)	PVd (N=145)
Grade 4	113/212 (53%)	53/160 (33%)	18/81 (22%)	20/60 (33%)
Grade 5	0	0	0	0
Action taken (% based on participants with an event) [a,b]				
Dose not changed	161/212 (76%)	123/160 (77%)	81/81 (100%)	53/60 (88%)
Dose interrupted/delayed or reduced	121/212 (57%)	67/160 (42%)	24/81 (30%)	22/60 (37%)
Dose interrupted/delayed	113/212 (53%)	63/160 (39%)	18/81 (22%)	17/60 (28%)
Dose reduced	91/212 (43%)	32/160 (20%)	12/81 (15%)	10/60 (17%)
Study treatment withdrawn	7/212 (3%)	2/160 (1%)	0/81	0/60
Dose increased	3/212 (1%)	0/160	0/81	0/60
Not applicable	8/212 (4%)	8/160 (5%)	10/81 (12%)	8/60 (13%)
Worst outcome (% based on participants with an event)				
Recovered/resolved	142/212 (67%)	121/160 (76%)	64/81 (79%)	43/60 (72%)
Recovered/resolved with sequalae	8/212 (4%)	7/160 (4%)	0/81	0/60
Recovering/resolving	11/212 (5%)	4/160 (3%)	4/81 (5%)	2/60 (3%)
Not Recovered/not resolved	51/212 (24%)	24/160 (15%)	13/81 (16%)	15/60 (25%)
Missing	0/212	4/160 (3%)	0/150	0/145

AESI = adverse event of special interest; BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib and dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone; PVd = pomalidomide, bortezomib, dexamethasone

a Participants may be included in more than 1 category for 'Event Characteristics' and 'Action Taken'.

b 'Action Taken' counts actions related to any of the study treatments.

Note: In DREAMM-7 thrombocytopenia is based on a hybrid of terms identified in the eCRF, and the terms thrombocytopenia and platelet count decreased.

Note: In DREAMM-8, an AE of 'Thrombocytosis' was also flagged as a Thrombocytopenia AESI in error by the investigator. The event has been updated and is no longer flagged as an AESI in the database following interim analysis database lock.

Note: In DREAMM-8, thrombocytopenia is based on a hybrid of terms identified in the eCRF, and a list of terms identified by GSK internal review. The terms are thrombocytopenia and platelet count decreased.

The main complication of thrombocytopenia is bleeding, but the incidence of concomitant Grade 3 or 4 platelet count decreased and Grade $\geq$2 bleeding event was low in the BLENREP arms in both studies (7% and 3%, respectively) (Table 35).

Table 35 DREAMM-7 and DREAMM-8: Summary of Thrombocytopenia and Bleeding Events for (Safety Population)

Thrombocytopenia and Bleeding Events, n (%)	DREAMM-7		DREAMM-8	
	BVd (N=242)	DVd (N=246)	BPd (N=150)	PVd (N=145)
Any Grade 3/4 platelet count decreased [a]	178 (74%)	118 (48%)	61 (41%)	46 (32%)
Any Grade 2 or above bleeding event [b]	34 (14%)	22 (9%)	16 (11%)	8 (6%)

Thrombocytopenia and Bleeding Events, n (%)	DREAMM-7		DREAMM-8	
	BVd (N=242)	DVd (N=246)	BPd (N=150)	PVd (N=145)
Concomitant Grade 3/4 platelet count decreased and Grade 2 or above bleeding event [c]	17 (7%)	14 (6%)	4 (3%)	5 (3%)

BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib and dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone; PVd = pomalidomide, bortezomib, dexamethasone
a In DREAMM-7 and DREAMM-8, platelet count decreased event is identified based on the platelet count decreased laboratory assessments with an increase to Grade 3 or 4.
b In DREAMM-7, bleeding events included bleeding AEs (investigator-reported), or minor/major bleeding associated with thrombocytopenia AEs. In DREAMM-8, bleeding events included a hybrid of terms identified in the eCRF (investigator reported thrombocytopenia associated minor/major bleeding), and a list of terms identified by GSK internal review (Hemorrhage terms).
c In DREAMM-7 and DREAMM-8, a Grade 2 or above bleeding event was considered as concomitant if the start date was within 3 days of a Grade 3/ 4 platelet count decreased laboratory assessment.
Note: Thrombocytopenia is based on a hybrid of terms identified in the eCRF, and the terms thrombocytopenia and platelet count decreased.

Overall, the rate of thrombocytopenia in the BLENREP arms ranged from 88% (Grade 3/4: 73%) in DREAMM-7 to 54% (Grade 3/4: 38%) in DREAMM-8. Thrombocytopenia AESIs were more pronounced in DREAMM-7 (in both BVd & DVd arms) and could represent the possible additive effects with bortezomib.

7.12.2 Infections and Infestations

Infections are frequently reported as AEs in patients with RRMM. Pneumonias and respiratory tract infections are noted as common ADRs in MM patients treated with bortezomib (combination partner in DREAMM-7) regardless of indication (Velcade USPI 2021) and in patients treated with pomalidomide and dexamethasone (combination partners in DREAMM-8) (Pomalyst USPI 2025). A summary of infections and infestations for DREAMM-7 and DREAMM-8 with exposure adjusted incidence rates is provided in Table 36.

In the BLENREP arms, upper respiratory tract infection, pneumonia, and COVID-19 were the most frequently reported PTs in the Infections and Infestations SOC. The incidence of infections (all PTs in the Infections and Infestations SOC) was 73% in DREAMM-7 and 83% in DREAMM-8. The higher incidence of infections including severe (Grade 3/4) infections in DREAMM-8 compared with DREAMM-7 could be explained by the additive toxicity of pomalidomide compared with bortezomib, and/or by the fact that DREAMM-7 participants received a triplet combination of BLENREP, bortezomib and dexamethasone for only the first 8 cycles followed by BLENREP monotherapy, while the DREAMM-8 participants received a triplet combination of BLENREP, pomalidomide, and dexamethasone throughout the study duration.

Infections reported in the BLENREP arms were characterized by high resolution rates, low treatment discontinuation rates, and low rates of fatal SAEs.

Table 36 DREAMM-7 and DREAMM-8: Summary of Infections and Infestations SOC (Safety Population)

	DREAMM-7				DREAMM-8			
	BVd (N=242)		DVd (N=246)		BPd (N=150)		PVd (N=145)	
	n (%)	EAIR (100 PY)	n (%)	EAIR (100 PY)	n (%)	EAIR (100 PY)	n (%)	EAIR (100 PY)
Any Infections and Infestations SOC Event	176 (73)	43.747	167 (68)	48.705	124 (83)	49.757	101 (70)	65.851
Grade 3/4/5 Infections and Infestations SOC Event	80 (33)	19.885	49 (20)	14.291	78 (52)	31.299	39 (27)	25.428

BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib and dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone; EAIR = exposure adjusted incidence rate; PT = MedDRA preferred term; PVd = pomalidomide, bortezomib, dexamethasone; PY = person year; SOC = MedDRA system organ class
Note: Exposure-adjusted event rates are calculated as the total number of participants with an event divided by the total PY (per 100 PY). Total PY is the sum of all participant exposure calculated as (last dose - first dose + 1) / 365.25.

7.13 Other Adverse Events of Clinical Interest

7.13.1 Infusion-related Reactions

Infusion-related reactions are expected for biologic agents administered as infusions and include events such as pyrexia, chills, diarrhea, nausea, asthenia, hypertension, lethargy, and tachycardia. Overall, across all monotherapy and combination therapy studies, the incidence of IRRs in BLENREP arms ranged from 2% in DREAMM-7 to 7% in DREAMM-8. Premedication for IRR prophylaxis is not required prior to infusion in the DREAMM program, unless deemed medically appropriate by the investigator.

7.13.2 Hepatobiliary Disorders

7.13.2.1 Hepatobiliary Disorders Adverse Events

In the registrational studies, the incidence of Hepatobiliary disorders AEs in the BLENREP arms was ≤3% for individual preferred terms in both DREAMM-7 and DREAMM-8. Increases in various liver tests in the Investigations SOC were generally more pronounced in the BVd and BPd arms when compared to their respective comparators.

Changes in ALT (ALT ≥5xULN) and other biochemical parameters of liver function were seen in a higher proportion of participants in the BLENREP arm in DREAMM-7, and in DREAMM-8 in similar proportions vs. the comparator arms. Based on the totality of available information from all combination and monotherapy studies, ALT, AST, and GGT increases are considered as adverse reactions for BLENREP.

Biochemical/potential Hy's Law cases in both registrational studies were balanced between treatment arms and were confounded with respect to causality. There were no biochemical/potential Hy's Law cases in the monotherapy studies.

7.13.2.2 Nodular Regenerative Hyperplasia and Veno-Occlusive Disease

In DREAMM-6, there were one cases of nodular regenerative hyperplasia (NRH), and one case of veno-occlusive disease (VOD). There was also 1 literature case of VOD with a fatal outcome. Both cases of NRH and both cases of VOD had a history of stem cell transplantation during the course of their illness (often years prior to receiving a BLENREP containing regimen).

The 2 cases of NRH in DREAMM-6 were both treated with BLENREP, bortezomib, and dexamethasone.

7.14 Safety Conclusions

The overall safety of BLENREP in triplet combinations from DREAMM-7 and DREAMM-8 is broadly consistent with the known stable safety profile of BLENREP and/or individual components in the triplet regimens. Ocular events that occur with BLENREP are generally reversible with time and effectively managed with dose modifications, allowing participants to remain on treatment and derive benefit.

The most commonly reported AEs (>20% of participants) in DREAMM-7 and DREAMM-8 included two AESIs occurring in the majority of participants, ocular (79%, 89%) and thrombocytopenia (87%, 55%). Thrombocytopenia reported in the BLENREP arms for both studies were characterized by low SAE rates, low and balanced rates of Grade 3/4 decreased platelet count associated with Grade ≥2 bleeding events, high resolution rates, and low treatment discontinuation rates due to thrombocytopenia.

The ocular safety profile was comparable between the BLENREP containing treatment arms in DREAMM-7 and DREAMM-8 studies, despite the different dosing schedules.

- Vision blurred and dry eye were the most commonly reported AEs by CTCAE. Ocular AEs occur on average after the second dose and the majority of ocular AEs were reversible with adequate follow-up, with an average resolution time of approximately 3 months
- Worsening of BCVA, as assessed by the clinically meaningful change to bilateral Snellen score of 20/50 or worse was experienced by a third of participants and was transient with returning to baseline within a median of 2 months. Participants who had a worsening experienced this for a mean of 11% to 14% of their total time on treatment in the two pivotal trials. More severe clinically meaningful BCVA changes to bilateral 20/200 or worse were infrequent (7 participants, 2%) and resolved to baseline in most (5 of 7) participants where follow-up data were available.
- Corneal events (KVA, a composite scale of BCVA changes and corneal examination findings) occurred in most participants. Of the participants who experienced a KVA event, the majority had their first corneal event within the first 2 cycles, and most had

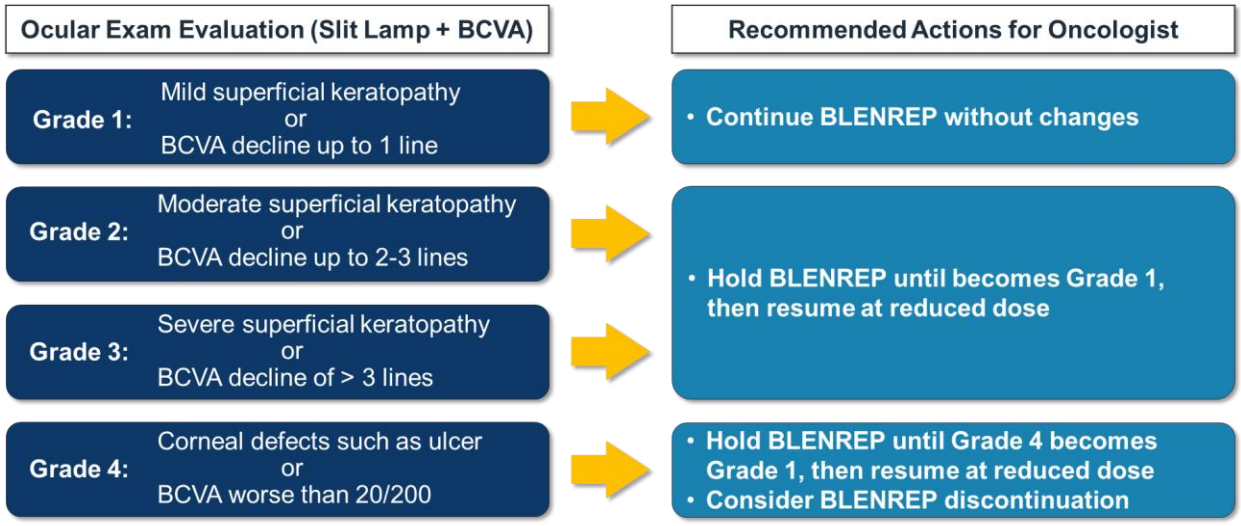
experienced their first event within 4 cycles. Corneal events were managed with dose modifications, and most events resolved with adequate follow-up, after which the participants could receive subsequent dosing with BLENREP. Corneal ulcers with stromal involvement and infection are infrequent across the program with only three confirmed events among approximately 1700 participants in the clinical development program.

- Importantly, despite more ocular events occurring in the BLENREP arms, overall patient-reported QOL was maintained over time, as demonstrated by EORTC QLQ-C30 Global Health Status/QOL domain scores.

The exposure-adjusted rates for SAEs in DREAMM-7 and DREAMM-8 were balanced between the BLENREP arms and comparator arms, underscoring that the addition of BLENREP to the SoC combinations does not increase severe toxicity burden. The incidence of any fatal SAEs (including fatal infections), and any fatal SAEs related to any study treatment were low and balanced (<5% difference across all four arms in DREAMM-7 and DREAMM-8).

Dose modifications in both studies in the form of dose reduction and dose delays allowed participants to continue receiving BLENREP by managing ocular events and other AEs without compromising efficacy. Participants were monitored by eye care professionals who communicated ocular findings to the oncologist to guide dosing decisions as illustrated in Figure 27.

Figure 27 Dose Modification Guidance for the Management of Ocular Events



BCVA = best corrected visual acuity

Despite the different dosing posology of BLENREP in the two registrational studies, the incidence of dose modifications for ocular events was comparable between DREAMM-7 and DREAMM-8. The ocular safety profile of BLENREP in the combination studies was generally consistent with the known safety profile of BLENREP.

8 RISK MITIGATION PLAN

A comprehensive approach to ocular risk management will include labeling, enhanced pharmacovigilance and a REMS with Elements to Ensure Safe Use (ETASU). BLENREP will be available only through a restricted program called the BLENREP REMS because of the risk of ocular events. Notable requirements of the ETASU include the following:

- Prescribers must be certified in the BLENREP REMS by enrolling and completing training; they will be required to pass a test to confirm their understanding of the information provided.
- Prescribers must counsel patients receiving BLENREP on the risk of ocular events, the need for monitoring via ophthalmic examinations, and provide patients with the BLENREP REMS Patient Guide. Prescribers must attest that they have educated the patients and patients must attest that they have received the education through a Patient Enrollment form.
- Healthcare settings that dispense BLENREP must be certified in the BLENREP REMS by enrolling and must verify prescribers are certified in the BLENREP REMS prior to dispensing.
- Wholesalers and distributors must distribute BLENREP only to certified healthcare settings.
- The training for health care providers includes the following educational materials: Program Overview, Education Program for Prescribers and Knowledge Assessment.

GSK will be responsible for oversight of the REMS and ensuring compliance with the REMS through regular audits. Additionally, routine pharmacovigilance activities will be enhanced with the use of a targeted follow-up form for reports of visual disturbances arising from post-marketing use of BLENREP

Lastly, GSK has prepared a supplemental educational program for eyecare professionals across the US. A dedicated team of specialists will focus exclusively on educating eyecare professionals, including both ophthalmologists and optometrists. Education will center on accurate grading of ocular events and the importance of promptly sharing eye exam results with hematologists/oncologists to support safe and effective use of BLENREP. GSK is partnering with at least one eye care health professional society to host live educational events, and on-demand educational content will be developed and made available through a trusted peer-to-peer platform. GSK also plans to support healthcare professionals and patients with eye care professionals who have been trained on BLENREP. There will also be on demand access to patient services representatives who can help with appropriate training of patients and eyecare professional inquiries.

9 BENEFIT-RISK CONCLUSIONS

With the results of the MAIA, CEPHEUS, IMROZ and PERSEUS studies in the recent years, (Mikhael 2019, Dimopoulos 2021, Moreau 2021, NCCN 2024), triplet and quadruplet regimens incorporating PIs, IMiDs, and anti-CD38 antibodies are emerging as SoC for patients with newly diagnosed MM. The widespread use of lenalidomide and anti-CD38 antibodies in newly diagnosed MM has increased the incidence of disease refractory to these agents at first relapse. As patients are increasingly exposed to lenalidomide and daratumumab in the frontline setting, there is an increasing unmet medical need for alternative treatment options with novel mechanisms of action in patients with RRMM.

Overall, the benefit-risk profile of BLENREP is strongly favorable. The registrational studies, DREAMM-7 and DREAMM-8, demonstrated clinically meaningful improvements in PFS and OS (i.e., statistically significant improvement in PFS, including 2 year increase in median PFS, in both studies; statistically significant improvement in OS in DREAMM-7). Both studies also demonstrated a benefit in secondary endpoints (ORR, MRD negativity, and DoR) corroborating the overall benefit conferred by BLENREP. The PFS improvement was observed across all subgroups, including in the participants refractory to lenalidomide, participants who are refractory to anti-CD38 treatments, and in those with high-risk cytogenetics and EMD, providing a fundamental improvement versus the respective comparator arms.

The safety profile is manageable, and ocular events were generally reversible when managed with dose reductions or dose delays enabling participants to continue treatment. Across both studies, ocular events were the most commonly reported safety events in the BLENREP groups. Ocular events led to drug discontinuation in 10% and 11% of participants the in the DREAMM-7 and DREAMM-8 studies. The efficacy of BVd and BPd was maintained in participants with dose modifications and importantly, QoL assessments showed no significant detrimental impact in the BLENREP arms vs. the comparator arms. The proposed REMS with ETASU ensures that BLENREP is prescribed by physicians and dispensed to patients who are educated about the risk of ocular events and the need for monitoring via ophthalmic examinations and is considered appropriate to manage the ocular safety risk associated with BLENREP.

Further, BLENREP provides significant improvement over existing anti-BCMA therapies. BLENREP is easily administered without the need for hospitalization or prophylactic use of IVIG. BLENREP has a short 30-minute outpatient infusion with convenient dosing schedules, enabling patients to maintain their quality of life and daily activities. BLENREP is also the only anti-BCMA therapy not requiring systemic premedication or post-infusion monitoring for CRS. Further, BLENREP has been shown not to impact the levels of sBCMA at the time of progression or the binding of the BCMA target, supporting the potential for utilizing BLENREP ahead of other anti-BCMA therapies in MM without loss of efficacy. Further, BLENREP has been shown not to impact the levels of sBCMA at the time of progression or the binding of the BCMA target. In addition, treatment with

BLENREP is not associated with T cell exhaustion supporting the potential for utilizing BLENREP ahead of other anti-BCMA therapies in MM without loss of efficacy

Considering the robust efficacy with BLENREP in the registrational DREAMM-7 and DREAMM-8 studies, and the safety profile of participants in those studies, GSK considers BVd and BPd to have a favorable benefit-risk profile and represents a critical addition to the treatment options for patients with RRMM.

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11 APPENDICES

11.1 Clinical Studies of BLENREP Relevant for this Application

The table below summarizes the study design, objectives, population, and status for the clinical studies discussed in this briefing document.

Appendix Table 1 Key Clinical Studies of BLENREP as Monotherapy and in Combination

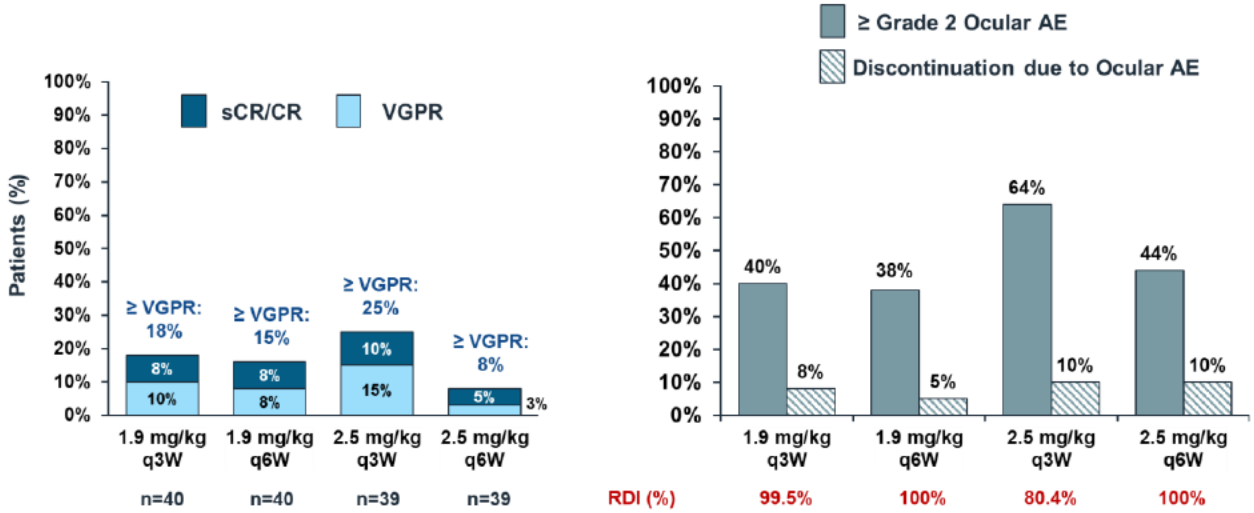
Study/ Phase	Design and Objectives	Study Population	Study Arms and Participants (ITT/Safety Analysis Set)	Study Status
Registrational Studies on Triplet Combination Therapy				
DREAMM-7 Phase 3 (Section 6.2)	Multicenter, randomized, open -label Efficacy, safety, and tolerability	Participants had to have at least 1 prior line of MM therapy	Total: 494/488 Study Arm A (**BVd**): 243/242 Study Arm B (**DVd**): 251/246	Ongoing Primary analysis cut-off date: 02 October 2023 OS update: 07 October 2024
DREAMM-8 Phase 3 (Section 6.3)	Multicenter, randomized, open -label Efficacy and safety	Participants had to have at least 1 prior line of MM therapy including lenalidomide	Total: 302/295 Study Arm A (**BPd**): 155/150 Study Arm B (**PVd**): 147/145	Ongoing Primary analysis cut-off date: 29 January 2024)
Supportive Studies on Triplet Combination Therapy				
DREAMM-6 Phase 1/2[a] (Section 6.4)	Non-randomized, open -label, dose escalation and expansion Safety, tolerability, and clinical activity	Participants had to have at least 1 prior line of MM therapy	Study Arm B (**BVd**): 107[b] 1.9 mg/kg Q6W Stretch: 12 1.9 mg/kg Q3W Single: 12 2.5 mg/kg Q6W Step down Stretch: 12 2.5 mg/kg Q6W Stretch: 12 2.5 mg/kg Q3W Split: 13 2.5 mg/kg Q3W Single: 18 3.4 mg/kg Q3W Split: 12 3.4 mg/kg Q3W Single: 16	Ongoing [c] Final analysis cut-off date: 28 February 2023
ALGONQUIN Investigator Supportive Study; Phase 1/2[a] (Section 6.5)	Multicenter, open -label, dose escalation and expansion RP2D, safety and efficacy	Participants had to have at least 1 prior line of MM therapy	Single arm, multiple dosing cohorts (**BPd**): 87/87 participants (All Treated Population) • Part 1 dose-exploration phase: 61/87 participants • Part 2 dose-expansion phase: 26/87 participants (BPd 2.5 mg/kg Q8W) • RP2D treatment: 38/87 participants (12 in Part 1 and 26 in Part 2)	Ongoing

Study/ Phase	Design and Objectives	Study Population	Study Arms and Participants (ITT/Safety Analysis Set)	Study Status
Supportive Studies on Monotherapy				
DREAMM-14 Phase 2[d] (Section 6.6)	Randomized, Open Label Safety, efficacy, and PK	Participants had to have at least 3 prior lines of MM therapy	Total: 177/175 • Arm A (Control; 2.5 mg/kg Q3W): 40/39 • Arm B (1.9 mg/kg Q3W): 40/40 • Arm C (2.5 or 1.9 mg/kg Q6W): 40/39 • Arm D (1.9 mg/kg Q6W): 40/40 • Arm E (1.9 mg/kg Q6W): not relevant for this submission	Ongoing

AutoSCT = autologous stem cell transplant; BLA = Biologics License Application; BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib and dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone; IA = interim analysis ;OS = overall survival; PK = pharmacokinetic; Pd = pomalidomide and dexamethasone; PVd = pomalidomide, bortezomib, and dexamethasone
a Study arms relevant to this submission are presented.
b All Treated Population.
c DREAMM-6 final analysis has been completed, and the final CSR was published in January 2024. The clinical study is ongoing to provide participants with continued access to study treatment post final analysis.
d Included in PK analyses.

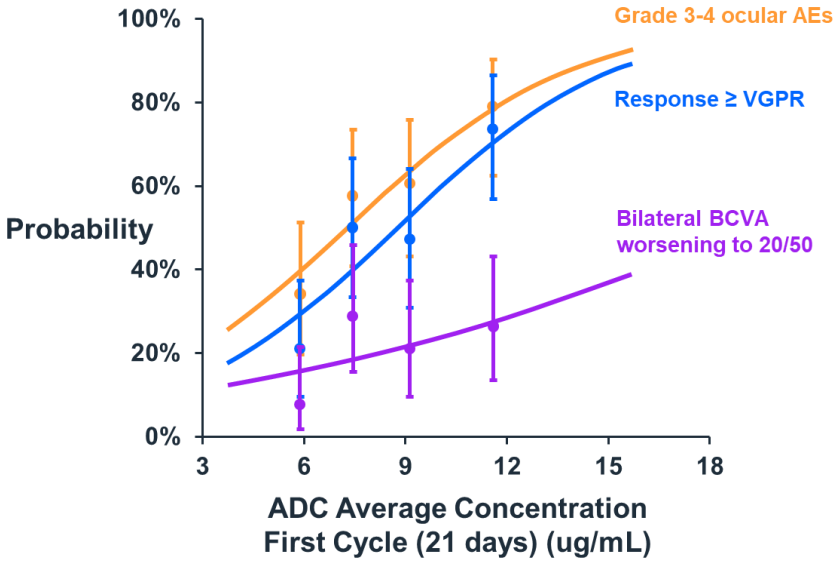
11.2 DREAMM-6, DREAMM-7, DREAMM-8, DREAMM-14 Supplemental Figures - Dose Rationale

Appendix Figure 1 DREAMM-14: Efficacy vs. Tolerability Across Dose and Dose Schedules



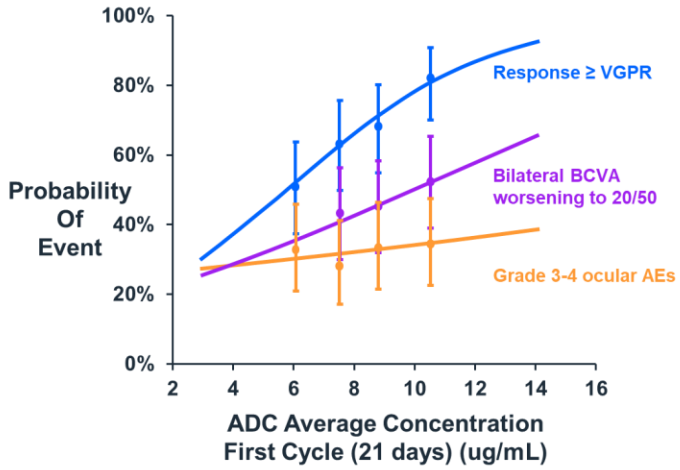
AE = adverse event; CR = complete response; q#W = every # of weeks; sCR = stringent complete response; VGPR = very good partial response
Note: This study investigated different BLENREP monotherapy doses/schedules in 4L+ RRMM; Due to the short treatment exposure period, the RDIs in this study are higher compared to the RDI values from the BLENREP combination therapy studies in 2L+ RRMM. RRMM.

Appendix Figure 2 DREAMM-6: Integrated Exposure-Response Relationship



ADC = antibody-drug conjugate (i.e., BLENREP); BCVA = best corrected visual acuity; VGPR = very good partial response
Note: The independent variable was divided into quartiles. Points and error bars represent the observed proportions and 95% CIs for each quartile (plotted at the median exposure within each quartile), respectively. The curves represent the prediction of the univariate logistic regression model.

Appendix Figure 3 DREAMM-7: Integrated Exposure-Response Relationship

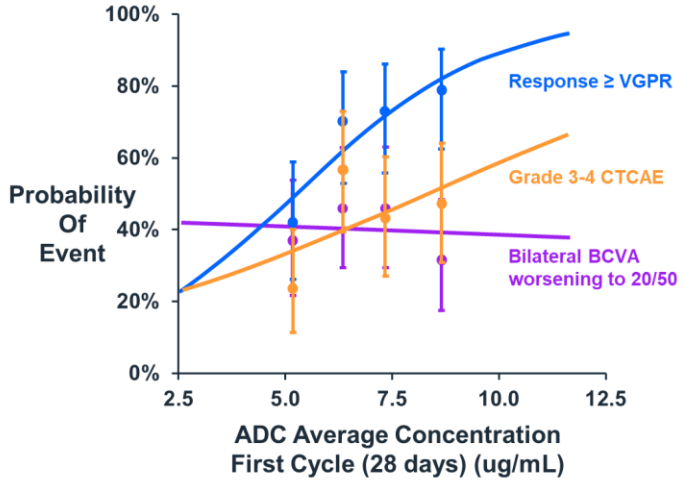


Multivariate Model Prediction
include effect of disease factors

Probability, %	1.9 mg/kg	2.5 mg/kg
VGPR+ response	53	68
CR+ response*	35	35
Gr 3+ Ocular AEs*	32	32
Bilateral worsening to 20/50 or worse*	38	38

ADC = antibody-drug conjugate (i.e., BLENREP); BCVA = best corrected visual acuity; CR = complete response; VGPR = very good partial response
Note: The independent variable was divided into quartiles. Points and error bars represent the observed proportions and 95% CIs for each quartile (plotted at the median exposure within each quartile), respectively. The curves represent the prediction of the univariate logistic regression model. Multivariate model predictions were obtained based on average exposure value of 7.83 ug/mL for 2.5 mg/kg and 5.95 ug/mL for 1.9 mg/kg using linear proportion assumption.

Appendix Figure 4 DREAMM-8: Integrated Exposure-Response Relationship

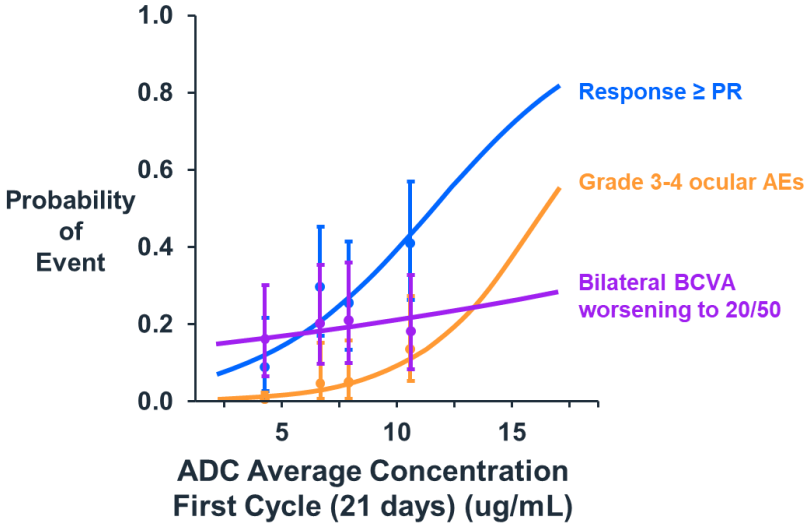


Multivariate Model Prediction
include effect of disease factors

Probability, %	1.9 mg/kg	2.5 mg/kg
VGPR+ response	75	80
CR+ response	23	45
Gr 3+ Ocular AEs	43	43
Bilateral worsening to 20/50 or worse	36	36

ADC = antibody-drug conjugate (i.e., BLENREP); BCVA = best corrected visual acuity; VGPR = very good partial response
Note: The independent variable was divided into quartiles. Points and error bars represent the observed proportions and 95% CIs for each quartile (plotted at the median exposure within each quartile), respectively. The curves represent the prediction of the univariate logistic regression model. Multivariate model predictions were obtained based on average exposure value of 6.7 ug/mL for 2.5 mg/kg and 5.09 ug/mL for 1.9 mg/kg, using linear proportion assumption.

Appendix Figure 5 DREAMM-14: Integrated Exposure-Response Relationship



ADC = antibody-drug conjugate (i.e., BLENREP); BCVA = best corrected visual acuity; PR = partial response
Note: The independent variable was divided into quartiles. Points and error bars represent the observed proportions and 95% CIs for each quartile (plotted at the median exposure within each quartile), respectively. The curves represent the prediction of the univariate logistic regression model.

11.3 DREAMM-7 and DREAMM-8 Supplemental Participant and Efficacy Information

11.3.1 Study Endpoints

DREAMM-7	DREAMM-8
Primary Endpoint The primary endpoint for DREAMM-7 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.	**Primary Endpoint** The primary endpoint for DREAMM-8 was PFS, defined as the time from randomization until the earliest date of documented disease progression based on IRC-assessment per IMWG criteria, or death due to any cause.
Key Secondary Endpoints Key secondary endpoints evaluated in DREAMM-7 included: • Overall Survival (OS): defined as the time from the date of randomization until the date of death due to any cause • Duration of Response: defined as the time from first documented evidence of PR or better until progressive disease (PD) or death due to any cause. • Minimal Residual Disease Negativity Rate: defined as the percentage of participants who are MRD negative by next-generation sequencing (NGS) at 10-5 threshold at least once during the time of confirmed CR or better. All categories of disease response - sCR, CR, VGPR, MR, PR, SD, and PD – used in the calculation of study endpoints were determined by an IRC using IMWG 2016 criteria.	**Key Secondary Endpoints** Key secondary endpoints included: • Overall Survival: defined as the time from the randomization until the date of death due to any cause • Duration of Response: defined as the time from first documented evidence of PR or better until PD or death due to any cause. Response will be based on IRC-assessment per IMWG criteria. Minimal Residual Disease Negativity Rate: defined as the percentage of participants who achieve MRD 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.
Other Secondary Endpoints Secondary endpoints to further assess the efficacy of BLENREP in combination with Bd include: • Objective Response Rate (ORR): defined as the percentage of participants with a confirmed PR or better (i.e. PR, VGPR, CR, sCR) • Complete Response Rate (CRR): defined as the percentage of participants with a confirmed CR or better (i.e., CR, sCR) • Clinical Benefit Rate (CBR): defined as the percentage of participants with a confirmed MR or better per IMWG • Time to Response: defined as the time between the date of randomization and the first documented evidence of response (PR or better) among participants who achieve confirmed PR or better	**Other Secondary Endpoints** Secondary endpoints to further assess the efficacy of BLENREP in combination with Pd include: • Complete Response Rate: defined as the percentage of participants with a confirmed CR or better (i.e., CR, sCR).based on IRC-assessment per IMWG • Very Good Partial Response or Better: defined as the percentage of participants with a confirmed VGPR or better (i.e., VGPR, CR, sCR).based on IRC-assessment per IMWG • Objective Response Rate: defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR, sCR) based on IRC-assessment per IMWG criteria • Time to Response: defined as the time between the date of randomization and the first documented evidence of response (PR or better) among participants who achieve a

DREAMM-7	DREAMM-8
• Progression Free Survival 2 (PFS2): defined as time from randomization to disease progression after initiation of new anti-myeloma therapy or death from any cause, whichever is earlier. If disease progression after new anti-myeloma therapy could not be measured, a PFS event is defined as the date of discontinuation of new anti-myeloma therapy, or death from any cause, whichever is earlier • Quality of Life (QoL): Change from baseline in health-related (HR) QoL as measured by EORTC QLQ-C30 and EORTC IL52 (disease symptoms domain from the EORTC QLQ-MY20)	response (confirmed PR or better) based on IRC-assessment per IMWG criteria • Progression Free Survival 2: defined as time from randomization to disease progression (investigator assessed response) after initiation of new anti-myeloma therapy or death from any cause, whichever is earlier. If disease progression after new anti-myeloma therapy could not be measured, a PFS event is defined as the date of discontinuation of new anti-myeloma therapy, or death from any cause, whichever is earlier • Quality of Life: Change from baseline in health-directed quality of life as measured by EORTC QLQ-C30, EORTC QLQ-MY20, and EORTC IL52 (EORTC IL52 applies to participants enrolled under the original Protocol; EORTC QLQ-MY20 applies to participants enrolled under Protocol Amendment 1).

11.3.2 Prior and Subsequent Lines of Therapy

Appendix Table 2 DREAMM-7 and DREAMM-8: Prior Lines of Therapy (Intent to Treat Population)

	DREAMM-7		DREAMM-8	
	BVd (N=243)	**DVd (N=251)**	**BPd (N=155)**	**PVd (N=147)**
Prior lines of therapy completed prior to screening, n (%)				
Mean (SD)	2.0 (1.29)	1.9 (1.25)	1.9 (1.22)	2.0 (1.44)
Median (min, max)	1.0 (1, 7)	2.0 (1, 7)	1.0 (1, 6)	1.0 (1, 9)
1 line	125 (51%)	125 (50%)	82 (53%)	77 (52%)
2 line	54 (22%)	63 (25%)	32 (21%)	33 (22%)
3 line	34 (14%)	36 (14%)	22 (14%)	15 (10%)
≥4 lines	30 (12%)	27 (11%)	19 (12%)	22 (15%)
Prior Proteasome Inhibitor	218 (90%)	216 (86%)	140 (90%)	136 (93%)
Refractory to PI	22 (9%)	24 (10%)	40 (26%)	35 (24%)
Bortezomib	210 (86%)	211 (84%)	134 (86%)	130 (88%)
Refractory to bortezomib	4 (2%)	0	16 (10%)	8 (5%)
Carfilzomib	31 (13%)	35 (14%)	34 (22%)	37 (25%)
Refractory to carfilzomib	12 (5%)	17 (7%)	18 (12%)	23 (16%)
Ixazomib	13 (5%)	11 (4%)	11 (7%)	15 (10%)
Refractory to ixazomib	7 (3%)	8 (3%)	8 (5%)	11 (7%)
Prior Immunomodulatory Agent (IMiD)	198 (81%)	216 (86%)	155 (100%)	147 (100%)
Refractory to IMiDs	94 (39%)	104 (41%)	127 (82%)	111 (76%)
Thalidomide	121 (50%)	144 (57%)	49 (32%)	48 (33%)
Refractory to thalidomide	16 (7%)	22 (9%)	9 (6%)	6 (4%)

	DREAMM-7		DREAMM-8	
	BVd (N=243)	**DVd (N=251)**	**BPd (N=155)**	**PVd (N=147)**
Lenalidomide	127 (52%)	130 (52%)	155 (100%)	147 (100%)
Refractory to lenalidomide	79 (33%)	87 (35%)	125 (81%)	111 (76%)
Pomalidomide	25 (10%)	19 (8%)	-	1 (<1%)
Refractory to pomalidomide	17 (7%)	12 (5%)	-	-
Prior anti-CD38	-	-	38 (25%)	42 (29%)
Daratumumab	3 (1%)	4 (2%)	36 (23%)	39 (27%)
Refractory to daratumumab	-	-	33 (21%)	34 (23%)
Isatuximab	-	-	2 (1%)	3 (2%)
Refractory to Isatuximab	-	-	2 (1%)	2 (1%)
Prior AutoSCT	164 (67%)	173 (69%)	99 (64%)	82 (56%)

AutoSCT = autologous stem cell transplant; BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib and dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone; IMiD = immunomodulatory agent; PI = proteasome inhibitor; SD = standard deviation; PVd = pomalidomide, bortezomib, dexamethasone

Appendix Table 3 DREAMM-7 and DREAMM-8: Subsequent Lines of Therapy

	DREAMM-7		DREAMM-8	
Subsequent antimyeloma therapy n (%)[b]	**BVd (N=243)**	**DVd (N=251)**	**BPd (N=155)**	**PVd (N=147)**
Any subsequent anti-myeloma therapy	**87 (36%)**	**130 (52%)**	**47 (30%)**	**85 (58%)**
Steroids	77 (32%)	107 (43%)	40 (26%)	66 (45%)
Anti-CD38 antibodies	61 (25%)	14 (6%)	24 (15%)	58 (39%)
Proteasome inhibitor Carfilzomib	46 (19%) 26 (11%)	80 (32%) 54 (22%)	28 (18%) 16 (10%)	39 (27%) 25 (17%)
Immunomodulator Pomalidomide	60 (25%) 41 (17%)	92 (37%) 47 (19%)	17 (11%) -	35 (24%) -
BCMA-targeting therapy [b]	9 (4%)	34 (14%)	6 (4%)	24 (17%)
Non-BCMA BiTEs [c]	5 (2%)	5 (2%)	6 (4%)	12 (8%)
Transplant	3 (1%)	2 (<1%)	2 (1%)	5 (3%)
T/NK cell therapy	1 (<1%)	3 (1%)	0	1 (<1%)

a Two participants in the ITT population were randomized, not treated, rescreened, and rerandomized. They are counted as 4 unique participants in this output. [b] Since multiple categories per participant are possible, the total percentage may be >100%.

b BCMA targeting therapy included BLENREP (BVd, n=2; DVd, n=22) (BPd, n=0; PVd, n=10), teclistamab (BVd, n=6; DVd, n=5) (BPd, n=5; PVd, n=7), TNB 383B (BVd, n=0; DVd, n=5), elranatamab (BVd, n=1; DVd, n=1) (BPd, n=1; PVd, n=3), HPN217 (BVd, n=0; DVd, n=1), EMB-06 (BPd, n=0; PVd, n=1), and linvoseltamab (BVd, n=0; DVd, n=1) (BPd, n=0; PVd, n=3).

c Bispecific antibodies that have other targets include talquetamab (BVd, n=1; DVd, n=2) (BPd, n=3; PVd, n=3), cevostamab (BVd, n=3; DVd, n=0) (BPd, n=2; PVd, n=3), investigational antineoplastic agent (BVd, n=0; DVd, n=2), and forimtamig (BVd, n=0; DVd, n=1) (BPd, n=1; PVd, n=2).

As of 07-Oct-2024 DCO

11.3.3 Efficacy Results

Appendix Table 4 DREAMM-7 and DREAMM-8: Progression-Free Survival Based on Independent Reviewer-Assessed Response (Intent to Treat Population)

	DREAMM-7		DREAMM-8 DCO: 29 January 2024		DREAMM-8 Post-hoc analysis (DCO 07 October 2024)	
	BVd (N=243)	DVd (N=251)	BPd (N=155)	PVd (N=147)	BPd (N=155)	PVd (N=147)
Number of participants, n (%)						
Progressed or died (event)	91 (37%)	158 (63%)	62 (40%)	80 (54%)	68 (44%)	89 (61%)
Disease progression	67 (28%)	139 (55%)	46 (30%)	66 (45%)	51 (33%)	74 (50%)
Death	24 (10%)	19 (8%)	16 (10%)	14 (10%)	17 (11%)	15 (10%)
Censored, follow-up ended	44 (18%)	41 (16%)	25 (16%)	34 (23%)	28 (18%)	37 (25%)
Censored, follow-up ongoing	108 (44%)	52 (21%)	68 (44%)	33 (22%)	59 (38%)	21 (14%)
Estimates for time variable (months)						
Q1 (95% CI)	14.5 (9.5, 17.5)	6.4 (4.9, 7.0)	10.3 (5.6, 14.0)	5.5 (3.7, 6.5)	10.3 (5.6, 14.0)	5.5 (3.7, 6.5)
Median (95% CI)	36.6 (28.4, -)	13.4 (11.1, 17.5)	- (20.6, -)	12.7 (9.1, 18.5)	32.6 (21.1, -)	12.5 (9.1, 17.6)
Q3 (95% CI)	- (-, -)	33.1 (26.3, -)	- (-, -)	- (20.3, -)	- (-, -)	29.5 (21.2, -)
Hazard ratio [a] (95% CI)	0.41 (0.31, 0.53)		0.52 (0.37, 0.73)		0.49 (0.35,0.68)	
Stratified log-rank [b] P-value	<0.00001		<0.001		NR	
Progression-free survival rate						
Time-to-event endpoint at 6 months (95% CI)	0.88 (0.83, 0.91)	0.77 (0.71, 0.82)	0.82 (0.75, 0.87)	0.72 (0.64, 0.79)	0.82 (0.75, 0.87)	0.72 (0.64, 0.79)
Time-to-event endpoint at 12 months (95% CI)	0.78 (0.72, 0.83)	0.53 (0.47, 0.60)	0.71 (0.63, 0.78)	0.51 (0.42, 0.60)	0.71 (0.63, 0.78)	0.51 (0.41, 0.59)
Time-to-event endpoint at 18 months (95% CI)	0.69 (0.62, 0.75)	0.43 (0.36, 0.49)	0.62 (0.54, 0.70)	0.43 (0.34, 0.52)	0.63 (0.54, 0.70)	0.41 (0.32, 0.50)

BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib and dexamethasone; CI = confidence interval; DVd = daratumumab, bortezomib, and dexamethasone; PVd = pomalidomide, bortezomib, dexamethasone; Q1 = first quartile; Q3 = third quartile

a Hazard ratios were estimated using a Cox Proportional Hazards model

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

Appendix Table 5 DREAMM-7 and DREAMM-8: Summary of Overall Survival (ITT Population)

	DREAMM-7 Interim Analysis 1 DCO: 03 Oct 2023		DREAMM-7 Interim Analysis 2 DCO: 07 Oct 2024		DREAMM-8	
	BVd (N=243)	DVd (N=251)	BVd (N=243)	DVd (N=251)	BPd (N=155)	PVd (N=147)
Number of participants, n (%)						
Died (event)	54 (22%)	87 (35%)	68 (28%)	103 (41%)	49 (32%)	56 (38%)
Censored, follow-up ended	20 (8%)	28 (11%)	26 (11%)	33 (13%)	12 (8%)	7 (5%)
Alive date obtained	6 (2%)	12 (5%)	12 (5%)	16 (6%)	-	-
No alive date obtained	14 (6%)	16 (6%)	14 (6%)	17 (7%)	-	-
Censored, follow-up ongoing	169 (70%)	136 (54%)	149 (61%)	115 (46%)	94 (61%)	84 (57%)
Estimates for time variable (months)[a]						
Q1 (95% CI)	33.9 (21.9, -)	15.2 (12.3, 21.1)	33.9 (21.9,44.5)	15.2 (12.3,21.1)	19.0 (12.2, 23.3)	12.7 (8.0, 18.5)
Median (95% CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR (41.0, NR)	NR (33.0, NR)	NR (25.2, NR)
Q3 (95% CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)	NR(NR, NR)	NR (NR, NR)	NR (NR, NR)
Hazard ratio [b] (95% CI)	0.57 (0.40, 0.80)		0.58 (0.43,0.79)		0.77 (0.53, 1.14)	
Stratified log-rank [c] p-value	0.00049		0.00023		0.095	
Overall Survival rate						
Time-to-event endpoint at 6 months (95% CI)	0.91 (0.87,0.94)	0.89 (0.84,0.92)			0.93 (0.88, 0.96)	0.88 (0.81, 0.92)
Time-to-event endpoint at 12 months (95% CI)	0.87 (0.81,0.90)	0.81 (0.75,0.85)			0.83 (0.76, 0.88)	0.76 (0.68, 0.82)
Time-to-event endpoint at 18 months (95% CI)	0.81 (0.75,0.85)	0.73 (0.67,0.78)			0.76 (0.69, 0.82)	0.69 (0.61, 0.76)
Time-to-event endpoint at 24 months (95% CI)	0.79 (0.73,0.84)	0.67 (0.61,0.73)				
Time-to-event endpoint at 36 months (95% CI)			0.74 (0.68,0.79)	0.60 (0.54,0.66)		

BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib and dexamethasone; CI = confidence interval; DVd =daratumumab, bortezomib, and dexamethasone; NR = not reported; PVd = pomalidomide, ortezomib, dexamethasone; Q1 = first quartile; Q3 = third quartile

a CIs were estimated using the Brookmeyer Crowley method.
b HRs were estimated using a Cox Proportional Hazards
c P-value from 1-sided stratified log-rank test

Appendix Table 6 DREAMM-7 and DREAMM-8: Duration of Response Based on Independent Reviewer-Assessed Response (Intent to Treat Population)

	DREAMM-7		DREAMM-8	
	BVd (N=243)	DVd (N=251)	BPd (N=155)	PVd (N=147)
n	201	179	120	106
Progressed or died (event)	68 (34%)	105 (59%)	39 (33%)	49 (46%)
Disease Progression	55 (27%)	97 (54%)	30 (25%)	43 (41%)
Death	13 (6%)	8 (4%)	9 (8%)	6 (6%)
Censored, follow-up ended	27 (13%)	22 (12%)	15 (13%)	24 (23%)
Censored, follow-up ongoing	106 (53%)	52 (29%)	66 (55%)	33 (31%)
Q1 (95% CI)	18.8 (13.2, 23.5)	9.0 (6.4, 10.4)	15.7 (10.3, 19.6)	5.6 (4.5, 8.2)
Median (95% CI)	35.6 (30.5, -)	17.8 (13.8, 23.6)	NR (24.9, NR)	17.5 (12.1, 26.4)
Q3 (95% CI)	- (35.6, -)	33.9 (30.4, -)	NR (NR , NR)	NR (26.4, NR)
Time-to-event endpoint at 6 months (95% CI)	0.93 (0.88,0.96)	0.85 (0.78,0.89)	0.91 (0.85, 0.95)	0.75 (0.65, 0.82)
Time-to-event endpoint at 12 months (95% CI)	0.83 (0.77,0.88)	0.61 (0.53,0.68)	0.79 (0.71, 0.86)	0.61 (0.50, 0.70)
Time-to-event endpoint at 18 months (95% CI)	0.76 (0.69,0.81)	0.49 (0.41,0.56)	0.72 (0.62, 0.79)	0.38, 0.60)

BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib and dexamethasone; CI = confidence interval; DVd =daratumumab, bortezomib, and dexamethasone; PVd = pomalidomide, ortezomib, dexamethasone; Q1 = first quartile; Q3 = third quartile

a CIs for time variables were estimated using the Brookmeyer Crowley method.

Note: In DREAMM-7, there were 2 participants in the ITT Population who were randomized, not treated, re-screened, and re-randomized. They were counted as 4 unique participants in this table.

Appendix Table 7 DREAMM-7 and DREAMM-8: Summary of Independent Reviewer-Assessed Best Response with Confirmation (IMWG Criteria) and MRD Negativity (ITT Population

	DREAMM-7		DREAMM-8	
	BVd (N=243)	DVd (N=251)	BPd (N=155)	PVd (N=147)
ORR, n (%)a				
sCR+CR+VGPR+PR	201 (82.7%)	179 (71.3%)	120 (77%)	106 (72%)
95% CI [b]	(77.4%, 87.3%)	(65.3%, 76.8%)	(70.0%, 83.7%)	(64.1%, 79.2%)
Difference in ORR (95% CI)	11.4% (3.1%, 18.8%)		5% (-6.0%, 16.5%)	
Best response, n(%)[a]				
sCR	34 (14.0%)	13 (5.2%)	14 (9%)	4 (3%)
CR	50 (20.6%)	30 (12.0%)	48 (31%)	20 (14%)
VGPR	76 (31.3%)	73 (29.1%)	37 (24%)	32 (22%)
PR	41 (16.9%)	63 (25.1%)	21 (14%)	50 (34%)

	DREAMM-7		DREAMM-8	
	BVd (N=243)	**DVd (N=251)**	**BPd (N=155)**	**PVd (N=147)**
VGPR+ rate, n (%)[a]				
sCR+CR+VGPR	160 (65.8%)	116 (46.2%)	99 (64%)	56 (38%)
95% CI [b]	(59.5%, 71.8%)	(39.9%, 52.6%)	(55.8%, 71.4%)	(30.2%, 46.5%)
Difference in VGPR+ (95% CI for difference)	19.6% (10.5%, 28.2%)		26% (14.6%, 36.5%)	
Complete response rate, n (%)[a]				
sCR+CR	84 (34.6%)	43 (17.1%)	62 (40%)	24 (16%)
95% CI [b]	(28.6%, 40.9%)	(12.7%, 22.4%)	(32.2%, 48.2%)	(10.7%, 23.3%)
Difference in CRR (95% CI)	17.4% (9.5%, 25.1%)		24% (12.5%, 34.4%)	
MRD negativity rate [a b]	**60 (24.7%)**	**24 (9.6%)**	37 (23.9%)	7 (4.8%)
95% CI [b]	(19.4%, 30.6%)	(6.2%, 13.9%)	(17.4%, 31.4%)	(1.9%, 9.6%)

BVd = BLENREP, bortezomib, dexamethasone; BPd = BLENREP, pomalidomide, dexamethasone; CI = confidence internal; CR = complete response; DVd = daratumumab, bortezomib, and dexamethasone; IMWG = International Myeloma Working Group; MRD = minimal residual disease; PVd = pomalidomide, bortezomib, dexamethasone;;sCR = stringent CR; VGPR = very good partial response

a Participants without MRD assessment were assumed to be non-negative.

b MRD negativity rate was defined as the percentage of participants who were MRD negative by NGS based on a sensitivity of 10^{-5}.

11.4 DREAMM-7 and DREAMM-8 Supplemental Safety Information

11.4.1 Study Disposition

Appendix Table 8 Participant Disposition and Treatment Status

	DREAMM-7		DREAMM-8	
	BVd N = 243	**DVd N = 251**	**BPd N = 155**	**PVd N = 147**
Participant Disposition				
Died	50 (21%)	77 (31%)	48 (31%)	54 (37%)
Ongoing	169 (70%)	135 (54%)	94 (61%)	84 (57%)
On study treatment [a]	81 (33%)	51 (20%)	65 (42%)	33 (22%)
In follow-up	88 (36%)	84 (33%)	29 (19%)	51 (35%)
Withdrawn from study	24 (10%)	39 (16%)	13 (8%)	9 (6%)
Primary reason for study withdrawal [b]				
Lost to Follow-up	1 (<1%)	3 (1%)	0	1 (<1%)
Physician Decision	4 (2%)	10 (4%)	1 (<1%)	0
Protocol Deviation	0	0	1 (<1%)	0
Withdrawal by Participant	19 (8%)	26 (10%)	11 (7%)	8 (5%)
Treatment Status				
Ongoing	81 (33%)	51 (20%)	56 (36%)	31 (21%)
Discontinued	161 (66%)	195 (78%)	99 (64%)	116 (79%)
Primary Reason for BLENREP or Daratumumab/Bortezomib Discontinuation [c,d]				
Progressive Disease	59 (24%)	148 (59%)	44 (28%)	71 (48%)
Adverse Event	45 (19%)	22 (9%)	25 (16%)	23 (16%)
Physician Decision	33 (14%)	10 (4%)	19 (12%)	14 (10%)
Ocular	NR	NR	3 (2%)	0
Withdrawal by Participant	22 (9%)	13 (5%)	10 (6%)	8 (5%)
Ocular	NR	NR	4 (3%)	0

BVd = BLENREP, bortezomib, dexamethasone; BPd = BLENREP, pomalidomide, dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone; NR = not reported; PVd = pomalidomide, bortezomib, dexamethasone

a Any study treatment component.

b Participants may have only one primary reason for study withdrawal.

c Treatment status for Daratumumab is reported for the DREAMM-7 comparator arm and Bortezomib for the DREAMM-8 comparator arm.

d Participants may have only one primary reason for treatment discontinuation. Only primary reasons reported for more than 1 participant in the treatment arm are summarized in this table.

Note: Based on primary analysis DCO for each study.

11.4.2 Common Adverse Events

Appendix Table 9: DREAMM-7 and DREAMM-8: Common Adverse Events by Preferred Term (≥20%[a])

Preferred Term	DREAMM-7		DREAMM-8	
	BVd N = 242	DVd N = 246	BPd N = 150	PVd N = 145
Any Event	**242 (100%)**	**246 (100%)**	**149 (>99%)**	**140 (97%)**
Eye Disorders	**195 (81%)**	**97 (39%)**	**136 (91%)**	**57 (39%)**
Vision blurred	165 (68%)	27 (11%)	120 (80%)	23 (16%)
Dry eye	129 (53%)	19 (8%)	92 (61%)	14 (10%)
Photophobia	120 (50%)	6 (2%)	69 (46%)	6 (4%)
Eye irritation	110 (45%)	14 (6%)	77 (51%)	14 (10%)
Foreign body sensation in eyes	111 (46%)	12 (5%)	91 (61%)	11 (8%)
Eye pain	81 (33%)	9 (4%)	49 (33%)	8 (6%)
Cataract	51 (21%)	28 (11%)	42 (28%)	16 (11%)
Visual acuity reduced	13 (5%)	5 (2%)	33 (22%)	8 (6%)
Corneal epithelial microcysts	1 (<1%)	0	34 (23%)	0
Punctate keratitis	2 (<1%)	1 (<1%)	33 (22%)	1 (<1%)
Infections and infestations	**176 (73%)**	**167 (68%)**	**124 (83%)**	**101 (70%)**
COVID-19	63 (26%)	52 (21%)	58 (39%)	33 (23%)
Upper respiratory tract infection	54 (22%)	54 (22%)	42 (28%)	26 (18%)
Pneumonia	48 (20%)	23 (9%)	38 (25%)	18 (12%)
Blood and lymphatic system disorders	**187 (77%)**	**159 (65%)**	**98 (65%)**	**83 (57%)**
Thrombocytopenia	169 (70%)	122 (50%)	54 (36%)	43 (30%)
Anaemia	48 (20%)	65 (26%)	37 (25%)	41 (28%)
Neutropenia	36 (15%)	28 (11%)	76 (51%)	51 (35%)
General disorders and administration site condition	**131 (54%)**	**128 (52%)**	**85 (57%)**	**82 (57%)**
Fatigue	49 (20%)	48 (20%)	42 (28%)	32 (22%)
Investigations	**143 (59%)**	**101 (41%)**	**85 (57%)**	**55 (38%)**
Neutrophil count decreased	9 (4%)	16 (7%)	32 (21%)	20 (14%)
Platelet count decreased	51 (21%)	40 (16%)	30 (20%)	23 (16%)
Alanine aminotransferase increased	48 (20%)	30 (12%)	25 (17%)	13 (9%)

Preferred Term	DREAMM-7		DREAMM-8	
	BVd N = 242	DVd N = 246	BPd N = 150	PVd N = 145
Gastrointestinal disorders	**148 (61%)**	**149 (61%)**	**74 (49%)**	**74 (51%)**
Diarrhoea	80 (33%)	78 (32%)	37 (25%)	34 (23%)
Constipation	49 (20%)	56 (23%)	25 (17%)	35 (24%)
Nervous system disorders	**165 (68%)**	**160 (65%)**	**57 (38%)**	**81 (56%)**
Peripheral sensory neuropathy	61 (25%)	51 (21%)	5 (3%)	16 (11%)
Neuropathy peripheral	50 (21%)	55 (22%)	12 (8%)	35 (24%)

BPd = BLENREP, pomalidomide, dexamethasone; BVd = BLENREP, bortezomib and dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone; PVd = pomalidomide, bortezomib, dexamethasone
a ≥ 20% in at least one of the BLENREP arms
As of 07-Oct-2024 DCO

11.4.3 Adverse Events Leading to Dose Modification

Appendix Table 10: DREAMM-7 and DREAMM-8: Summary of Adverse Events Leading to Dose Reduction of Study Treatment in ≥2% of Participants in Any Treatment Group by Preferred Term (Safety Population)

Preferred Term, n (%)	Treatment	
DREAMM-7	**BVd (N=242)**	**DVd (N=246)**
Any event	181 (75%)	146 (59%)
Exposure-adjusted rate (per 100 person years)	44.990	42.580
Thrombocytopenia	69 (29%)	24 (10%)
Peripheral sensory neuropathy	33 (14%)	31 (13%)
Neuropathy peripheral	24 (10%)	33 (13%)
Platelet count decreased	22 (9%)	8 (3%)
Vision blurred	27 (11%)	2 (<1%)
Insomnia	12 (5%)	13 (5%)
Fatigue	8 (3%)	12 (5%)
Polyneuropathy	9 (4%)	8 (3%)
Neuralgia	8 (3%)	7 (3%)
Hyperglycaemia	4 (2%)	9 (4%)
Diarrhoea	2 (<1%)	8 (3%)
Oedema peripheral	4 (2%)	3 (1%)
Peripheral swelling	0	7 (3%)
Visual impairment	7 (3%)	0
Dry eye	6 (2%)	0
Eye pain	5 (2%)	0
Photophobia	5 (2%)	0
Face oedema	0	4 (2%)

Preferred Term, n (%)	Treatment	
Hypertension	4 (2%)	0
Keratitis	4 (2%)	0
Keratopathy	3 (1%)	0
Weight decreased	4 (2%)	0
DREAMM-8	**BPd (N=150)**	**PVd (N=145)**
Any event	94 (63%)	88 (61%)
Exposure-adjusted rate (per 100 person years)	37.719	57.375
Neutropenia	24 (16%)	7 (5%)
Neutrophil count decreased	15 (10%)	5 (3%)
Fatigue	11 (7%)	10 (7%)
Muscular weakness	11 (7%)	6 (4%)
Insomnia	9 (6%)	7 (5%)
Platelet count decreased	6 (4%)	1 (<1%)
Thrombocytopenia	6 (4%)	9 (6%)
Agitation	5 (3%)	0
Tremor	5 (3%)	0
Asthenia	4 (3%)	8 (6%)
Mood altered	5 (3%)	0
Neuropathy peripheral	4 (3%)	25 (17%)
Oedema peripheral	4 (3%)	4 (3%)
Dyspepsia	3 (2%)	1 (<1%)
Pneumonia	2 1%)	0
Vision blurred	3 (2%)	0
Neuralgia	2 (1%)	6 (4%)
Diarrhoea	2 (1%)	4 (3%)
Polyneuropathy	1 (<1%)	4 (3%)
Peripheral sensory neuropathy	0	10 (7%)
Dizziness	0	3 (2%)

AE = adverse event; BPd = BLENREP, pomalidomide, dexamethasone; and dexamethasone; BVd = BLENREP, bortezomib, dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone; KVA = Keratopathy Visual Acuity; PVd = pomalidomide, bortezomib, dexamethasone

11.4.4 Adverse Events Leading to Fatality

Appendix Table 11: DREAMM-7and DREAMM-8: Summary of Fatal Adverse Events (Safety Population)

	DREAMM-7		DREAMM-8	
Preferred Term, n (%)	**BVd (N=242)**	**DVd (N=246)**	**BPd (N=150)**	**PVd (N=145)**
Any event	**26 (11%)**	**20 (8%)**	**19 (13%)**	**18 (12%)**
Pneumonia	7 (3%)	2 (<1%)	2 (1%)	1 (<1%)
COVID-19	3 (1%)	5 (2%)	2 (1%)	2 (1%)

	DREAMM-7		DREAMM-8	
Preferred Term, n (%)	**BVd (N=242)**	**DVd (N=246)**	**BPd (N=150)**	**PVd (N=145)**
COVID-19 pneumonia	2 (<1%)	5 (2%)	5 (3%)	2 (1%)
Sepsis	3 (1%)	3 (1%)	0	2 (1%)
Respiratory failure	3 (1%)	0	-	-
Septic shock	3 (1%)	0	1 (<1%)	
Acute kidney injury	-	-	1 (<1%)	0
Acute myeloid leukaemia	-	-	0	1 (<1%)
Acute myocardial infarction	1 (<1%)	0	-	-
Acute pulmonary oedema	-	-	0	1 (<1%)
Acute respiratory failure	0	1 (<1%)	-	-
Cardiac arrest	-	-	0	1 (<1%)
Cerebral haemorrhage	1 (<1%)	0	-	-
Cerebrovascular accident	0	1 (<1%)	0	1 (<1%)
Chest pain	-	-	1 (<1%)	0
Colitis	1 (<1%)	0	-	-
Colon cancer metastatic	-	-	0	1 (<1%)
Coronavirus pneumonia	1 (<1%)	0	-	-
Death	-	-	0	3 (2%)
Dyspnoea	1 (<1%)	0	-	-
Encephalitis herpes	-	-	1 (<1%)	0
Fall	0	1 (<1%)	-	-
Febrile neutropenia	1 (<1%)	0		
Gastrointestinal cancer metastatic	-	-	1 (<1%)	0
Gastrointestinal haemorrhage	1 (<1%)	0	-	-
General physical health deterioration	-	-	0	1 (<1%)
Glioblastoma	1 (<1%)	0	-	-
Haemorrhage intracranial	0	1 (<1%)	-	-
Hyperkalaemia	0	1 (<1%)	-	-
Hyperthermia	0	1 (<1%)	-	-
Ischaemic stroke			1 (<1%)	0
Injury	0	1 (<1%)	-	-
Multiple organ dysfunction syndrome	1 (<1%)	0	-	-
Myocardial infarction	-	-	1 (<1%)	0
Pneumonia aspiration	-	-	0	1 (<1%)
Pneumonia influenza	1 (<1%)	0		
Peritonitis	1 (<1%)	0	-	-
Pulmonary embolism			1 (<1%)	0

	DREAMM-7		DREAMM-8	
Preferred Term, n (%)	**BVd (N=242)**	**DVd (N=246)**	**BPd (N=150)**	**PVd (N=145)**
Respiratory tract infection/lower respiratory tract infection	2 (<1%)	0	0	1 (<1%)
Second primary malignancy	-	-	1 (<1%)	0
Subdural haemorrhage	1 (<1%)	0	-	-
Sudden death	-	-	1 (<1%)	0
Thrombosis mesenteric vessel	1 (<1%)	0	-	-
Septic shock	-	-	1 (<1%)	0
Sepsis	-	-	0	2 (1%)

BPd = BLENREP, pomalidomide, dexamethasone; and dexamethasone; BVd = BLENREP, bortezomib, dexamethasone; DVd = daratumumab, bortezomib, and dexamethasone; PVd = pomalidomide, bortezomib, dexamethasone