14 December 2023
EMA/72045/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Blenrep

International non-proprietary name: Belantamab mafodotin

Procedure No. EMEA/H/C/004935/R/0017

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure:	26 Feb 2023	26 Feb 2023	☐
☐	CHMP and PRAC Rapporteurs Joint Assessment Report	28 Mar 2023	29 Mar 2023	☐
☐	CHMP and PRAC members comments	03 Apr 2023	03 Apr 2023	☐
☐	Updated CHMP and PRAC Rapporteurs Joint Assessment Report	05 Apr 2023	05 Apr 2023	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	14 Apr 2023	14 Apr 2023	☐
☐	Request for supplementary information	26 Apr 2023	26 Apr 2023	☐
☐	MAH responses to (RfSI)	30 May 2023	30 May 2023	☐
☐	Re-start	31 May 2023	31 May 2023	
☐	CHMP and PRAC Rapporteurs' joint assessment report	7 Jun 2023	7 Jun 2023	☐
☐	PRAC endorsed relevant sections of the assessment report3	8 Jun 2023	8 Jun 2023	☐
☐	Comments from CHMP	12 Jun 2023	12 Jun 2023	
☐	Updated CHMP and PRAC Rapporteurs Joint Assessment Report	15 Jun 2023	15 Jun 2023	☐
☐	Request for supplementary information	22 Jun 2023	22 Jun 2023	☐
☐	Submission Deadline	14 Aug 2023	14 Aug 2023	☐
☐	Start of procedure	16 Aug 2023	16 Aug 2023	☐
☐	CHMP Rapporteurs Joint Assessment Report	30 Aug 2023	30 Aug 2023	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	31 Aug 2023	31 Aug 2023	☐
☐	CHMP and PRAC members comments	04 Sep 2023	04 Sep 2023	☐
☐	Updated CHMP and PRAC Rapporteurs Joint Assessment Report	07 Sep 2023	11 Sep 2023	☐
☐	Opinion	14 Sep 2023	14 Sep 2023	☐
☐	Submission of the Applicant's grounds for re-examination	27 Oct 2023	27 Oct 2023	☐
☐	Start of the re-examination procedure -	28 Oct 2023	28 Oct 2023	☐
☐	Preliminary re-examination CHMP Rapporteur Assessment Report	17 Nov 2023	17 Nov 2023	☐
☐	Preliminary re-examination CHMP Co-	17 Nov 2023	17 Nov 2023	☐

Status of this report and steps taken for the assessment				
	Rapporteur Assessment Report			
☐	Comments from CHMP	24 Nov 2023	24 Nov 2023	☐
☐	SAG Meeting	01 Dec 2023	01 Dec 2023	☐
☐	Updated re-examination CHMP Rapporteur Assessment Report	05 Dec 2023	05 Dec 2023	☐
☐	Updated re-examination CHMP Co- Rapporteur Assessment Report	06 Dec 2023	06 Dec 2023	☐
☐	Oral Explanation (OE) at CHMP	12 Dec 2023	12 Dec 2023	☐
☒	CHMP re-examination Opinion	14 Dec 2023	14 Dec 2023	☐

Declarations

☒(Non-Clinical/Clinical/Pharmacovigilance) The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report, including in the Product Information, if any.

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

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1. Background information on the annual renewal

The European Commission issued on 25 August 2020, a conditional marketing authorisation (MA) for BLENREP. This implied that, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 5 of Commission Regulation (EC) No 507/2006, the marketing authorisation holder (MAH) has to complete ongoing studies, or to conduct new studies, as listed in Annex II.E of the MA, the so-called Specific Obligations (SOBs). These data form the basis of the renewal of the conditional MA.

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

A conditional MA is valid for one year and may be renewed annually upon request by the MAH. Therefore, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 6(2) of Commission Regulation (EC) No 507/2006, the MAH GlaxoSmithKline (Ireland) Limited, submitted to the Agency on 7 February 2023 an application for renewal of the conditional MA for BLENREP. The expiry date of the MA is 26 August 2023.

The period covered by this annual renewal is from 7 November 2021 to 01 December 2022.

2. Overall conclusions and benefit-risk balance

2.1. Specific Obligations (SOBs)

Compliance of SOB data submitted

During the period covered by this annual renewal data on the SOBs have been submitted that overall are compliant in terms of adherence to deadlines and are compliant in terms of acceptability of data submitted.

As part of this annual renewal the CHMP is of the opinion that the following obligation SOB-clin-003 has been fulfilled:

> "*In order to confirm the efficacy and safety of BLENREP in relapsed/refractory multiple myeloma adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy, the MAH should submit the results of the DREAMM-2 (205678) study investigating the efficacy of belantamab mafodotin in patients with multiple myeloma who had 3 or more prior lines of treatment, are refractory to a proteasome inhibitor and an immunomodulatory agent and have failed an anti-CD38 antibody*".

The primary analysis and additional data updates from SOB-clin-004 were also submitted as part of this annual renewal as the final CSR of the DREAMM-3 (207495) study is due in July 2024.

Updated list of specific obligations (SOBs)

At the time of submission of the dataset covered by this annual renewal period, the following measures were still required to be completed within the stated timeframe at the time of submission of the dataset covered by this annual renewal period, the following measures were still required to be completed within the stated timeframe:

Number	Description	Due date
SOB-clin-004	In order to confirm the efficacy and safety of BLENREP in multiple myeloma adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy, the MAH should submit the results of the DREAMM-3 (207495) study comparing the efficacy of belantamab mafodotin vs. pomalidomide plus low dose dexamethasone (pom/dex) in patients with relapsed/refractory multiple myeloma.	July 2024

Since the last annual reassessment, SOB-clin-003 and SOB-clin-004 were outstanding (see below).

2.1.1. SOB-clin-003: final results of the DREAMM-2 (205678) study

The MAH has provided the final study results of DREAMM-2 (205678); a phase II, open label, randomized, two-arm study to investigate the efficacy and safety of two dose levels (2.5 and 3.4 mg/kg) of Blenrep in participants with multiple myeloma who had 3 or more prior lines of treatment, are refractory to a proteasome inhibitor and an immunomodulatory agent and have failed an anti-CD38 antibody.

The data cut for the final analysis occurred on 04 May 2022 and the final clinical study report was published on 10 October 2022. As of 01 December 2022, 46 months since the Last Subject First Visit (LSFV), there are 3 participants receiving BLENREP (belantamab mafodotin) in the Post-Analysis Continuation of Treatment Phase of the study.

Final analysis consisted of 196 participants with relapsed, refractory multiple myeloma (RRMM) randomized to either belantamab mafodotin (frozen solution) 2.5 mg/kg cohort (n=97) or 3.4 mg/kg cohort (n=99), with a median duration of follow-up of 12.5 months and 13.8 months respectively. In a third independent cohort, 25 participants received a lyophilized presentation of belantamab mafodotin at 3.4 mg/kg dose.

The demonstrated objective response rate (ORR) was 32% in the 2.5 mg/kg cohort with the median Duration of Response (DoR) of 12.5 months.

The median Overall Survival (OS) was 15.3 months (95% CI: 9.9 to 18.9) in the 2.5 mg/kg cohort.

The provided final study results of DREAMM-2 with regard to efficacy are in line with the results provided during the MA evaluation (13-month FU data cut-off date of 31 January 2020). At that time 11% (10/95) of participants in the 2.5 mg/kg cohort in the main study were still receiving study treatment, with the median DoR of 11 months and with the median OS estimate of 13.7 months.

No new safety findings were identified with longer follow-up.

The SOB-clin-003 is considered fulfilled.

2.1.2. SOB-clin-004: the results of the DREAMM-3 (207495) study

The MAH provided the primary analysis of DREAMM-3 (207495); a phase III, open-label, randomized trial evaluating the efficacy and safety of single-agent belantamab mafodotin compared to pomalidomide and dexamethasone (PomDex) in patients with RRMM. The CSR is being prepared and is not available for inclusion in this annual renewal submission. However, the results of the DREAMM-3 primary analysis have been described within the Interim Report for SOBs. The data cut-off for the initial interim report was 12 September 2022. Further data updates were provided during the renewal process (latest data

cut-off 3 July 2023).

A total of 325 participants were randomized in a 2:1 ratio to receive either single agent belantamab mafodotin administered as a 2.5 mg/kg dose every 3 weeks (Q3W), or PomDex. Pomalidomide was administered daily on days 1 to 21 of each 28-day cycle, with dexamethasone administered once weekly (days 1, 8, 15, and 22 of each cycle).

The study did not meet its primary endpoint of superiority in investigator-assessed Progression Free Survival (PFS). There was no statistically significant difference in PFS between the 2 treatment groups, as demonstrated by an Hazard Ratio (HR) of 1.03 (95% CI: 0.72, 1.47), based on the stratified Cox model (p=0.558).

Based on the results of the DREAMM-3 primary analysis, GSK initiated the process for withdrawal of the US marketing authorization for BLENREP (belantamab mafodotin) on 14 November 2022 at the request of the US FDA.

In a second (unplanned), updated PFS analysis (DCO: 3 July 2023) an additional 23 PFS events occurred, 13 in the belantamab mafodotin group and 10 in the pom/dex group. The updated HR is 0.90 (95% CI: 0.65, 1.24), and median PFS 11.2 vs. 7.0 months favoring belantamab mafodotin. This ad hoc analysis is not alpha protected. Updated OS data based on an unplanned analysis were also provided. The provided primary analysis of the DREAMM-3 clinical study did not meet its primary endpoint PFS, and the HR for OS was 1.03 (95% CI: 0.74, 1.43).

The SOB-clin-004 is due in July 2024. The MAH anticipates that the next planned interim analysis for OS is planned to occur in November 2023. Based on current projections the analysis would provide only 12 additional events (a total of approximately 170 events, 52% maturity; 68% IF).

2.2. Benefit-risk Balance

During the period covered by this annual renewal, new data have emerged. These data are considered to have an impact on the benefit-risk of Blenrep in its approved indication.

Blenrep received a CMA for the late-line treatment of myeloma patients having exhausted well-established treatment options known to prolong PFS and/or OS. This was based on an ORR deemed promising, along with a DoR showing responses sufficiently long to potentially translate into clinical benefit.

However, due to the limited amount of available data, as well as the absence of a reference treatment arm (the study compared two active doses of Blenrep), the effect of the product on PFS or OS could not be isolated. Therefore, the dataset was deemed non-comprehensive. Having fulfilled the requirements under the relevant regulatory framework, Blenrep received a CMA.

The DREAMM-3 study was proposed by the applicant as a relevant specific obligation, to confirm the efficacy, safety and B/R of Blenrep. This was agreed as an appropriate measure by the CHMP.

As described above, the DREAMM-3 study was not positive in its inferential analysis of PFS. Therefore, the required confirmation of efficacy in the context of a CMA, was not achieved. The study also failed to show a beneficial effect of Blenrep on OS.

Concerning safety, the toxicity profile of Blenrep is non-negligible, with a significant proportion of patients suffering from ocular adverse effects such as blurred vision, dry eye, photophobia and eye pain.

A SAG was consulted (7th of September 2023), concerning available efficacy and safety data for Blenrep. The SAG concluded that the efficacy of Blenrep has not been confirmed on the basis of DREAMM-3 (See Section 11.3).

In summary, Blenrep was approved based on a promising level of activity (ORR), which was considered likely to translate into clinical benefit, notwithstanding the abovementioned toxicity profile. The DREAMM-3 study was agreed as SOB to confirm the assumption of clinical benefit. Since this study failed to confirm the positive B/R balance of Blenrep in its approved indication it is recommended not to renew the CMA.

Scientific conclusions

Overall summary of the scientific evaluation

The European Commission issued on 25 August 2020, a conditional marketing authorisation (MA) for Blenrep. As specific obligations (SOB), the marketing authorisation holder (MAH) was requested to perform and submit the results from the clinical study DREAMM-2 (205678) and to perform and submit the results from an additional clinical study DREAMM-3 (207495) to confirm safety and efficacy of Blenrep.

- Efficacy issues

DREAMM-2 (205678)

The provided final study results of DREAMM-2 with regard to efficacy are in line with the results provided during the MA evaluation.

No new safety findings were identified with longer follow-up.

This SOB is considered fulfilled.

DREAMM-3 (207495)

Blenrep (belantamab mafodotin) was approved based on promising activity in terms of ORR. However, the data available at time of initial marketing authorisation were not deemed comprehensive. In particular, there was no demonstration of a positive impact of the product on time-dependent endpoint including PFS and OS. Therefore, a CMA was granted subject to SOB.

The applicant proposed the DREAMM-3 study as a SOB to confirm the efficacy and safety of Blenrep in relapsed/refractory multiple myeloma patients. This was accepted by the CHMP.

The DREAMM-3 (207495) study investigates the efficacy of belantamab mafodotin in patients with multiple myeloma who had had previously been treated with at least 2 prior lines of therapy, including 2 consecutive cycles of lenalidomide and a proteasome inhibitor. The study is a phase III, open-label, randomized trial designed to demonstrate the superiority of BLENREP monotherapy compared to pomalidomide and dexamethasone (PomDex).

The MAH submitted the main results of DREAMM-3 as part of the annual renewal procedure (EMEA/H/C/004935/R/0017)). The study did not meet its primary endpoint of superiority in investigator-assessed Progression Free Survival (PFS), as there was no statistically significant difference in PFS between the 2 treatment groups, as demonstrated by a Hazard Ratio (HR) of 1.03 (95% CI: 0.72, 1.47). The HR of the Overall Survival (OS) was 1.03 (95%CI: 0.74. 1.43) at the most

updated available analysis. Thus, the efficacy of Blenrep was not confirmed.

Key outcomes from the agreed SOB's have now been delivered and the data's totality are now considered comprehensive. Therefore, the CHMP concludes that efficacy of Blenrep in the approved indication has not been demonstrated.

Grounds for refusal of the renewal

Whereas

- The Committee re-assessed the benefit/risk of Blenrep as part of the annual renewal procedure, taking into account the totality of data, which includes the data at the time of the conditional approval and, the additional data from studies DREAMM-2 and DREAMM-3 generated as per the specific obligations.

- Evidence for the use of Blenrep in its approved indication was based on the objective response rate observed in a trial without a reference treatment arm allowing for the isolation of effects on PFS and OS. Therefore, efficacy was expected to be confirmed in a randomized controlled trial with a relevant reference regimen (DREAMM-3 (207495)). However, the primary analysis of the confirmatory study for Blenrep failed to demonstrate clinical benefit in terms of progression free survival or overall survival. Thus, the favourable benefit/risk balance of Blenrep in its approved indication has not been confirmed as required in the setting of a CMA.

Therefore, the CHMP has recommended not to renew the conditional marketing authorisation.

Annex: Rapporteurs' assessment comments on the renewal

PRAC input:

In this annual renewal,	Yes	No
- RMP submitted (If yes is ticked, discussion should be included in the Risk management plan section of the Annex)	☒	☐
- Outstanding SOB is a non-interventional PASS study (If yes is ticked, the relevant discussion should be included in the sub-section Outstanding Specific Obligations – status report for period covered of the Annex)	☐	☒
- There are issues originating from a parallel/recent PSUR or signal assessment to be flagged to the CHMP rapporteur (If yes is ticked, the relevant discussion should be included in the Clinical safety section of the Annex)	☐	☒
- PhV inspections have been conducted/are ongoing with an impact on the MA under annual Re-Assessment (If yes is ticked, the relevant discussion should be included in the Pharmacovigilance inspections section of the Annex)	☐	☒

3. Specific Obligations

3.1. Specific Obligations adopted with the initial marketing authorisation

Table 1. Full list of SOBs as adopted with the initial marketing authorisation

Number	Description	Status
SOB-clin-003	In order to confirm the efficacy and safety of BLENREP in relapsed/refractory multiple myeloma adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy, the MAH should submit the results of the DREAMM-2 (205678) study investigating the efficacy of belantamab mafodotin in patients with multiple myeloma who had 3 or more prior lines of treatment, are refractory to a proteasome inhibitor and an immunomodulatory agent and have failed an anti-CD38 antibody.	Fulfilled
SOB-clin-004	In order to confirm the efficacy and safety of BLENREP in multiple myeloma adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy, the MAH should submit the results of the DREAMM-3 (207495) study comparing the efficacy of belantamab mafodotin vs. pomalidomide plus low dose dexamethasone (pom/dex) in patients with relapsed/refractory multiple myeloma.	Ongoing / due date July 2024

Currently, the MAH has submitted the final clinical study report for DREAMM-2 for the SOB-clin-003 and the primary analysis for DREAMM-3 for the SOB-clin-004, as part of this annual renewal application.

3.2. Outstanding Specific Obligations – status report for period covered

SOB-clin-003: Description

With this SOB, the MAH was requested to submit the final results of the pivotal study DREAMM-2 and provide further information on resolution of the AEs.

During the period covered by the 1st annual renewal, the MAH proposed to postpone the end of study report due date for the SOB-clin-003 from April 2021 to November 2022 with a type IB variation (EMEA/H/C/004935/IB/0002, approved 27 January 2021).

The deadline for the DREAMM-2 SOB was further extended from November 2022 to February 2023 via a type IB variation (EMEA/H/C/004935/IB/0014, approved 26 September 2022). This was done to facilitate assessment of the DREAMM-2 final analysis as part of a grouped type II variation with the DREAMM-3 primary analysis, where safety data would be pooled across the two studies. The planned primary analysis of DREAMM-3 was delayed due to a slower rate of PFS events.

The final analyses with updated efficacy and safety results of the study are reported based on a data cut-off (DCO) of 31 March 2022. The median duration of follow-up at the time of final analysis was 12.5 months. The final clinical study report was published on 10 October 2022. As of 01 December 2022, 46 months since the Last Subject First Visit (LSFV), there were 3 participants receiving BLENREP (belantamab mafodotin) in the Post-Analysis Continuation of Treatment Phase of the study.

Objectives

The objective of this SOB-clin-003 is to confirm the efficacy and safety of BLENREP in relapsed/refractory multiple myeloma adult patients who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

The primary endpoint was ORR, defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR and stringent CR), according to the 2016 IMWG Response Criteria by IRC. Secondary objectives included CBR, DOR, TTR, PFS, TTP, OS, safety (AEs, SAEs, AESIs, ocular findings on ophthalmic examinations), PK, ADAs, PROs and exploratory endpoints.

Results

The final analysis consisted of 196 participants with RRMM randomized to either belantamab mafodotin (frozen solution) 2.5 mg/kg cohort (n=97) or 3.4 mg/kg cohort (n=99), with a median duration of follow-up of 12.5 months and 13.8 months respectively. In a third independent cohort, 25 participants received a lyophilized presentation of belantamab mafodotin at 3.4 mg/kg dose (not included in the results below).

Outcomes and estimation

Participants in both cohorts received a median of 3 treatment cycles. The median time on treatment was 9.3 weeks in the 2.5 mg/kg cohort.

The ORR as assessed by IRC was 32% in the 2.5 mg/kg cohort and 35% in the 3.4 mg/kg cohort. Of the responders 58% and 69% had a response of VGPR or better. The median DoR was 12.5 months in the

2.5 mg/kg cohort and 6.2 months in the 3.4 mg/kg cohort. In the subgroup analysis patients with extramedullary disease have a lower ORR (4.5%, 1/22).

The time to response was similar for both cohorts (median: 1.5 months and 1.4 months). The median PFS was 2.8 months and 3.9 months.

The median OS was 15.3 months (95% CI: 9.9 to 18.9) in the 2.5 mg/kg cohort and 14.0 months (95% CI:10.0 to 18.1) in the 3.4 mg/kg cohort.

In the final analysis as of DCO 31 March 2022, 73% of participants in the 2.5 mg/kg cohort and 82% of participants in the 3.4 mg/kg cohort had died. Of these, 82% (57 of 69) of participants in the 2.5 mg/kg cohort and 78% (63 of 81) of participants in the 3.5 mg/kg cohort died due to disease under study.

As of 01-December-2022, there are 3 participants receiving belantamab mafodotin in the post-analysis continuation of treatment phase.

Adverse events

Overall, 98% of participants in the 2.5 mg/kg cohort and 100% of participants in the 3.4 mg/kg cohort had AEs, and 84% and 83% respectively had Grade 3 or 4 AEs. Overall, the most commonly reported AE by preferred term (CTCAE) in both cohorts was keratopathy (71% and 75%). Other commonly reported AEs by PT were anemia (27% and 38%), nausea (25% and 32%), thrombocytopenia (24% and 46%), vision blurred (23% and 30%), and pyrexia (23% and 25%).

The most common treatment-related Grade ≥2 AEs reported (≥10% of participants in either cohort) were keratopathy (59% and 64%), thrombocytopenia (14% and 27%), vision blurred (13% and 18%), infusion related reaction (IRRs) (13% and 5%), anemia (6% and 10%), and neutropenia (4% and 10%).

Serious adverse event/deaths/dose reductions and discontinuation

45% of participants in the 2.5 mg/kg cohort and 54% in the 3.4 mg/kg cohort had SAEs.

The most frequent SAEs (≥3 participants at any dose) were pneumonia (7% and 14%), pyrexia (7% and 5%), anaemia (1% and 3%), IRR (3% and 2%), thrombocytopenia (1% and 3%), gastrointestinal haemorrhage (2% and 2%), and sepsis (2% and 2%).

There were 4% and 9% of participants with fatal SAEs. Of these, 3 participants had a fatal SAE considered related to study drug (sepsis, cerebral haemorrhage and haemophagocytic lymphohistiocytosis).

36% (2.5 mg/kg) and 44% (3.4 mg/kg) of participants had an AE leading to dose reduction. 54% (2,5 mg/kg) and 62% (3.4 mg/kg) of participants had AEs leading to dose delays. In both cohorts, 12% of participants had AEs that led to permanent discontinuation of the study treatment. Overall, the most common AE leading to permanent discontinuation was keratopathy (3% and 3%).

AESIs identified are corneal events, thrombocytopenic events, and IRRs.

Ocular safety:

Keratopathy (based on objective ocular exams by an ophthalmologist) was the most frequently reported AE (71% and 75%) with 30% and 25% Grade 3 or 4 events. There were 3 participants who had treatment-emergent severe visual impairment of 20/200 or worse (fulfilling the criteria for legal blindness) in both eyes. These events were reversible but the return to baseline required weeks to months.

Dry eye events (18% and 25%) and blurred vision (25% and 36%) were common; CTCAE Grade 3 events for dry eyes and blurred vision were infrequent (<5%).

The median time to onset for ocular events (keratopathy, dry eye, blurred vision, GSK Scale Grade ≥2) ranged from 22 to 51.5 days, and the median duration of onset ranged from 42 to 120 days for both doses. Based on PRO instruments, participants noted changes in visual acuity usually by around Week 7.

Dose modifications and specifically dose delays appear to be the most important mitigation strategy. Concomitant use of preservative-free artificial tear drops might also be beneficial though they are not expected to prevent the occurrence of the epithelopathy. Given the association of dry eye with the higher probability of developing corneal events, lubricating drops may be beneficial. Permanent treatment discontinuations due to corneal events occurred in <5% of participants.

Based on limited follow-up data, vision returned to or near to baseline in most cases. Median time to resolution post-treatment exposure was 36 days and 27 days. Permanent loss of vision was not reported.

The ocular sub-study results provided no evidence that corticosteroid eye drops would be an effective mitigation strategy for keratopathy/corneal events.

Furthermore, the final study report provides additional results for ocular safety (corneal events by GSK scale, examination findings (ophthalmological, Schirmer's test, tear break-up time, intraocular pressure, visual acuity, follow-up after cataract surgery) and PROs related to ocular safety). These results are in line with known adverse effects and do not alter the B/R profile of belantamab mafodotin.

Thrombocytopenic events

Thrombocytopenic events occurred in 38% and 57% participants during the study treatment. In the 3.4 mg/kg cohort, more Grade ≥3 events were observed (34%) compared with 2.5 mg/kg cohort (22%). 1% and 6% were considered SAEs. There were 2 thrombocytopenic events associated with fatal bleeding in the 3.4 mg/kg cohort, compared with none in the 2.5 mg/kg cohort. Thrombocytopenic events led to dose reduction in 17% and 23% of participants with the event and to dose delays in 6% and 11% of participants with the event. The median time to onset for the first thrombocytopenic event was 25.5 days and 21 days. The median time to first event resolution was 21.5 days and 22.5 days.

IRRs

21% and 16% participants had an IRR, of which 4% and 2% were SAEs. The most frequent (≥3%) preferred terms representing IRRs were IRR (17% and 10%) and pyrexia (5% and 6%). Most IRRs were Grade 1 and Grade 2 (18% and 15%), while 3% and 1% were Grade 3. No Grade 4 or Grade 5 IRRs were reported. In participants with IRR events, events were reported resolved in 90% and 94% of participants. One participant (3.4 mg/kg) required a dose delay and one participant (2.5 mg/kg) who discontinued due to an IRR. Prior to Cycle 1, 23% and 27% of participants had a premedication for IRR. Among the remaining participants who did not have premedication prior to Cycle 1, 16% and 14% experienced IRR. At Cycle 1, the cumulative incidence of IRR events was 19% and 14%. At Cycle 2, the cumulative incidence of IRR events was 20% and 16%, which was close to the maximum incidences of 21% and 16%.

Discussion

Efficacy

Conclusions for the 2.5 mg/kg cohort from the final efficacy data (DCO March 2022), when compared to the primary analysis (DCO 21 June 2019) and to DCO 31 January 2020, indicate that,

- the final ORR by IRC (32%) is consistent with the primary analysis (31%) and with DCO 31 January 2020 (32%)
- the final CBR of 36% is consistent with primary analysis (34%)
- the final median DOR (12.5 months) is consistent with DCO 31 January 2020 (11 months)
- the final estimated probability of having a DoR of ≥12 months (53%) is consistent with primary analysis (50%) and to 51% at the time of the 2nd annual renewal
- the final median TTR (1.5 months) and the median time to best response (2.2 months) are consistent with the primary analysis (1.2 months and 2.2 months, respectively)
- the final median PFS (2.8 months) is consistent with the primary analysis (2.9 months) and with the 2nd annual renewal (2.8 months)
- the final median OS is 15.3 months and thus slightly longer than at DCO 31 January 2020 analysis (13.7 months), immature at primary analysis
- at the final analysis 69 patients (73%) had died, compared to primary analysis with 32 patients who died during the study

Safety

Conclusions for the 2.5 mg/kg cohort from the final safety data (DCO March 2022), when compared to the primary analysis (DCO 21 June 2019), to DCO 20 September 2019, and to DCO 31 January 2020, indicate that

- at the final analysis AEs were reported for 98% of the patients and AEs related to study treatment were reported for 88% of the patients (unchanged through previous three DCOs)
- at the final analysis SAEs were reported for 45% of patients, consistent with DCOs 21 Jun 2019 and 20 Sep 2019 (40%) and with DCO 31 Jan 2020 (42%)
- at the final analysis AEs leading to dose reduction were reported for 36% thus demonstrating a minor increase from 21 Jun 2019 (29%), 20 Sep 2019 (34%), and 31 Jan 2020 (35%)
- at the final analysis AEs leading to dose interruption/delay were reported for 54%, unchanged through previous DCOs
- at the final analysis AEs leading to permanent discontinuation were reported for 12% of the patients, and thus consistent with 21 Jun 2019 (8%), 20 Sep 2019 and 31 Jan 2020 (9%)
- at the final analysis the most frequent (>20%) AEs by SOC and PT in ≥10% of patients are keratopathy (71%), anaemia (27%), nausea (25%) thrombocytopenia (24%), vision blurred and pyrexia (23%), aspartate aminotransferase increased (22%). This AE profile is consistent with earlier DCOs.

Rapporteur assessment/comment:

The Rapporteur is of the opinion that Specific Obligation SOB-clin-003 has been fulfilled, and therefore recommends its deletion from the Annex II.

SOB-clin-004: Description

The objective of SOB-clin-004 is to confirm the efficacy and safety of BLENREP in multiple myeloma patients.

With this SOB, the MAH was requested to provide results of the confirmatory study DREAMM-3, a phase III study of single agent belantamab mafodotin versus pomalidomide plus low-dose dexamethasone in participants with relapsed/refractory multiple myeloma. A randomised study should be able to provide more comprehensive analysis of both favourable and unfavourable effects of belantamab mafodotin than the pivotal study DREAMM-2. DREAMM-3 enrolled participants with RRMM who had been previously treated with at least 2 prior lines of therapy, including 2 consecutive cycles of lenalidomide and a PI, (given separately or in combination) and must have had documented progression (a) on, or within 60 days of completion of the last therapy or (b) must have been nonresponsive while on last treatment where non-responsive is defined as not achieving at least MR after 2 complete treatment cycles.

The primary analysis of the DREAMM-3 clinical study occurred during the reporting period and the MAH has submitted a preliminary report of the primary analysis for PFS, as well as results of an ocular sub-study that was conducted to assess whether the use of BCLs during belantamab mafodotin treatment might help mitigate the associated corneal toxicity by aiding the resolution of corneal epithelial lesions and alleviating symptoms.

Study progress and protocol amendments

At the time of the 1st annual renewal of BLENREP, the MAH was asked to provide an update of this study at the time of 2nd annual renewal: Briefly, as of 03 December 2021, 384 subjects had been screened, 276 subjects had been enrolled, 165 had discontinued treatment and 81 had discontinued from the study (63 due to death). Since the 1st annual renewal two protocol amendments (PA 02 and PA 03) had been implemented and introduced to the Rapporteurs. An additional OS interim analysis was introduced, and PFS futility analysis revised (PA 02). Last Subject Last Visit date (LSFV) was delayed by 4 months and was expected in February 2022, and the global enrolment cap (limit) for participants who have received ≤3 prior lines was increased from 40% to 55% (PA 03). The submission for DREAMM-3, based on the primary endpoint analysis was projected to occur by the end of 2022 (planned submission date August 2022) and is based on the slowing of PFS events observed in the study.

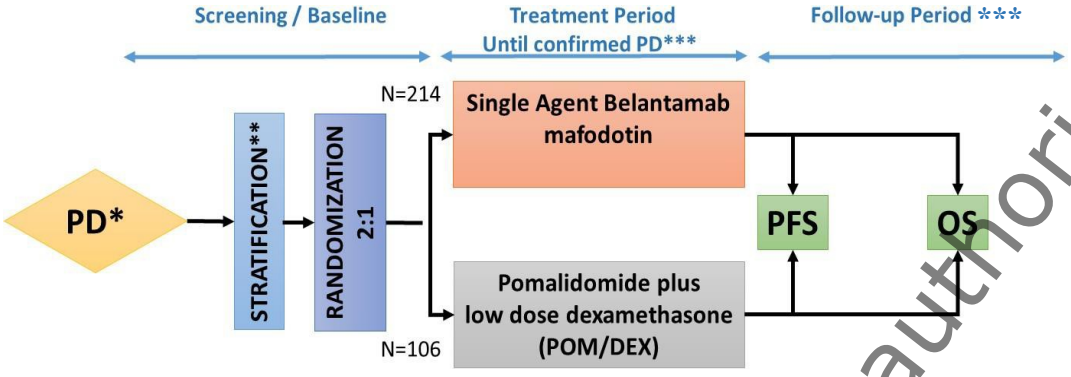
Protocol amendment 4 was implemented during the reporting period for this 3rd annual renewal. This PA 4 was issued after the timeframe for study completion was re-estimated based on the slower than originally anticipated accrual rate of PFS events. It revised the power for final PFS analysis from 95.6% to at least 90%, allowing the final PFS analysis to be triggered when at least 151 events were accrued and the first 320 randomized participants had been followed for a minimum of 4 months, with an anticipated median follow-up of approximately 10 months by the time 151 PFS events accrued. The PFS futility interim analysis was removed as this would coincide with the updated final PFS analysis.

Furthermore, protocol amendment 5 was implemented during the reporting period. It included updates to the method for the primary analysis of efficacy endpoints from being based on algorithm-derived confirmed response and dates per IMWG [Kumar, 2016] criteria, to being based on investigator-assessed responses and dates per IMWG. The primary efficacy analysis will be supported by a pre-specified IRC audit for the analysis of the efficacy endpoints. In addition, the definition for DoR was updated, the countries included in the Northeast Asia subgroup were defined, the required number of events for the primary PFS analysis was aligned, the language for anti-myeloma therapy was updated, and the post analysis continued treatment phase language including ocular follow-up was updated.

Study design

DREAMM-3 is a Phase 3, open-label, randomized, multicenter clinical study to evaluate the efficacy and safety of single agent belantamab mafodotin compared with pom/dex in participants with RRMM (see Figure 1 below).

Figure 1. Study design

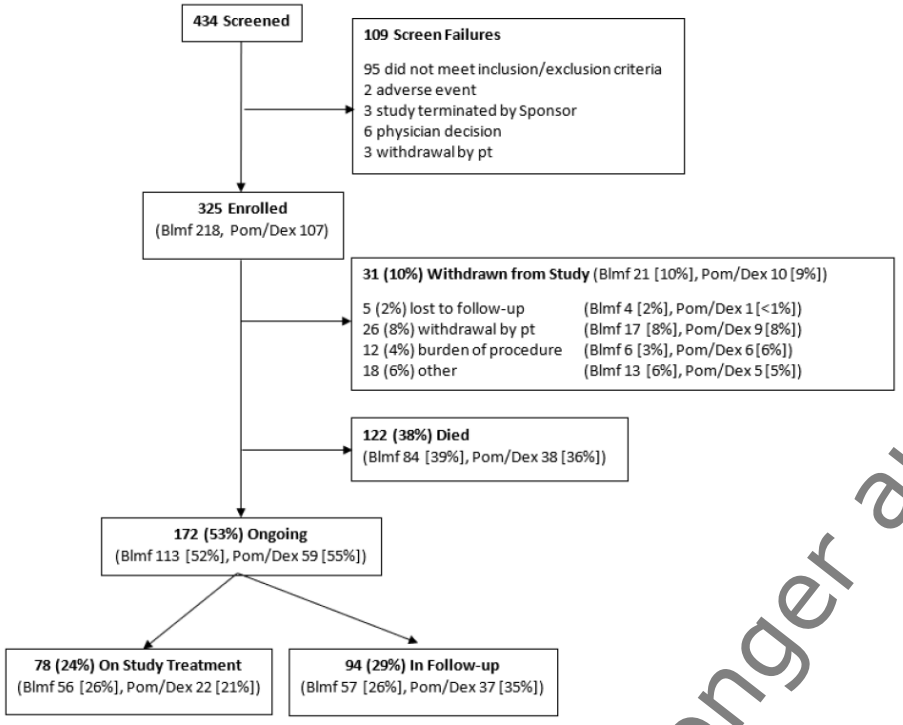


Key criteria included having a histologically or cytologically confirmed diagnosis of MM according to IMWG [Rajkumar, 2014], had undergone autologous stem cell transplant or were transplant ineligible, and received at least 2 prior lines of anti-myeloma treatments, including at least 2 consecutive cycles of both lenalidomide and a PI. Participants must have had documented disease progression on or within 60 days of completion of the last treatment or been nonresponsive. Participants with prior BCMA-targeted therapy or prior pomalidomide treatment were excluded as well as participants with current corneal epithelial disease except for mild punctate keratopathy.

The objective of the **ocular sub-study** was to assess whether the use of BCL during belantamab mafodotin treatment may help mitigate the associated corneal toxicity by aiding the resolution of corneal epithelial lesions and alleviating symptoms. Up to 60 evaluable participants who received at least 1 dose of belantamab mafodotin and developed KVA (keratopathy visual acuity) Grade ≥2 treatment-related corneal toxicities were to be centrally randomized 1:1 into the open-label ocular sub-study to receive either a BCL or routine management per a qualified eye care specialist.

Enrolment for the main study was completed on 25 March 2022. At the time that the last subject was randomized into the main study (18-April-2022), 449 subjects had been screened, with 325 subjects randomized. At data-cutoff of 12-September-2022 the median follow-up was 11.53 months for belantamab mafodotin (n=218) and 10.78 months for pom/dex (n=107). Of the 172 patients ongoing in the study, 78 were on study treatment (56 with belantamab mafodotin, 22 on pom/dex) and 94 in follow-up. 122 patients had died (39% in belantamab mafodotin arm, 36% in pom/dex). Follow-up anti-cancer therapy was initiated in 39% and 49% of participants, respectively with more than half of these patients only receiving 1 subsequent therapy at the time of data cut-off.

Figure 2. Study design



At data cut-off, the percentage of participants who discontinued study treatment was similar between the belantamab mafodotin, pomalidomide, and low-dose dexamethasone treatments (74%, 75%, and 75%, respectively). The median time on study treatment was 4.14 months (0.4, 22.9). Dose delays were reported in 12% of participants treated with belantamab mafodotin, and reductions were reported in 41% of patients (one dose reduction of belantamab mafodotin was allowed during the study).

Study population

Overall, the baseline characteristics were balanced between the treatment arms. The types of prior anti-cancer therapies participants received were similar between treatment groups, including the percentage of participants with prior anti-CD38 antibody therapy (42% and 39%), for which there was a 40% global enrollment cap. The percentage of participants refractory to different types of prior anti-cancer therapies was generally similar between treatment groups. The percentage of participants who were triple refractory to anti-CD38 antibody, PI, and IMiD therapy was 21% and 21%. However, some imbalances were noted: The median number of lines of prior anti-myeloma therapy was higher in the belantamab mafodotin group compared with the pom/dex group (4 lines vs. 3 lines). In the belantamab mafodotin group, 55% of participants had more than 3 lines of prior therapy compared with 49% of participants in the pom/dex group. In the belantamab mafodotin group, 15.1% of participants (33/218) had 6 or more lines of prior therapy compared with 7.5% of participants (8/107) in the pom/dex group.

Efficacy

Analysis of efficacy endpoints was based on investigator-assessed response with the ITT Population. The DREAMM-3 study did not meet the primary endpoint for investigator-assessed PFS. There was no statistically significant difference in the primary analysis for PFS between the 2 treatment groups, as demonstrated by an HR of 1.03 (95% CI: 0.72, 1.47), based on the stratified Cox model (p=0.558). The median PFS was longer in the belantamab mafodotin group with 11.2 (95% CI: 6.4, 14.5) months vs. 7.0 (95% CI: 4.6, 10.6) months in the pom/dex group.

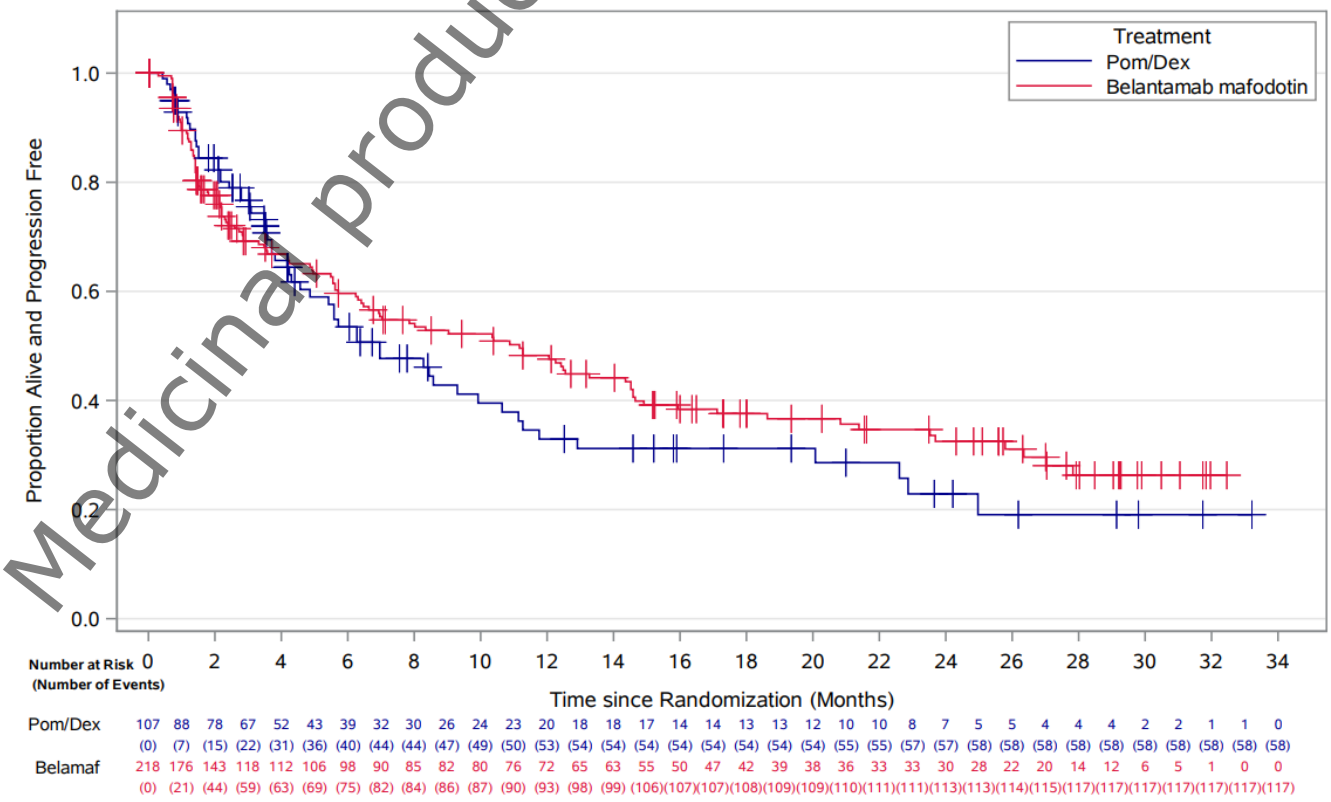
Table 29 Progression-Free Survival Based on Investigator-Assessed Response and Primary Censoring Rule (ITT Population)

	Belantamab Mafodotin (N=218)	Pom/Dex (N=107)
Number of participants, n (%)		
Progressed or died (event)	104 (48)	48 (45)
Censored, follow-up ended	53 (24)	36 (34)
Censored, follow-up ongoing	61 (28)	23 (21)
Event summary, n (%)		
Disease progression	92 (42)	38 (36)
Death	12 (6)	10 (9)
Estimates for time variable (months)[a]		
1st quartile (95% CI)	2.2 (1.4, 3.5)	3.1 (2.1, 3.8)
Median (95% CI)	11.2 (6.4, 14.5)	7.0 (4.6, 10.6)
3rd quartile (95% CI)	NE	NE (11.3, NE)
Stratified hazard ratio[b]		
Estimate (95% CI)	1.03 (0.72, 1.47)	
P-Value	0.558	
PFS probability at 6 months (95% CI)	0.60 (0.52, 0.66)	0.55 (0.43, 0.65)

a. CIs estimated using the Brookmeyer-Crowley method.
b. Hazard ratios are estimated using the Cox Proportional Hazards. A hazard ratio <1 indicates a lower risk of progressive disease or death with belantamab mafodotin compared with pom/dex. Hazard ratio and 1 sided p-value from stratified log-rank test are adjusted for previous treatment with anti-CD38 (yes, no), ISS staging (I/II, III), and number of prior lines of therapy (≤3, >3).
Source: Table 2.0050

In the most recent PFS analysis, an additional 23 PFS events occurred compared to the primary analysis, 13 (6%, including 1 death) in the belantamab mafodotin group and 10 (9%, including 2 deaths) in the PomDex group bringing the PFS maturity to 54%. The median PFS was 11.2 (95% CI: 6.5, 14.5) months vs. 7.0 (95% CI: 4.6, 10.6), and the HR 0.90 (95% CI 0.65, 1.24), Figure 3.

Figure 3. Kaplan-Meier curves for PFS (data update DCO 3 July 2023)

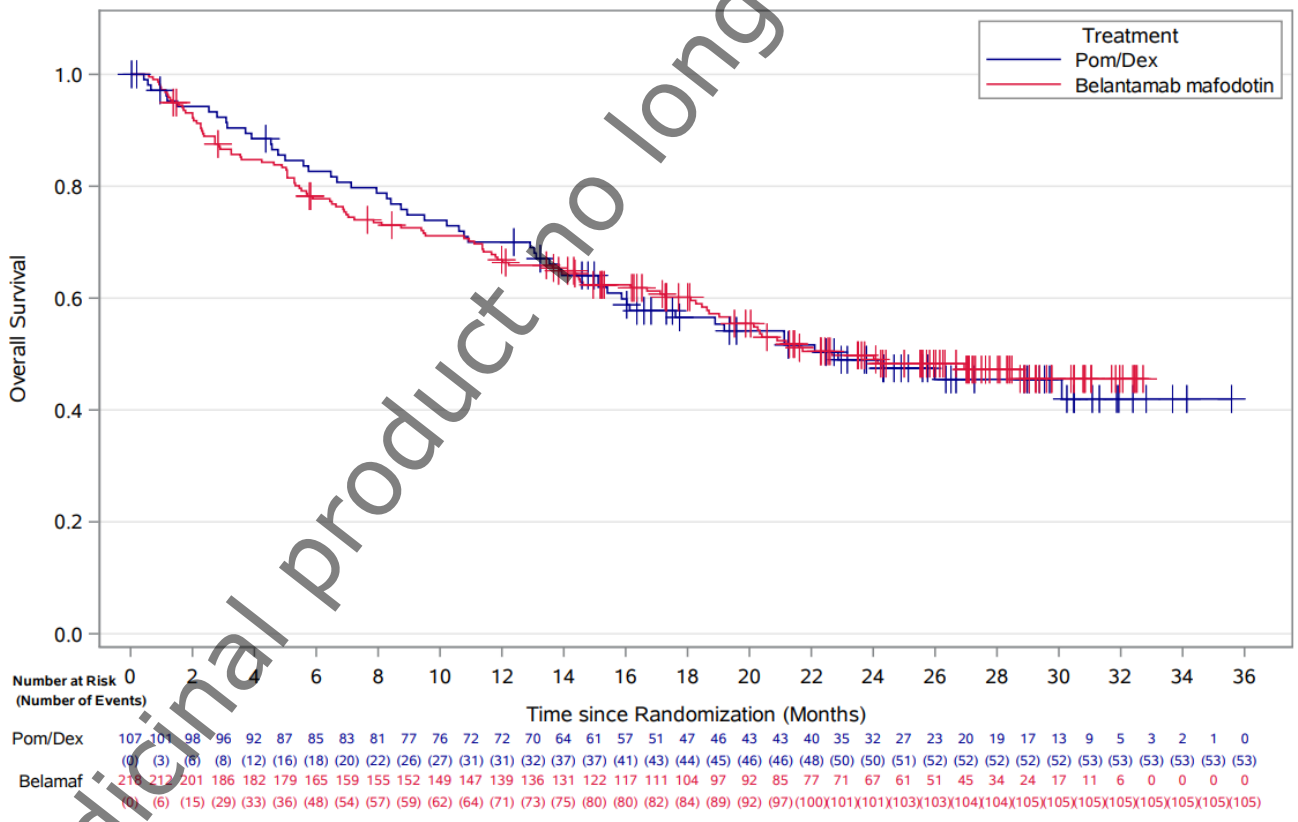


The pre-planned PFS analysis using the RMST method, which can be utilized as a sensitivity analysis for time-to-event outcomes when the proportional hazards assumption is possibly violated, showed no statistically significant difference between treatment groups using a cut-off of 22.9 months (RMST HR = 1.07).

At the time of the primary analysis, OS data were immature (37.5% [122/325] overall maturity and information fraction 48.8% [122/250], where 250 were the planned deaths for OS analysis according to the SAP). The median OS was similar between treatment groups and was 21.2 (95% CI: 18.7, NE) months for belantamab mafodotin and 21.1 (95% CI: 15.1, NE) months for pom/dex, with an HR of 1.14 (95% CI: 0.77, 1.68).

In the updated +10M FU OS analysis, an additional 36 OS events (11% of 325) were reported as compared to the primary analysis DCO, 21 (10% of 218) in the belantamab mafodotin group and 15 (14% of 107) in the PomDex group, increasing the overall OS maturity from 37.5% to 48.6%. The additional 10 months of follow-up have resulted in a change of OS HR from 1.14 to 1.03 (95% CI: 0.74, 1.43), Figure 4.

Figure 4. Kaplan-Meier curves for OS (update DCO 3 July 2023)



The ORR was 41% for belantamab mafodotin and 36% for PomDex. Belantamab mafodotin demonstrated a higher rate of deeper responses when compared with PomDex (25% VGPR or better with belantamab mafodotin compared to 8% with PomDex). The median DoR was 25.6 months for belantamab mafodotin (95% CI: 20.7, NE) vs 9.9 months (95% CI: 7.6, --) for PomDex (DCO 3 July 2023).

Safety

Table 43 Adverse Event Overview (Safety Population)

Adverse events, n (%)	Belantamab Mafodotin (N=217)	Pom/Dex (N=102)
Any AE	211 (97)	95 (93)
AEs related to study treatment[a]	182 (84)	78 (76)
Grade 3 or 4 AEs[b]	164 (76)	71 (70)
Grade 3 or 4 AEs related to study treatment[a]	123 (57)	55 (54)
Any SAE	94 (43)	40 (39)
SAEs related to study treatment[a]	25 (12)	12 (12)
Fatal SAEs	16 (7)	11 (11)
Fatal SAEs related to study treatment[a]	0	1 (<1)
AEs leading to dose modification		
AEs leading to dose interruption/delay	133 (61)	52 (51)
AEs leading to dose reduction	79 (36)	36 (35)
AEs leading to permanent discontinuation of study treatment	33 (15)	17 (17)

Note 1: Summary only includes treatment-emergent AEs.
Note 2: Treatment-emergent AEs leading to dose modifications do not include protocol-recommended dose modifications due to KVA greater than or equal to Grade 2, unless there was a concurrent AE that was captured as a reason for dose modification.
a. Any combination constituent.
b. Maximum grades reported during AE.
Source: Table 3.0240

Ocular AESIs by CTCAE (66% vs. 8%) and corneal events by KVA Scale (75% vs. 31% all corneal events; 70% vs. 23% investigator-assessed) were more frequently reported in the belantamab mafodotin group than in the pom/dex group. Ocular toxicity was manageable with dose modifications. Approximately half of the participants in the belantamab mafodotin group with a corneal event (by KVA Scale) of Grade ≥2 experienced 1 occurrence of these events. The first occurrence of corneal event (by KVA Scale) of Grade ≥2 was considered resolved in 78% of participants and at the time of data cut-off, and the median resolution time was 65.0 days. Overall, 62% of the corneal events resolved during treatment, but 20% of the events had not resolved at the time of the data cut-off. Transient corneal exam findings and visual acuity worsening were consistent with the safety pattern previously reported for belantamab mafodotin and there were no new safety signals related with the study findings, even after further exploration in post-hoc analyses. Thrombocytopenia was the most frequently reported AESI and treatment-emergent AE in both belantamab mafodotin and pom/dex groups (34% vs. 30%), which is consistent with what would be expected for the study population and treatments.

Ocular sub-study explored the use of BCL inserted into both eyes by the qualified eye care specialist within 14 days of KVA Grade 2 corneal event diagnosis. 25 participants in the belantamab mafodotin group were enrolled into the sub-study. Considering that the number of participants enrolled in the ocular sub-study was small, no conclusions could be drawn on whether the use of BCLs during belantamab mafodotin treatment might help mitigate the associated corneal toxicity.

Overall, deaths were balanced between the 2 treatment groups. At data cut-off, 83 (38%) of participants in the belantamab mafodotin group had died vs. 38 (37%) in the pom/dex group. The proportion of participants who died within 30 days of last dose of study treatment was 11% in the pom/dex group compared to 7% in the belantamab mafodotin group. The number of participants who died in the first 3 months post randomization is greater in the belantamab mafodotin group than in the pom/dex group. The main cause of death attributed by the investigator in both groups was cancer (57 and 22 patients,

respectively). The second most common cause of death in both treatment groups was "Other non-cardiovascular cause" (8% in belantamab mafodotin group and 11% in pom/dex group). A breakdown of these deaths revealed that most events were related to infections, such as COVID-19 and pulmonary/respiratory infections.

Discussion

The confirmatory study DREAMM-3 failed to meet the primary endpoint for investigator-assessed PFS. The initial approval of Blenrep was based on the observed ORR of 32% with a median duration of response of 12.5 months, and the assumption that the observed responses would be translated to clinically relevant improvement in time-to-event endpoints. However, the available data failed to demonstrate that the observed anti-disease activity as the response rate, depth of response and duration of response in the DREAMM-3 study would be translated to clinically relevant improvement in PFS and/or OS. A caveat is the fact that DREAMM-3 enrolled a less heavily pre-treated population in which generally higher activity is expected than in more heavily pre-treated subjects.

DREAMM-3 was conducted against an active comparator. Although the comparator is not optimal, its efficacy has been demonstrated, and pom/dex was accepted as the comparator for the confirmatory study.

The median PFS was longer in the belantamab mafodotin group with 11.2 (95% CI: 6.4, 14.5) months vs. 7.0 (95% CI: 4.6, 10.6) months in the pom/dex group, albeit not statistically significant (HR of 1.03 (95% CI: 0.72, 1.47), based on the stratified Cox model, p=0.558). In the second (unplanned), updated PFS analysis (DCO: 3 July 23) an additional 23 PFS events occurred, 13 in the belantamab mafodotin group and 10 in the pom/dex group. The updated HR is 0.90 (95% CI (0.65, 1.24), and median PFS 11.2 (6.5, 14.5) vs. 7.0 (4.6, 10.6) months favoring belantamab mafodotin.

An initial drop in the PFS curve for belantamab mafodotin was observed during the first 3 months of treatment. This was not clearly explained by dose delays or dose reductions due to adverse events or censoring. Overall, the patient characteristics were well balanced between the treatment arms. However, some imbalances were observed: for example, the median number of lines of prior anti-myeloma therapy was higher in the belantamab mafodotin group compared with the pom/dex group (4 lines vs. 3 lines), and 55% of participants had more than 3 lines of prior therapy compared with 49% of participants in the pom/dex group. In addition, there was a relatively high rate of stratification errors (16% for belantamab mafodotin and 15% for PomDex) mostly due to incorrect ISS stage entered at the time of randomization when central lab data was not available at the time the ISS stage had to be entered. Closer comparison of early progressors revealed some imbalances, with higher proportion of heavily pre-treated patients, and more prior lines of therapy in a shorter period of time suggesting a more aggressive disease trajectory in the belantamab mafodotin group. However, no clear explanation was identified in the comparison of these small sub-groups.

The chosen intercurrent event strategy led to high number of censored patients, e.g due to censoring when starting new anti-myeloma therapy and censoring after extended loss to follow-up. The censoring rules applied were not in line with the EMA guidance. In the primary analysis (September DCO) 24% of the patients in belantamab mafodotin group and 34% of the patients in pom/dex group were censored and follow-up had ended, and 28% and 21%, respectively, were censored with ongoing follow-up. While the updated PFS and OS data both appear to show slight improvement in both PFS and OS results, these *ad hoc* analyses are no longer alpha protected as the primary PFS analysis has occurred and failed, and cannot formally support efficacy claims. The next interim analysis for OS is expected to occur later in November 2023.

The OS data is immature (37.5% overall maturity and information fraction 48.8%). While the median OS was similar between treatment groups, HR of 1.14 (95% CI: 0.77, 1.68) was reported and more

deaths were observed during the first three months of the treatment. The additional ~10 months of follow-up and increased data maturity to 48.6% have resulted in a change of OS HR from 1.14 (95% CI 0.77, 1.68) to 1.03 (95% CI 0.74, 1.43). No specific concerns were identified suggesting a detrimental effect of the treatment upon assessment of the fatal events. Majority of the deaths were due to multiple myeloma (59% vs. 36%), and the other causes of death were similar between the groups, and no toxicity-related concerns were identified. In order to determine if additional follow-up will be able to provide information that could have an impact the B/R assessment, the MAH was requested to clarify how many new events will be available in the next planned data cut-off and discuss the best- and worst-case scenarios the further data updates could provide. The MAH has provided the possible scenarios (estimate of future events) regarding the outcome of the next planned OS analysis which is not likely to change the current finding of no OS benefit of belantamab mafodotin vs. pom/dex.

The ORR is slightly higher (41%) as compared to the pivotal study, which is expected considering that the study population is not as heavily treated as in DREAMM-2 (median number of prior lines of therapy 4 vs. 7, respectively). However, the ORR of the pom/dex arm is only slightly lower (36%). The median DoR was 25.6 months for belantamab mafodotin (95% CI: 20.7, NE) vs 9.9 months (95% CI: 7.6, NE) for PomDex (DCO 3 July 2023). The DoR data do not raise concerns on maintenance of the treatment effect, but no conclusions can be drawn based on this non-randomised comparison.

The incidences of all AEs (97% vs. 93%), Grade 3 and 4 AEs (76% vs. 70%), and SAEs (43% vs. 39%) were similar between the belantamab mafodotin and the pom/dex groups. The number of deaths were balanced across the 2 treatment groups (38% vs. 37%). The main cause of death in both arms was cancer. Ocular AESIs by CTCAE (66% vs. 8%) and corneal events by KVA Scale (75% vs. 31% all corneal events; 70% vs. 23% investigator-assessed) were more frequently reported in the belantamab mafodotin group than in the pom/dex group. The corneal toxicity resulted in adverse events including blurred vision (40% vs. 2%), dry eye (28% vs 2%), photophobia (21% vs. 1%), visual acuity reduced (19% vs. >1%) and eye pain (16% vs. 0%), and regular eye exams and supportive local treatment is needed. Thrombocytopenia was equally common in both arms. In general, the safety findings of DREAMM-3 are consistent with prior data.

Conclusion

The SOB-clin-004 is due to be fulfilled by July 2024. The interim reports submitted as a part of this renewal provide an overview of the efficacy and safety results, and updated PFS and OS data were provided in response to a MO raised during the renewal procedure. Fifty-three percent of the patients in belantamab mafodotin group were still in the study, and 24% of the patients were still on study treatment at the time of the time of the performed interim data cut-off.

Based on the interim results of the DREAMM-3 study, the positive B/R determined based on the pivotal SAT cannot be considered to be confirmed. The study failed to demonstrate superiority of belantamab mafodotin over pom/dex in PFS, despite slightly higher ORR and proportion of patients who achieved VGPR or better. The study did not demonstrate improvement in overall survival. The toxicity profile is non-negligible, with a significant proportion of patients suffering from ocular adverse effects such as blurred vision, dry eye, photophobia and eye pain.

The DREAMM-3 failed to confirm efficacy as agreed when the CMA was granted. Available data is considered to be sufficient to conclude that the positive B/R has not been confirmed. A Scientific Advisory Group was consulted, and the experts concluded that efficacy has not been confirmed on the basis of DREAMM-3 in the target population.

3.3. Overall conclusion on Specific Obligations

During the period covered by this annual renewal, new data regarding SOBs have emerged. The new data emerged are compliant in terms of adherence to deadlines and are compliant in terms of acceptability of data submitted.

The SOB-clin-003 is considered fulfilled. The SOB-clin-004 was initially due to be fulfilled in July 2024 when the final clinical study report will be available. However, as the results of the primary analysis for PFS are already available, it can be concluded that the study has failed to confirm efficacy as requested at the time the initial CMA was granted.

Last remaining SOB04 cannot be considered fulfilled as the study failed to confirm the efficacy of Blenrep for the treatment of multiple myeloma in adult patients, who received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

4. Additional scientific data provided relevant for the assessment of the benefit/risk balance

4.1. Quality

N/A

4.2. Non-clinical

Since the 2nd Conditional Renewal, in vitro investigations of the uptake and the ocular toxicity studies have been conducted. In these studies, the cytotoxic effect of fluorescently labelled belantamab mafodotin and GSK2857914 (parent antibody) in the presence of chemical inhibitors of endocytosis or intravenous immunoglobulin, or cysmcMMAF, into corneal epithelial cells (HCEC) and renal proximal tubule epithelial cells (RPTEC) have been conducted.

In addition, a gene expression (transcirtomics) analysis in HCEC have been conducted to determine the cell type most affected by treatment with belantamab mafodotin and, the sensitivity of limbal stem cells to the cytotoxic effects of belantamab mafodotin. In this assay, no transcriptomic differences between small proliferative and large squamous cells was identified. Of limbal stem cell-like markers, downregulation of human beta-catenin gene and microtubule-related gene, and upregulation of nucleolar protein gene WDR74 was noted in belantamab mafodotin treated cells compared to GSK2857914.

Investigations generated no further information that would alter the original conclusions regarding the safety of belantamab mafodotin or altered the benefit:risk evaluation.

4.3. Clinical pharmacology

The MAH has provided clinical pharmacology data from DREAMM-3, which has not been previously assessed. In general, the data seems to be consistent with earlier findings.

4.4. Clinical efficacy

Outside of the SOBs, there have been no new significant efficacy related findings from clinical trials and/or non-interventional studies involving belantamab mafodotin during the period covered by the addendum of clinical overview (ACO).

4.5. Clinical safety

Outside of the SOBs, there have been no new significant safety related findings from clinical trials and/or non-interventional studies involving belantamab mafodotin during the period covered by the addendum of clinical overview (ACO).

The final analysis of DREAMM-2 (205678); a phase II, open label, randomized, two-arm study to investigate the efficacy and safety of two dose levels (2.5 and 3.4 mg/kg) of the antibody drug conjugate GSK2857916 in participants with multiple myeloma who had 3 or more prior lines of treatment, are refractory to a proteasome inhibitor and an immunomodulatory agent and have failed an anti-CD38 antibody, was completed during the reporting period. The final CSR, based on DCO of 31 March 2022, was provided by the MAH in this annual renewal application (see 5.1. for further details).

During the reporting period, 4 new validated signals, since the DLP of the last PBRER up to the DLP of the renewal, underwent assessment:

• Validated Signal 1: Tumor lysis syndrome was newly identified and closed as a refuted signal during the reporting period.

• Validated Signal 2: Hemorrhagic events was closed as a refuted signal and continues to be monitored as part of the important identified risk of thrombocytopenia.

• Validated Signal 3: Changes to the corneal nerve plexus and decreased corneal sensitivity was identified during the reporting period and the assessment is ongoing at the DLP of this report.

• Validate Signal 4: Pneumonitis was newly identified during the reporting period and the assessment is ongoing at the DLP of this report.

5. Risk management plan

The MAH has submitted an updated RMP within the annual renewal procedure.
The main changes include:

- Removal of the completed Specific Obligation relating to Study 205678 (DREAMM-2).
- Update of the status and due dates for Category 3 Studies 209626 (DREAMM-12) and 209627 (DREAMM-13).

Safety concerns

Table 2. Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye

Summary of safety concerns	
Important potential risks	• Nephrotoxicity • Increased risk of infections due to immunosuppression and/or neutropenia
Missing information	• Safety in patients with severe renal impairment • Safety in patients with hepatic impairment

No change is proposed to the safety specification within this procedure.

Considering the data in the safety specification, the safety concerns listed by the MAH are appropriate.

Pharmacovigilance plan

Table 3. On-going and planned studies in the post-authorisation pharmacovigilance development plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances				
~~205678 (DREAMM-2): Open-label, randomized study of two doses of belantamab mafodotin in participants with relapsed/refractory multiple myeloma who have failed prior treatment with an anti-CD38 antibody - Ongoing~~	~~Primary: To evaluate the clinical efficacy of 2 doses of belantamab mafodotin in participants with relapsed/refractory multiple myeloma~~ ~~Secondary:~~ ~~To further evaluate the clinical measures of efficacy of belantamab mafodotin in participants with RRMM~~ ~~To evaluate the safety of belantamab mafodotin in participants with RRMM~~ ~~To evaluate the pharmacokinetic profile of belantamab mafodotin~~ ~~To assess anti-drug antibodies (ADAs) against belantamab mafodotin~~ ~~Participant self-reported symptomatic adverse effects by evaluation of tolerability of belantamab mafodotin~~ ~~To evaluate disease and treatment related symptoms and impact on function and health-related quality of life~~	~~Standard clinical and laboratory tests~~ ~~Collection of AEs and SAEs~~ ~~AEs of special interest~~ ~~Ocular findings on ophthalmic exam~~ ~~Further characterization of important identified and potential risks:~~ ~~• Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye~~ ~~• Nephrotoxicity~~ ~~• Increased risk of infections due to immunosuppression and/or neutropenia~~	~~Final study report~~ ~~Final study report submission~~	~~Sep 2022~~ ~~Feb 2023~~
207495 (DREAMM-3): Phase III Study of Single Agent Belantamab Mafodotin versus Pomalidomide plus Low-dose	Primary: To compare the efficacy with belantamab mafodotin vs pomalidomide plus low dose dexamethasone (pom/dex) in participants with relapsed/refractory multiple myeloma	Incidence of AEs and changes in laboratory parameters	~~Projected Primary endpoint analysis~~	~~Oct 2022~~

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma – Ongoing	Key Secondary: To compare the overall survival with belantamab mafodotin vs pom/dex in participants with RRMM Secondary: To compare other markers of efficacy of belantamab mafodotin vs pom/dex in participants with RRMM To evaluate the safety and tolerability of belantamab mafodotin vs pom/dex in participants with RRMM To evaluate the pharmacokinetic profile of belantamab mafodotin To assess anti-drug antibodies (ADAs) against belantamab mafodotin To evaluate the tolerability of belantamab mafodotin vs pom/dex based on self-reported symptomatic adverse effects To evaluate and compare changes in symptoms and health-related quality of life (HRQOL)of belantamab mafodotin to pom/dex To assess Minimal Residual Disease (MRD) in participants who achieve ≥VGPR or better for belantamab mafodotin vs pom/dex	Ocular findings on ophthalmic exam Symptomatic adverse effects as measured by the PRO-CTCAE and OSDI Changes in safety assessments, including vital signs and ECGs Further characterization of important identified and potential risks: • Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye • Nephrotoxicity • Increased risk of infections due to immunosuppression and/or neutropenia	~~Study report submission~~ Overall survival and Final analysis	~~Q1 2023~~ Jul 2024
Category 3- Required additional pharmacovigilance activities				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
209626 (DREAMM-12): A Phase 1 open label study of GSK2857916 in relapsed/refractory multiple myeloma patients with renal impairment	Primary: To describe the effects of renal impairment on the pharmacokinetics of belantamab mafodotin in participants with RRMM and with severe renal impairment, ESRD (not on dialysis) or ESRD (on dialysis) compared to participants with normal renal function Secondary: To evaluate safety and tolerability using parameters, including adverse events, vital signs, ECGs, and clinical laboratory assessments in participants with RRMM who have normal or impaired renal functions	Safety of belantamab mafodotin in patients with severe renal impairment Plasma belantamab mafodotin, total mAb, and cys-mcMMAF pharmacokinetic parameters; dialysate PK parameters, as data permit Change from baseline in vital signs (blood pressure and heart rate), monitoring and incidence of adverse events, toxicity grading of clinical laboratory tests, ECG findings, and physical examinations	Final study report	~~1Q2025~~3Q2025
209827 (DREAMM-13): A Phase 1 open label study of GSK2857916 in patients with relapsed/refractory multiple myeloma and hepatic impairment	Primary: To evaluate the effects of hepatic impairment on the PK of belantamab mafodotin in RRMM participant with impaired hepatic function as compared to RRMM participants with normal hepatic function Secondary: To evaluate the safety, and tolerability parameters, including AEs, vital signs, ECGs, and clinical laboratory assessments in participants with RRMM who have normal or impaired hepatic functions	Safety of belantamab mafodotin in patients with hepatic impairment Plasma belantamab mafodotin, total mAb, and cys-mcMMAF pharmacokinetic parameters	Final study report	~~2Q2028~~4Q2026

The study 205678 (DREAMM-2) listed as Category 2 has been completed and is removed from the table.

In addition, the due dates for the category 3 studies have been updated.

The proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

Routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 4. Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation activities
Identified Risks	
Keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye	Routine risk communication: SmPC Sections 4.2: Posology and method of administration 4.4: Special warnings and precautions for use 4.8: Undesirable effects PL Sections 2. What you need to know before you take Belantamab mafodotin 4. Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommended treatment modifications are provided in SmPC section 4.2. Instruction regarding symptom evaluation, treatment modifications and interventions are provided in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: - Prescription only medicine - Use restricted to physicians experienced in the use of anticancer medicinal products
Potential Risks	
Nephrotoxicity	Routine risk communication: Routine risk minimisation activities recommending specific clinical measures to address the risk: Other routine risk minimisation measures beyond the Product Information: - Prescription only medicine - Use restricted to physicians experienced in the use of anticancer medicinal products
Increased risk of infections due to immunosuppression and/or neutropenia	Routine risk communication: Routine risk minimisation activities recommending specific clinical measures to address the risk: Other routine risk minimisation measures beyond the Product Information: - Prescription only medicine - Use restricted to physicians experienced in the use of anticancer medicinal products
Missing Information	
Safety in patients with severe renal impairment	Routine risk communication: Routine risk minimisation activities recommending specific clinical measures to address the risk: Other routine risk minimisation measures beyond the Product Information: - Prescription only medicine - Use restricted to physicians experienced in the use of anticancer medicinal products
Safety in patients with hepatic impairment	Routine risk communication: Routine risk minimisation activities recommending specific clinical measures to address the risk: Other routine risk minimisation measures beyond the Product Information:

Safety concern	Routine risk minimisation activities
	- Prescription only medicine - Use restricted to physicians experienced in the use of anticancer medicinal products

Additional Risk Minimisation Measures

Educational Materials for Healthcare Professionals and Patients

Objectives:

To mitigate the possible risks of keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye in patients taking belantamab mafodotin.

Rationale for the additional risk minimisation activity:

To help oncologists, eye care professionals and patients understand the corneal risks associated with belantamab mafodotin, so that corneal examination findings, and/or visual changes can be promptly identified and managed according to the product labelling.

Patients will receive educational materials to help them understand the corneal risks and potential visual impairment associated with taking belantamab mafodotin. This includes guidance on screening exams as well as treatment with preservative-free artificial tears, and how to speak with their doctors about their symptoms.

Oncologists will receive educational materials to help them understand the corneal risks associated with prescribing belantamab mafodotin and how this risk is best managed and mitigated. They will be encouraged to work closely with the eye care professional since their treatment plan may be impacted by the eye care professional's exam findings.

Eye care professionals will receive educational materials to help them understand the corneal risks associated with belantamab mafodotin with the aim to optimise symptom recognition and reporting. They will be encouraged to work closely with the treating oncologist as their findings may impact the oncologist's treatment plan.

Target audience and planned distribution path:

Oncologists and eye care professionals will receive educational materials to help them understand the corneal risks associated with belantamab mafodotin.

Patients taking belantamab mafodotin will receive educational materials from their treating oncologist focusing on the possible risks of keratopathy (or MEC) in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, or dry eye and the main required actions to be taken in order to prevent and minimize these risks.

Following approval of the EU RMP, the Applicant will oversee and follow local processes in each member state to ensure implementation of the education materials, which includes submission to the national competent authority and will include the proposed tools to be used and a local communication and distribution plan to the predetermined target audience.

No changes were introduced to the approved risk minimization measures.

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Elements for a public summary of the RMP

The proposed updates to elements for a public summary of the RMP are in line with the changes in the RMP and are acceptable.

Annexes

The RMP annexes have been updated appropriately.

5.1. Overall conclusion on the RMP

☒The RMP version 3 is acceptable.

6. Changes to the Product Information

Not applicable.

7. Request for Supplementary Information - RfSI

The MAH should provide the following supplementary information in response to Day 60 RfSI

7.1. Major objections

1. In DREAMM-3, both PFS and OS K-M curves demonstrate increased number of events in belantamab mafodotin treated patients during the first months of treatment. The Applicant is requested to provide data on patients with early progression events and deaths including patient characteristics, previous treatments etc.

7.2. Other concerns

Clinical aspects

1. OS results cannot be reliably interpreted in a single arm study, and should be removed from SmPC section 5.1, table 5 in line with the current CHMP policy.

8. Assessment of the MAH responses to the RfSI

8.1. Major objections

Clinical aspects

Question 1

In DREAMM-3, both PFS and OS K-M curves demonstrate increased number of events in belantamab mafodotin treated patients during the first months of treatment. The Applicant is requested to provide data on patients with early progression events and deaths including patient characteristics, previous treatments etc.

Summary of the MAH's response

As per the EMA's request, GSK conducted an analysis of baseline demographic and disease characteristics of DREAMM-3 participants with early progression events and early deaths in both treatment groups to better help to understand the outcome of the DREAMM-3 study.

In addition, GSK would like to provide the EMA with an updated data-cut of the DREAMM-3 OS and PFS analysis, which was conducted approximately 6 months post the primary analysis.

Characteristics of Participants with Early Progression

The initial PFS KM curve in the belantamab mafodotin group is driven by a higher rate of progression events in the first 2 months followed by a slower event rate in the belantamab mafodotin group in months 3 and 4 before the PFS curves cross at 4 months post randomisation (Table 1) (Interim Report for Specific Obligations Section 3.5.1, Figure 3). At the 4 months PFS KM curve cross-over point, the proportions of PFS event and censors were similar between both arms (see Table 1). After the 4-month KM curve cross-over, more participants progressed on the pom/dex group, as compared to the belantamab mafodotin group. Given that the largest disparity of PFS event rate is in the first 2 months post randomisation (44/218 events in the belantamab mafodotin group, 15/107 events in the pom/dex group (see Table 1) a time frame of 0-2 months post randomisation was applied for the requested analysis of characteristics of early progression events. The following stratification factors were used: International Staging System (ISS; I/II or III), number of prior lines of therapy (≤3 or >3), and prior anti-CD38 mAb treatment (yes or no).

Table 1 Progression status 0-4 months post randomisation

	Belantamab mafodotin (N=218)				PomDex (n=107)			
	Progressed	Died [1]	Ongoing	Censored	Progressed	Died [1]	Ongoing	Censored
0-<1M	18	3	175	22	4	3	88	12
1-<2M	20	3	141	11	5	3	78	2
Total 0-<2M	**38 (17%)**	**6 (3%)**	**141 (65%)**	**33 (15%)**	**9 (8%)**	**6 (6%)**	**78 (73%)**	**14 (13%)**
2-<3M	12	2	117	10	6	1	67	4
3-<4M	3	1	110	3	8	1	52	6
Total 2-<4M	**15 (7%)**	**3 (1%)**	**110 (50%)**	**13 (6%)**	**14 (13%)**	**2 (2%)**	**52 (49%)**	**10 (9%)**
Total 0-<4M	**53 (24%)**	**9 (4%)**	**110 (50%)**	**46 (21%)**	**23 (21%)**	**8 (7%)**	**52 (49%)**	**24 (22%)**

[1] Death without prior progression. For all deaths during this time frame see Table 4

The outcome of the early progression event analysis should be viewed and interpreted in the context of the baseline demographic and disease characteristics of the entire DREAMM-3 population. Overall, the baseline characteristics were balanced in participants in the belantamab mafodotin group respect to most factors, however the participants in the belantamab mafodotin group were more heavily pre-treated with a higher median of prior lines of therapy, and higher proportion of patients with 5 or more prior lines of therapy (Table 2, imbalances bolded).

Table 2 Baseline Characteristics in DREAMM-3 for the entire population

unit displayed is [n (%)] unless stated otherwise	**Belantamab mafodotin (N=218)**	**Pom/Dex (N=107)**
Female	100 (46)	41 (38)
Age, Median (Min, Max)	68.0 (43, 86)	68.0 (38, 90)
>=65; >=75	137 (63), 47 (22)	64 (60), 23 (21)
Race: WHITE	162 (76)	84 (81)
BMI (kg/m2), Median (Min, Max)	26.49 (16.0, 45.7)	26.99 (18.3, 42.8)
ECOG PS 0, PS 1, PS 2	**79 (36), 116 (53), 23 (11)**	**49 (46), 50 (47), 8 (7)**
ISS stage I, II, III	76 (35), 89 (41), 52 (24)	37 (35), 41 (38), 28 (26)
IgG Multiple Myeloma	148 (74)	62 (67)
Kappa Light Chain Myeloma	129 (69)	67 (68)
Serum M-Protein, g/L Median (Min, Max)	18 (0, 102)	18.4 (0, 78)
Urine M-protein, mg/day, Median (Min, Max)	14.7 (0, 12887)	7.3 (0, 5759)
Extramedullary Disease	39 (18)	19 (18)
Lytic Bone Lesions	164 (75)	79 (74)
Lines of prior therapy, median (min Max)	**4.0 (2, 12)**	**3.0 (2, 13)**
>3 lines (per CRF)	110 (50)	53 (50)
>5 lines (per CRF)	**33 (15)**	**8 (7.5)**
Prior Anti-CD38 (per CRF)	91 (42)	42 (39)
Prior ASCT	111 (51)	55 (51)
Time from initial diagnosis (years)	5.23 (1.1, 22.5)	5.05 (0.8, 19.6)
High Risk Cytogenetics [1]	57 (26)	34 (32)
Moderate Renal Impairment (>=30, <60) [2]	61 (28)	35 (33)
Severe Renal Impairment (>=15, <30) [2]	4 (2)	1 (<1)
sBCMA (ug/L), median (Min, Max)	56.5 (2,1176)	57.0 (5, 771)
Beta-2 Microglobulin (nmol/L), Median (Min, Max)	311 (113, 1569)	291.5 (113, 1521)
Albumin (g/L), Median (Min, Max)	38 (4,52)	39 (4, 51)
Lactate Dehydrogenase (IU/L), Median (Min, Max)	198 (84, 969)	205 (98, 810)

Imbalances between groups are shown in **bold**
[1] If the subject has any of the following cytogenetics: t(4;14), t(14;16) or 17p13del., [2] per eGFR (ml/min/1.73 m^2)

Table 3 shows baseline demographics and disease characteristics of participants that progressed, died, or were event-free and ongoing during the first 2 months post randomisation. This table allows for a between-group comparison of early progression of baseline characteristics by status (e.g. characteristics of early progressors in the belantamab mafodotin group compared to the early progressors on the pom/dex group), but also an intra-group comparison of baseline characteristic (e.g. characteristics of early progressors in the belantamab mafodotin group compared to ongoing participants in the same group).

The between-group comparison (belantamab mafodotin early progressors vs pom/dex early progressors) of baseline characteristic, showed only few baseline characteristics were more prominent in the early progressors in the belantamab mafodotin group: slightly younger age, more heavily pre-treated (number or prior lines of treatment, prior ASCT, shorter time since initial diagnosis) and higher sBCMA at baseline. Early progressors in the belantamab mafodotin group are less likely to have high risk cytogenetics and moderate renal impairment.

The intra-group comparison (early progressors vs ongoing) in both groups showed that early progressors are more likely to be male, have higher ECOG PS, have EMD, have lytic bone lesions, had prior ASCT, and/or had prior anti-CD38. In both treatment groups participants with a progression event of death are more likely to have ISS stage III, higher secretion of M-protein, higher baseline sBCMA, higher Beta-2 Microglobulin (B2M) and higher Lactate dehydrogenase (LDH).

Soluble BCMA levels were identified as important contributing factors in both, the intra and inter-group comparison. The cut-off values were not pre-defined and, for the purpose of this analysis the median sBCMA levels were selected as a cut-off point.

Median values for baseline sBCMA were higher for early progressors and deaths in both arms (Table 3). This confirms previously published observation that sBCMA may be reflective of a disease burden and a prognostic factor for treatment response, regardless of treatment modality [Forslund, 2019]. A KM analysis for PFS in participants with high and low baseline sBCMA levels (< vs. >=56.86 ug/L) clearly shows an impact of baseline sBCMA level on treatment outcome (Figure 1). The higher number of early progression in the belantamab mafodotin group is also apparent in this subgroup analysis and shows that sBCMA alone is not the driver for this observation, but the factors identified earlier may have contributed to the outcome.

Figure 1 Graph of Kaplan-Meier Curves of PFS by Baseline sBCMA (ITT)

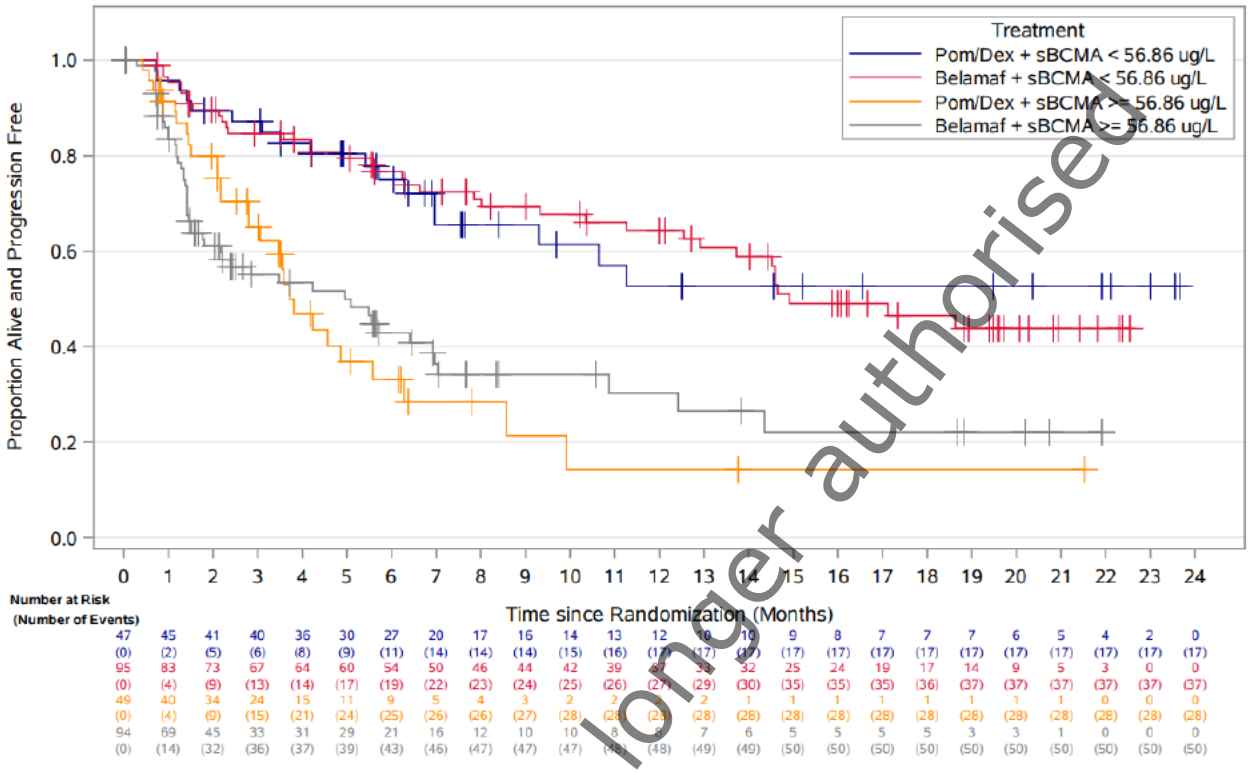


Table 3 Baseline Characteristics by Progression Status (progressed, died, ongoing) 0-2 months post randomisation)

	Status: Progressed		Status: Death		Status: Ongoing	
unit displayed is [n (%)] unless stated otherwise	Belantamab mafodotin (N=218)	Pom/Dex (N=107)	Belantamab mafodotin (N=218)	Pom/Dex (N=107)	Belantamab mafodotin (N=218)	Pom/Dex (N=107)
Number of Subjects in the Subgroup	**38**	**9**	**6**	**6**	**141**	**78**
Female	11 (29)	1 (11)	2 (33)	3 (50)	73 (52)	32 (41)
Age, Median (Min, Max)	65 (44, 86)	73 (48, 76)	61 (43, 73)	64.5 (51, 78)	69 (43, 85)	68 (38, 84)
>=65; >=75	19 (50), 5 (13)	6 (67), 1 (11)	2 (33), 0	3 (50), 1 (17)	98 (70), 36 (26)	49 (63), 17 (22)
Race: WHITE	31 (82)	7 (88)	5 (83)	5 (100)	103 (76)	62 (81)
BMI (kg/m2) Median (Min, Max)	28.5 (18.3, 39.8)	28.5 (24.2, 31.8)	25.46 (22.6, 28)	28.95 (25.7, 34)	26.94 (16, 45.7)	26.86 (18.3, 42.8)
ECOG PS 0	13 (34)	8 (89)	2 (33)	0	53 (38)	34 (44)
ECOG PS 1	18 (47)	1 (11)	4 (67)	4 (67)	77 (55)	39 (50)
ECOG PS 2	7 (18)	0	0	2 (33)	11 (8)	5 (6)
ISS stage I, II	9 (24), 20 (53)	3 (33), 4 (44)	1 (17), 1 (17)	0, 1 (17)	55 (39), 55 (39)	30 (38), 29 (37)
ISS stage III	9 (24)	2 (22)	4 (67)	5 (83)	30 (21)	18 (23)
IgG Multiple Myeloma	24 (73)	5 (83)	3 (50)	4 (67)	101 (77)	44 (66)
Kappa Light Chain Myeloma	27 (77)	5 (56)	4 (80)	5 (83)	80 (67)	49 (70)
Serum M-Protein, g/L, Median (Min, Max)*	18.7 (0, 77.2)	7.7 (0.5, 33.8)	25.4 (2.4, 36.4)	33.3 (17.7, 77.9)	17.95 (0, 102)	19.8 (0, 69.6)
Urine M-protein, mg/day, Median (Min, Max)*	17.99 (0, 12887)	0 (0, 0)	1241.5 (0, 7497)	54.5 (5.5, 5759)	9.6 (0, 4618)	5.2 (0, 3137)
Extramedullary Disease	15 (39)	3 (33)	2 (33)	1 (17)	14 (10)	11 (14)
Lytic Bone Lesions	36 (95)	8 (89)	5 (83)	6 (100)	96 (68)	54 (69)
Lines of prior therapy, median (min Max)	4.0 (2, 12)	3.0 (2, 5)	3.5 (2, 7)	5.5 (2, 6)	3 (2, 10)	3 (2, 13)
>3 lines (per CRF)	26 (68)	4 (44)	3 (50)	5 (83)	66 (47)	38 (49)
>5 lines (per CRF)	8 (21)	0	2 (33)	3 (50)	17 (12)	5 (6)
Prior Anti-CD38 (per CRF)	25 (66)	5 (56)	3 (50)	2 (33)	50 (35)	29 (37)
Prior ASCT	27 (71)	6 (67)	5 (83)	3 (50)	65 (46)	40 (51)
Years from initial diagnosis, median (Min, Max)	4.91 (1.4, 17.3)	5.15 (1.8, 8.7)	4.34 (1.8, 13.5)	5.58 (1.8, 16)	5.65 (1.1, 22.5)	5.07 (1.0, 19.6)
High Risk Cytogenetics [1]	7 (18)	3 (33)	1 (17)	2 (33)	35 (25)	25 (32)
Moderate Renal Impairment (>=30, <60) [2]	7 (18)	3 (33)	1 (20)	3 (50)	41 (29)	24 (31)
Severe Renal Impairment (>=15, <30) [2]	2 (5)	0	0	1 (17)	2 (1)	0
sBCMA (ug/L), median (Min, Max)*	137 (6, 865)	23.3 (10, 128)	554 (307, 1176)	354 (57, 771)	39.6 (2, 699)	49.4 (5, 665)
Beta-2 Microglobulin (nmol/L), Median (Min, Max)*	314 (114, 817)	247 (148, 410)	599 (218, 1473)	822 (460.2, 1521.2)	294 (113, 1102)	283.9 (123, 1286)
Albumin (g/L), Median (Min, Max)	38 (24, 52)	39.7 (33, 34)	33.5 (26, 48)	28.5 (23, 51)	38.9 (4, 51)	38.6 (4, 48)
Lactate Dehydrogenase (IU/L), Median (Min, Max)	218 (91, 670)	185 (157, 297)	394 (198, 866)	282 (227, 686)	196 (90, 969)	205 (98, 810)

[1] If the subject has any of the following cytogenetics: t(4;14), t(14;16) or 17p13del., [2] per eGFR (ml/min/1.73 m2), Note: Subjects censored for PFS in this timeframe are not shown in this table summary, hence the overall number to not add up to 325.
* some numbers maybe rounded

The assessment of early progression events highlights several important points:

- With the overall small numbers of early progressors, no one specific characteristic could be identified that would explain the larger proportion of early progressors in the belantamab mafodotin group.

- There are many baseline characteristics that distinguish early progressors from early ongoing participants equally in both groups. Most of these characteristics are reflective of an advanced disease, higher disease burden and are known characteristics (e.g. ISS stage, prior treatments, LDH, B2M, lytic bone lesions, EMD, sBCMA) for an inferior prognosis in RRMM, irrespective of treatment
- There are few baseline characteristics that distinguish early belantamab mafodotin progressors from early pom/dex progressors, and these may offer some insight in the overall outcome of DREAMM-3:
    - Early progressors in the belantamab mafodotin group were more heavily pretreated, and while the stratification included prior lines of therapy (≤3 vs. >3), the number of prior lines of therapy was imbalanced at baseline where participants in the belantamab mafodotin, by chance, appear to have been more heavily pre-treated than participants in the pom/dex group, which may have contributed to the overall outcome
    - Early progressors in the belantamab mafodotin group had more prior lines of therapy in a shorter period of time (as indicated by the shorter time since initial diagnosis) and this could further indicate a more aggressive disease trajectory, as compared to participants in the PomDex group

Characteristics of Participants Experiencing Early Death

While the KM curves for OS show a great degree of overlap between belantamab mafodotin and pom/dex (Interim Report for Specific Obligations Section 3.5.2, Figure 5), the initial flattening of the belantamab mafodotin KM curves occurs at around 4 months. This timepoint also coincides with the PFS KM crossing of the curves, and a classification of "early" deaths using a 2-month cut-off similar to the PFS analysis would have resulted in too few events to allow a meaningful analysis, a classification of death within 4 months post randomisation was considered as 'early death'.

For early deaths, the proportion of participants who died in the first 30 days post randomization is similar between treatment groups (2.8% in each group), however a larger proportion of participants in the belantamab mafodotin group died between 1- and 3-months post randomization (Table 4). Most of the deaths in the first 4 months in both groups were due to disease progression. Death due to adverse events were infrequent and were similar between groups.

Deaths in relation to last dose, instead of in relation to time from randomisation, showed that the proportion of participants who died within 30 days of last dose of study treatment was higher in the pom/dex group compared to the belantamab mafodotin group (11% vs 7%) (Interim Report for Specific Obligations Section 3.6.2.1, Table 49).

Table 4 Nature of Early Deaths by Time Period (ITT)

Time period	belantamab mafodotin (N= 218)		Pom/Dex (N=107)	
	n	Cause of death	n	Cause of death
0-<1M	n=6 (2.8%)	Multiple Myeloma x3	n=3 (2.8%)	Heart Failure
		Sepsis		Multiple Myeloma
		Road traffic accident		Septicemia
		Cardiac arrest		
1-<2M	n=9 (4.1%)	Multiple Myeloma x6	n=3 (2.8%)	Covid-19
		Sepsis		cardiac arrest
		Trauma/Femur Fracture		Multiple Myeloma
		Sepsis/Pneumonia		
2-<3M	n=13 (6%)	Multiple Myeloma x7	n=1 (0.9%)	Covid-19
		Pulmonary infection x2		
		Febrile infection		
		Multiple Myeloma & haemorrhagic stroke		
		Covid-19		
		Septic shock, bronchopneumonia & Multiple Myeloma		
3-<4M	n=4 (1.8%)	Multiple Myeloma x3	n=4 (3.7%)	Multiple Myeloma x2
		Cardiac arrest		Unknown
				Sepsis
Total 0-4M	**N=32 (15%)**		**n=11 (10%)**	

The between-group comparison (belantamab mafodotin early deaths vs pom/dex early deaths) of baseline characteristic (Table 5), bearing in mind the 2:1 randomisation, the small subgroups and overlapping ranges, as before, showed few baseline characteristics more prominent in the early deaths in the belantamab mafodotin group vs the pom/dex group, which are aligned with an advanced/difficult to treat disease status: participants in this group are more likely to have a higher urine M protein secretion and are more likely to have EMD. Interestingly, the 11 (10%) early deaths in the pom/dex group as compared to early death in the belantamab mafodotin group, participants were likely to have more prior lines of therapy and a shorter time from diagnosis, and are more likely to have high risk cytogenetics, and moderate renal impairment.

The intra-group comparison (early progressors vs ongoing) in both groups showed that participants with early death were more likely to be slightly younger, had higher ECOG PS and ISS stage, higher serum M-protein, and higher sBCMA.

Consequently, the analysis of early deaths, similar to the analysis of early progression, did not show one specific characteristic that could identify participants at risk of earlier death in the belantamab mafodotin group. Rather, patients who died early have shown characteristics related to more advanced disease.

Table 5 Baseline Demographics and Disease Characteristics by Time of Death (<4 months, >=4 months)

	Time of Death: <4 Months		Time of Death: >=4 Months	
unit displayed is [n (%)] unless stated otherwise	**Belantamab mafodotin (N=218)**	**Pom/Dex (N=107)**	**Belantamab mafodotin (N=218)**	**Pom/Dex (N=107)**
Number of Subjects in the Subgroup	**32**	**11**	**52**	**27**
Female	13 (41)	5 (45)	24 (46)	12 (44)
Age, Median (Min, Max)	65 (43, 81)	65 (51, 78)	67 (43, 86)	72 (46, 48)
>=65; >=75	16 (50), 4 (13)	6 (55), 1 (9)	29 (56), 14 (27)	19 (70), 7 (26)
Race: WHITE	25 (81)	9 (90)	39 (78)	24 (92)
BMI (kg/m2) Median (Min, Max)	26.97 (20.3, 37.8)	27.36 (22, 34)	26.51 (18.3, 39.8)	26.83 (20.5, 40.7)
ECOG PS 0, PS 1, PS 2	10 (31), 15 (47), 7 (22)	2 (18), 7 (64), 2 (18)	20 (38), 27 (52), 5 (10)	12 (44), 13 (48), 2 (7)
ISS stage I, II, III	7 (22), 11 (34), 14 (44)	2 (18), 2 (18), 7 (64)	14 (27), 25 (48), 13 (25)	4 (15), 16 (59), 7 (26)
IgG Multiple Myeloma	16 (57)	7 (64)	38 (81)	17 (71)
Kappa Light Chain Myeloma	21 (72)	9 (90)	32 (70)	15 (60)
Serum M-Protein, g/L	21.6 (0, 67.5)	26.3 (7.7, 77.9)	17.8 (0, 77.2)	19.8 (0.2, 66.4)
Urine M-protein, mg/day	92.2 (0, 12887)	7.6 (0, 5759)	14.1 (0, 3650)	71.5 (0, 2194)
Extramedullary Disease	11 (34)	1 (9)	13 (25)	5 (19)
Lytic Bone Lesions	28 (88)	10 (91)	47 (90)	19 (70)
Lines of prior therapy, median (Min Max)	4 (2, 7)	5 (2, 6)	4 (2, 12)	3 (2, 8)
>3 lines (per CRF)	18 (56)	6 (55)	34 (65)	9 (33)
>5 lines (per CRF)	5 (15)	4 (36)	6 (12)	2 (7)
Prior Anti-CD38 (per CRF)	15 (47)	5 (45)	33 (63)	14 (52)
Months since last anti-CD38, median (Min, Max)	3 (1, 27)	5.7 (1, 29)	4 (1, 31)	1.8 (1, 20)
Prior ASCT	21 (66)	4 (36)	32 (62)	15 (56)
Years from initial diagnosis, median (Min, Max)	4.09 (1.5, 22.5)	3.19 (1.3, 16)	4.52 (1.3, 18.9)	4.10 (1.8, 14.4)
High Risk Cytogenetics [1]	12 (38)	5 (45)	17 (33)	14 (52)
Moderate Renal Impairment (>=30, <60) [2]	10 (32)	5 (45)	17 (33)	14 (52)
Severe Renal Impairment (>=15, <30) [2]	0	1 (9)	1 (2)	0
sBCMA (ug/L), median (Min, Max)	215 (20, 1179)	313 (14, 771)	99 (5, 699)	106 (13, 611)
Beta-2 Microglobulin (nmol/L), Median (Min, Max)	379 (218, 1553)	474 (164, 1521)	318 (172, 1569)	327 (148, 1286)
Albumin (g/L), Median (Min, Max)	35 (24, 50)	31 (23, 51)	38 (19, 51)	37 (4, 45)
Lactate Dehydrogenase (IU/L), Median (Min, Max)	281 (866)	278 (173, 686)	227 (84, 969)	212 (98, 733)

[1] If the subject has any of the following cytogenetics: t(4;14), t(14;16) or 17p13del., [2] per eGFR (ml/min/1.73 m2), Note: Subjects censored for PFS in this show time period are not shown in this table summary, but data are available in the source

PFS2, defined as time from randomization to disease progression after initiation of new anti-cancer therapy or death from any cause, whichever is earlier, can be used to help bridging the data gap between PFS and OS, especially if OS is still relatively immature [Matulonis, 2015]. GSK therefore performed an exploratory analysis of PFS2 on the subgroup of participants that experienced progression in the first 4 months versus PFS2 for participants who progressed on study treatment after 4 months post randomization Table 6.

This analysis needs to be caveated with several considerations requiring interpretation with caution: more participants in the belantamab mafodotin group were still on study treatment (26% vs pom/dex 21%), hence less participants in the belantamab mafodotin group will have had the opportunity to receive subsequent therapy; subgrouping by PFS time period is a post-randomisation factor, hence stratification factors may not be balanced and the ITT principle does not hold; some subgroups and number of events in the subgroups are relatively small.

Table 6 shows that participants with early disease progression (<4 months post randomization) in the pom/dex group appear to experience higher efficacy on subsequent therapies than participants in the belantamab mafodotin group, which also aligns with the previous observation that in DREAMM-3 the early progressors in the belantamab mafodotin group, by chance, had more aggressive disease, hence are also less likely to respond to subsequent therapy.

Participants with disease progression later than 4 months post randomisation in the belantamab mafodotin group appear to experience higher efficacy on subsequent therapies than participants in the pom/dex group, which is likely to be driven by the longer DOR in this groups (Interim Report for Specific Obligations Section 3.5.4, Table 40), and no detriment from subsequent treatment.

Table 6 Summary of Progression-Free Survival 2 by PFS Progression (<4 months, >=4 months)

	PFS Event: Progressed Time Period: <4 Months		PFS Event: Progressed Time Period: >=4 Months	
	Belantamab mafodotin (N=218)	Pom/Dex (N=107)	Belantamab mafodotin (N=218)	Pom/Dex (N=107)
Number of Subjects in the Subgroup	**53**	**23**	**39**	**15**
Subject Status, n (%)				
PD or death (event)	41 (77)	14 (61)	18 (46)	8 (53)
Censored, FU ended	3 (6)	0	5 (13)	1 (7)
Censored, FU ongoing	9 (17)	9 (39)	16 (41)	6 (40)
Event Summary, n (%)				
Disease Progression	20 (38)	10 (43)	13 (33)	5 (33)
Death	21 (40)	4 (17)	5 (13)	3 (20)
Estimates for PFS2 (Months) [1]				
1st Quartile	2.9	6.4	13.3	10.6
95% CI	(1.7,4.0)	(3.1,10.4)	(7.9,16.7)	(7.1,11.5)
Median	**5.5**	**11.4**	**18.7**	**12.7**
95% CI	**(4.0,7.5)**	**(6.7,-)**	**(15.7,24)**	**(8.6,-)**
3rd Quartile	14.6	-	24.0	-
95% CI	(7.3,21.7)	(13.7,-)	(18.7,24)	(11.5,-)
PFS2 Probability				
PFS2 at 6 Months	0.42	0.78	0.97	1.00
95% CI	(0.28,0.55)	(0.55,0.90)	(0.83,1.00)	(-,-)

[1] Confidence intervals for time variables are estimated using the Brookmeyer-Crowley method.

Updated DREAMM-3 OS and PFS analysis

GSK conducted a data-cut after the primary analysis, with an additional 25 weeks/5.6 months of follow-up (primary analysis DCO: 12-September-2022, repeat DCO: 03- March-2023) to provide an update to the OS and an analysis of the PFS was performed at the same time. It must be noted that this data-cut was proactively conducted to be able to share with regulatory authorities in advance of the next planned, formal, OS interim analysis that will be conducted to coincide with the DREAMM-7/DREAMM-8 primary analysis. The final updated OS and PFS analyses will be included in the final DREAMM- 3 CSR, which will be submitted to EMA as part of a future regulatory procedure.

In the updated DREAMM-3 OS analysis (DCO: 3Mar23), an additional 23 OS events were reported, 14 in the belantamab mafodotin group and 9 in the pom/dex group, increasing the overall OS maturity from 37.5% to 44.6% (Table 7). It should be noted that 10 of these events occurred prior to the 12-September-2022 primary data-cut off, but those patients were considered censored for the primary analysis due to the loss of follow up. Upon further intense follow-up and use tracking through public databases and registries GSK was able to recover the information on those 10 patients and included it in the updated analysis. The additional ~6 months of follow-up and increased data maturity have resulted in a change of OS HR from 1.14 to 1.10. The ratio of the RMST analysis has not changed. Patients continue to be followed in the DREAMM-3 study.

Table 7 DREAMM-3 Primary OS analysis and updated OS

	Primary DCO (12Sep2022)		Updated DCO (3Mar23)	
	Belantamab Mafodotin (N=218)	Pom/Dex (N=107)	Belantamab Mafodotin (N=218)	Pom/Dex (N=107)
Number of participants, n (%)				
Died (event)	84 (39)	38 (36)	98 (45%)	47 (44%)
Censored, follow-up ended	21 (10)	10 (9)	16 (7%)	8 (7%)
Censored, follow-up ongoing	113 (52)	59 (55)	104 (48%)	52 (49%)
Event summary, n (%)				
Death	84 (39)	38 (36)	98 (45%)	47 (44%)
Estimates for OS (months)[a]				
1st quartile (95% CI)	7.9 (5.5, 11.7)	8.7 (5.7, 13.0)	7.0 (5.3, 11.4)	8.9 (5.6, 13.5)
Median OS (95% CI)	21.2 (18.7, NE)	21.1 (15.1, NE)	21.7 (18.7, NE)	22.9 (16.0, NE)
3rd quartile (95% CI)	24.0 (24.0, NE)	NE	NE	NE
Stratified hazard ratio[b]				
Estimate (95% CI)	1.14 (0.77, 1.68)		1.10 (0.77, 1.56)	
P-Value	NA[c]		NA[c]	
Survival probability				
at 6 months (95% CI)	0.79 (0.73, 0.84)	0.83 (0.74, 0.89)	0.78 (0.72, 0.83)	0.83 (0.74, 0.89)
at 12 months (95% CI)	0.67 (0.60, 0.73)	0.67 (0.56, 0.76)	0.67 (0.61, 0.73)	0.70 (0.60, 0.78)
at 18 months (95% CI)	0.59 (0.51, 0.66)	0.57 (0.44, 0.67)	0.60 (0.53, 0.67)	0.58 (0.47, 0.67)
RMST Estimates at t* (months)				
Estimate (95% CI)	16.6 (15.4, 17.9)	17.0 (15.2, 18.8)	19.6 (18.0, 21.2)	19.9 (17.7, 22.1)
Difference between RMST at t* from Pom/Dex (months)				
Estimate (95% CI)	-0.4 (-2.5, 1.8)		-0.3 (-3.0, 2.4)	
Ratio of RMST at t*				
Belantamab mafodotin RMST / Pom/Dex RMST (95% CI)	0.98 (0.86, 1.11)		0.98 (0.86, 1.13)	

a. CIs estimated using the Brookmeyer-Crowley method.
b. Hazard ratios are estimated using the Cox Proportional Hazards. A hazard ratio <1 indicates a lower risk of death with this treatment compared with Pom/Dex. Hazard ratio and 1 sided p-value from stratified log-rank test are adjusted for previous treatment with anti-CD38 (yes, no), ISS staging (I/II, III), and number of prior lines of therapy (£3, >3).
c. P-value not applicable because the primary analysis of PFS failed and no further significance testing is performed
Note: The RMST is the expected survival time restricted to a specific time horizon t*. The cutoff t* for determining the RMST is the smallest value among the largest observed time across study interventions. *t* = 24.2 months for the 12Sep22 DCO and t* = 30.2 months for the 3MarDCO*

In the updated PFS analysis (DCO: 3Mar23) an additional 15 PFS events occurred, 8 in the belantamab mafodotin group and 7 in the pom/dex group. Given the 2:1 randomisation ratio, the proportion of events since the primary DCO is higher in the pom/dex group.

The additional ~6 months of follow-up have resulted in a change to the PFS HR from 1.03 to 0.92, with the point estimate now being <1 (Table 8) and the RMST difference and ratio changed in line with the PFS HR, increasingly favouring belantamab mafodotin.

Table 8 DREAMM-3 Primary PFS analysis and updated PFS

	Primary DCO (12Sep2022)		Updated DCO (3Mar23)	
	Belantamab Mafodotin (N=218)	**Pom/Dex (N=107)**	**Belantamab Mafodotin (N=218)**	**Pom/Dex (N=107)**
Number of participants, n (%)				
Progressed or died (event)	104 (48)	48 (45)	112 (51%)	55 (51%)
Censored, follow-up ended	53 (24)	36 (34)	57 (26%)	37 (35%)
Censored, follow-up ongoing	61 (28)	23 (21)	49 (22%)	15 (14%)
Event summary, n (%)				
Disease progression	92 (42)	38 (36)	100 (46%)	44 (41%)
Death	12 (6)	10 (9)	12 (6%)	11 (10%)
Estimates for time variable (months)[a]				
1st quartile (95% CI)	2.2 (1.4, 3.5)	3.1 (2.1, 3.8)	2.2 (1.4,3.5)	3.1 (2.1, 3.8)
Median (95% CI)	11.2 (6.4, 14.5)	7.0 (4.6, 10.6)	11.2 (6.6, 14.5)	7.0 (4.6, 9.9)
3rd quartile (95% CI)	NE	NE (11.3, NE)	27.8 (23.5, NE)	22.6 (11.3, NE)
Stratified hazard ratio[b]				
Estimate (95% CI)	1.03 (0.72, 1.47)		0.92 (0.66, 1.29)	
P-Value	0.558		NA[c]	
PFS probability at 6 months (95% CI)	0.60 (0.52, 0.66)	0.55 (0.43, 0.65)	0.60 (0.53, 0.67)	0.53 (0.41, 0.63)
RMST Estimates at t* (months)				
Estimate (95% CI)	11.2 (6.4, 14.5)	7.0 (4.6, 10.6)	13.6 (11.8, 15.3)	11.9 (9.4, 14.4)
Difference between RMST at t* from Pom/Dex (months)				
Estimate (95% CI)	0.7 (-1.7, 3.2)		1.6 (-1.4, 4.5)	
Ratio of RMST at t*				
Belantamab mafodotin RMST / Pom/Dex RMST (95% CI)	1.07 (0.86, 1.33)		1.13 (0.90, 1.43)	

a. CIs estimated using the Brookmeyer-Crowley method.

b. Hazard ratios are estimated using the Cox Proportional Hazards. A hazard ratio <1 indicates a lower risk of progressive disease or death with belantamab mafodotin compared with pom/dex. Hazard ratio and 1 sided p-value from stratified log-rank test are adjusted for previous treatment with anti-CD38 (yes, no), ISS staging (I/II, III), and number of prior lines of therapy (≤3, >3).

c. P-value no applicable because the primary analysis of PFS failed and no further significance testing is performed

Note: The RMST is the expected survival time restricted to a specific time horizon t*. The cutoff t* for determining the RMST is the smallest value among the largest observed time across study interventions. *t* = 22.9 months for the 12Sep22 DCO and t* = 28.5 months for the 3MarDCO*

Conclusion

GSK acknowledges the relative increase in the number of early progression events and deaths in the belantamab mafodotin treatment group in the initial months of the study.

Based on the additional analyses that have been conducted, the larger proportion of early progressors in belantamab mafodotin group could be attributed to few factors. The slight imbalance in the number of prior lines of therapy, where participants in the belantamab mafodotin treatment group, appear to have been more heavily pre-treated than participants in the pom/dex group, may have contributed to the outcome. In addition, the shorter time from the diagnosis and higher number of median prior lines indicate a more aggressive disease trajectory for participants in the belantamab mafodotin treatment group. Importantly, in most cases participants coming off study treatment early for progression were on full dose of belantamab mafodotin, and dose reductions/dose holds for adverse events are not an explanation for more early PD in the belantamab mafodotin group (Interim Report for Specific Obligations Section 3.5.1, Table 31).

Similarly, in case of death, the leading cause was MM and death due to adverse events were infrequent and were similar between groups.

It should be noted that an increased number of PFS events in belantamab mafodotintreated participants during the first months of treatment was also observed in the DREAMM-2 study (DREAMM-2 final CSR Section 6.4 (eCTD sequence 0039)), as well as with teclistamab (BCMA-CD38 bispecific antibody) in the RRMM MajesTEC-1 clinical trial [Moreau, 2022]. The 'steep drop' of early progression with belantamab mafodotin in DREAMM-3 is also not dissimilar to the hyper-progression phenomenon observed with single agent immunotherapy [Frelaut, 2019]. In contrast, published data with pom/dex in the RRMM MM-003 trial [San Miguel, 2013], showed a linear progression, again, not dissimilar to the data observed in the pom/dex group in DREAMM-3.

Still, despite the higher number of events reported in the initial few months, belantamab mafodotin demonstrated numerical improvement in mPFS (11.2 vs 7.0 months), deeper clinical responses (ORR 41% vs 36%, ≥VGPR 25% vs 8%, MRD negativity 7% vs 0%), and clinically meaningful improvement in duration of response (mDoR [NR vs 8.5 months]; DoR rate at 12-months [77% vs 50%]) when compared to pom/dex in the primary analysis of the DREAMM-3 study. While still based on immature data, the additional OS analysis conducted since the primary analysis with an additional 23 OS events, demonstrates a change in HR from 1.14 to 1.10 (37.5% vs 44.6% OS data maturity). The longer DoR and the kinetics of the DoR in the belantamab mafodotin group is expected to translate to improved OS in favour of belantamab mafodotin in future data-cuts. The corresponding additional PFS analysis demonstrates a change in HR from 1.03 to 0.92. Further updates are planned for both endpoints: PFS and OS later in 2023 to coincide with DREAMM-7 and DREAMM-8 read out, and in early 2024.

Considering the strong monotherapy activity in a significant proportion of participants, who derived benefit over prolonged period of time together with a manageable safety profile, GSK believes that belantamab mafodotin remains an important treatment option for MM.

Assessment of the MAH's response

The MAH has provided data and several different lines of argumentation so as to explain the possible reasons behind the observation that both PFS and OS K-M curves demonstrated increased number of events in belantamab mafodotin treated patients during the first months of treatment in DREAMM-3.

Regarding the characteristics of participants with early progression, it is noted that the participants in the belantamab mafodotin group were more heavily pre-treated with a higher median of prior lines of

therapy, and higher proportion of patients with 5 or more prior lines of therapy in the entire DREAMM-3 population.

Regarding the characteristics of participants by progression status 0-2 months post randomization, early progressors in the belantamab mafodotin group were slightly younger age, more heavily pre-treated (number or prior lines of treatment, prior ASCT, shorter time since initial diagnosis) and higher sBCMA at baseline.

While the results identified with cut-off values of soluble BCMA levels are interesting with median values for baseline sBCMA higher for early progressors and deaths in both arms, is does not actually explain the observation with both PFS and OS K-M curves.

For early deaths (1- and 3-months post randomization), a larger proportion of participants in the belantamab mafodotin group died. From the data provided, in it not completely clear, whether these participants were also early progressors, but it would seem likely as 59% of the early deaths were due to MM in belantamab mafodotin group. The between-group comparison seems also to point out that participants in the belantamab mafodotin group who died early had an advanced/difficult to treat disease status (taking into consideration the small number of patients in the subgroups and 2:1 randomisation).

In addition to requested data on patients with early progression events and deaths, the MAH has provided updated DREAMM-3 OS and PFS analysis with an additional 25 weeks/5.6 months of follow-up. This was not a preplanned analysis, next formal OS interim analysis that will be conducted to coincide with the DREAMM-7/DREAMM-8 primary analysis later in 2023 and final updated OS and PFS analyses will be included in the final DREAMM- 3 CSR and submitted to fulfill the SOB (due July 2024).

The additional ~6 months of follow-up and increased data maturity (from 37.5% to 44.6%) have resulted in a change of OS HR from 1.14 to 1.10 and a change to the PFS HR from 1.03 to 0.92, with the point estimate now being <1 and the RMST difference and ratio changed in line with the PFS HR, somewhat favouring belantamab mafodotin.

With more mature data, both PFS and OS results are in line with the earlier observations, showing no difference in PFS while OS being still immature.

The MAH did not provide updated PFS and OS K-M curves entire DREAMM-3 population. In addition, due the observed differences in the baseline characteristics to in the belantamab mafodotin arm (participants were more heavily pre-treated with a higher median of prior lines of therapy and more patients were with ECOG 1 and 2), the MAH could have performed subgroup PFS and OS analyses to support the assumption that participants with advanced/difficult to treat disease actually had increased number of events in belantamab mafodotin arm during the first months of treatment.

Conclusion

The MAH has provided possible reasoning behind the increased number of events in belantamab mafodotin treated patients during the first months of treatment which is acknowledged.

Based on the interim results from study DREAMM-3, the positive B/R determined based on the pivotal SAT cannot be considered to be confirmed. The study failed to demonstrate superiority in PFS, and the preliminary OS results, while not yet mature, are concerning. It needs to be assessed if the SOB-clin-004 can be considered to be fulfilled, and if other regulatory actions need to be taken.

Comments

CHMP Member Comments were received from two member states.

MS1: It is agreed with the Rap that the interim results DREAMM-3 are of concern, and it can be questioned whether the positive B/R in 4+ line can be confirmed by this study. The data do seem to confirm anti-disease activity as the response rate, depth of response and duration of response in the DREAMM-3 study seem to be at least similar than what was observed inDREAMM-2. Such an argumentation would allow to conclude that despite its failure this study does address the uncertainty regarding efficacy as identified at the time of CMA. Caveat is the fact that DREAMM-3 enrolled a less heavily pre-treated population in which generally higher activity is expected than in more heavily pre-treated subjects. Importantly, and disappointingly, the slightly higher difference in ORR and substantial longer DOR, relative to the control arm (PomDex), does not seem to translate into a clinically relevant benefit in terms of PFS (or OS), as such questioning the validity of basing an estimation of benefit on a product's activity. Given these considerations, the SAG's input on the (expected) benefit for 4+lines MM patients could be sought, together with the need to (further) confirm the B/R in this setting. Although it is noted that CSR is not yet available, it is not expected that the data would change substantially, a conclusion on the impact of the failure of this study on the B/R in approved indication should be made within this procedure. As such it is preferred to consult the SAG within this procedure instead of waiting for the final CSR in the upcoming SOB procedure

MS2: The SOB for Blenrep, DREAMM-3; has failed on its primary endpoint, PFS. Therefore, this confirmatory study is not positive, and will not become positive in a formal sense. Moreover, there is a suggestion of a detrimental effect on OS, in relation to the active comparator Pom/Dex. Therefore, one may question whether B/R remains positive in the approved indication.

Our concern is that if we affirm a positive B/R in the present Renewal process, having assessed the negative SOB, this decision will de facto not be possible to alter. Moreover, we are presently not sure we can agree that B/R is positive for the approved use.

We propose that it be discussed at the CHMP how to take this forward; e.g., whether a SAG consultation within the present procedure is possible, on whether clinical utility remains for Blenrep.

Issue *not* solved.

The MS comments are acknowledged, and thus the impact of the results on the B/R in the approved indication is raised as a Major Objection.

8.2. Other concerns

Clinical aspects

Question 1

OS results cannot be reliably interpreted in a single arm study, and should be removed from SmPC section 5.1, table 5 in line with the current CHMP policy.

Summary of the MAH's response

The Product Information has been updated to remove DREAMM-2 OS results from SmPC section 5.1 Table 5 as requested.

Assessment of the MAH's response

The MAH removed DREAMM-2 OS results from SmPC section 5.1 (table 5) as requested.

Conclusion

Issue solved.

9. Request for Supplementary Information – 2. RfSI

The MAH should provide the following supplementary information in response to Day 60 RfSI

9.1. Major Objection

Clinical aspects

1. Given the outcome of the inferential PFS analysis of study DREAMM-3, the positive B/R determined based on the pivotal SAT has not been confirmed. Moreover, given the immaturity of OS data, uncertainty about the impact on OS remains. Therefore, the applicant should justify that the benefit/risk balance remains positive in the approved indication.

9.2. Other concerns

Clinical aspects

2. Considering the number of patients still in follow-up regarding OS, the MAH should clarify how many new events will be reached in the next planned data cut-off and discuss several reasonable favourable and unfavourable scenarios the further data updates could provide, along with likelihood of these scenarios given the current data.

10. Assessment of the MAH responses to the 2. RfSI

10.1. Major objection

Clinical aspects

Question 1

Given the outcome of the inferential PFS analysis of study DREAMM-3, the positive B/R determined based on the pivotal SAT has not been confirmed. Moreover, given the immaturity of OS data, uncertainty about the impact on OS remains. Therefore, the applicant should justify that the benefit/risk balance remains positive in the approved indication.

Summary of the MAH's response

DREAMM-3 was a head-to-head study of belantamab mafodotin monotherapy against a combination treatment of two drugs, pomalidomide plus dexamethasone (PomDex), in patients who have failed at least 2 prior lines of treatment. While statistically significant superiority of belantamab mafodotin has not been demonstrated based on Progression Free Survival (PFS), the clinically meaningful single agent activity of belantamab mafodotin in heavily pre-treated Multiple Myeloma (MM) patients was confirmed with these data.

To provide a comprehensive response, GSK will touch upon several distinct topics in support of the justification for a positive benefit risk balance of belantamab mafodotin in the approved indication:

- Review of the efficacy of belantamab mafodotin, including the following:
  - o Characterisation of early progressors
  - o Comparison of DREAMM-3 to DREAMM-2
  - o Most recent updates of OS, PFS and DoR since the primary analysis of the DREAMM-3 study
- Assessment of the performance of the comparator in DREAMM-3
- Review of the safety of belantamab mafodotin
- Highlight of the Patient reported outcomes in DREAMM-3

Efficacy of Belantamab Mafodotin

In DREAMM-3, the median PFS (mPFS) at the time of the primary analysis (12-Sep- 2022) was 11.2 months in the belantamab mafodotin group vs. 7.0 months in the PomDex group; the one-year PFS survival probabilities were 48% vs. 35% respectively (Table 2).

Despite this observed benefit in mPFS and one-year PFS rate in favour of the belantamab mafodotin group, the trial failed to meet the primary endpoint based on PFS (HR = 1.03, p =0.558) (Table 2). A higher proportion of early progression in the belantamab mafodotin group relative to the PomDex group in the first 2 months, as evident by the early 'drop' of fast progressing patients and crossing observed in the PFS Kaplan-Meier (KM) curve has contributed to the negative PFS outcome of the DREAMM-3 study.

There are many baseline characteristics that distinguish early progressors from early ongoing participants equally in both groups. Most of these characteristics are reflective of an advanced disease, higher disease burden and are known poor prognostic factors (e.g. ISS stage, prior treatments, LDH, B2M, lytic bone lesions, EMD, sBCMA) for an inferior outcome in RRMM, irrespective of treatment. The phenomenon of early progression in DREAMM-3 could be potentially attributed to the biology of the late stages of MM disease, where some patients progress quickly, and early in the treatment. The larger proportion of early progressors in belantamab mafodotin group may be attributed to an imbalance in the number of prior lines of therapy. As part of a previous response within the ongoing annual renewal procedure (EMEA/H/C/004935/R/0017; eCTD sequence 043), GSK previously described that early progressors (0-2 months post randomisation) in the belantamab mafodotin treatment group appear to have been more heavily pretreated than participants in the PomDex group. The shorter time from diagnosis (4.91 vs 5.15 years) and higher median number of prior lines of therapy (4.0 [2-12] vs 3.0 [2-5]) could indicate a more aggressive disease trajectory for a subgroup of participants in the belantamab mafodotin treatment group. a subgroup of participants in the belantamab mafodotin treatment group.

The side-by-side comparison of the ITT population of the belantamab mafodotin groups in DREAMM-3 and DREAMM-2 (2.5 mg/kg) indicates that the efficacy of belantamab mafodotin in the DREAMM-2 study, as demonstrated by the response rate and depth/durability of response was confirmed in the DREAMM-3 study, acknowledging the differences in the study population between DREAMM-2 and DREAMM-3 (**Table 1**).

Table 1 Overview of DREAMM-2 and DREAMM-3 Data

	DREAMM-2 (Final Analysis)	DREAMM-3 (Primary analysis)	
	Belamaf N = 97	Belamaf N = 218	PomDex N = 107
Median follow up (months)	12.5	11.53	10.78
Demography			
Age, median (range)	65 (39, 85)	68.0 (43, 86)	68.0 (38, 90)
Prior lines of therapy; median (range)	7 (3 - 21)	4 (2 - 12)	3 (2 - 13)
> 5 prior lines (%)	66	15	8
TCR (%)	100	13	14
prior ASCT (%)	75	51	51
Time from diagnosis, median (years)	5.50	5.23	5.05
ECOG score ≥ 1 at screening (%)	67	64	54
ISS Stage at screening, I II III (%)	22, 34, 43	35, 41, 24	35, 38, 26
High risk cytogenetics at screening* (%)	27	16	15
EMD at screening (%)	23	18	18
Efficacy			
ORR (%), (95%CI)	32 (22.9, 42.2)	41 (34.2, 47.7)	36 (26.5, 45.4)
VGPR+ (%)	19	25	8
DOR (months), median (95%CI)	12.5 (4.2, 19.3)	NE (17.9, NE)	8.5 (7.6, NE)
PFS, n (%) median (95%CI)	75 (77) 2.8 (1.6, 3.6)	104 (48) 11.2 (6.4, 14.5)	48 (45) 7.0 (4.6, 10.6)
OS, n (%) OS (months), median (95%CI)	70 (72) 15.3 (9.9, 18.9)	84 (39) 21.2 (18.7, NE)	38 (36) 21.1 (15.1, NE)

NE = not evaluable

Updated PFS, OS, and DOR Data

At the time of the DREAMM-3 primary analysis, the median follow-up was 11.5 months for the belantamab mafodotin group and 10.7 months for the PomDex group. Despite the similar response rate between groups (B: 41%, Pd: 36%), more deep and durable responses were observed in the belantamab mafodotin group resulting in longer DoR, longer mPFS, and a higher probability of not a having experienced a PFS event at 6 and 12 months.

Following the primary analysis DCO, two additional data cuts were performed: first one with an additional 6 months of follow-up [+6M FU analysis]) and the second with an additional 10 months of follow-up [+10M FU analysis]). Both provide an update on the PFS and OS and allow monitoring of trends in direction. An updated analysis of DoR was also performed at the +10M FU analysis. A final updated OS and PFS analyses will be included in the DREAMM-3 Final Analysis CSR, which will be submitted to EMA as part of a future regulatory procedure.

Updated Progression-Free Survival

In the +10M FU PFS analysis, an additional 23 PFS events occurred compared to the primary analysis, 13 (6%, including 1 death) in the belantamab mafodotin group and 10 (9%, including 2 deaths) in the PomDex group bringing the PFS maturity to 54%. Given the 2:1 randomisation ratio, the proportion of events since the primary analysis DCO is higher in the PomDex group.

The additional 10 months of follow-up have resulted in a change to the PFS HR from 1.03 to 0.90 (Table 2) increasingly favouring belantamab mafodotin. The RMST difference and ratio changed in line with the PFS HR.

In addition, there was a relatively high rate of stratification errors (16% for belantamab mafodotin and 15% for PomDex) in the DREAMM-3 study at the time of randomization. These errors were mostly due to incorrect ISS stage entered in the interactive response technology (IRT) due to operational constraints where central lab data was not always available at the time the ISS stage had to be entered. Therefore, in most instances investigators were entering ISS stage based on local results. This was resolved 18 months after study start, but at that time 264 patients were already enrolled and stratified. GSK conducted a predefined sensitivity analysis using stratification data entered in the clinical database, instead of the IRT. In this analysis, the additional 10 months of follow-up have resulted in a change to the PFS HR from 0.98 to 0.85.

Table 2 DREAMM-3 Primary PFS analysis and updated PFS analyses

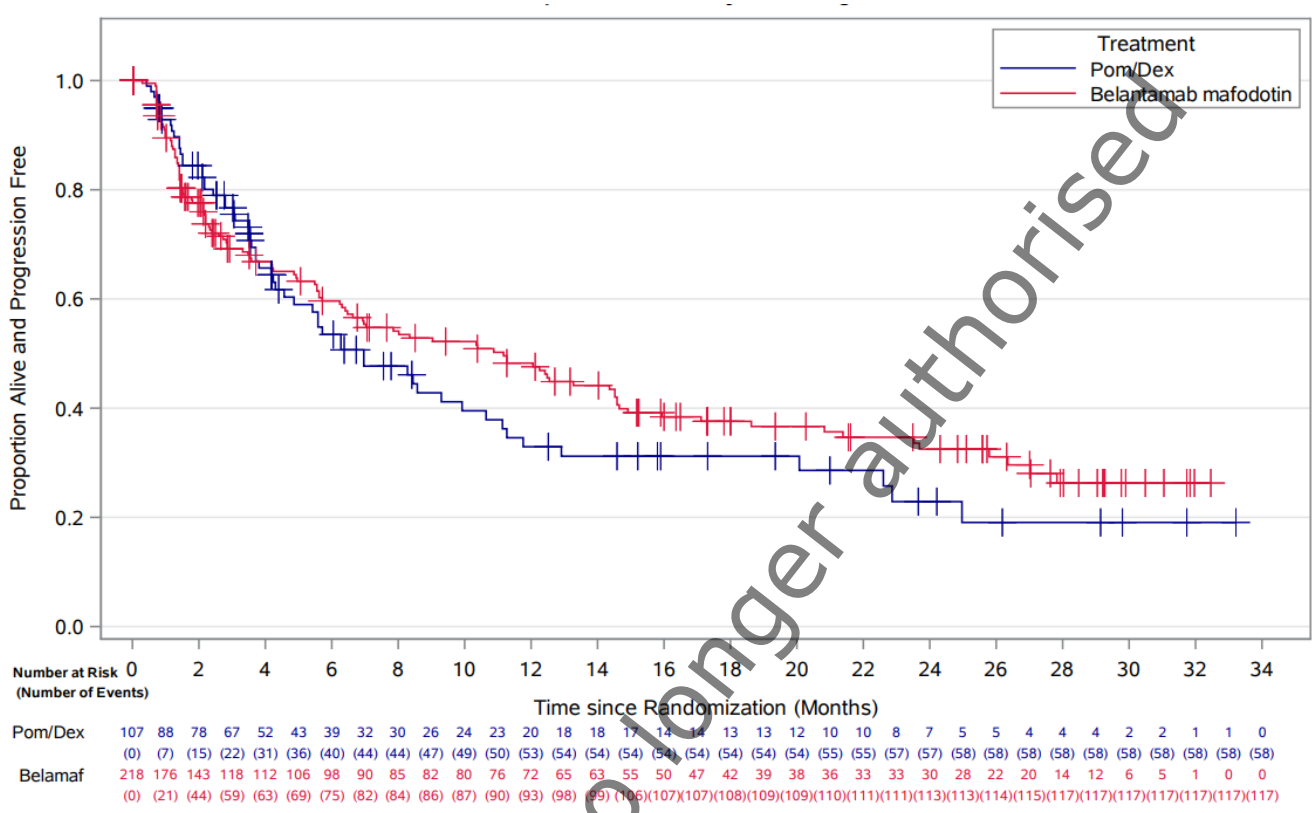
	Primary Analysis DCO (12Sep2022)		+6M FU (3Mar23)		+10M FU (3Jul23)	
	Belamaf (N=218)	**PomDex (N=107)**	**Belamaf (N=218)**	**PomDex (N=107)**	**Belamaf (N=218)**	**PomDex (N=107)**
Number of subjects, n(%)						
Progressed or died	104 (48)	48 (45)	112 (51)	55 (51)	117 (54)	58 (54)
Censored, FU ended	53 (24)	36 (34)	57 (26)	37 (35)	57 (26)	37 (35)
Censored, FU ongoing	61 (28)	23 (21)	49 (22)	15 (14)	44 (20)	12 (11)
Event summary, n (%)						
Disease progression	92 (42)	38 (36)	100 (46)	44 (41)	104 (48)	46 (43)
Death	12 (6)	10 (9)	12 (6)	11 (10)	13 (6)	12 (11)
Estimates for time variable (months)[a]						
1st quartile (95% CI)	2.2 (1.4, 3.5)	3.1 (2.1, 3.8)	2.2 (1.4,3.5)	3.1 (2.1, 3.8)	2.2 (1.4,3.3)	3.1 (2.1, 3.8)
Median (95% CI)	11.2 (6.4, 14.5)	7.0 (4.6, 10.6)	11.2 (6.6, 14.5)	7.0 (4.6, 9.9)	11.2 (6.5, 14.5)	7.0 (4.6, 10.6)
3rd quartile (95% CI)	NE	NE (11.3, NE)	27.8 (23.5, NE)	22.9 (11.3, NE)	NE (23.7 NE)	22.9 (11.3, NE)
PFS probability at 6 months (95% CI)	0.60 (0.52, 0.66)	0.55 (0.43, 0.65)	0.60 (0.53, 0.67)	0.53 (0.41,0.63)	0.60 (0.52, 0.66)	0.53 (0.42,0.64)
PFS probability at 12 months (95% CI)	0.48 (0.40, 0.56)	0.35 (0.23, 0.48)	0.49 (0.41, 0.56)	0.33 (0.22, 0.45)	0.48 (0.41, 0.55)	0.33 (0.22, 0.44)
Stratified hazard ratio[b]						
Estimate (95% CI)	1.03 (0.72, 1.47)		0.92 (0.66, 1.29)		0.90 (0.65, 1.24)	
P-Value	0.558		NA[c]		NA[c]	
Stratified hazard ratio, sensitivity analysis[d]						
Estimate (95% CI)	0.98 (0.69, 1.40)		NA		0.85 (0.61,1.18)	
RMST at t* (months)[e]						
Estimate (95% CI)	11.7 (10.3, 13.1)	11.0 (8.8, 13.2)	13.6 (11.8, 15.3)	11.9 (9.4, 14.4)	14.7 (12.7, 16.6)	12.4 (9.6, 15.1)
RMST Difference at t* from PomDex (months)						
Estimate (95% CI)	0.7 (-1.7, 3.2)		1.6 (-1.4, 4.5)		2.1 (-1.1, 5.4)	
Ratio of RMST at t*						
Belamaf RMST/ Pom/ Dex RMST (95% CI)	1.07 (0.86, 1.33)		1.13 (0.90, 1.43)		1.17 (0.91, 1.49)	

NA = not applicable, ND = not done, NE = not evaluable

a. CIs estimated using the Brookmeyer-Crowley method.
b. Hazard ratios are estimated using the Cox Proportional Hazards. A hazard ratio <1 indicates a lower risk of progressive disease or death with belantamab mafodotin compared with PomDex. Hazard ratio and 1 sided p-value from stratified log-rank test are adjusted for previous treatment with anti-CD38 (yes, no), ISS staging (I/II, III), and number of prior lines of therapy (≤3, >3).
c. P-value no applicable because the primary analysis of PFS failed and no further significance testing is performed.
d. Same as 'b' with Hazard ratio adjusted based on stratification factors as reported in the clinical database, rather than the IRT
e. Note: The RMST is the expected survival time restricted to a specific time horizon t*. The cutoff t* for determining the RMST is the smallest value among the largest observed time across study interventions. t* = 22.9 months for the 12Sep22 DCO, t* = 28.5 months for the 03Mar23 DCO, and t* = 32.5 months for the 03Jul23 DCO

The updated PFS KM curves (Figure 1) show clear and continued separation of the curves in favour of belantamab mafodotin after the early crossing.

Figure 1 Graph of Kaplan-Meier Curves of Progression-Free Survival Based on Investigator-Assessed Response (+10 Month Follow-Up Analysis)



Overall Survival

In the updated +10M FU OS analysis, an additional 36 OS events (11% of 325) were reported as compared to the primary analysis DCO, 21 (10% of 218) in the belantamab mafodotin group and 15 (14% of 107) in the PomDex group, increasing the overall OS maturity from 37.5% to 48.6% (Table 3). While the mOS remain similar, the additional 10 months of follow-up and increased data maturity have resulted in a change of OS HR from 1.14 to 1.03. These updated results show that there is no clinically meaningful difference in survival between the treatment groups.

In the sensitivity analysis using the stratification factors as entered in the clinical database, rather than the IRT, the additional 10 months of follow-up have resulted in a change to the OS HR from 1.04 to 0.97. The ratio of the RMST analysis has changed marginally, in line with the OS HR. Patients continue to be followed in the DREAMM-3 study.

Table 3 DREAMM-3 Primary OS analysis and updated OS analyses

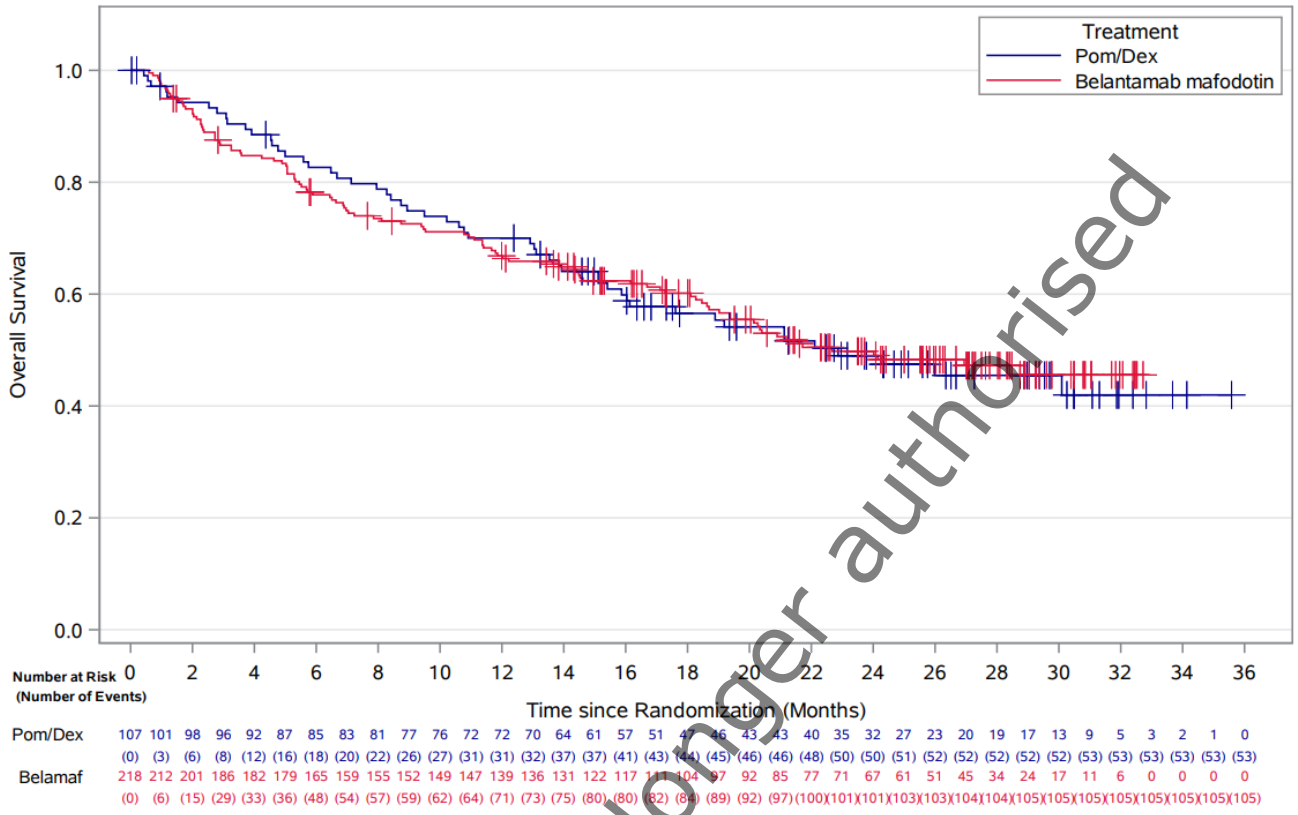
	Primary Analysis DCO (12Sep2022)		+6M FU (3Mar23)		+10M FU (3Jul23)	
	Belamaf (N=218)	PomDex (N=107)	Belamaf (N=218)	PomDex (N=107)	Belamaf (N=218)	PomDex (N=107)
OS maturity	37.5%		44.6%		48.6%	
Number of subjects, n(%)						
Died (event)	84 (39)	38 (36)	98 (45)	47 (44)	105 (48)	53 (50)
Censored, FU ended	21 (10)	10 (9)	16 (7)	8 (7)	15 (7)	8 (7)
Censored, FU ongoing	113 (52)	59 (55)	104 (48)	52 (49)	98 (45)	46 (43)
Estimates for OS (mths)[a]						
1st quartile (95% CI)	7.9 (5.5, 11.7)	8.7 (5.7, 13.0)	7.0 (5.3, 11.4)	8.9 (5.6, 13.5)	7.0 (5.3, 11.4)	8.9 (5.6, 13.5)
Median OS (95% CI)	21.2 (18.7, NE)	21.1 (15.1, NE)	21.7 (18.7, NE)	22.9 (16.0, NE)	22.7 (19.0, NE)	22.9 (15.9, NE)
3rd quartile (95% CI)	24.0 (24.0, NE)	NE	NE	NE	NE	NE
Stratified hazard ratio[b]						
Estimate (95% CI)	1.14 (0.77, 1.68)		1.10 (0.77, 1.56)		1.03 (0.74,1.43)	
P-Value	NA[c]		NA[c]		NA[c]	
Stratified hazard ratio, sensitivity analysis[d]						
Estimate (95% CI)	1.04 (0.70, 1.53)		ND		0.97 (0.69, 1.36)	
Survival probability						
at 6 months (95% CI)	0.79 (0.73, 0.84)	0.83 (0.74, 0.89)	0.78 (0.72, 0.83)	0.83 (0.74, 0.89)	0.78 (0.72, 0.83)	0.83 (0.74, 0.89)
at 12 months (95% CI)	0.67 (0.60, 0.73)	0.67 (0.56, 0.76)	0.67 (0.61, 0.73)	0.70 (0.60, 0.78)	0.67 (0.60, 0.73)	0.70 (0.60, 0.78)
at 18 months (95% CI)	0.59 (0.51, 0.66)	0.57 (0.44, 0.67)	0.60 (0.53, 0.67)	0.58 (0.47, 0.67)	0.60 (0.53, 0.66)	0.57 (0.46, 0.66)
RMST[d] at t* (months)						
Estimate (95% CI)	16.6 (15.4, 17.9)	17.0 (15.2, 18.8)	19.6 (18.0, 21.2)	19.9 (17.7, 22.1)	20.8 (19.1, 22.5)	20.9 (18.5, 23.2)
RMST Difference at t* from PomDex (months)						
Estimate (95% CI)	-0.4 (-2.5, 1.8)		-0.3 (-3.0, 2.4)		-0.1 (-3.0, 2.8)	
Ratio of RMST at t*						
Belamaf RMST / Pom Dex RMST (95% CI)	0.98 (0.86, 1.11)		0.98 (0.86, 1.13)		0.99 (0.87, 1.14)	

NA = not applicable, ND = not done, NE = not evaluable

a. CIs estimated using the Brookmeyer-Crowley method.
b. Hazard ratios are estimated using the Cox Proportional Hazards. A hazard ratio <1 indicates a lower risk of death with this treatment compared with PomDex. Hazard ratio and 1-sided p-value from stratified log-rank test are adjusted for previous treatment with anti-CD38 (yes, no), ISS staging (I/II, III), and number of prior lines of therapy (<=3, >3).
c. P-value not applicable because the primary analysis of PFS failed and no further significance testing is performed.
d. Same as 'b' with Hazard ratio adjusted based on stratification factors as reported in the clinical database, rather than the IRT
e. Note: The RMST is the expected survival time restricted to a specific time horizon t*. The cutoff t* for determining the RMST is the smallest value among the largest observed time across study interventions. t* = 24.2 months for the 12Sep22 DCO, t* = 30.2 months for the 03Mar23 DCO, and t*=32.7 for the 03Jul23 DCO

The updated Graph of OS KM is shown in Figure 2.

Figure 2 Graph of Kaplan-Meier Curves of Overall Survival (+10 Month Follow-Up Analysis)

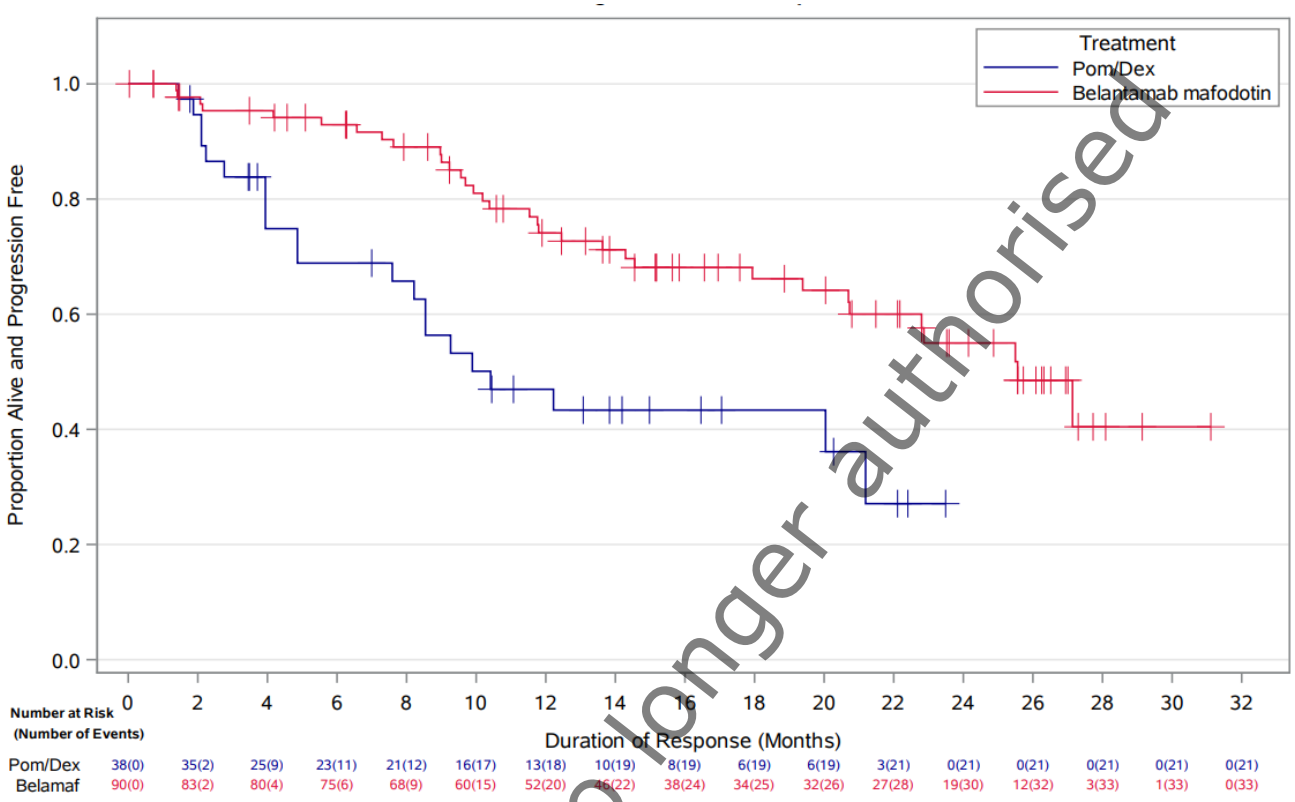


Duration of Response

For the +10M FU DoR analysis, 1 more patient in the belantamab mafodotin analysis population has experienced a response, and none in the PomDex group. The updated analysis shows a response rate of 41% vs. 36% with a mDoR for belantamab mafodotin of 25.6 months vs 9.9 months with PomDex. There were 52 (58%) participants in the belantamab mafodotin group and 13 (34%) participants in the PomDex group who had an ongoing response at 12 months.

The DoR KM curves (Figure 3) show a continued separation between the treatment groups favoring belantamab mafodotin. At the +10 Month FU DCO, 40 participants (44%) in the belantamab mafodotin group were censored and have not progressed but continued to be followed (vs n=10 [26%] in the PomDex group). Therefore, it is expected the DoR may further improve for belantamab mafodotin with additional follow up.

Figure 3 Graph of Kaplan-Meier Curves of Duration of Response Based on Investigator-Assessed Response (+10 Month Follow-Up Analysis)



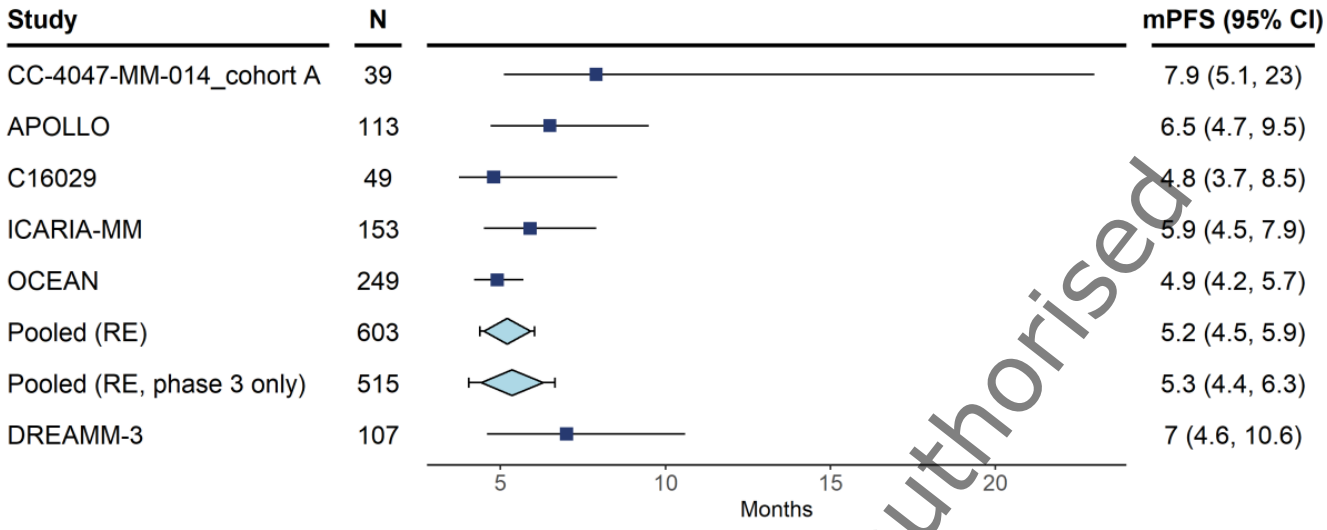
The longer duration, kinetics, and maturity of the DoR in the belantamab mafodotingroup observed in the primary PFS analysis was expected to translate into further improvements in PFS and OS with longer follow-up. Indeed, the updated efficacy data in the 2 subsequent data cuts (+6mFU, +10m FU) already demonstrated improvements for OS and PFS. Given the mechanism of action of belantamab mafodotin and the postulated induction of immunogenic cell death phenomenon, it is likely the ultimate benefit of belantamab mafodotin monotherapy is most adequately demonstrated with a longer follow-up.

Assessment of the Efficacy of PomDex in DREAMM-3

The statistical assumption for DREAMM-3 was based on the MM-03 trial where median PFS with PomDex was 4 months [Miguel, 2013]. Studies with PomDex which followed since then have demonstrated variable level of activity for mPFS in the range of 4.7 to 6.5 months (Table 5), which is exceeded with the 7 mPFS for PomDex observed in DREAMM-3.

To assess how the DREAMM-3 PomDex results compared to concurrent (2022-present) studies in the same patient populations, GSK conducted a meta-analysis of clinical trials with PomDex with matching key eligibility criteria of DREAMM-3 obtained from the CERTARA [Certara, 2023] RRMM database. The data obtained was pooled through random-effects meta-analysis (Figure 4).

Figure 4 PomDex Efficacy in 3L+ RRMM (2020-Present)



RE, random effects meta-analysis. Pooled estimates exclude DREAMM-3 [Weisel 2023]. 95% prediction intervals with and without phase 2 trial data are (4.4, 6.0) and (4.0, 6.7), respectively. APOLLO results are from 3L/4L subgroup. mPFS assumption for PomDex arm in DREAMM-3 based on mPFS of 4.0 (95% CI: 3.6, 4.7) from MM-03 trial [Miguel,2013]. In the RE analysis, the chevrons indicate the 95% CI for the overall average effect, whereas the error bars indicate the prediction interval for the study-specific effect.

The estimate of mPFS with PomDex from the meta-analysis was 5.3 months compared to the 7 months observed in DREAMM-3. With the primary efficacy analysis for DREAMM-3 having been a comparison of the distribution of PFS events between the two treatment groups, and an expected HR of 0.57 (corresponding to an increase in median PFS from 4 months to 7 months), a comparator arm that performed considerably better than previously reported will have impacted the primary efficacy analysis.

Safety of Belantamab Mafodotin

Belantamab mafodotin at 2.5mg/kg Q3W had a comparable safety profile to the DREAMM-2 study and there were no new safety signals on either treatment arm.

Specifically, ocular findings (transient corneal exam findings and visual acuity worsening) were consistent with the pattern previously reported for belantamab mafodotin in DREAMM-2 and there were no new ocular safety signals. In DREAMM-3, ocular AESIs by CTCAE (66% vs. 8%) and corneal events by KVA Scale (75% vs. 31% all corneal events; 70% vs. 23% investigator-assessed) were, as expected more frequently reported in the belantamab mafodotin group than the PomDex group. Ocular toxicity was manageable with dose modifications (dose holds and reductions). DREAMM-3 safety data were reviewed every 6 months by an Independent Data Monitoring Committee (IDMC) and are consistent with DREAMM-2 based on periodic safety reviews, and on primary safety analysis. Dose delays were more frequent with belantamab mafodotin, but a similar percentage of patients on both arms required dose reductions. The discontinuations from treatment due to an AE were 15% for belantamab mafodotin, and 17% for PomDex.

The percentage of patients experiencing an AE, or SAE were similar, with PomDex having more fatal SAEs (11 vs 7%). Thrombocytopenia was more frequent with belantamab mafodotin treatment, while neutropenia was more frequent with PomDex.

Although the incidence of AEs in the Infections and infestations SOC was similar between the 2 treatment groups, Grade ≥ 3 infections were more commonly reported in the PomDex group than the belantamab mafodotin group, including COVID-19 pneumonia (4% vs. <1%, respectively) and pneumonia (11% vs. 4%, respectively). In addition, there were fewer fatal AEs in the belantamab mafodotin group.

As expected, ocular AEs by CTCAE were noted primarily in the belantamab mafodotin group in 143 (66%) participants. The most frequently (>20%) reported preferred termswere: vision blurred (40%), dry eye (28%), foreign body sensation (26%), eye irritation (23%), and photophobia (21%). Most of these events were G1-2 in severity. The median time to onset of first ocular AE was 40 days (min 1, max 231), and the median time to resolution was 65.5 days (1-526). At database cut-off, the majority of ocular AEs (77%) were resolved. In the PomDex group, 8 (8%) of participants had an ocular AE, 5 had their event resolve prior to end of treatment exposure.

Ocular exams were performed in both treatment groups in accordance with the protocol. The resulting corneal exam findings and changes to best corrected visual acuity (BCVA) were used to derive a Keratopathy Visual Acuity (KVA) grade. The KVA grade was designed specific to participants treated with belantamab mafodotin, . The derived KVA algorithm was applied to both treatment arms providing a more objective analysis.

Corneal events as per the derived KVA Scale were reported by 80% (161/202) of participants in the belantamab mafodotin arm, with n=82 (41%) experiencing KVA Grade 3 and n=19 (9%) experiencing KVA Grade 4. The median time to resolution of the first occurrence of derived KVA Grade 2 or higher events was 66 days (range: 8-419), and most events were resolved as of last follow-up (77%). Keratopathy was reported by investigators as an adverse event in 12% of participants who received belantamab mafodotin but was present in 80% of patients on ocular exam. Fifty percent (50%) of the keratopathy present on ocular exam was Grade 3, or greater, which is very similar to the data reported in DREAMM-2. Of note, keratopathy is an abnormality of the cornea identified on eye exam and does not always correlate with clinically significant ocular symptoms such as decline in visual acuity.

Corneal events per the derived KVA Scale were reported in 48% (25/52) of patients in the PomDex arm (all G1-2, no ≥G3). The dose modifications, especially dose delays, were slightly more frequent for belantamab mafodotin than PomDex, but did not contribute to the outcome of the study with patients experiencing deep and durable responses despite dose modifications. Most patients who discontinued belantamab mafodotin treatment early did so because of disease progression and many without the need for prior dose modification, while most patients who derived long term benefit may have required a dose modification at some point in their treatment journey. Extended dose delays (>63 days) occurred in 27/218 (12%) patients in the belantamab mafodotin arm; responses were maintained or deepened in all but 3 patients during dose delays. These findings support the dose of 2.5mg/kg on Q3W schedule as an appropriate dose for monotherapy treatment with belantamab mafodotin.

In 50 patients who received long-term treatment (≥52 weeks) in DREAMM-3 (primary analysis DCO), the safety profile of belantamab mafodotin was consistent with previous reports. The majority of AEs reported occurred at, or before cycle 17 (51 weeks). For the most common AEs (>40%, any grade), few additional events occurred after cycle 17 (1 new occurrence each of dry eye, reduced visual acuity, eye irritation, and thrombocytopenia after cycle 17). Few infections (any grade) occurred after cycle 17 (COVID-19, n=5; viral infection, n=1; pneumonia influenza, n=1). No patients permanently discontinued treatment due to AEs considered related to belantamab mafodotin. This analysis further supports the safety of long-term treatment with belantamab mafodotin.

Ocular adverse events from DREAMM-3 were consistent in nature with the cumulative data which has been reported from marketed use of monotherapy belantamab mafodotin (including compassionate use/expanded access, US REMS and spontaneous reports), across the clinical programme, and the observed safety profile of belantamab mafodotin [PSUR (Reporting period 05-Aug-2022 to 04-Feb-2023; EMEA/H/C/PSUSA/00010869/202302)]. The safety data were reviewed every 6 months by an IDMC who have been informed of the data and recommended to continue the DREAMM-3 study according to the protocol with no changes to study conduct.

MAH`s conclusion

Based on GSK analysis, the outcome of DREAMM-3 does not alter the overall B/R of belantamab mafodotin (BLENREP) monotherapy, which remains positive.

The long-term benefit of belantamab mafodotin was demonstrated by a clinically meaningful response rate and the fact that, among the patients who do respond to treatment, many achieve deep responses, which in turn translate into a long duration of response. This is also reflected with the improved PFS and OS treatment effect as observed with longer follow-up in the **+10M FU** analysis.

It was noted that for a large proportion (15%) of patients, stratification factors for prior anti-CD38 treatment (1%); ISS staging (11%); prior LoT (4%) were incorrectly assigned at randomization in the IRT. This has negatively impacted the stratified hazard ratio estimate for the primary analysis which used the IRT assigned strata. A pre-defined sensitivity analysis that used the correct stratification values per the baseline CRF showed incremental improvement in these estimates in favor of belantamab mafadotin for both PFS and OS.

The updated **+10M FU** DREAMM-3 PFS analysis changed the stratified HR estimate from 1.03 to 0.90, (from 0.98 to 0.85 if stratification from the clinical database was used instead from the IRT). The PFS KM curve show clear and continued separation of the curves in favour of belantamab mafodotin after the initial crossing. Updated OS analysis changed HR estimate from 1.14 to 1.03 (1.04 to 0.97 if using the stratification as assigned at baseline from the clinical database), indicating no clinically relevant difference between arm, and no detriment. Although ORR remained similar between the two arms (41% vs. 36%), the updated DoR analyses continue to demonstrate long term efficacy for responders with a mDoR of 25.6 month for belantamab mafodotin compared to 9.9 months for the PomDex arm. More patients in the belantamab mafodotin arm maintained their response at 12 months (52/90 [58%] vs. 13/38 [34%]. More responders remain in follow-up in the belantamab mafodotin arm (40/90 [44%] vs. 10/38 [26%]) at the time of the **+10** Month **FU**. The more than two and a half times improvement in the mDoR further illustrates the clinically meaningful benefit observed with belantamab mafodotin in this difficult to treat population. Therefore, the data from the DREAMM-3 study confirm the outcome from the DREAMM-2 study as seen with the response rate and the depth/durability of response. No new safety signals were observed, even for participants on treatment for a year or longer. Corneal events are manageable with dose modifications, which in turn do not impact efficacy. PRO data indicate that belantamab mafodotin is tolerable, that patients feel less fatigued, a common complaint in patient receiving treatment for MM, and that patients are 'little bothered' by the side effects of belantamab mafodotin.

Importantly, there are two additional large phase 3 randomized trials with Blenrep expected to read out later this year (DREAMM-7 and DREAMM-8). Both studies are conducted in combination with SOC treatments, and in less heavily pre-treated patients with RRMM. If positive, they will deliver additional evidence to support the value of Belamaf as an additional treatment option for patients.

There are many treatment options for MM patients for first and second line, but options are limited post exposure to immunomodulatory drugs and/or anti-CD38 and treatment with a different mechanism of action give patients a better chance of prolonged response to subsequent treatment. The available data from DREAMM-3 and the totality of the in the approved indication as determined during the initial conditional marketing authorisation based on the results from the DREAMM-2 study.

Assessment of the MAH's response

The MAH has provided updated DREAMM-3 OS and PFS analysis with an additional ~10 months of follow-up (data cut-off 3rd of July 2023, primary analysis 12th of September 2022). This was not a preplanned analysis, next formal OS interim analysis that will be conducted to coincide with the DREAMM-7/DREAMM-8 primary analysis later in 2023 and final updated OS and PFS analyses will be included in the final DREAMM- 3 CSR and submitted to fulfill the SOB (due July 2024).

The results of the several data updates (both additional ~6 and ~10 months of follow-up) and increased OS data maturity (from 37.5% to 48.6%) resulted in a change of OS HR from 1.14 to 1.03 and a change to the PFS HR from 1.03 to 0.90, with the point estimate now being <1 and the RMST difference and ratio changed in line with the PFS HR.

While the updated PFS and OS data both appear to show slight improvement in both PFS and OS results, these *ad hoc* analyses do not provide suffiencient evidence to overcome to originally negative primary analysis as per protocol. Further on, while the data updates seem to confirm that no detrimental OS results will be expected at the time of the final analysis, no benefit in terms of improved PFS or OS (belantamab mafodotin vs. pom/dex) are likely to occur, either.

To assess how the DREAMM-3 PomDex results compared to concurrent (2022-present) studies in the same patient populations, GSK conducted a meta-analysis of clinical trials with PomDex with matching key eligibility criteria of DREAMM-3 obtained from the CERTARA RRMM database. The estimate of mPFS with PomDex from the meta-analysis was 5.3 months compared to the 7 months observed in DREAMM-3. The results demonstrate considerable variety in responses between studies, and confirm that the efficacy assumption of PFS of 4 months for pom/dex used for study planning was overly optimistic.

The Applicant also provided arguments related to patient-reported outcomes (PROs). However, the value is considered limited, as the study was open label.

Conclusion

Based on the interim results from study DREAMM-3 (and from two additional, not preplanned analyses), the positive B/R determined based on the pivotal SAT cannot be considered to be confirmed. The study failed to demonstrate superiority in PFS, and the preliminary OS results, while not yet mature, are concerning. It needs to be assessed if the SOB-clin-004 can be considered to be fulfilled, and if other regulatory actions need to be taken. The outcome of the SAG consultation (7th of September 2023) is awaited.

Comments

CHMP Member Comments were received from one member state, supporting the Rapporteur's assessment and conclusion.

10.2. Other concerns

Clinical aspects

Question 2

Considering the number of patients still in follow-up regarding OS, the MAH should clarify how many new events will be reached in the next planned data cut-off and discuss several reasonable favourable and unfavourable scenarios the further data updates could provide, along with likelihood of these scenarios given the current data.

Summary of the MAH's response

As described in the response to the Major Objection above, in the updated +10M FU DREAMM-3 OS analysis (DCO: 03Jul23), an additional 36 OS events were reported as compared to the primary DCO, 21 (10%) in the belantamab mafodotin group and 15 (14%) in the PomDex group, increasing the overall OS maturity from 37.5% to 48.6 % (Table 3). The additional +10M FU data and increased data maturity of 48.6% resulted in a change of OS HR from 1.14 to 1.03 (1.04 to 0.97 if using baseline stratification values instead of IRT). Patients continue to be followed in the DREAMM-3 study.

This updated data provide emerging OS data from the study, and demonstrate a trend in direction which may offer insight into potential scenarios for planned future data cuts.

The next data cut-off from the study is planned to occur on 01-November-2023, which based on current projections would provide a total of approximately 170 events (52% maturity; 68% IF).

Assuming a similar trend in event accrual as currently seen, it is predicted that another 12 events will be accrued; 6 (3%) in the belantamab mafodotin arm and 6 (6%) in the PomDex arm. A central forecast for the 01-November-2023 data cut-off will be a stratified HR = 1.00. This reflects the survival patterns observed from the primary analysis and can be considered the most likely scenario. A theoretical scenario that would be most favourable to belantamab mafodotin would be if 12 additional events were all observed in the PomDex group. This is forecast to give a stratified HR = 0.86. Conversely, the scenario that would be least favorable to belantamab mafodotin would be if all 12 additional events are observed in the belantamab mafodotin group, with 0 in the PomDex group. This is forecast to give a stratified HR = 1.13. Both this and the opposite scenario described above represent extremes and are unlikely given observed event accrual. A more likely scenario would be to observe a slower accrual of OS events in the belantamab arm relative to PomDex due to the substantially greater durability of response and the greater number of responders that remain on study without disease progression or death. This can be confirmed with continued follow-up.

The Final OS analysis from the DREAMM-3 study will be included in the DREAMM-3 Final Analysis CSR, which will be submitted to EMA as part of a future regulatory procedure to fulfil the DREAMM-3 Specific Obligation (SOB-clin-004). The due date for this Specific Obligation is July 2024. GSK are monitoring the event rate of the DREAMM-3 study and will submit a request for an extension to the Specific Obligation deadline via a separate regulatory procedure if needed.

Assessment of the MAH's response

The MAH has provided the possible scenarios regarding the outcome of the final OS analysis. The expected number of future events is low. In any case, the impact of the future data updates are not likely to change the current observation with no OS benefit of belantamab mafodotin vs. pom/dex. Interestingly, the efficacy in the advanced/difficult to treat disease status subjects (like in the currently authorized indication) seems to be worse in subjects treated belantamab mafodotin, further questioning also the benefit-risk of Blenrep in the currently authorized indication.

Conclusion

The MAH has provided the possible scenarios regarding the outcome of the final OS analysis which is not likely to change the current finding with no OS benefit of belantamab mafodotin vs. pom/dex. The proposed extension to the Specific Obligation deadline via a separate regulatory procedure (if needed) is thus considered to be of no additional value.

10.3. Questions to be posed to additional experts

Questions for consultation with the SAG-Oncology:

1. Given that DREAMM-3 failed to establish a PFS Benefit, and the immaturity of OS data, does the SAG consider that available evidence overall supports efficacy in the target population (5L+)?
2. How does the SAG view the safety profile of Blenrep considering the currently approved 5L+ indication?

Responses from the SAG-Oncology held on September 7th, 2023:

Given that DREAMM-3 failed to establish a PFS Benefit, and the immaturity of OS data, does the SAG consider that available evidence overall supports efficacy in the target population (5L+)?

The DREAMM-3 trial trial did not demonstrate the planned significant superiority on true clinical endpoints PFS, OS or HR-QOL comparing Blenrep with POM/DEX and is so far a negative trial. The SAG agreed that the primary analysis and exploratory analyses presented from DREAMM-3 fail to provide evidence of efficacy in the approved indication.

Although visual exploration of the PFS curves and point estimates of the hazard ratio show a similar range to POM / DEX, also in terms of objective response rate in DREAMM-3, this cannot be understood as demonstrating similar efficacy according to scientific standards, also in view of the width of the confidence intervals and the effect of POM / DEX on PFS that is known to be relatively limited. In addition, the PFS curves may be affected by informative censoring possibly due to rapid progressions; this further hampers any conclusion about a possible similar effect. Any formal comparison of PFS would also need to rule out informative censoring, for example, considering different reasons for discontinuation (toxicity v. other), to explore the possible impact of informative censoring.

In conclusion, efficacy has not been confirmed on the basis of DREAMM-3 in the target population.

Notwithstanding the lack of evidence of efficacy, it was also agreed that the patient population of DREAMM-3 is different than in the approved indication, which is a more advanced population with more lines of prior therapies. This would have further hampered a demonstration of efficacy due to the necessary assumptions and extrapolation, even if the trial had been positive.

The SAG members agreed that in multiple myeloma, even acknowledging the availability of numerous approved treatments in relapsed / refractory disease, there are limited situations where patients are not eligible for other available effective options for example due to frailty or important ongoing toxicity (e.g. neurotoxicity). In such individual patients, a product like Blenrep with an interesting antitumor activity (32% durable response rate in the phase 2 DREAMM-2 study) may potentially be considered as a useful "last-line" option in individual patients with no other established therapeutic options.

However, the activity in this "last line" population requires strong assumptions since Blenrep activity is not known in this population (the phase 2 study was conducted in a different population with likely better prognosis and other characteristics).

How does the SAG view the safety profile of Blenrep considering the currently approved 5L+ indication?

Overall, the toxicity was considered significant and the ocular toxicity was considered of concern. However, it is acknowledged that management of the toxicity may improve over time and in some situations the lack of infections may be an advantage compared to other treatment options. Thus, the toxicity profile needs to be considered in the benefit-risk balance, especially in a heavily pretreated patient population as the target population. Given the lack of evidence of efficacy, the balance may be questionable but in the end this remains to be decided by patients and doctors in the right clinical context.

11. Re-examination of the initial CHMP Opinion

11.1. Introduction

In accordance with Article 9(2) of Regulation (EC) No. 726/2004, the MAH for Blenrep requested the re-examination of the CHMP opinion for BLENREP Annual renewal on 21 September 2023 and provided a detailed justification for this re-examination request.

In addition, the MAH requested a Scientific Advisory Group to support the re-examination request.

Finally, in response to the negative CHMP Opinion, the MAH proposed the following modified indication for Blenrep monotherapy (modifications from the currently approved indication in bold):

*BLENREP is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody**, who have** demonstrated disease progression on the last therapy, **and where there is no other suitable alternative treatment option (see Section 5.1)**.*

11.2. Grounds for re-examination as submitted by the MAH

The MAH presented their detailed grounds in writing on 25 October 2023 and at an oral explanation on 12 December 2023. The MAH's grounds for re-examination are presented below.

11.2.1. BLENREP Demonstrated Robust ORR and DoR Across Clinical Studies, Real World Data (RWD) and Expanded Access Programs (EAP) in Patients with RRMM

11.2.1.1. DREAMM-2 (2.5 mg/kg Q3W dose arm)

The DREAMM-2 study enrolled a highly refractory MM patient population. Participants were triple class refractory (TCR) and had a median of 7 or more lines of prior therapy (range 3-21).

BLENREP showed a clinically relevant activity with deep and durable responses, with an ORR of 32% and a mDoR of 12.5 months in DREAMM-2 (**Table 1**). These are meaningful results in this heavily pre-treated population with otherwise short, expected survival (**Figure 9**).

Table 1. Efficacy data in DREAMM-2 Final Analysis (2.5 mg/kg)

	BLENREP **N=97**
ORR (%) (95% CI)	32 (23, 42)
sCR (%)	2
CR (%)	7
VGPR (%)	9
PR (%)	13

Minimal response (%)	4
Stable disease (%)	28
Progressive disease (%)	30
Time to Response, months (95% CI)	1.5 (1.0, 2.1)
Median DoR, months (95% CI)[a]	12.5 (4.2, 19.3)
Median PFS, months (95% CI)	2.8 (1.6, 3.6)
Median OS, months (95% CI)	15.3(9.9, 18.9)

a Median duration of response in months defined as: the time from first documented evidence of partial response (PR) or better until the earliest date of documented disease progression (PD) per IMWG, or death due to PD among participants who achieved an overall response, i.e., confirmed PR or better.

CHMP comment

While the DREAMM-2 study indicated a potential treatment effect from Blenrep in RRMM, it cannot be regarded as confirmatory of efficacy or provide the foundation for a positive/benefit risk assessment.

Since the last patient in DREAMM-2 was enrolled, the treatment field in RRMM has changed dramatically with the authorisation of Abecma, Carvykti, Tecvayli, Talvey and Elrexfio (on 13-OCT-2023, awaiting marketing authorisation). This is of particular concern with regard to the potential efficacy of Blenrep, as four of these products also target BCMA (all except Talvey). The Applicant argues that some patients are too frail for treatment with CAR-T cell products or bispecific antibodies and Blenrep would be a suitable medicinal product for such patients.

However, patients could have been exposed to BCMA-directed therapies in earlier lines –rather than in very late lines– or in last line setting, where the MAH argues that Blenrep should be an option. With the current available data, there is uncertainty regarding both efficacy and safety of Blenrep in patients with prior exposure to BCMA-directed therapies. Thus, the results on treatment effect from DREAMM-2 cannot be used to support the extrapolation implied by the proposed modified indication.

11.2.1.2. DREAMM-3

The clinical activity of Blenrep monotherapy from DREAMM-2 has been replicated in the Phase 3, randomized, controlled study DREAMM-3, as demonstrated by the response rate, depth of response, and DoR, while acknowledging the differences in the study populations between DREAMM-2 and DREAMM-3. The primary analysis of DREAMM-3 was conducted in September 2022 (**Table 2**). An updated analysis of efficacy was conducted in July 2023 with 10 months of additional follow-up. The latter analysis is descriptive only without formal statistical comparisons. However, due to the randomized nature of the study, and no change in study conduct or schedule of follow-up since the primary analysis, the treatment estimates allow for reliable interpretation.

In the updated 10 Month Follow-up Analysis (03 July 2023) the ORR remained the same (41% vs. 36%), and patients receiving Blenrep also achieved deep responses, with 28% achieving VGPR or

better compared to 13% on the Pom/Dex arm (**Table 2**). The median DoR was 25.6 months for the Blenrep monotherapy group and 10.4 months for the Pom/Dex group (**Figure 1**).

K-M plot for DoR by Investigator in the primary analysis showed a clear and early separation in favour of Blenrep which was maintained over time (

Figure 2).

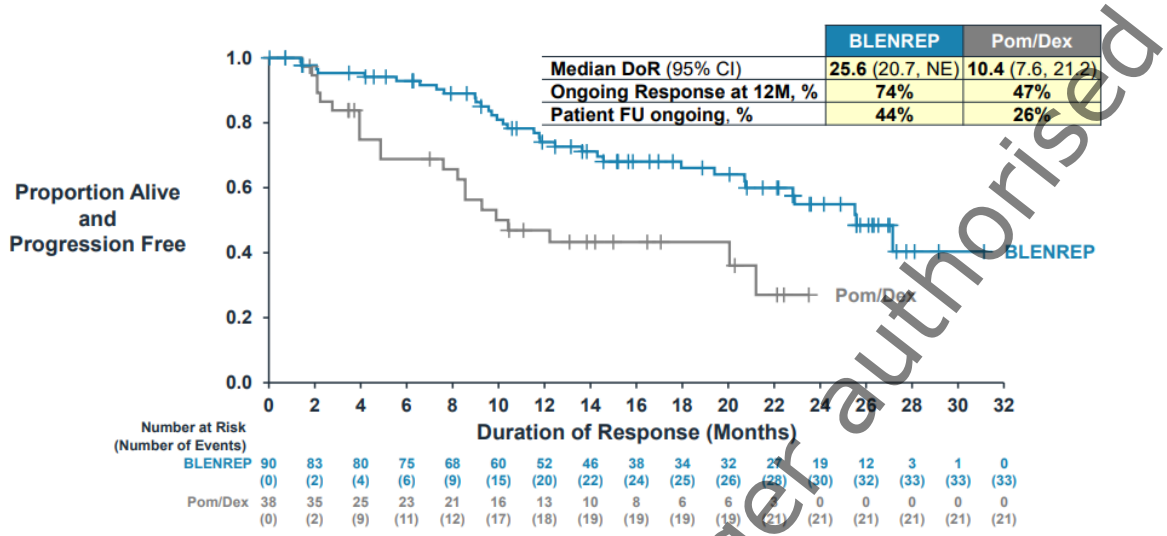
Patients in the Blenrep arm had a 74% chance of maintaining their response at 12 months compared to 47% with Pom/Dex. In addition, 44% of the Blenrep responders had not progressed yet and were censored at the time of analysis, compared to 26% of Pom/Dex responders. Consequently, the DoR may further improve with additional follow-up.

Table 2 DREAMM-2 and DREAMM-3 ORR and DoR Results

	DREAMM-2 Final Analysis	**DREAMM-3 Primary Analysis**		**DREAMM-3 +10M FU Analysis**	
	BLENREP (N=97)	**BLENREP (N=218)**	**Pom/Dex (N=107)**	**BLENREP (N=218)**	**Pom/Dex (N=107)**
Overall Response Rate, n (%) sCR+CR+VGPR+PR	31 (32)	89 (41)	38 (36)	90 (41)	38 (36)
95% CI	(23, 42)	(34, 48)	(26, 45)	(35, 48)	(27, 45)
Responders ≥ VGPR, %	18	25	8	28	13
Median time to response, months (range)	1.5 (1.0, 2.1)[a]	2.10 (0.7, 12.5)	1.53 (0.7, 18.8)	ND	ND
Estimates for DoR PD and all deaths					
N	31	89	38	90	38
Progressed or died	19 (61)	21 (24)	13 (34)	33 (37)	21 (55)
Censored, follow-up ended	12 (39)	15 (17)	7 (18)	17 (19)	7 (18)
Censored, follow-up ongoing	0	53 (60)	18 (47)	40 (44)	10 (26)
Median (95% CI), months	12.5 (4.2,19.3)[b]	NE (17.9, NE)	8.5 (7.6, NE)	25.6 (20.7, NE)	10.4 (7.6, 21.2)
Probability of Maintaining Response at 12 Months (95%CI)	53% (32, 70)	77% (64, 85)	48% (26, 68)	74% (63, 83)	47% (30, 63)

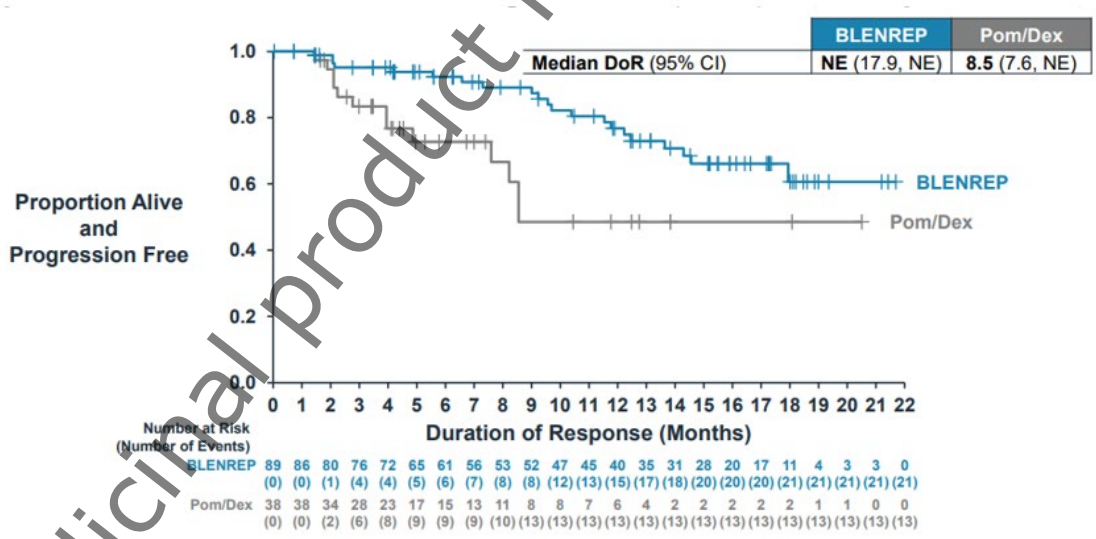
a. 95% CI, b. Analyzed based on deaths due to PD.

Figure 1. Kaplan-Meier Curve of DoR (10 Month Follow-up Analysis)



CI: confidence interval; DoR: duration of response; FU: follow up; NE: not estimable
Data cutoff 03 July 2023

Figure 2. Kaplan-Meier Curve of DoR based on Investigator-assessed response (primary analysis)



CI: confidence interval; DoR: duration of response; NE: not estimable
Data cutoff 12 September 2022

CHMP comment

The MAH is right that the findings of DREAMM-3 corroborate the data on ORR/DoR that supported the initial approval in the absence of comprehensive data. However, the purpose of this study was to provide confirmation of efficacy in the form of evidence of an impact on PFS and OS. In addition, as duration of response only occurs in responders, between arm comparisons of DoR are not randomised comparisons. PFS would be the appropriate comparison, which encompasses the impact of DoR.

The DREAMM-3 study failed to demonstrate statistical superiority of Blenrep over Pom/Dex with regard to the primary endpoint of PFS. Additionally, the OS curves show a higher proportion of early deaths in the Blenrep arm.

In conclusion, results on DoR (from the limited proportion of responders) of DREAMM-3 does not confirm efficacy of Blenrep in the population studied in DREAMM-3, and data cannot be extrapolated to confirm a positive benefit/risk of Blenrep treatment in the proposed modified indication.

11.2.1.3. RWE and compassionate use data confirm durable response rates

Outside of clinical trials, efficacy data on Blenrep are available from published real-world evidence and compassionate use studies on approximately 800 patients. Most (~80%) of these patients are in the 5L+ TCR population.

Consistent efficacy and safety data are also observed from Blenrep real-world evidence and expanded access programs in France, Spain and the United Kingdom (**Table 3**). These data independently corroborate the results from interventional clinical trials led by GSK, based on the objective endpoint of ORR and DoR. Some of those results have already been published in peer reviewed journals. Due to the late line target population and the objectivity of the endpoint (response rate), the real-world data provide further evidence of benefit in clinical practice.

The results from EAP and Named Patient Programme (NPP) studies from France, and Spain, and the UK are consistent with the DREAMM-2 data with ORR ranging from 27% to 62%.

Table 3 ORR and DoR for 5L+ TCR Patients in EAP/Compassionate Use Studies

	DREAMM-2 N=97	**EAP France N=153**	**EAP Spain N=100**	**NPP UK N=56**
Patients with a response ≥PR	36	41	36	35
ORR (95% CI), %	32 (23, 42)	27 (20, 34)	36 (27, 46)	62 (48, 75)
DoR (events)	19	23	NA	10
Median DoR (95% CI), months	12.5 (4.2,19.3)[a]	9.0 (3.3, 16.6)	NA	15.9 (3.2, 15.9)

Note: Populations were based on 5L+ TCR patients and also those who had ≥4 LoT before receiving BLENREP.

Source: Data on file

[a] Analyzed based on deaths due to PD.

Published RWE, EAP, and NPP data from non-comparative studies (**Table 4**) with majority of patients being triple class refractory demonstrated that heavily pre-treated patients who responded to

treatment derived a clinical benefit that corroborates the benefits observed in DREAMM-2 (Table 1). Studies were chosen based on the latest publication with the longest follow-up time.

The outcomes from 6 independent studies in more than 400 patients show the consistent benefit of BLENREP in heavily pre-treated, triple class refractory MM with an ORR between 31-52%.

Table 4 Published Real World, EAP, and NPP Studies with Triple Class Refractory Patients

	DREAMM-2 (Final Analysis) N=97	Spanish Cohort N = 156	Israel Cohort N = 106	French Cohort N = 97	Mayo Clinic N = 36	Italian Cohort N=67	Athens Cohort N = 27
Type of Study	Clinical Trial	EAP	EAP	EAP	RWE	NPP/EAP/EMN	NPP
Publication year	2022	2023	2022	2023	2021	2023	2023
Median Follow-up (mos)	12.5	10.9	11.9	Not reported	6	12	Not reported
Age (median, range)	65 (39-85)	73 (40-89)	69 (36-88)	66 (37-82)	61 (37-83)	66 (42-82)	65 (41-81)
Prior lines (median, range)	7 (3-21)	5 (1-10)	6 (2-11)	5 (3-12)	8 (7-11)	6 (4-10)	5 (4-10)
Triple-class refractory (%)	**100%**	**88%**	**73%**	**56.7%**	**100%**	**100%**	**100%**
Median PFS (mos)	2.8	3.6	4.7	3.5	2	3.7	2
Median OS (mos)	15.3	11.1	14.5	9.3	6.5	12.8	16
ORR (%)	**32%**	**41.8%[b]**	**45.5%**	**38.1**	**33%**	**31%**	**52%**
Median DoR (mos)	**12.5[a]**	**13.9[b]**	**8.1**	**9**	**5**	**13.8**	**Not reported**
Time to Response	1.5 months	1 month	23 days	Not reported	Not reported	Not reported	Not reported

Sources:de la Rubia, 2023;Ntanasis-Stathopoulos, 2023; Offidani, 2023; Shragai, 2023; Talbot, 2023; Vaxman, 2021, 2021, [a] Analyzed based on deaths due to PD, [b] ORR and DoR for the Spanish cohort is defined by ≥MR (MR: n=3); all other cohorts ORR and DoR based on ≥PR.

CHMP comment:

The Applicant has presented observational data in support of their efficacy claim for Blenrep. Due to limited sample size, selection bias, lack of randomisation and lack of a relevant comparator, observational data cannot be used to isolate or confirm efficacy for Blenrep. When assessing the data from the triple class refractory (TCR) population, it is noted that median PFS varies between 2 and 3.7 months in a rather young RRMM population (average age at diagnosis for multiple myeloma is around 70 years).

In conclusion, the observational data presented do not confirm the efficacy of Blenrep treatment in the proposed modified indication and cannot be used to replace the failed SOB-clin-004 (DREAMM-3).

11.2.2. Further evaluation of DREAMM-3 efficacy results

11.2.2.1. Additional analyses of PFS and OS

The data from DREAMM-3 show that Blenrep monotherapy is at least as active as the Pom/Dex combination. Furthermore, responders are observed to have a substantial clinical benefit demonstrating a ~2.5 times longer median duration of response compared to responders in the Pom/Dex group.

In addition, the 10M Follow-Up Analysis shows a trend for the Blenrep PFS and OS Hazard Ratios to improve over time (**Table 5**). The HR for Blenrep versus Pom/Dex for both PFS and OS consistently improved from the Primary Analysis to the Follow-Up Analyses with an additional 10 months.

Table 5. HRs for PFS and OS analyses

	Primary Analysis (DCO 12Sep2022)		**+10M FU Analysis (DCO 03Jul2023)**	
	Belamaf (N=218)	**Pom/Dex (N=107)**	**Belamaf (N=218)**	**Pom/Dex (N=107)**
Estimates for PFS (months)				
Median (95% CI)	11.2 (6.4, 14.5)	7.0 (4.6, 10.6)	11.2 (6.5, 14.5)	7.0 (4.6, 10.6)
Stratified hazard ratio Estimate (95% CI)	1.03 (0.72, 1.47)		0.90 (0.65, 1.24)	
PFS rate at 12 months Estimate (95% CI)	0.48 (0.40,0.56)	0.35 (0.23,0.48)	0.48 (0.41,0.56)	0.33 (0.22,0.44)
Estimates for OS				
OS maturity	37.5%		48.6%	
Median OS (95% CI)	21.2	21.1	22.7	22.9

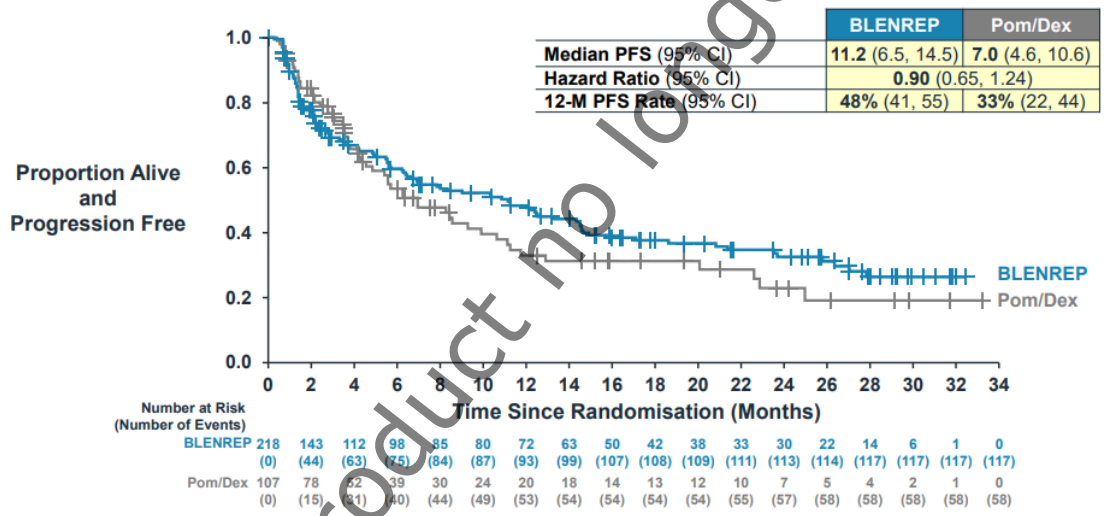
	(18.7, NE)	(15.1, NE)	(19.0, NE)	(15.9, NE)
Stratified Hazard Ratio				
Estimate (95% CI)	1.14 (0.77, 1.68)		1.03 (0.74,1.43)	

NE = not evaluable

Stratified Hazard ratios are estimated using the Cox Proportional Hazards, accounting for previous treatment with anti-CD38 (yes, no), ISS staging(I/II, III), and number of prior lines of therapy (≤3, >3) as stratification factors. A hazard ratio <1 indicates a lower risk of progressive disease or death with belantamab mafodotin compared with Pom/Dex.

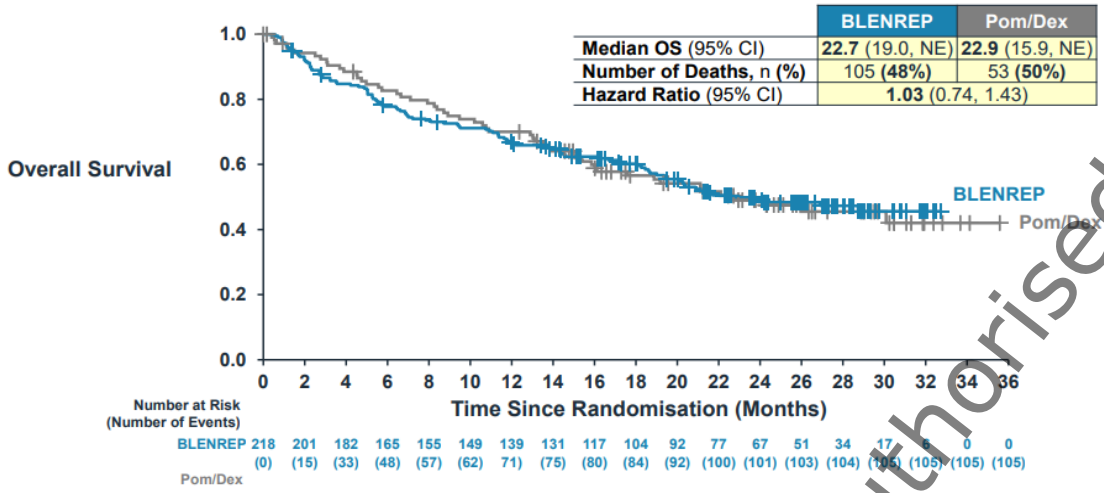
Kaplan-Meier curves for PFS (**Figure 3**) and OS (**Figure 4**) from the 10-Month Follow-up Analysis are provided for reference and comparison. The additional 10-month follow-up showed a clear separation between arms for PFS in favour of Blenrep, with a HR of 0.9 (95%CI: 0.65,1.24) and a 12-month PFS rate of 48% vs. 33%. Due to the fact that there are more responding patients in the Blenrep arm that remain on treatment, it is expected that DoR, and with that PFS and OS, may further improve for Blenrep with longer follow up.

Figure 3 Kaplan-Meier Curve of PFS Based on Investigator-Assessed Response (10 Month Follow-up Analysis)



CI: confidence interval; PFS: progression-free survival
Data cutoff 03 July 2023

Figure 4 Kaplan-Meier Curve of OS (10 Month Follow-up Analysis)



CI: confidence interval; NE: not estimable; OS: overall survival
Data cutoff 03 July 2023

CHMP comment

The DREAMM-3 study was set up with a superiority design, in order to confirm the efficacy and safety of Blenrep in a randomised setting, using pom/dex as comparator. The study did not have a non-inferiority design, and it is not evident that this would have been accepted.

The study results may be interpreted as to say, that there is no large differences between the efficacy of Blenrep and Pom/dex in the study population. However, there is no solid statistical basis for that inference. In addition, no consideration to non-inferiority was made in the planning of the DREAMM-3 study. For instance, there was no predefined non-inferiority margin and the sample size determination was based on a superiority design. Therefore, in terms of PFS and OS, the statistical analysis from DREAMM-3 does not demonstrate that Blenrep monotherapy is at least as active as the pom-dex combination.

In the KM curve for PFS an increased rate of early progression in the Blenrep arm is noted, suggesting limited activity of Blenrep. Later a crossing of the curves is noted. The Applicant has provided additional 10 months follow-up and an updated HR (not alpha protected). Dose modifications and interruptions due to ocular toxicity were common in the Blenrep arm and this is a potential explanation for the rate of early progressors.

While the PFS results fail to show any benefit of Blenrep over pom-dex, the OS data are even more concerning and raise suspicion of potentially fatal risks associated with Blenrep treatment with a HR of 1.14 (0.77, 1.68) at the time of primary analysis. The survival curves first cross after approximately 13 months due to an increased number of early deaths in the Blenrep arm. A potentially increased risk of early death would be of concern in any treatment line, but this becomes of utmost importance for Blenrep in its approved 5L+ indication and in the intended use of the product as a "last resort" with the new modified proposed indication. There are no randomised data available for Blenrep that support a PFS or OS benefit of the drug. On the contrary, there is potential OS detriment in 3L+ setting in the DREAMM-3 trial. When extrapolating to the approved 5L+ indication , there is concern for even less likelihood of efficacy and worse toxicity for Blenrep as multiple myeloma is characterized by clonal evolution to a more resistant and less treatment sensitive disease, and heavily treated patients are in general much weaker and susceptible to toxicity. And, with the recent evolution in the treatment landscape, many potential candidates for Blenrep in 5L+ will already have been exposed to, and progressed on, other BCMA-targeting agents, adding further uncertainty to the purported benefit of Blenrep. Clinical benefit of Blenrep in terms of PFS and OS in any target population has not been established based on the DREAMM-3 study and the significant risks associated with Blenrep treatment were reproduced.

11.2.2.2. Additional interpretation of DREAMM3 results

Several factors may have contributed to the outcome of the primary analysis in this study, including enrolment imbalances at baseline, and early progressors.

Enrolment imbalances at baseline

As would be expected from an earlier line of therapy, DREAMM-3 enrolled less heavily pre-treated participants compared to DREAMM-2 (**Table 6**). While the number of prior lines was a stratification factor in DREAMM-3, it was only grouping participants into groups of ≤3 and >3 prior lines. This stratification scheme did not allow to control for the distribution of participants who were treated with a greater number of lines and, by chance, Blenrep-treated participants were more heavily pre-treated than those participants randomized to Pom/Dex, with a median number of prior lines of 4 for Blenrep

compared with 3 for Pom/Dex. There was also a higher proportion of participants with an Eastern Cooperative Oncology Group (ECOG) performance status of ≥1 in the Blenrep group (64%) in DREAMM-3 as compared to the Pom/Dex group (55%). An analysis of the potential impact of baseline risk factors on efficacy outcomes in DREAMM-3 was conducted (see below).

Table 6. DREAMM-2 and DREAMM-3 Participant Baseline Characteristics

	DREAMM-2 Final Analysis (31 Mar 2022)	DREAMM-3 Primary Analysis (12 Sep 2022)	
	BLENREP N = 97	BLENREP N = 218	Pom/Dex N = 107
Age, median (range)	65 (39 - 85)	68.0 (43 - 86)	68.0 (38 - 90)
Prior lines of therapy; median (range)	7 (3 - 21)	4 (2 - 12)	3 (2 - 13)
> 5 prior lines	66%	15%	7%
TCR (%)	100%	13%	14%
Prior ASCT (%)	75%	51%	51%
Refractory to anti-CD38 antibody	100%	34%	34%
Refractory to proteasome inhibitor	100%	68%	63%
Refractory to immunomodulatory agent	100%	72%	77%
Time from diagnosis, medium (years)	5.50	5.23	5.05
ECOG score ≥ 1 at screening	67%	64%	55%
ISS Stage II or III multiple myeloma	77%	65%	65%
High risk cytogenetics at screening*	27%	26%	32%
EMD at screening	23%	18%	18%

ASCT: autologous stem cell transplantation; ECOG: Eastern Cooperative Oncology Group; EMD: extramedullary disease; ISS: International Staging System; TCR: triple-class refractory
*Includes t(4;14), t(14;16), and 17p13del; after completion of data cleaning of FISH bone marrow field; numbers were updated for the primary data cutoff.

CHMP comment

This is an RCT, the size of which was suggested by the MAH to suffice for the demonstration of superior PFS of Blenrep versus pom/dex. Considering the 2:1 treatment allocation and the fact there were only 107 patients in the control arm, there may be imbalances in some prognostic parameters.

These imbalances are considered minor and most baseline characteristics appear to be balanced. It is acknowledged that the median prior lines of therapy were 4 in the Blenrep arm and 3 in the pom-dex arm and that the proportion of patients # with ECOG ≥1 was 64% vs. 55% respectively. However, it should also be noted that there was a higher fraction of patients with high-risk cytogenetics at screening in the pom-dex arm (32% vs 26%) which could potentially favour the Blenrep arm. Additionally, refractoriness to immunomodulatory agent was more common (77% vs 72%) in the pom-dex arm which could also favour the Blenrep arm as pomalidomide is an immunomodulatory agent.

Overall, imbalances are considered minor and bidirectional and are not believed to have had a substantial impact on the study results.

Early progression led to early crossing of PFS curves and to violation of proportional hazard assumptions

A higher proportion of early progression in the Blenrep group relative to the Pom/Dex group in the first 2 months was evident by the early 'drop' of fast progressing participants and crossing observed in the PFS Kaplan-Meier curve. The initial PFS KM curve in the Blenrep group is driven by a higher rate of

progression events in the first 2 months followed by a change in that trend with more events in the Pom/Dex arm beyond 3 months.

Comprehensive investigations of early progression during the first 2 months were conducted, where baseline disease characteristics and prior therapy were considered. There was no evidence for possible causal link to any safety issues related to Blenrep for participants with early progression. Most of the PFS events were disease progressions, which occurred at a higher proportion in the Blenrep group in the first 2 months and were not associated with dose modifications. Deaths in the first 2 months in both groups were mostly due to disease progression and not a result of safety events. Death due to AEs were infrequent and were similar between groups.

Investigation of baseline characteristics of early progressors showed that many baseline characteristics distinguish early progressors from early ongoing participants equally in both groups. Most of these characteristics are reflective of an advanced disease, higher disease burden, and are known poor prognostic factors for an inferior outcome in RRMM, irrespective of treatment (e.g., ISS stage, prior treatments, LDH, B2M, lytic bone lesions, EMD, sBCMA).

More recently, GSK conducted a post-hoc multivariate analysis adjusting for baseline prognostic factors. As previously mentioned, some of the baseline characteristics do not appear to be balanced between the treatment groups on DREAMM-3. The investigated factors included in the analysis were as follows: ISS at diagnosis (stage 3 vs stage <3), prior lines of therapy (>5 vs ≤5), anti-CD38 treatment (yes vs no), high risk cytogenetics (high risk vs other), and ECOG performance status (2 vs 0/1).

Results from the multivariate analysis that adjusted for these baseline covariates showed that for the additional 10-month follow-up, the PFS HR was 0.84 (95% CI 0.58, 1.23), as compared to the updated unadjusted PFS HR of 0.9 (95% CI 0.65, 1.24) (**Table 7**).

Table 7. Covariate Analysis for PFS Analysis in DREAMM-3

	Primary Analysis	**10 Month Follow-up Analysis**
Unadjusted PFS HR, 95%CI	1.03 (0.72, 1.47)	0.9 (0.65, 1.24)
Covariate-adjusted[a] PFS HR, 95% CI	0.90 (0.59, 1.35)	0.84 (0.58, 1.23)

a. Covariates were ISS at diagnosis (stage 3 vs stage <3), prior lines of therapy (>5 vs ≤5), anti-CD38 treatment (yes vs no), high risk cytogenetics (high risk vs other), and ECOG performance status (2 vs 0/1).

CHMP comment

The results of DREAMM-3 suggest that the utility of Blenrep relative to Pom/dex may vary within the studied population (heterogeneity of response). However, this does not impact the fact that the study failed to meet its primary endpoint.

Delayed separation of Kaplan-Meier curves not accounted for within the original statistical assumptions for sizing of study

The DREAMM-3 PFS curve clearly showed a violation of the proportional hazards (PH) assumption due to the early crossing. This phenomenon has been commonly observed in monotherapy studies of anti-PD1/PDL1 agents versus chemotherapy in solid tumours [Borghaei, 2015]. Unless such a departure

from the PH assumption is accounted for at the design stage, this will lead to significant loss in study power, therefore resulting in negative trial outcomes [Lin, 2020].

The DREAMM-3 study had 90% power to detect a HR of 0.57 (median PFS of 4 months vs. 7 months) with 151 total events. However, with a 2-month delay on the original protocol assumption before the KM curves separate, this would result in a study with only ~41% power.

The statistically negative PFS outcome in DREAMM-3 may have been influenced by several factors including imbalances in baseline characteristics, possibly leading to an early crossing of the KM curves. Post hoc multivariate analysis, adjusting for key baseline prognostic factors showed directional improvement in the PFS HR. The early crossing of KM curves has led to the violation of the proportional hazard assumption and potentially resulted in a loss in power to detect a statistically significant difference. Despite this, the study showed numerical improvement in median PFS and one-year PFS rate. Importantly, Blenrep demonstrated a deeper response and ~2.5-fold improvement in median DoR over Pom/Dex.

CHMP comment

None of these post hoc considerations alter the fact that efficacy was not confirmed by the DREAMM-3 study. Post-hoc power calculations are not considered to support the claimed benefits of Blenrep.

11.2.3. The Safety and Tolerability Profile of BLENREP has been consistent in clinical trials and in RWE and EAP studies

More than 9000 patients have been treated with Blenrep globally, and these data confirm the safety profile of Blenrep. Cumulative global post-marketing exposure to Blenrep is estimated as 2068 patient-months, as of June 2023. About 6400 MM patients have been treated in Europe through prescriptions or with an expanded access program. In addition, more than 2700 patients have been treated with Blenrep in the United States. Of those, over 2400 patients had been treated in the Blenrep Risk Evaluation Mitigation Strategy (REMS) as of 06 June 2022 [REMS Assessment report, 2022].

Data on ocular events remain consistent and unchanged across the belantamab mafodotin program. For DREAMM-3, the ocular findings based on ophthalmologic examination (transient corneal exam findings and visual acuity worsening) were consistent with the safety pattern previously reported for Blenrep in DREAMM-2, and there were no new ocular safety signals. Importantly, ocular toxicity was manageable with dose modifications and did not lead to treatment discontinuation in most participants (2% discontinued Blenrep due to an ocular AE).

In DREAMM-3, ocular AESIs including blurred vision, dry eye, and decreased visual acuity, occurred in 66% of participants, were mostly Grade 1-2 in severity, and the majority (77%) had resolved as of the Primary Analysis data cut. These events are quickly identified and effectively managed with dose modifications (dose holds / reductions). Visual acuity changes greater than grade 2 occurred in 39% of participants in the Blenrep group, median time to onset was 65 days, the median duration was 39 days and 91% of these events resolved, with median duration 39 days. In the Blenrep group, 18% of participants experienced a drop in visual acuity to 20/50 or worse (moderate impairment of visual acuity), but these changes were also temporary with 95% of participants recovering. Severe impairment of visual acuity (20/200 or worse) was observed in 5 (2%) participants.

The Blenrep REMS provides the longest real world follow-up data for Blenrep. The last REMS assessment report prepared was for a 24-month reporting period [REMS, 2022], at which time over 2400 patients had been treated with Blenrep. The ocular safety data collected from the Blenrep REMS are consistent in nature with the known safety profile of Blenrep. Keratopathy and Visual acuity

reduced were the most frequently reported ocular events, and where outcome was available, there was evidence of recovery. Cumulatively, with additional follow-up, higher rates of re-occurrence of corneal adverse events were seen in patients on treatment for longer durations, however, the adverse events were manageable.

Ongoing, routine pharmacovigilance has shown no change for belantamab mafodotin and infections [PBRER: 05 February 2023 to 04 August 2023]. Pneumonia and upper respiratory tract infection are included as listed events in the BLENREP monotherapy prescribing information, with a low incidence of Grade 3 and 4 events (7% and 0, respectively) [BLENREP SPC, 2022]. Comparative data from the DREAMM-3 study showed that more Grade $\geq$ 3 infections (pneumonia, COVID-19, COVID-19 pneumonia, febrile neutropenia, and sepsis) occurred in the Pom/Dex treatment group than the Blenrep group (25% vs. 13%, respectively). Infection-related SAEs occurred more frequently in the Pom/Dex group than in the belantamab mafodotin group. Other BCMA-targeting therapies such as teclistamab and idecabtagene vicleucel are associated with cytokine release syndrome and severe, fulminant infections [TECVAYLI USPI, 2023; ABECMA USPI, 2021]. Blenrep may therefore provide an alternative treatment option with a more manageable safety profile for patients with RRMM.

CHMP comment

The ocular toxicity remains a major concern with the use of Blenrep. It is acknowledged that the safety profile of Blenrep seems consistent across clinical trials and in post-marketing follow-up. In this regard, the very high rates of ocular toxicity (including grade 3 and 4) leading to dose interruptions, modifications and discontinuations are of utmost importance.

Keratopathy (corneal epithelium changes) were found in patients treated with Blenrep at both dose levels in the DREAMM-2 study. The most common grade 1–2 adverse event was keratopathy, and the most common grade 3–4 adverse events in the safety population were keratopathy (in 26 [27%] of 95 patients in the 2·5 mg/kg cohort and 21 [21%] of 99 patients in the 3·4 mg/kg cohort). Keratopathy led to the majority of dose adjustments (23% of 95 patients and 27% of 99 patients), treatment delays (47% of 95 patients and 48% of 99 patients), and discontinuations (1% of 95 patients and 3% in 99 patients). Patients who underwent dosing delays were usually able to re-initiate treatment with a median treatment initiation time of 83 days (2.5 mg/kg cohort) and 63 days (3.4 mg/kg cohort).

In the DREAMM-3 study, ocular AEs by CTCAE were reported in the Blenrep group in 143 of 217 (66%) participants. Grade 3 and worse ocular AESIs were reported in 64 (29%) of 217 patients in the Blenrep group. Grade 4 KVA (Keratopathy and Visual Acuity) scale events occurred in 21 (10%) of 217 patients in the Blenrep group (comprising 16 corneal erosions, two keratopathy, two best corrected visual acuity worse than 20/200, and one corneal erosion and ulcer).

For all adverse events and KVA events, dose modifications, delays, or reductions were reported in 155 (71%) of 217 patients. Dose reductions were 84 of 217 (39%), while delays were 147 (68%) of 217. Extended dose delays (>63 days) occurred in 27 (12%) of 217 patients in the Blenrep group. Discontinuations due to ocular AESIs happened in four (2%) of 217 Blenrep treated patients.

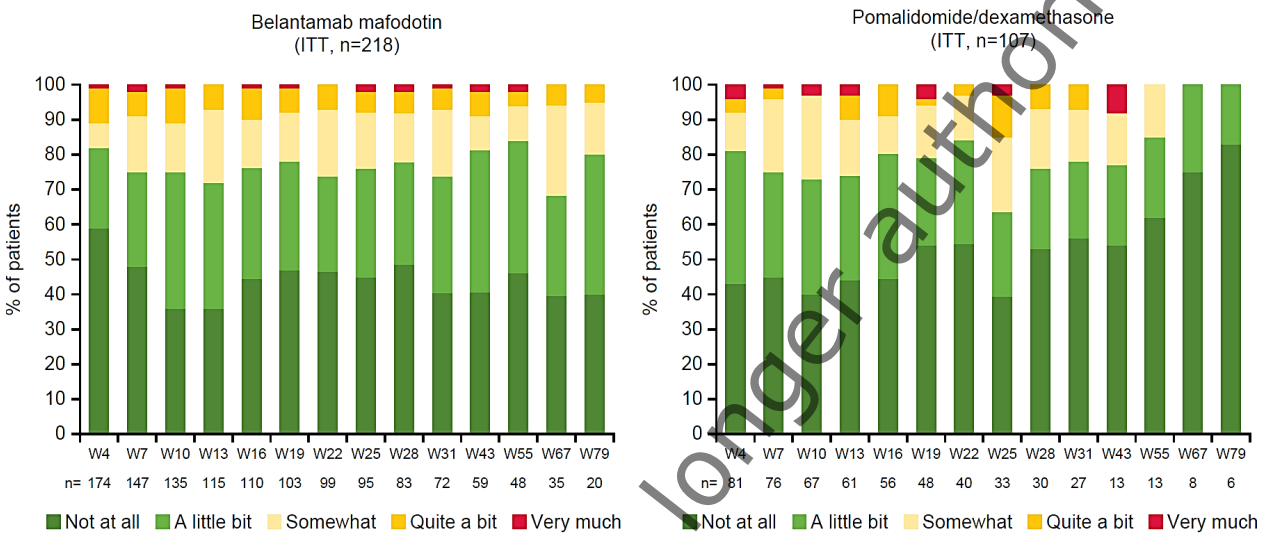
In conclusion, the likelihood of considerable ocular toxicity (and related visual acuity consequences) reaches nearly two thirds of patients exposed to Blenrep.

Patient-reported outcomes

In DREAMM-3, the improvements observed in disease-related symptoms and key HRQoL domains demonstrate the overall positive impact of belantamab mafodotin on participants in this study.

Despite the side effects participants experienced, based on the FACT-GP5, more than 70% of participants indicated being 'Not at All Bothered' or only 'A Little Bothered' by treatment side effects in both groups across most study visits in DREAMM-3 (**Figure 5**).

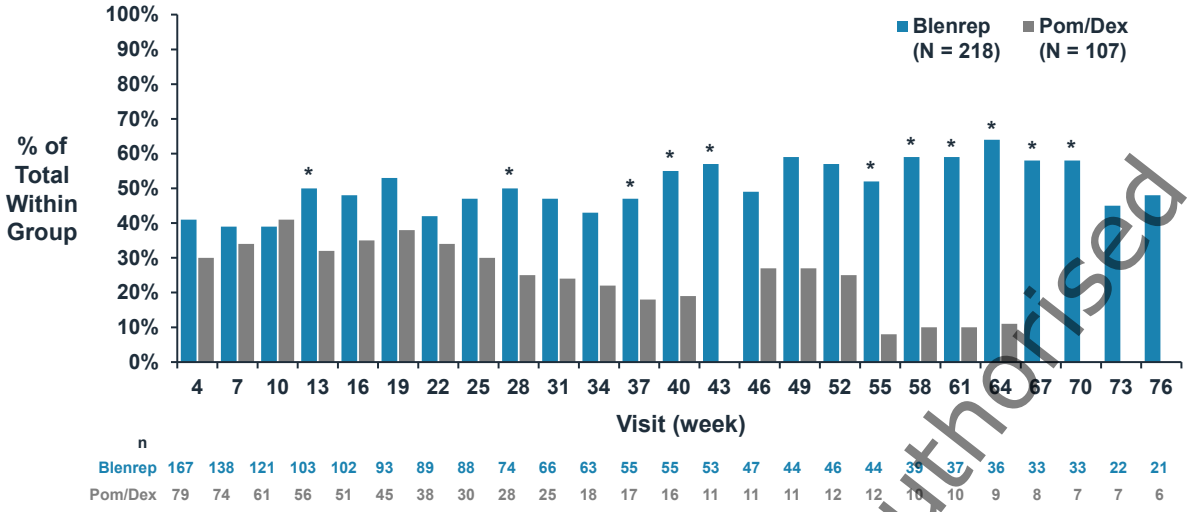
Figure 5. DREAMM-3: Patient-reported tolerability related to treatment side effects (FACT-GP5) (Primary Analysis)



Apart from blurred vision, patient-reported tolerability of Blenrep was generally good in DREAMM-3, with most participants indicating on the PRO-CTCAE either none or mild (or infrequent) other AEs at each visit throughout the study. Similar tolerability results were observed for participants treated with Pom/Dex.

An important and difficult-to-manage symptom of multiple myeloma is fatigue, which directly affects quality of life and patient functionality. Fatigue can be a direct result of cancer but is also further potentiated by frequently reported anaemia in participants with multiple myeloma. Over the course of DREAMM-3, the EORTC Fatigue domain data demonstrated that 40% to 60% of participants treated with Blenrep at each visit experienced meaningful improvement, defined as a 10-point change in the Fatigue domain score from baseline. At multiple time points, significantly more participants receiving Blenrep experienced improvement in fatigue compared to Pom/Dex (**Figure 6**), bearing in mind the reduced numbers per treatment group at later timepoints.

Figure 6 DREAMM-3: Proportion of Participants with Meaningful Improvement from Baseline in Fatigue Over Time (Primary Analysis**)**



* Nominal significance ($p < 0.05$) from the mixed model for repeated measures analysis

Based on EORTC QLQ-Q-C30 Fatigue Domain, where meaningful improvement is a 10-point change from baseline

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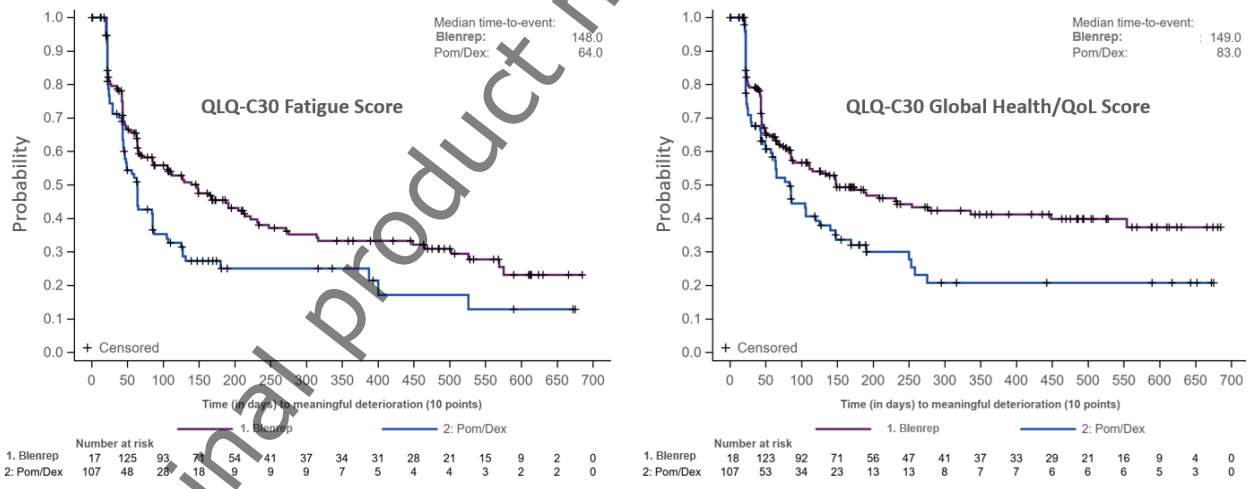
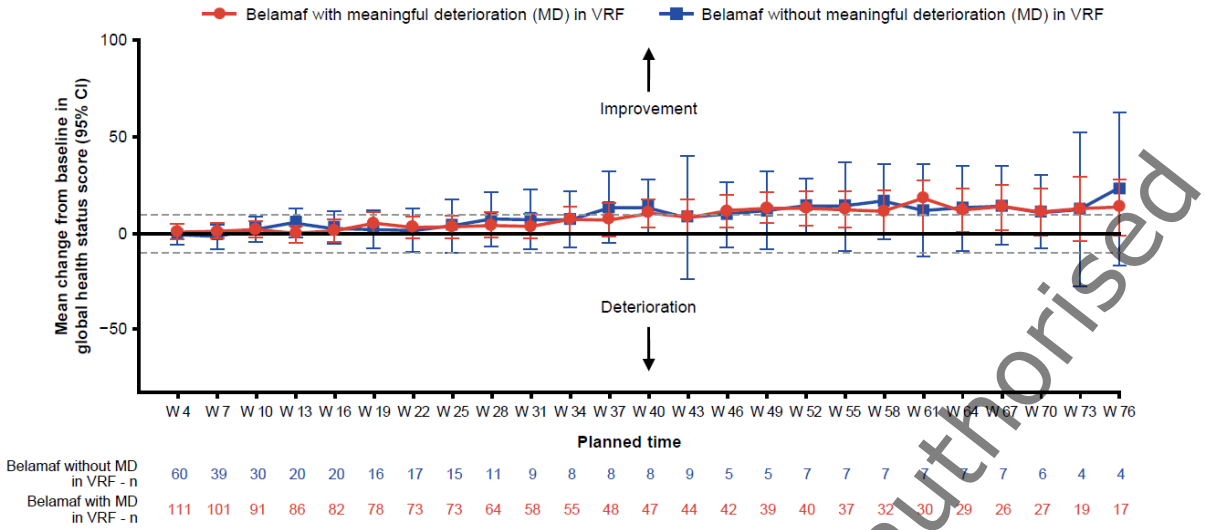
Further, time to meaningful deterioration in fatigue and global health status/QoL was evaluated in a post-hoc analysis, and results showed there was a significant delay in deterioration for participants receiving BLENREP compared with Pom/Dex (fatigue: median time of 148 days vs. 64 days; global health status: 149 days vs. 83 days; both p<0.01) (**Figure 7**).

Figure 7 DREAMM-3: Time to First Meaningful Deterioration in EORTC QLQ-C30 Fatigue and Global Health/QoL (Primary Analysis)



Though a majority of participants (67%) in the belantamab mafodotin group experienced meaningful (≥12.5 point) change) deterioration in their vision-related functioning (VRF) at some point during DREAMM-3, their mean global health and functioning scores remained stable over time and were similar to participants receiving belantamab mafodotin who did not experience meaningful deterioration in VRF (**Figure 8**) [Dimopoulos, 2023]. This was consistent with published findings from a similar post-hoc analysis conducted using DREAMM-2 data (13-month follow-up; cut-off date 31 January 2020) [Popat, 2020].

Figure 8 Change from baseline in Global Health Status for BLENREP-treated Participants in DREAMM-3 (EORTC QLQ-C30)



CHMP comment

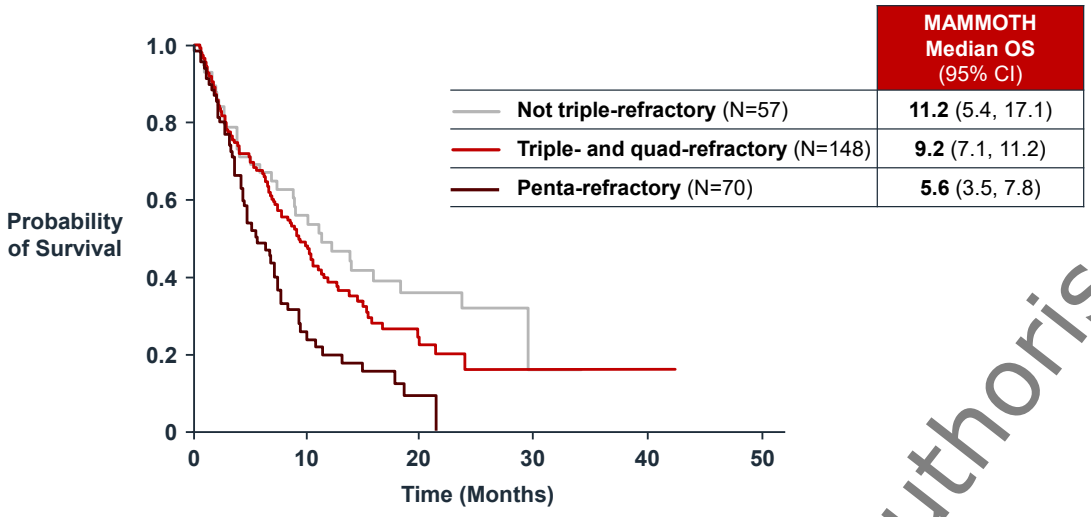
These data suffer from the usual issues with PRO's, including substantial attrition of respondents, as well as the obvious selection of patients tolerating the drugs over time. This makes the appropriate estimand, which as usual seems not pre-specified, difficult to surmise. Moreover, any claims of a difference would be based on non-type-1 error-controlled data in a study that is overall statistically negative. In addition, the proportion of patients who responded the PRO surveys decreases to 50% of the ITT (103/218 in Blenrep and 56/107 in pom/dex) as of W10, which undermines interpretation of PROs in an open label trial. No specific conclusion can be drawn from these data.

11.2.4. Unmet Medical Need in Patients with 5L+ TCR Multiple Myeloma

11.2.4.1. The treatment options in 5L+ TCR MM patients are limited and often associated with poor outcomes

There are many treatment options for MM patients for first and second line, but options are limited post exposure to three major classes of drugs: immunomodulatory agents, PIs, and/or anti-CD38, of which many are used in combinations. Once myeloma becomes triple-class-refractory, patient outcomes are poor. As shown by the MAMMOTH study, survival diminishes as myeloma becomes more refractory, with median survivals between 5.6 and 9.2 months for more heavily pre-treated patients [Gandhi, 2019]. The triple- and quad-refractory population, shown by the middle red line, is most comparable to the TCR patient population in DREAMM-2 (**Figure 9**).

Figure 9. Probability of Survival by Treatment Status

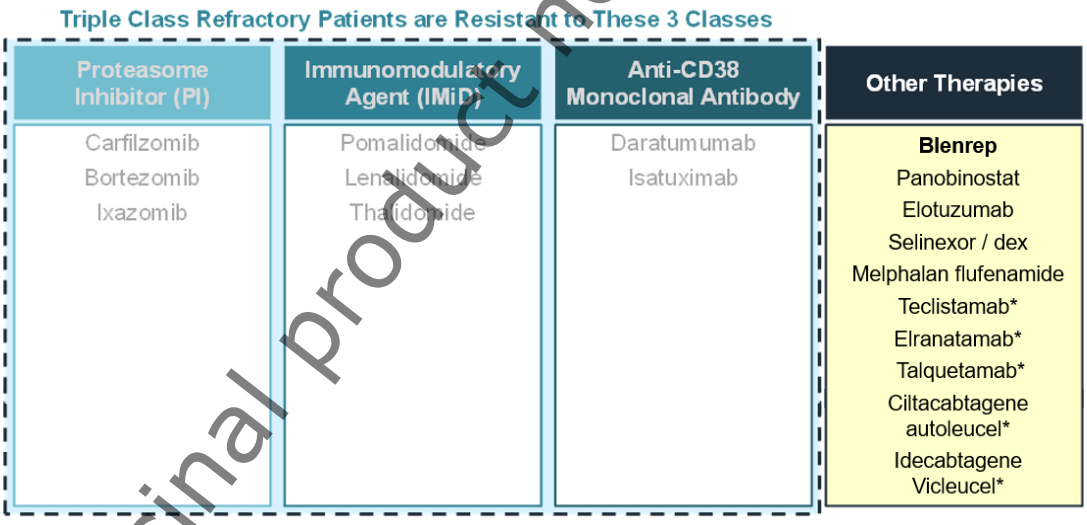


CI: confidence interval; OS: overall survival, Source: Gandhi, 2019

As indicated by this real-world study, treatment options for the Blenrep approved indication (5L+ TCR) are limited, as by then most patients have exhausted the three most effective drug classes commonly used as standard of care: PIs, immunomodulatory agents, and anti-CD38 antibodies.

5L+ TCR patients have a need for effective products with different mechanisms of action that can overcome the resistance to existing therapies. Those treatments are included on the "Other Therapies" list, which summarizes the options currently available to patients in the EU (Figure 9).

Figure 10. Treatment Options for Relapse Refractory Multiple Myeloma in the EU



*Administered in hospital setting

Except for BCMA-targeting agents, most options listed under "Other Therapies" in Figure 10 have limited activity and are characterized by significant toxicities (Selinexor, Farydak [panobinostat]) **Table 8** . In addition to limited efficacy, Empliciti (elotuzumab) [Trudel, 2019] and Farydak have no/very limited single agent activity and are indicated as add-on to standard of care for less heavily pre-treated patients. Targeting BCMA antigen through various mechanisms: antibody drug conjugate, bispecific antibodies, or CAR-Ts represent novel, validated and effective treatments. The bispecific antibody (teclistamab) and CAR-Ts (idecabtagene vicleucel, ciltacabtagene autoleucel) targeting BCMA became recently licensed and are characterized by strong efficacy. However, their use is associated with significant toxicities in a high proportion of patients: cytokine release syndrome; infections, and

neurotoxicity [Raje, 2023; Morris, 2022]. They require access to hospitals in an academic setting, and availability of highly trained personnel to manage the SAEs. In addition, CAR-Ts have very limited availability, and require the patient to be stable for a few weeks during the autologous T cell preparation process. Patients previously treated with 5 or more lines rarely are stable enough to be able to wait and require an immediate treatment.

Table 8. Outcomes of Other Treatment Options for 5L+ MM Patients

	Selinexor/Dex	**Panobinostat**	**Elostuzumab**	**Ide-cel**	**Cilta-cel**	**Elranatamab**	**Teclistamab**	**Talquetamab**
Trial	**STORM Part 2** **N=122**	**PANORAMA1** **N=768 (total)** **N=387 (pano)**	**ELOQUENT2** **N=646 (total)** **N=321 (elo)**	**KARMMA3** **N=386** **N=254 (ide-cel)**	**CARTITUDE-1** **N=97**	**MagnetisMM-3** **N=123**	**MajesTEC-1** **N=165**	**MonumenTAL-1 QW/Q2W** **N=232 (IV+SC talq)** **N=30 (QW SC)/** **N=44 (Q2W SC)**
Phase	2b	3	3	3	1b/2	2	1/2	1
Median pLOT	7 (3-18)	Not reported	2 (1-4)	3 (2-4)	6 (4-8)	5 (2-12)	5 (2-14)	6 (2-14)/5 (2-17)
TCR (%)	100	Not reported	Not reported	65	88	96.9	77.6	74 / 69
ORR (%)	26.2	60.7	79	71	98	57.7	63	74 / 73
mPFS	3.7 (3.0, 5.3)	11.99 (10.33, 12.94)	19.4 (16.6, 22.2)	13.3 (11.8, 16.1)	34.9 (25.2, NE)	NE (9.9, NE)	11.3 (8.8, 17.1)	7.5/11.9
mDoR	4.4 (3.7, 10.8)	13.14 (11.76, 14.92)	21.9 (18.4, 26.6)	14.8 (12, 18.6)	33.9 (25.5, NE)	NE (NE, NE)	18.4 (14.9, NE)	Not reported
mOS	8.6 (6.2, 11.3)	48.3 (40.3, 51.9)	48.3 (40.3, 51.9)	NE	NE	NE (13.9, NE)	18.3 (15.1, NE)	Not reported

	Selinexor/Dex	Panobinostat	Elostuzumab	Ide-cel	Cilta-cel	Elranatamab	Teclistamab	Talquetamab
Infection (%)/ Grade 3-4 (%)	Not reported	Not reported	81 / Not reported	58 / 24	58 / 20	69.9 / 39.8	76.4 / 44.8	58 / 22 65 / 16

Sources: [Chari, 2019; San Miguel, 2014; San Miguel, 2016; Lonial, 2015; Dimopoulos, 2020; Rodriguez, 2023; Berdeja, 2021; Lesokhin, 2023; Moreau, 2022; Schinke, 2023]

Since its approval, BLENREP has narrowed this treatment gap for those patients by providing a clinically meaningful efficacy with long lasting remissions in responding patients with manageable adverse events.

CHMP comment:

It is agreed that the efficacy of available last line options for triple refractory patients is low. Thus, there is an unmet medical need in this pospulation as stated by the MAH. In cross-trial comparisons (with all its limitations), ORRs, and mPFS estimates for other BCMA targeting therapies are more encouraging than what is seen for Blenrep. It is acknowledged that there are limitations regarding CAR-T cell therapies as these products are not available off the shelf and the patients often require bridging therapies while waiting for manufacturing of the CAR-T product. However, bispecific antibodies (teclistamab, elranatamab and talquetamab) are available as off-the-shelf products that are injected subcutaneously. Due to risk of CRS, close monitoring is recommended initially when treating with bispecific antibodies. However, once the CRS risk has diminished, close monitoring is no longer necessary in subsequent treatment cycles. Blenrep treatment is given intravenously and frequent co-management by an eye care professional is necessary throughout the treatment due to high frequency of ocular toxicities.

11.2.4.2. Infection risk and immunoglobulin use are less pronounced for BLENREP compared with other BCMA-targeting agents

MM patients have an increased susceptibility to infection due to immunodeficiency associated with myeloma and immunosuppressive effects of previous myeloma therapies [Nucci, 2009] (Figure 10). MM patients commonly experience secondary immune deficiencies such as hypogammaglobulinemia (HGG), a disorder defined by low serum IgG levels (<400 mg/dL). HGG increases infection risk with encapsulated bacteria and is associated with decreased overall survival [Raje, 2023; Garfall, 2023]. Patients may receive immunoglobin replacement therapy as prophylaxis or treatment.

Frequent HGG and an increased risk for opportunistic infections, have been observed with bispecific antibodies and CAR-Ts, resulting in the recommendation for universal use of immunoglobulin replacement therapy in patients receiving anti-BCMA bispecific antibody therapy [Garfall, 2023]. Broad use of immunoglobulin replacement therapy can represent a significant burden to health care systems and can pose a significant disadvantage especially in the event of a shortage of IVIG.

In the Phase 2 study of teclistamab (MAJESTIC-1), infections occurred in 76.4% of participants, and 44.8% were severe (Grade 3-4). In addition, 39.3% of participants received immunoglobulin to address hypogammaglobulinemia [Moreau, 2022]. In the Phase 2 study of elranatamab (MAGNETISMM-3), infections occurred in 69.9% of participants and were severe (Grade 3–4) in 39.8% and fatal in 6.5% of participants [Lesokhin, 2023]. The most frequent TEAEs leading to dose interruptions were infections (50.4%). Also, 43.1% of participants received immunoglobulin replacement during the study. Many of the infections observed in these studies were unusual opportunistic infections including but not limited to progressive multifocal leukoencephalopathy, pseudomonas pneumonia, adenovirus hepatitis and adenoviral pneumonia.

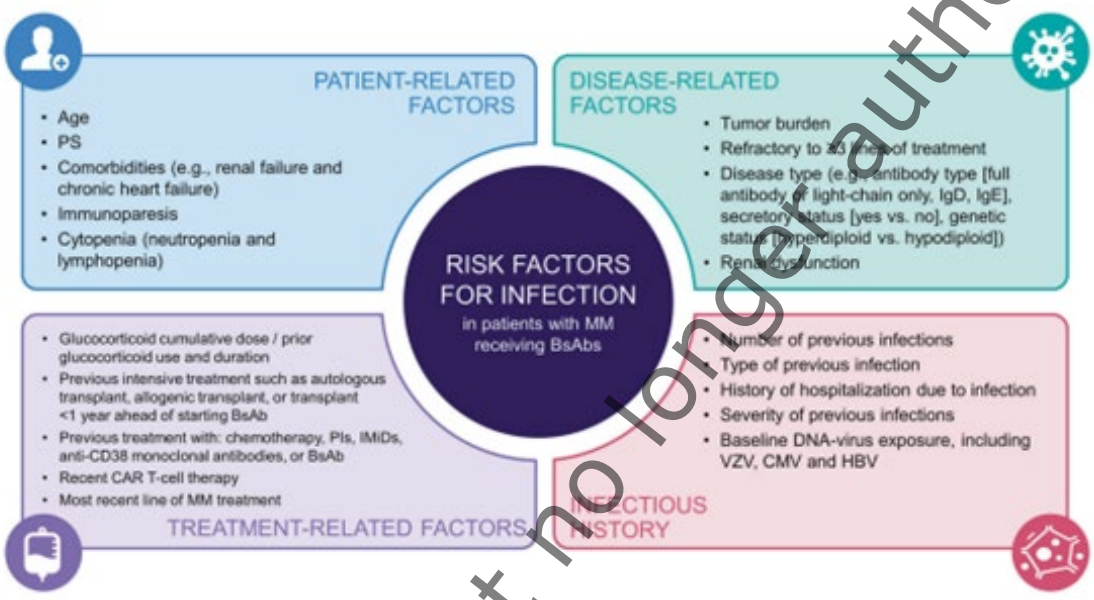
In the Phase 3 KARMMA-3 trial, infections occurred in 58% of participants in the ide-cel group and were severe in 24% and fatal in 4% of participants [Rodriguez-Otero, 2023]. In the Phase 3 CARTITUDE-4 trial, infections occurred in 62.0% in the cilta-cel group and were severe in 26.9% of

participants. 65.9% of participants received immunoglobulin to treat hypogammaglobulinemia. The risk of infection can significantly limit the eligibility of 5L+ TCR patients for CARTs and bispecific antibodies.

In DREAMM-3, Grade ≥ 3 infections were reported in 13% of subjects in the belantamab group, with 7 fatal infections (3%). In DREAMM-2, infections (all grades) occurred in 45% of participants in the 2.5 mg/kg arm, and fatal infections in 3 participants (3%).

BLENREP's lower risk for severe infection compared to a standard treatment such as other BCMA targeting agents as well as Pom/Dex, may make it a good treatment option for many 5L+ TCR patients.

Figure 11 Risk factors contributing to infection in patients with MM



BsAb bispecific antibody, CAR-T chimeric antigen receptor T-cell, CMV cytomegalovirus, HBV hepatitis B virus, IMiD immunomodulatory drug, MM multiple myeloma, PI proteasome inhibitors, PS propensity score, VZV varicella zoster virus.

Source: Raje, 2023

Importantly, the relatively low infection risk observed with Blenrep has been demonstrated with very limited/negligible utilization of immunoglobulin replacement. In the DREAMM-2 study, 1 participant in the 2.5 mg/kg arm (N=95, 1%) reported an AE of HGG, and only 8 participants in the 2.5 mg/kg arm (N=95, 8%) received IVIG. In the DREAMM-3 study, there were no AE reports of HGG in the BLENREP group, and 2 participants in the Blenrep group (N=218, <1%) received IVIG support. One participant in the Pom/Dex group experienced HGG, and 3 participants (3%) received IVIG support.

The low rates of infection and low rates of immunoglobulin replacement therapy in patients receiving BLENREP is in stark contrast to the high rates of unusual, opportunistic infections, and high rates of HGG with BCMA-directed bi-specific antibodies (reported at >70% in the Phase 2 studies of teclistamab and elranatamab). This data supports Blenrep as a more accessible option for RRMM patients with a differentiated safety profile relative to the bi-specifics and CAR-Ts.

CHMP comment

The MAH claims that risk of infections is lower with Blenrep treatment compared with other BCMA-directed therapies. There are no clinical trials with direct comparisons. There are caveats to comparing infection risk across different trials. Firstly, the patient populations can be different. Of particular importance is the number of prior lines of treatment and drug class exposure/refractoriness. There can also be heterogeneity with regard to disease related factors such as ISS stage, extramedullary disease, and high-risk cytogenetics.

The DREAMM-3 study included patients who had received at least two prior lines of therapy and only 21% of patients were triple-class-refractory. The patient populations included in the SAT trials that led to CMAs for ide-cel, cilta-cel, teclistamab, elranatamab and talquetamab had much higher rates of triple class refractory (TCR) patients and patients who had received more prior lines of therapy.

Secondly, in comparison with Blenrep, more patients responded to treatment with teclistamab, elranatamab, and talquetamab and patients stayed on treatment for longer time (= considerably higher exposure), thus increasing the risk of acquiring an infection while on protocol due to exposure time alone.

In DREAMM-3 the median time on study treatment was 4.1 months (0.4, 22.9). In DREAMM-3, Grade ≥3 infections were reported in 13% of subjects in the belantamab group, with 7 fatal infections (3%).

In DREAMM-2 The median time on study treatment was 2.2 months in the 2.5 mg/kg cohort. In DREAMM-2, infections (all grades) occurred in 45% of participants in the 2.5 mg/kg arm, and fatal infections in 3 participants (3%).

In MajesTEC-1 (teclistamab), the median time of treatment was 7.1 months and seventy-five subjects (50.0%) remained on treatment at data cutoff. All grade infection rate was 76%.

In MagnetisMM-3 (elranatamab) the median time on study treatment was 5.6 months (range: 0.03–24.4 months). All grade infection rate was 70%.

In MonumenTAL-1 (talquetamab), 51.7% of patients received treatment dose of 800 ug/kg biweekly up to 7 months and 55.2% received treatment dose of 400 ug/kg weekly up to 6 months. All grade infection was 58-65%.

Rates of infection were higher in trials investigating bispecific antibodies when compared to Blenrep, but time on treatment was also longer.

In conclusion, when considering the heterogeneity of the study populations and differences in time on treatment (overall exposure) comparisons between Blenrep and treatment with bispecific antibodies are highly uncertain. Thus, it cannot be concluded with certainty that Blenrep has a lower risk of infection than bispecific antibodies in the target indication.

11.2.5. BLENREP fills the treatment gap for patients who are unlikely candidates for bi-specific agents, or CAR-T Therapy

Patients with medical characteristics who may be unable or ineligible to receive CAR-T treatment or bispecific antibodies can be treated with BLENREP monotherapy and show clinically meaningful ORR and DoR. A retrospective analysis was conducted to evaluate outcomes in patients with certain demographic and disease characteristics that would be unlikely candidates for bi-specific agents or CAR-Ts. These characteristics included elderly patients, those with poor renal function, and those with

poor ECOG performance status. For the elderly population, the rate of infections in bi-specific agents and CAR-Ts may pose a challenge in terms of polypharmacy [Chacon, 2023]. The NCCN and EMN guidelines on the management of infections in patients with multiple myeloma recommend multiple interventions and prophylaxis for bispecific agents and CAR-Ts [Wood, 2021; Ludwig, 2023], whereas for BLENREP, prophylaxis management is generally limited to preservative-free lubricant eyedrops and periodic eye exams.

Data from DREAMM-2 and DREAMM-3 were pooled to specifically look at the outcomes for participants who, due to those characteristics, are less likely to be considered suitable candidates for bispecific agents or CAR-Ts (Table 9). These included patients who were elderly (age ≥ 65, age ≥ 75), having renal impairment (eGFR < 40 mg/mL/min) and poor performance status (ECOG PS ≥2).

11.2.5.1. Efficacy data

Both ORR and DoR were maintained and comparable between the elderly age groups analysed and the overall total population (**Table 9**). Notably, the ORR for the ≥ 75-year-old group was 49% and the mDoR was estimated to be 19.4 months. This is a subset of participants who are very unlikely to be considered for CAR-T therapy or for bispecific antibody treatment.

Analysis of subjects with renal impairment and those with poor ECOG performance status also demonstrated benefit from Blenrep treatment, although these groups were more limited in size.

In a retrospective review of RRMM patients evaluated at a US medical centre who were on the "waitlist" to receive ide-cel in 2021 and who could not secure a slot, the mortality rate was higher than those who received ide-cel due to lack of comparable alternatives. The article stated that "Belantamab mafodotin was the most favoured alternative for patients who did not have prompt access to CAR-T in our study population, however, it was withdrawn from the US market in November 2022" [Ahmed, 2023]. Insufficient treatment options may lead to a similar unmet medical need in the EU.

Table 9. Outcomes with BLENREP (DREAMM-2 and DREAMM-3 pooled analysis) in participants who may not be suitable candidates for bispecific agents or CAR-Ts

Parameter	**N**	**Subjects with Response**	**ORR, %**	**Median DoR (95%CI), months**
DREAMM-2[a]	97	31	32	12.5 (4.2,19.3)
DREAMM-3[b]	218	90	41	25.6 (20.7, NE)
DREAMM-2/DREAMM-3 Pool	315	122	38	21.4 (14.6, 27.1)
≥65 years	188	87	46	22.8 (14.3, 27.1)
≥75 years	59	29	49	19.4 (10.4, NE)
eGFR <40 mg/mL/min	22	5	23	NE (12.4, NE)
ECOG PS ≥2	39	10	26	14.6 (1.4, NE)

a. Final Analysis, b. 10 Month Follow-up Analysis, c. DoR events = responders who progress or died due to any cause

Similarly, the efficacy data from real-world evidence and expanded access programs in France, Spain and the UK show clinical benefit from Blenrep treatment in patients who are elderly, patients with renal impairment or ECOG score of ≥ 2 (Table 10). These data show consistency with the results from interventional clinical trials led by GSK.

Table 10. RWE Data for Subgroups of 5L+ TCR Patients

	EAP France N=153		**EAP Spain N=100**		**NPP UK N=56**	
	ORR, % (95% CI)	**mDoR, M (95% CI)**	**ORR, % (95% CI)**	**mDoR, M (95% CI)**	**ORR, % (95% CI)**	**mDoR, M (95% CI)**
Age group, y						
≥65	30 (22, 39)	10.7 (3.4, NE)	42 (31, 55)	NA	62 (41, 80)	23.3 (4.3, NE)
≥75	27 (15, 42)	NE	38 (20, 59)	NA	67 (22, 95)	NE
eGFR <40	19 (7, 39)	11.5 (1.3, NE)	NA	NA	60 (15, 95)	1.6 (1, NE)
ECOG PS ≥2	10 (4, 23)	10.7 (1.3, NE)	19 (7, 36)	NA	54 (23, 83)	8.9 (0.1, NE)

The results from the DREAMM-2/DREAMM-3 pooled analysis and from RWE data, in subgroups that are less likely to be candidates for therapy with CAR-Ts or bispecific agents, demonstrate these patients have a good chance to respond to BLENREP, and to achieve durable benefit from this treatment.

CHMP comment

The MAH proposes that Blenrep is a more suitable option than other approved BCMA-targeting agents in a subset of patients defined as elderly (age ≥ 65, age ≥ 75), and/or having renal impairment (eGFR < 40 mg/mL/min) and/or poor performance status (ECOG PS ≥2). Concerning relative safety, see comment above. This remains speculative as neither the DREAMM-2 or DREAMM-3 study populations were selected on the basis of not being eligible for T-cell redirecting therapies. Both the DREAMM-2 and DREAMM-3 study had exclusion criteria that excluded patients with ECOG PS≥3, active infection, poor bone marrow reserves, psychiatric disorders and severe renal, cardiac, pulmonary and hepatic disorders. Across the DREAMM-2 and DREAMM-3 trials 87.6% of patients were ECOG PS 0 or 1, underlining that these were not particularly frail populations. There is a high degree of overlap between inclusion criteria among the DREAMM-2 and DREAMM-3 studies and the pivotal single arm trials for ide-cel, cilta-cel, teclistamab, elranatamab and talquetamab, so it is likely that patients included into the DREAMM-2 or DREAMM-3 could also fulfilled the inclusion criteria for studies with T-cell redirecting therapies.

The MAH proposed that a reasonable subset of these patients will experience benefit with Blenrep, in the form of reasonably durable objective responses.

That objective responses do occur in approximately a third of patients, and in these patients objective response are reasonably lasting, is not questioned. The CHMP, however, considered that in the absence of confirmation of efficacy in terms of an impact on PFS or OS, comprehensive data have not confirmed the benefit suggested by this anti-tumoral activity.

The claim that Blenrep fills the treatment gap for patients who are unlikely candidates for bi-specific agents or CAR-T Therapy is not considered supported by the submitted data.

11.2.5.2. Safety data

Safety Analysis from the selected Pooled sub-populations in DREAMM-2/DREAMM-3

Patients who are elderly, have significant comorbidities, or renal impairment represent a difficult to treat population, and are unlikely candidates for CAR-T, or bispecific agents. To illustrate that those patients can achieve similar benefit from Blenrep as the remaining population a pooled analysis from DREAMM-2 and DREAMM-3 was performed.

Regardless of patients age the overall AE profile was similar across the age sub-groups, in the pooled DREAMM-2/DREAMM-3 analysis (**Table 11**).

Patients with eGFR<40 and ECOG PS ≥2 appear to have slightly higher incidence of SAE, which may be related to co-morbidities, but also a reflection of smaller number of participants in these 2 sub-groups. The incidence of AEs leading to discontinuation was similar across all subgroups. Ocular AEs leading to discontinuation were also infrequent in all subgroups.

Table 11. Overview of AEs in Sub-groups (Pooled DREAMM-2/DREAMM-3 data)

	Age			**eGFR**	
Subjects, n (%)	**<65 N=124**	**≥65 N=188**	**≥75 N=59**	**<40 N=22**	**ECOG PS ≥2 N=39**
Any AE	119 (96)	185 (98)	56 (95)	21 (95)	37 (95)

SAE	52 (42)	85 (45)	22 (37)	13 (59)	24 (62)
AE leading to discontinuation	17 (14)	26 (14)	7 (12)	2 (9)	8 (21)
Ocular AE leading to discontinuation	4 (3)	4 (2)	0	1 (5)	1 (3)

Similarly, the analysis of AEs of special interest shows generally similar incidences across the subgroups for each category (**Table 12**). Events coded to the Eye disorders SOC were the most frequent AE reported across all age groups with similar frequency and in the ECOG ≥2 sub-group, and in patients with renal impairment. The incidence of infections was similar across the groups with no notable increase in elderly, renal impaired, or poor performance patients. The efficacy outcomes for those subpopulations are discussed in **Table 9.**

Table 12 AEs of Special Interest in Sub-groups (Pooled DREAMM-2/DREAMM-3 data)

	Age (Years)			**eGFR <40 N=22**	**ECOG PS ≥2 N=39**
	<65 N=124	**≥65 N=188**	**≥75 N=59**		
Eye disorders SOC					
Any AE	82 (66%)	137 (73%)	44 (75%)	12 (55%)	23 (59%)
Keratopathy	39 (31%)	53 (28%)	14 (24%)	7 (32%)	14 (36%)
Vision blurred	36 (29%)	72 (38%)	19 (32%)	6 (27%)	8 (21%)
Dry eye	28 (23%)	47 (25%)	15 (25%)	5 (23%)	9 (23%)
Foreign body sensation in eyes	16 (13%)	41 (22%)	12 (20%)	5 (23%)	3 (8%)
Photophobia	14 (11%)	39 (21%)	8 (14%)	3 (14%)	2 (5%)
Visual acuity reduced	14 (11%)	32 (17%)	14 (24%)	1 (5%)	5 (13%)
Eye irritation	10 (8%)	44 (23%)	13 (22%)	5 (23%)	3 (8%)
Eye pain	10 (8%)	27 (14%)	5 (8%)	2 (9%)	4 (10%)
Punctate keratitis	7 (6%)	17 (9%)	6 (10%)	0	1 (3%)
Infections and Infestations SOC					
Any AE	51 (41%)	82 (44%)	23 (39%)	11 (50%)	13 (33%)
COVID-19	11 (9%)	17 (9%)	3 (5%)	2 (9%)	4 (10%)
Pneumonia	8 (6%)	9 (5%)	2 (3%)	2 (9%)	4 (10%)
Upper respiratory tract infection	5 (4%)	11 (6%)	2 (3%)	0-	1 (3%)

Urinary tract infection	5 (4%)	16 (9%)	7 (12%)	2 (9%)	1 (3%)
Investigations SOC					
Any AE	60 (48%)	87 (46%)	27 (46%)	12 (55%)	19 (49%)
Platelet count decreased	14 (11%)	29 (15%)	8 (14%)	2 (9%)	6 (15%)
Blood and lymphatic system disorders SOC					
Any AE	58 (47%)	95 (51%)	27 (46%)	17 (77%)	17 (44%)
Thrombocytopenia	39 (31%)	57 (30%)	18 (31%)	9 (41%)	9 (23%)
Injury, poisoning and procedural complications SOC					
Any AE	22 (18%)	50 (27%)	18 (31%)	6 (27%)	6 (15%)
Infusion related reaction	10 (8%)	25 (13%)	7 (12%)	4 (18%)	4 (10%)

MAHs Conclusions

Based on the totality of the available efficacy and safety data, BLENREP has a favourable Benefit/Risk balance in patients with RRMM, therefore supporting the maintenance of the Conditional Marketing Authorisation for BLENREP. Specific reasons supporting this position are summarized below.

i. BLENREP is an effective, easy to use option with a novel mechanism of action that has demonstrated a robust efficacy in patients with advanced MM along with a manageable safety profile, with low infection risk. It does not have prophylactic therapy requirements or the need to be administered in a hospital setting, making it more easily accessible for all patients.

ii. BLENREP monotherapy has independently demonstrated clinically meaningful improvement in the objective endpoints of ORR and DoR, from two clinical trials (DREAMM-2 and DREAMM-3), RWE and EAPs, indicating a positive Benefit/Risk balance in 5L+ multiple myeloma patients. GSK considers that these data support further the evidence that BLENREP has benefit.

iii. BLENREP has a known, well-characterized safety profile supported by consistent safety data arising from clinical studies, RWE, post-marketing and Expanded Access Program use. Ocular events are primarily non-serious, can be managed through dose modifications, resolve for most patients, and infrequently lead to treatment discontinuation. Importantly, it has a differentiated

safety profile relative to other efficacious options in this population, due to its low rate of infections, neurotoxicity, and CRS.

iv. There is a significant unmet need in patients with 5L+ TCR multiple myeloma despite the availability of alternate therapies. BLENREP has been granted an orphan drug designation in EU. While CAR-Ts and bi-specifics have shown robust efficacy, there are considerable risks of severe or life-threatening infections and access barriers that limit its use in many patients. Other agents have sub-optimal efficacy with a non-negligible toxicity burden. Therefore, there is an important need for agents with novel mechanisms of action, with demonstrated efficacy and manageable safety profile that are easily accessible by all patients.

v. A retrospective analysis of efficacy from DREAMM-2/DREAMM-3 and RW studies in subgroups of patients unlikely to receive CAR-Ts or bispecific agents (e.g., elderly patients, those with poor renal function, poor performance status) consistently showed robust ORR and durability with BLENREP therapy.

Therefore, GSK appeals the negative recommendation of CHMP and proposes to renew the license for the conditional marketing application with a modified indication for BLENREP monotherapy. The proposed label is in line with the evidence of beneficial effect in terms of durable responses relevant to the proposed population (heavily treated patients with no or limited other options):

*BLENREP is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody**,** who have demonstrated disease progression on the last therapy, **and where there is no other suitable alternative treatment option (see Section 5.1)**.*

CHMP Comments
Based on available data, the CHMP considered that the efficacy of Blenrep was not confirmed in the DREAMM-3 study and the benefit/risk of the product is not positive in patients with MM, even as a last line resort. Please also see detailed discussion in section 13.7.1. on Importance of favourable and unfavourable effects.

12. Report from the SAG

Upon request from the Committee for Human Medicinal Products, a SAG Oncology meeting was convened in the context of a re-examination of the annual renewal procedure for Blenrep.

Question 1. The SAG is asked to comment on the CHMP grounds for refusal of the renewal for Blenrep:

The Committee re-assessed the benefit/risk of Blenrep as part of the annual renewal procedure, taking into account the totality of data, which includes the data at the time of the conditional approval and, the additional data from studies DREAMM-2 and DREAMM-3 generated as per the specific obligations.

Evidence for the use of Blenrep in its approved indication was based on the objective response rate observed in a trial without a reference treatment arm allowing for the isolation of effects on PFS and OS. Therefore, efficacy was expected to be confirmed in a randomized controlled trial with a relevant reference regimen (DREAMM-3 (207495)). However, the primary analysis of the confirmatory study for Blenrep failed to demonstrate clinical benefit in terms of progression free survival or overall survival. Thus, the favourable benefit/risk balance of Blenrep in its approved indication has not been confirmed as required in the setting of a CMA.

Therefore, the CHMP has recommended not to renew the conditional marketing

authorisation.

The SAG members agreed that belantamab mafodotin, a B Cell Maturation Antigen (BCMA) targeted agent, has been introduced on the basis of durable objective response rate as observed in the non-randomized DREAMM-2 trial leading to a conditional marketing authorisation in patients with 4 or more prior treatments. The SAG agreed about the high unmet medical need in patients progressing after 4 or more prior treatments, and that the confirmatory Phase 3 DREAMM-3 trial in patients with 3 or more prior treatments, did not meet its primary objective of showing superiority against the control arm pomalidomide plus dexamethasone (PomDex). The SAG agreed that the benefit-risk balance cannot be considered confirmed on the basis of DREAMM-3.

However, the majority of SAG agreed that the approved indication corresponds to a stage of the disease where the primary goal of care shifts from prolonging survival or control of the disease to improving the patient's quality of life. This is particularly true for frail patients that cannot tolerate aggressive treatment options with high risk of infections. This is a more advanced stage than patients selected in the DREAMM-3 study. While a positive DREAMM-3 study could have been used to confirm efficacy based on some assumptions, its failure to demonstrate the desired objective should not be understood as demonstration of lack of effect. Active treatments are still needed in this setting and belantamab represents a useful option for some patients.

The majority of the SAG concluded that the durable objective response observed in DREAMM-2 still represents a benefit in this advanced population where managing symptoms and quality of life of patients becomes the primary goal for some patients. In this context, durable remission (longer than one year for some patients) in about one-third of patients as evidenced from DREAMM-2 is a plausible clinical goal in some patients, as remission is expected to be associated with symptom improvement. Responses occur early in treatment, which can be interrupted to reverse any unacceptable toxicity. Patients who respond positively to treatment often experience a reduction in symptoms such as bone pain, fatigue, anaemia, kidney problems, and fractures. Patients might experience an improvement in their overall quality of life. Unfortunately, these effects have not been confirmed in a broader "real world" population. Further data should be collected to assess the impact of response to belantamab on symptom control and quality of life, to inform treatment decisions in the approved monotherapy setting in patients with 4 or more prior treatments.

The majority of SAG members, agreed that the goal of treatment and toxicity need to be discussed in details among patients and doctors to decide if treatment with belantamab is adequate to meet patient preferences and expectations. This should include an in-depth discussion of expected effects, including vision impairment, lack of improvement in terms of survival endpoints compared to PomDex, and uncertainties about the response rate and precise impact on quality of life in the real life setting. Providing careful patient information for clinical decisions was considered possible from a patient perspective, using effective risk minimisation tools.

The minority of the SAG agreed with the CHMP grounds. Notwithstanding all the limitations of DREAMM-3 in terms of studied population, this adequately powered study failed to show superiority of belantamab compared to PomDex. A switch to "non-inferiority" cannot be considered credible a posteriori and given the wide margins observed (upper limit of 1.24 and 1.43 for the HR for PFS and OS respectively, according to more recent analyses). The quality of life data presented also fail to show any convincing evidence of an effect on symptoms due to missing data, untestable assumptions, and multiplicity. The minority of SAG members also considered that the toxicity profile was unacceptable, including the visual impairment. For a product claimed to improve quality of life in patients who respond, it is expected that the toxicity profile would completely outweigh any claimed benefits. According to the minority of SAG members, there is now sufficient evidence to conclude that important

benefits in the approved indication are lacking and that patients are at high risk of important toxicity, resulting in a negative benefit-risk balance.

Question 2. Does available evidence support that Blenrep is a useful treatment option likely to provide clinical benefit in the company's proposed revised target population?

The SAG did not agree with a formal restriction of the indication beyond the currently approved indication although it is likely that treatment with belantamab would be preferred only by a small subgroup of patients. The majority of the SAG considered that it is generally understood that the balance of benefits and risks of belantamab, and its uncertainties in terms of evidence for an improvement in symptoms and quality of life, compared to available options, has to be discussed by patients and doctors.

13. Updated Benefit-risk balance

13.1. Therapeutic Context

13.1.1. Disease or condition

In the context of this re-examination of the CHMP negative opinion of the Renewal of the CMA of Blenrep, the MAH proposed the following amendment to the current indication **(bold)**:

*BLENREP is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody**,** who have demonstrated disease progression on the last therapy, **and where there is no other suitable alternative treatment option (see Section 5.1)**.*

13.1.2. Available therapies and unmet medical need

Current treatment of MM includes glucocorticoids, chemotherapy, primarily alkylating agents, including high dose chemotherapy followed by autologous stem cell transplantation (ASCT), IMiDs (such as lenalidomide, pomalidomide and thalidomide), PIs (such as bortezomib, carfilzomib and ixazomib), anti-CD38 antibodies (such as daratumumab and isatuximab), elotuzumab and the histone deacetylase inhibitor panobinostat.

In addition, BCMA targeted agents (CAR-T products and bispecific antibodies), a GPRC5D targeted bispecific antibody as well as melphalan flufenamide and selinexor have been approved in the EU in recent years.

Despite multiple therapeutic options, multiple myeloma remains incurable. Median OS in patients who have received at least three prior multiple myeloma lines of therapy and are refractory to both an IMiD and a PI is only 13 months (Kumar 2017). There is an unmet medical need for more treatment options capable of achieving deep and durable responses.

13.1.3. Main clinical studies

DREAMM-2

The initial authorisation of belantamab mafodotin was primarily supported by data from a phase II, open-label, 2-arm, randomized, multicentre study to evaluate the efficacy and safety of two doses (2.5 mg/kg or 3.4 mg/kg) belantamab mafodotin monotherapy in patients who had failed at least 3 prior lines of anti-myeloma treatments, including an anti-CD38 antibody alone or in combination, and was refractory to an immunomodulatory agent, and to a proteasome inhibitor. In addition, patients must had undergone stem cell transplant or be considered transplant ineligible. Prior treatment with anti-BCMA therapy was an exclusion criterion.

DREAMM-3

DREAMM-3 (SOB-clin-004), is a phase III, open-label, randomized study, evaluating the efficacy and safety of single agent belantamab mafodotin when compared to pom/dex in patients with relapsed/refractory myeloma who had been previously treated with at least 2 prior lines of therapy, including 2 consecutive cycles of lenalidomide and a PI, (given separately or in combination) and must have had documented progression (a) on, or within 60 days of completion of the last therapy or (b) must have been nonresponsive while on last treatment where non-responsive is defined as not achieving at least MR after 2 complete treatment cycles. In addition, patients must have undergone stem cell transplant or be considered transplant ineligible. Prior treatment with anti-BCMA therapy was an exclusion criterion.

13.2. Favourable effects

DREAMM-2

The ORR per IRC was 32% (97.5%CI: 21.7, 43.6) in the treatment arm with the subsequently approved posology (2.5 mg/kg). The median DOR was 11 months (95%CI: 4.2 to NR).

DREAMM-3

In the inferential PFS analysis, medians were 11.2 months vs. 7.0 months in the Blenrep and pom/dex groups, respectively. This difference was not statistically significant; HR 1.03 (95% CI: 0.72, 1.47). Hazards were non-proportional.

In a data update 10 months after the inferential analysis, the median OS was 22.7 months vs. 22.9 months, for Blenrep and pom/dex respectively; HR 1.03 (0.74,1.43).

ORR per Investigator was 41% vs. 36% for Blenrep and pom/dex respectively.

13.3. Uncertainties and limitations about favourable effects

DREAMM-2

This was a single arm trial. ORR is on the low end of what has been previously acceptable, and moreover might have been influenced by patient selection.

DREAMM-3

The study did not meet its primary endpoint of superiority in investigator-assessed PFS.

DREAMM-3 enrolled a less heavily pre-treated population (than DREAMM-2) in which generally higher activity (ORR) is expected than in more heavily pre-treated subjects.

13.4. Unfavourable effects

Ocular toxicity

The safety profile of Blenrep appears consistent across clinical trials and in post-marketing follow-up. Most notable are the very high rates of ocular toxicity (including grade 3 and 4) leading to dose interruptions, modifications and discontinuations.

In the DREAMM-2 study keratopathy (corneal epithelium changes) were found in patients treated with Blenrep at both dose levels in the DREAMM-2 study. The most common grade 1–2 adverse event was keratopathy, and the most common grade 3–4 adverse events in the safety population were keratopathy (in 26 [27%] of 95 patients in the 2·5 mg/kg cohort and 21 [21%] of 99 patients in the 3·4 mg/kg cohort). Keratopathy led to the majority of dose adjustments (23% of 95 patients and 27% of 99 patients), treatment delays (47% of 95 patients and 48% of 99 patients), and discontinuations (1% of 95 patients and 3% in 99 patients. Patients who underwent dosing delays were usually able to re-initiate treatment with a median treatment initiation time of 83 days (2.5 mg/kg cohort) and 63 days (3.4 mg/kg cohort).

In the DREAMM-3 study ocular AEs by CTCAE were reported in the Blenrep group in 143 of 217 (66%) participants. Grade 3 and worse ocular AESIs were reported in 64 (29%) of 217 patients in the Blenrep group. Grade 4 Keratopathy and Visual Acuity (KVA) scale events occurred in 21 (10%) of 217 patients in the Blenrep group (comprising 16 corneal erosions, two keratopathy, two best corrected visual acuity worse than 20/200, and one corneal erosion and ulcer).

For all adverse events and KVA events dose modifications, delays, or reductions were reported in 155 (71%) of 217 patients. Dose reductions were 84 of 217 (39%), delays were 147 (68%) of 217. Extended dose delays (>63 days) occurred in 27 (12%) of 217 patients in the Blenrep group. Discontinuations due to ocular AESIs happened in four (2%) of 217 Blenrep treated patients.

Thrombocytopenia

In DREAMM-2, thrombocytopenic events were reported in 38% of patients, while 22% of patients experienced thrombocytopenia grade 3-4. In DREAMM-3, the rate of thrombocytopenia (any grade) was 34% and 30% for Blenrep and Pom/Dex. The rate of grade ≥3 thrombocytopenia was 23% and 16% for the two treatment arms respectively.

Infections

In DREAMM-2, infections (all grades) occurred in 45% of participants in the 2.5 mg/kg arm, and fatal infections in 3 participants (3%).

In DREAMM-3, Grade ≥3 infections were reported in 13% of subjects in the belantamab group, with 7 fatal infections (3%). The rate of pneumonia (any grade) was 4% and 11% in the Blenrep and pom/dex arms, respectively. The rate of grade ≥3 pneumonia was 3% and 9% respectively.

13.5. Uncertainties and limitations about unfavourable effects

A single arm study setting impairs the causality assessment of non-signature adverse events. Therefore, a confirmation of the safety profile in a randomised controlled trial was required.

The sample size of DREAMM-3 is not large enough to identify rare adverse events. In addition, study investigators were not required to report pure corneal exam findings as AEs, so the incidence of

keratopathy reported by Common Terminology Criteria for Adverse Events (CTCAE) does not necessarily reflect the totality of cases occurred during the study.

The ocular safety of Blenrep depends on adequate monitoring. It is not known if monitoring in real life will be up to the same standard as in the trial.

13.6. Effects Tables

Table 13. Effects table for Belantamab mafodotin 2.5 mg/kg, as monotherapy for the treatment of adult patients with multiple myeloma who have received at least four prior therapies- cut-off date 03 July 2023.

Effect	Short Description	Unit	Belantamab mafodotin 2.5 mg/kg (N = 218)	Pomalidomide and dexamethasone (N = 107)	Uncertainties/ Strength of evidence	Ref
Favourable Effects						
Median PFS*	Time from randomisation until PD or death due to any cause	Months (95% CI)	11.2 (6.4, 14.5)	7.0 (4.6, 10.6)	No statistically significant difference between the 2 treatment groups, (HR 1.03 [95% CI: 0.72, 1.47]), based on the stratified Cox model (p=0.558).	DREAMM-3
Median OS**	Time from randomisation to death due to any cause	Months (95% CI)	22.7 (19.0, Not reached)	22.9 (15.9, Not reached) HR 1.03 (0.74, 1.43)		
Unfavourable Effects						
Ocular AE	- all grades -grade 3-4 KVA	% 	66 50	8 0		DREAMM-3
Pneumonia	- all grades - grade 3-4	%	4 3	11 9		
Thrombocytopenia	- all grades - grade 3-4	%	34 23	30 16		

Abbreviations: PFS: progression free survival, OS: overall survival; HR: hazard ratio; ORR: objective response rate; PR: partial response; CI: confidence interval; PD: progressive disease; AESI: Adverse events of special interest; KVA: Keratopathy and visual acuity events
Notes: *The primary analysis of DREAMM-3 was conducted in September 2022.
** OS and ORR data are presented with the latest available cut-off data, of 03 July 2023.

13.7. Benefit-risk assessment and discussion

13.7.1. Importance of favourable and unfavourable effects

In this re-examination procedure, the MAH challenged the negative CHMP opinion on the annual renewal of Blenrep, maintaining that B/R remains positive, at least in a subset of the approved

indication for whom other options are not suitable. This is notwithstanding the failure to statistically establish an effect on PFS or OS in the study agreed at time of conditional approval to confirm the benefit/risk balance of Blenrep.

The initial conditional approval of Blenrep was based on the single arm trial DREAMM-2 with an observed ORR of 32% with a median DoR of 11 months that improved to 12.5 months with longer follow up. Due to the known limitations of SATs, including lack of randomisation, lack of comparator, inability to isolate effects on PFS and OS, difficulty in causality attribution of adverse effects and potential selection bias, results from SATs in most cases cannot be considered comprehensive evidence for efficacy and safety in a disease like MM for which the prevalence does not preclude the conduct of randomised clinical trials. Thus, the company was requested to submit the results of DREAMM-3 where the efficacy and safety of Blenrep was to be compared with pom-dex in RRMM patients.

The assumption was that the observed responses would be translated to clinically relevant improvement in time-to-event endpoints. Current data show that this was not the case.

The median PFS (mPFS) at the time of the primary analysis (12 SEP 2022) was 11.2 months in the Blenrep group vs. 7.0 months in the Pom-Dex group. Despite the numerical difference in median PFS, the trial failed to meet the primary endpoint for superiority of Blenrep over pom-dex with a HR of 1.03, p =0.558 (stratified Cox model). According to the statistical analysis plan, step 1 was to test PFS at the final PFS analysis (12 SEP 2022). If not significant then further statistical testing should be stopped. The trial is thus formally negative.

In their grounds for re-examination, the applicant claims that "*the data from DREAMM-3 show that BLENREP monotherapy is at least as active as the Pom/Dex combination".* DREAMM-3 failed to meet its prespecified primary endpoint of Blenrep superiority over pom-dex. A failed trial for superiority does not automatically translate into statistically significant non-inferiority. In fact, no consideration of non-inferiority was made in the planning of the DREAMM-3 study. For instance, there was no predefined non-inferiority margin and the sample size determination was based on a superiority design. In terms of PFS and OS, the analysis from DREAMM-3 does not statistically demonstrate that Blenrep monotherapy is as least active as the pom-dex combination.

The MAH also argues that the overall safety profile of Blenrep, despite its marked ocular toxicity, is "manageable" in terms of the risk for discontinuation and impact on QoL. Overall discontinuation rates due to AE's were similar for Blenrep and PomDex in DREAMM-3.

Moreover, it is claimed that the risk of infectious adverse events is lower than for alternatives, including other BCMA targeting agents. However, when comparing infection risk across different trials it is important to consider that patient populations that are being compared can be different, especially with respect to the number of prior lines of treatment and drug class exposure/refractoriness.

The MAH also argues that Blenrep fills the treatment gap for patients who are unlikely candidates for bi-specific agents, or CAR-T Therapy. In support of that claim, the MAH presents data from the following subgroups: age ≥75, eGFR < 40 mg/mL/min and ECOG PS 2 (the MAH writes PS ≥ 2 but patients with PS 3 or greater could not be included into DREAMM-2 or DREAMM-3).

In agreement with the SAG it is acknowledged that there may be a patient group ineligible for treatment with CAR-T therapy and bispecific antibodies which potentially could benefit from Blenrep treatment. However, the CHMP considers that the benefit of Blenrep monotherapy has not been established in this subset of patients.

The CHMP also did not agree with the restriction of the indication as proposed by the MAH, as no data to support the efficacy of Blenrep in this indication were presented.

13.7.2. Balance of benefits and risks

From the available data and taking into account the uncertainties in relation to the patients that may benefit from Blenrep treatment, it is concluded that the favourable effects of Blenrep in the proposed indication do not outweigh the risks associated with this treatment.

Since the DREAMM-3 which had been agreed as the study to confirm the clinical benefit of Blenrep in its approved indication failed to do so, it is recommended not to renew the CMA.

Scientific conclusions

Overall summary of the scientific evaluation

The European Commission issued on 25 August 2020, a conditional marketing authorisation (MA) for Blenrep. As specific obligations (SOB), the marketing authorisation holder (MAH) was requested to perform and submit the results from the clinical study DREAMM-2 (205678) and to perform and submit the results from an additional clinical study DREAMM-3 (207495) to confirm safety and efficacy of Blenrep.

- Efficacy issues

DREAMM-2 (205678)

The provided final study results of DREAMM-2 with regard to efficacy are in line with the results provided during the MA evaluation.

No new safety findings were identified with longer follow-up.

This SOB is considered fulfilled.

DREAMM-3 (207495)

Blenrep (belantamab mafodotin) was approved based on promising activity in terms of ORR. However, the data available at time of initial marketing authorisation were not deemed comprehensive. In particular, there was no demonstration of a positive impact of the product on time-dependent endpoint including PFS and OS. Therefore, a CMA was granted subject to SOB.

The applicant proposed the DREAMM-3 study as a SOB to confirm the efficacy and safety of Blenrep in relapsed/refractory multiple myeloma patients. This was accepted by the CHMP.

The DREAMM-3 (207495) study investigates the efficacy of belantamab mafodotin in patients with multiple myeloma who had had previously been treated with at least 2 prior lines of therapy, including 2 consecutive cycles of lenalidomide and a proteasome inhibitor. The study is a phase III, open-label, randomized trial designed to demonstrate the superiority of BLENREP monotherapy compared to pomalidomide and dexamethasone (PomDex).

The MAH submitted the main results of DREAMM-3 as part of the annual renewal procedure (EMEA/H/C/004935/R/0017). The study did not meet its primary endpoint of superiority in investigator-assessed Progression Free Survival (PFS), as there was no statistically significant difference in PFS between the 2 treatment groups, as demonstrated by a Hazard Ratio (HR) of 1.03

(95% CI: 0.72, 1.47). The HR of the Overall Survival (OS) was 1.03 (95%CI: 0.74. 1.43) at the most updated available analysis. Thus, the efficacy of Blenrep was not confirmed.

Key outcomes from the agreed SOB's have now been delivered and the data are now considered comprehensive. Therefore, the CHMP concludes that efficacy of Blenrep in the approved indication has not been demonstrated.

Grounds for refusal of the renewal

Whereas

- The Committee re-assessed the benefit/risk of Blenrep as part of the annual renewal procedure, taking into account the totality of data, which includes the data at the time of the conditional approval and, the additional data from studies DREAMM-2 and DREAMM-3 generated as per the specific obligations.

- Evidence for the use of Blenrep in its approved indication was based on the objective response rate observed in a trial without a reference treatment arm allowing for the isolation of effects on PFS and OS. Therefore, efficacy was expected to be confirmed in a randomized controlled trial with a relevant reference regimen (DREAMM-3 (207495)). However, the primary analysis of the confirmatory study for Blenrep failed to demonstrate clinical benefit in terms of progression free survival or overall survival. Thus, the favourable benefit/risk balance of Blenrep in its approved indication has not been confirmed as required in the setting of a CMA.

Therefore, the CHMP has recommended not to renew the conditional marketing authorisation.