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RESEARCH**

APPLICATION NUMBER:

761158Orig1s000

OTHER REVIEW(S)

Memorandum to File

To: BLA 761158

From: Gerald J. Dal Pan, MD, MHS
Director, Office of Surveillance and Epidemiology

Date: 05 August 2020

Re: Risk Evaluation and Mitigation Strategy for Blenrep (belantamab mafodotin)

Blenrep (belantamab mafodotin) is a B-cell maturation antigen (BCMA)-directed antibody and microtubule inhibitor conjugate indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

In the clinical development program, ocular toxicity, in the form of keratopathy, was the most common adverse event in the DREAMM-2 study, occurring in 71% of patients at the 2.5 mg/kg dose and in 77% at the 3.4 mg/kg dose,¹ with ocular symptoms reported in 43% and 55% of those patients, respectively.² Worsening of visual acuity by a decrease of at least one line was reported in 53% of patients at the 2.5 mg/kg dose and in 48% at the 3.4 mg/kg dose, respectively.³

To address this toxicity in the clinical development program, and to inform dose modifications, the sponsor developed an ocular toxicity scale specifically for this product. The scale, known as the Keratopathy and Visual Acuity (KVA) scale, assesses both the extent of keratopathy and the best corrected visual acuity. For patients with an abnormal ocular exam, the extent of keratopathy and the change in best corrected visual acuity (relative to the previous ocular exam) are each recorded on a 4-point scale for each eye prior to each dose administration. These results are used to determine the Grade of ocular toxicity on a scale from 1 to 4. The overall grade is based on the most severe finding on the corneal or visual acuity exam.

In the clinical development program, dose modifications were common, occurring in 47% of patients at the 2.5 mg/kg dose and in 51% at the 3.4 mg/kg dose, respectively.⁴

Review staff in both the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) agree that a risk evaluation and mitigation strategy (REMS) is necessary for the benefits of belantamab mafodotin to exceed its risks. Specifically, the REMS will require that an eye specialist, either an ophthalmologist or an optometrist, perform a corneal examination to assess keratopathy and measure best corrected visual acuity and record the findings for each assessment or measurement

¹ FDA presentation at the July 14, 2020 meeting of the Oncologic Drugs Advisory Committee, slide 6, available at <https://www.fda.gov/media/140061/download>.

² FDA presentation, slide 14.

³ FDA presentation, slide 12.

⁴ FDA presentation, slide 15.

according to the KVA. The eye specialist, who will be consulted by the belantumab prescriber and will not be required to be enrolled in the REMS, forwards the results of the eye exam to the oncologist prescriber, who will be required to be enrolled in the REMS. The oncologist prescriber will then transcribe the results of the eye exam, including the results of the keratopathy assessment and the best visual acuity for each eye, onto the BLENREP™ REMS Patient Status Form, and, using these data, will determine the Grade of the ocular toxicity according to an algorithm that is printed on the form. For each Grade of ocular toxicity, the form indicates the type of dose modification that is necessary.

The specific disagreement between review staff in OND and OSE is the amount of information that needs to be recorded by the oncologist prescriber onto the BLENREP™ REMS Patient Status Form and forwarded to the Blenrep REMS Program. The OND staff maintain that the oncologist prescriber should record the data on keratopathy and best visual acuity for each eye along with the Grade of ocular toxicity and transmit this information to the REMS program. In support of its position, OND staff note that these details are necessary to determine whether the KVA scale is being used properly. The OSE staff maintain that the oncologist prescriber should record and transmit to the REMS program only the Grade of ocular toxicity. In support of its position, OSE staff note that only the Grade of ocular toxicity, and not the underlying keratopathy data and visual acuity data, is needed for the proper dose modification. OSE staff argue that the collection of the additional data on keratopathy and visual acuity imposes an undue burden on the oncologist prescriber, and that data on the result of the eye exam can be obtained by the company as part of their pharmacovigilance or postmarket study activities. OND staff maintain that collection of these data is necessary and thus does not impose an undue burden.

To assess the possibility of undue burden from the collection of the data on keratopathy and visual acuity, I reviewed the BLENREP™ REMS Patient Status Form to determine the amount of additional work that the oncologist prescriber must perform to record these details. For a patient with both eyes affected, the oncologist prescriber will need to check at most 16 boxes on the form. If only one eye is affected, the number drops to at most eight boxes.

On the basis of this review, I conclude that collection of data on keratopathy and visual acuity is clinically relevant for the determination of the Grade of ocular toxicity and thus for the determination of the appropriate dose modification. It is therefore necessary for the safe use of the drug and should not impose an undue burden. As part of the REMS assessment for this drug, there should be a measure of the burden that this data collection imposes.

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/s/

GERALD J DALPAN
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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761158
Date Received	December 5, 2019
Review Division	Division of Hematology Malignancies 2 (DHM2)
OSE RCM #	2019-2432; 2019-2434
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D., Risk Management Analyst Kate Heinrich Oswell, MA, Health Communications Analyst Carolyn Tieu, Pharm.D., MPH, Risk Assessment Analyst
Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	August 4, 2020
Subject	Interim comments for the proposed REMS
Established Name	belantamab mafodotin-blmf
Trade Name	Blenrep
Name of Applicant	GlaxoSmithKline Intellectual Property Development Ltd.
Therapeutic Class	B-cell maturation antigen (BCMA)-directed antibody-drug conjugate
Formulation(s)	100 mg lyophilized powder in a single-dose vial for reconstitution
Dosing Regimen	Administer belantamab mafodotin 2.5 mg/kg intravenously every three weeks until disease progression or unacceptable toxicity over 30 minutes infusion.

1 Introduction

This review provides comments and changes to the proposed risk evaluation and mitigation strategy (REMS) and the REMS materials for the new molecular entity (NME) Blenrep (belantamab mafodotin-blmf). On December 5, 2019, GlaxoSmithKline Intellectual Property Development Ltd. (GSK) submitted a Biologic Licensing Application (BLA) 761158 for Blenrep (belantamab mafodotin-blmf) with the proposed indication for the treatment of adult patients with relapsed or refractory multiple myeloma (MM) (b) (4)

This application is under review in the Division of Hematology Malignancies 2 (DHM2).

The Applicant's proposed REMS submitted on May 7 (Global Submit;GS), July 7 (email), July 10 (GS), July 17 (email), July 21 (GS) and July 24 (email), July 27 (docuBridge) and July 29 (email) and July 30 (docuBridge), 2020, are the subject of this review. Their proposed REMS consist of communication plan, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Blenrep outweigh the risks of serious adverse outcomes resulting from ocular toxicity. Division of Risk Management (DRM) and Division of Hematology Malignancies 2 (DHM2) agree that a REMS with ETASU A (prescriber certification), ETASU B (healthcare settings certification), ETASU D (patient enrollment with documentation of safe use condition) and ETASU E (monitoring) is required for the benefits of Blenrep to outweigh the risk of ocular toxicity.

2 Materials Reviewed

General comments on the Applicant's REMS document, REMS Supporting Document and REMS materials were provided on June 26, 2020. On July 10, 2020, the Applicant provided responses to the Agency's comments. FDA provided comments on July 22 and July 28, 2020, on attestations for the prescriber, healthcare setting and patient enrollment forms, which have been reviewed by the Offices of Regulatory Policy (ORP) and Chief Counsel (OCC). In addition to the review by the DRM, the REMS Document has been reviewed by the OCC.

The following materials have been reviewed and comments on these materials are appended to this review:

- Patient Status Form
- Eye Care Professional Consult Request Form

3 Comments to the Applicant

The Agency has reviewed the proposed Patient Status Form and Eye Care Professional Consult Request Form based on the teleconference on August 3, 2020. Please see the summary of comments below.

General Comment

Please note that REMS materials must align with the Prescribing Information.

The Agency has determined that a part of the assessment plan, a qualitative study is needed to inform the discussion about administrative burden on prescribers. The objective of the study is to investigate administrative burden and prescriber's attitudes and beliefs around the requirement for transcribing the ophthalmic examination findings from the Eye Care Professional Consult Request Form to the Patient Status Form. Submit your protocol for FDA review and comment within 60 days from the date of approval. Results of the qualitative study must be included in the Year 1 assessment report. The protocol should include but is not limited to the following:

- A timeline for study implementation
- A total of 12 participants (e.g. 3 per mini groups or triads, 6 per focus group, or 1 on 1 in-depth interviews)
- Topics to be addressed in the study
- All materials (e.g. screener script, moderator guide etc.)
- Shell tables of the participant's demographics
- Shell tables/figures of content and thematic analysis

I. REMS Materials

Eye Care Professional Consult Request Form:

Include summary finding for the ophthalmologist in the form as follows:

What is the current grading from the examinations finding(s) and BCVA? (Report the grade for the worst eye based on Keratopathy and Visual Acuity (KVA) scale)

Normal Grade 1 Grade 2 Grade 3 Grade 4

“Normal” must be defined and described as part of the question.

Patient Status Form:

As per the discussion between the Agency and the Applicant via teleconference on August 4, 2020, add “Corneal Clear” to all the Corneal Examination Finding” columns for the Question #3 and #4.

The Patient Status Form must include a question with a summary finding. Per the Prescribing Information, the oncologist needs to determine the summary finding from the eye exam to determine continuation of treatment, which must be summarized in the form as a new Question #5 as follows:

5. What is the current grading from the examinations finding(s) and BCVA? (Report the grade for the worst eye based on Keratopathy and Visual Acuity (KVA) scale)

Normal Grade 1 Grade 2 Grade 3 Grade 4

“Normal” must be defined and described as part of the Question # 5 in the ophthalmic assessment.

II. REMS Assessment Plan

Include this metric under Safe Use Behaviors following section 9.

10. Prescriber Burden Assessment (1-year assessment only)

- a. A qualitative study to assess administrative burden and prescribers' attitudes and beliefs around the requirement for transcribing the ophthalmic examination findings from the Eye Care Professional Consult Request Form to the Patient Status Form

Resubmission Instructions:

Your amendment must include the complete REMS, including the REMS document, all appended materials, and the REMS supporting document as a final submission. Submit Word version as well as a PDF version of each document, and single compiled PDF version of the REMS document and all the appended REMS Materials.

Respond to these comments and re-submit all documents as a REMS AMENDMENT by this afternoon August 4, 2020.

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/s/

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Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF ONCOLOGIC DISEASES
DIVISION OF HEMATOLOGIC MALIGNANCIES 2**

BLA #: 761158
Products: BLENREP (belantamab mafodotin), IV infusion
APPLICANT: GlaxoSmithKline (GSK)
FROM: Shanthy Marur MBBS MD, Associate Director for Safety (Acting)
DATE: August 4, 2020

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for BLENREP (belantamab mafodotin) to ensure that the benefits of the drug outweigh the risk of ocular toxicity. In reaching this determination, we considered the following:

- A. In the United States, for 2020, it is estimated approximately 32,270 new patients will be diagnosed with multiple myeloma and 12,830 multiple myeloma-related deaths are expected to occur (NCI SEER, 2020). In the United States, the lifetime risk of getting a diagnosis of multiple myeloma is 1 in 132 (0.76%). This estimate is based on key statistics for Multiple Myeloma from American Cancer Society's Cancer Statistics Center.
- B. While treatment for recurrent, refractory MM (RRMM) is individualized according to patient- and disease-related factors, patients with RRMM inevitably become resistant to current standard of care options (proteasome inhibitors [PIs], immunomodulatory agents, and monoclonal antibodies [mAbs]). With currently available treatments the median progression-free survival [PFS] is 3.4 months; and median overall survival [OS] is 6–9 months.
- C. Treatment with belantamab mafodotin 2.5 mg/kg Q3W IV resulted in an objective response rate (ORR) assessed by independent review committee (IRC) of 31% (97.5% CI: 20.8, 42.6). Among the responders, the achieved responses were partial response (38%) and very good partial response (VGPR) or better (62%). At the time of data cut-off with a median follow-up of 6.3 months, the median duration of response (per IRC assessment) was not reached. Secondary endpoints included progression free survival, with a median of 2.9 months.
- D. It is expected adult patients with RRMM who have received at least 4 prior therapies including an anti-CD38 antibody, a PI, and an immunomodulatory agent (triple-class refractory multiple myeloma), would receive treatment with Belantamab mafodotin until disease progression or unacceptable toxicity.
- E. Belantamab mafodotin 2.5 mg/kg poses the serious risk of severe ocular toxicity with the risk of bilateral vision loss. In the pivotal study, DREAMM2, among the patients who received 2.5mg/kg (n=97), the most commonly reported adverse event (AE) was keratopathy (71%) including microcyst-like epithelial changes [MECs], changes in the corneal epithelium observed on eye examination with or without symptoms. The incidence of Grade ≥ 3 keratopathy based on the Keratopathy Visual Analytic scale was 44%. A significant proportion of patients with keratopathy did not experience any ocular symptoms and were detected only by routine ophthalmic exam performed on trial. Approximately 17% of patients had a treatment-emergent decline in visual acuity to 20/50 or worse (a level at which patients may not be legally able to drive) in the better seeing eye. The ocular toxicities were primarily managed with dose modifications, including dose delays/interruptions, dose reductions, and/or permanent discontinuation of study treatment. Dose delays occurred in 54% of patients, and the most common cause for dose delay was keratopathy (47%) and blurred vision (5%). Dose reduction occurred in 29% of patients, and the most common AE leading to dose reduction was keratopathy (23%). Keratopathy led to permanent discontinuation of treatment in two patients treated with 2.5mg/kg. In addition to severe ocular

toxicity, belantamab mafodotin has been associated with thrombocytopenia and infusion related reactions.

- F. Belantamab mafodotin is an antibody drug conjugate (ADC) with an afucosylated, humanized anti-BCMA mAb conjugated to a microtubule disrupting agent, MMAF payload, which is a new molecular entity.

The elements of the REMS will be ETASU A (healthcare providers who prescribe belantamab mafodotin are specially certified), ETASU B (pharmacies and healthcare settings that dispense belantamab mafodotin are specially certified), ETASU D (each patient enrolled will have documentation of safe use conditions), ETASU E (each patient using belantamab mafodotin will be subject to certain monitoring), a communication plan, an implementation system, and a timetable for submission of assessments.

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/s/

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Ophthalmology Consult Review of BLA 761158

Consult Request Date: October 2, 2019
Submission: August 21, 2019
Review completed: July 31, 2020

Product name: Belantamab mafodotin

Applicant: GlaxoSmithKline

Division Request: For BLA 761158 (belantamab mafodotin), please review the ocular toxicity safety data and associated ocular exam reports and narratives, and the implementation/outcomes of corneal mitigation strategies for both the pivotal (205678) study and supportive study (BMA117159). Please comment specifically on ocular and corneal AEs, the outcomes of the mitigation strategies, and dose modifications due to ocular AEs. Also provide recommendations for monitoring and management of ocular toxicities to be incorporated in the USPI.

Please note that the Applicant is participating in the Real-Time Oncology Review (RTOR) pilot in the Oncology Center for Excellence (OCE) for submission of this BLA. The RTOR is similar to a rolling review with components of the BLA being submitted in batches. Submission of the final batch is planned on December 19, 2019; however, other portions of the BLA have already been submitted or will be submitted in October/November 2019. Refer to the attached timeline for further details. The Applicant is also participating in the OCE's Assessment Aid pilot program (<https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>). Our target action date for this BLA will be in March 2020. Please let us know if you have any questions, especially with regard to the above pilot programs for this application.

EDR Location: \\CDSESUB1\evsprod\BLA761158\0001

Study: A Phase II, Open Label, Randomized, Two-Arm Study to Investigate the Efficacy and Safety of Two Doses 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 (DREAMM 2)

Ocular Adverse Events: Corneal events are the most frequently reported adverse events associated with belantamab mafodotin in the clinic, which include keratopathy, blurred vision, dry eyes and photophobia. The proportion of participants who had corneal events based on examination findings (GSK scale) was comparable in both cohorts (71% for 2.5 mg/kg cohort, 77% for 3.4 mg/kg cohort) and Grade 3 and Grade 4 events were also comparable (47% for 2.5 mg/kg cohort; 49% for 3.4 mg/kg cohort). The time to onset of first occurrence was also comparable in both treatment cohorts (28 days for 2.5 mg/kg cohort, 22 days for 3.4 mg/kg cohort), as was the median duration of first occurrence (101.5 days and 91.5 days, respectively). These ocular events were managed with dose delays and reductions, which occurred frequently (52% and 46% of participants). Recovery data are limited, but in both cohorts, recovery to mild or baseline examination findings was observed in the majority

of participants for whom adequate follow-up was available, with a median duration of about 3 months. Participants with a history of dry eyes were found to be at higher risk for the development of Grade ≥ 2 corneal findings related to belantamab mafodotin ($p = 0.014$).

The ocular sub-study did not provide any evidence that the prophylactic use of steroid eye drops was beneficial to participants treated with belantamab mafodotin.

Reviewer's Comments: *Concur that ocular events were significant portion of the adverse events occurring in greater than 70% of treated patients. The prophylactic use of ophthalmic corticosteroids did not significantly impact the events.*

Dose Reductions:

There were 29% and 42% of participants who had at least 1 dose reduction. The most common AEs leading to dose reductions were keratopathy based on corneal examination finding and thrombocytopenia (see Section 7.2.4). Dose reductions tended to occur sooner in the 3.4 mg/kg cohort (51% by Cycle 3 Day 1) than in the 2.5 mg/kg cohort (26% by Cycle 3 Day 1)(Table 15). Per protocol, participants in the 3.4 mg/kg cohort were allowed a maximum of 2 dose reductions, and participants in the 2.5mg/kg cohort were allowed only 1 dose reduction.

Reviewer's Comments: *To date, dose reductions have been the only effective modifier for ocular adverse events.*

Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU)

A Risk Evaluation and Mitigation Strategy (REMS) proposal was submitted on February 17, 2020 and revised on April 13, 2020, in which GlaxoSmithKline (GSK) proposed a REMS with Elements to Assure Safe Use (ETASU), in addition to the previously proposed Communication Plan. Further updates to the proposed REMS were submitted on May 7, 2020 (BLA 761158; Seq 0046) Subsequently, on June 29, 2020, the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) Division of Division of Hematologic Malignancies 2 (DHM2) provided comments on the REMS materials submitted to date, with a response requested by July 10, 2020.

- The BLENREP REMs program will be a portal where prescribers, patients and healthcare settings (HCS) can enroll.
- Patient management will also occur via this portal.
- The paper forms will be available as a back-up option on the REMS website with the REMS Coordinating Center available to provide support.
- The high-level process flow for the portal, assuming enrollment is complete, is that the prescriber will log into the website and see a patient dashboard, select the appropriate patient, and complete the patient status information based on results from the eye exam.
- [REDACTED] ^{(b) (4)}
- The HCS can log in and see the patient is eligible for infusion, generate an authorization code and confirm the date and amount of drug dispensed.
- Once this has occurred, the system automatically makes the patient ineligible again until the prescriber submits another patient status form based on results of an updated eye exam.

- The prescriber must complete the patient status information prior to each dose for a patient to be eligible.
- The patient must be eligible for the HCS to generate an authorization code to dispense and the dispensing of drug makes the patient ineligible once again.
- This pattern repeats as long as a patient is on therapy.

Reviewer's Comments: *I concur with the proposed REMS with ETASU.*

Labeling: (Sections below are limited to areas of ophthalmologic concern)

WARNING: OCULAR TOXICITY

BLNREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms, such as blurred vision and dry eyes [see Warnings and Precautions (5.1)].

Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLNREP until improvement and resume, or permanently discontinue, based on severity [see Dosage and Administration (2.3), Warnings and Precautions (5.1)].

(b) (4) BLNREP is available only through a restricted program (b) (4) (b) (4) called the BLNREP REMS [see Warnings and Precautions (5.2)].

2 DOSAGE AND ADMINISTRATION

2.1 Important Safety Information

Perform an ophthalmic exam prior to initiation of BLNREP and during treatment [see Warnings and Precautions (5.1)].

Advise patients to use preservative-free lubricant eye drops and avoid contact lenses unless directed by an ophthalmologist [see Warnings and Precautions (5.1)].

2.3 Dosage Modifications for Adverse Reactions

The recommended dose reduction for adverse reactions is:

- BLNREP 1.9 mg/kg intravenously once every 3 weeks.

Discontinue BLNREP in patients who are unable to tolerate a dose of 1.9 mg/kg (see Tables 1 and 2).

Corneal Adverse Reactions

The recommended dosage modifications for corneal adverse reactions, based on both corneal examination findings and changes in best-corrected visual acuity (BCVA), are provided in Table 1 [see Warnings and Precautions (5.1)]. Determine the recommended dosage modification of BLNREP based on the worst finding in the worst affected eye. Worst finding should be based on either a corneal examination finding or a change in visual acuity per the Keratopathy and Visual Acuity (KVA) scale.

Table 1. Dosage Modifications for Corneal Adverse Reactions per the KVA Scale

Corneal Adverse Reaction		Recommended Dosage Modifications
Grade 1	<i>Corneal examination finding(s):</i> Mild superficial keratopathy ^a <i>Change in BCVA^b:</i> Decline from baseline of 1 line on Snellen Visual Acuity	Continue treatment at current dose.
Grade 2	<i>Corneal examination finding(s):</i> Moderate superficial keratopathy ^c <i>Change in BCVA^b:</i> Decline from baseline of 2 or 3 lines on Snellen Visual Acuity and not worse than 20/200	Withhold BLENREP until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at same dose.
Grade 3	<i>Corneal examination finding(s):</i> Severe superficial keratopathy ^d <i>Change in BCVA^b:</i> Decline from baseline by more than 3 lines on Snellen Visual Acuity and not worse than 20/200	Withhold BLENREP until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at reduced dose.
Grade 4	<i>Corneal examination finding(s):</i> Corneal epithelial defect ^e <i>Change in BCVA^b:</i> Snellen Visual Acuity worse than 20/200	Consider permanent discontinuation of BLENREP. If continuing treatment, withhold BLENREP until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at reduced dose.

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

^b Changes in visual acuity due to treatment-related corneal findings.

^c Moderate superficial keratopathy with or without patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity.

^d Severe superficial keratopathy with or without diffuse microcyst-like deposits, sub-epithelial haze (central), or a new central stromal opacity.

^e Corneal epithelial defect such as corneal ulcers.

5 WARNINGS AND PRECAUTIONS

5.1 Ocular Toxicity

Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%) and dry eye (19%) [*see Adverse Reactions (6.1)*]. Among patients with keratopathy (n = 165), 49% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

Keratopathy

Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% of patients recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

Visual Acuity Changes

A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 1.4%. Of the patients with decreased visual acuity of worse than 20/40, 88% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

Monitoring and Patient Instruction

Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity [see *Dosage and Administration (2.3)*].

Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist [see *Dosage and Administration (2.1)*].

Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery.

BLENREP is only available through a restricted program under a REMS [see *Warnings and Precautions (5.2)*].

5.2 BLENREP REMS

BLENREP is available only through a restricted program under a REMS called the BLENREP REMS because of the risks of ocular toxicity [see *Warnings and Precautions (5.1)*].

Notable requirements of the BLENREP REMS include the following:

- Prescribers must be certified with the program by enrolling and completing training in the BLENREP REMS.
- Prescribers must counsel patients receiving BLENREP about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose.
- Patients must be enrolled in the BLENREP REMS and comply with monitoring.
- Healthcare facilities must be certified with the program and verify that patients are authorized to receive BLENREP.
- Wholesalers and distributors must only distribute BLENREP to certified healthcare facilities.

Further information is available, at www.BLENREPREMS.com and 1-855-209-9188.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Ocular toxicity [see *Warnings and Precautions (5.1)*].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in *Warnings and Precautions* reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder. Among the 218 patients, 24% were exposed for 6 months or longer.

Relapsed or Refractory Multiple Myeloma

The safety of BLENREP as a single agent was evaluated in DREAMM-2 [see *Clinical Studies (14.1)*]. Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Among these patients, 22% were exposed for 6 months or longer.

Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation.

Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%).

Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%), and thrombocytopenia (5%).

The most common adverse reactions ($\geq 20\%$) were keratopathy, decreased visual acuity, nausea, blurred vision, pyrexia, infusion-related reactions, and fatigue. The most common Grade 3 or 4 ($\geq 5\%$) laboratory abnormalities were lymphocytes decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyl transferase increased.

Table 3 summarizes the adverse reactions in DREAMM-2 for patients who received the recommended dosage of 2.5 mg/kg once every 3 weeks.

Table 3. Adverse Reactions ($\geq 10\%$) in Patients Who Received BLENREP in DREAMM-2

Adverse Reactions	BLENREP N = 95	
	All Grades (%)	Grade 3-4 (%)
Eye disorders		
Keratopathy ^a	71	44
Decreased visual acuity ^b	53	28
Blurred vision ^c	22	4
Dry eyes ^d	14	1

^a Keratopathy was based on slit lamp eye examination, characterized as corneal epithelium changes with or without symptoms.

^b Visual acuity changes were determined upon eye examination.

^c Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.

^d Dry eyes included dry eye, ocular discomfort, and eye pruritus.

^e Fatigue included fatigue and asthenia.

^f Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthenia, hypertension, lethargy, tachycardia.

^g Upper respiratory tract infection included upper respiratory tract infection, nasopharyngitis, rhinovirus infections, and sinusitis.

Clinically relevant adverse reactions in <10% of patients included:

Eye Disorders: Photophobia, eye irritation, infective keratitis, ulcerative keratitis.

13.2 Animal Toxicology and/or Pharmacology

Increased mitoses of corneal epithelial cells with bilateral single cell necrosis were observed following intravenous administration of belantamab mafodotin-blmf in rats and rabbits.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Ocular Toxicity

- Advise patients that ocular toxicity may occur during treatment with BLENREP [see *Warnings and Precautions (5.1)*].
- Advise patients to administer preservative-free lubricant eye drops as recommended during treatment and to avoid wearing contact lenses during treatment unless directed by a healthcare professional [see *Dosage and Administration (2.3)*, *Warnings and Precautions (5.1)*].
- Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see *Warnings and Precautions (5.1)*].

BLENREP REMS

BLENREP is available only through a restricted program called BLENREP REMS [see *Warnings and Precautions (5.2)*]. Inform the patient of the following notable requirements:

- Patients must complete the enrollment form with their provider.
- Patients must comply with ongoing monitoring for eye exams [see *Warnings and Precautions (5.1)*].

MEDICATION GUIDE BLENREP (BLEN-REP) (belantamab mafodotin-blmf) for injection, for intravenous use
<p>What is the most important information I should know about BLENREP?</p> <p>Before you receive BLENREP, you must read and agree to all of the instructions in the BLENREP REMS. Before prescribing BLENREP, your healthcare provider will explain the BLENREP REMS to you and have you sign the Patient Enrollment Form.</p> <p>BLENREP can cause serious side effects, including:</p> <p>Eye problems. Eye problems are common with BLENREP. BLENREP can cause changes to the surface of your eye that can lead to dry eyes, blurred vision, worsening vision, severe vision loss, and corneal ulcer. Tell your healthcare provider if you have any vision changes or eye problems during treatment with BLENREP.</p> <ul style="list-style-type: none"> • Your healthcare provider will send you to an eye specialist to check your eyes before you start treatment with BLENREP, prior to each dose of BLENREP, and for worsening symptoms of eye problems. • Even if your vision seems fine, it is important that you get your eyes checked during treatment with BLENREP because some changes can happen without symptoms and may only be seen on an eye exam. • You should use preservative-free lubricant eye drops at least 4 times per day during treatment with BLENREP as instructed by your healthcare provider. • You should use caution when driving or operating machinery as BLENREP may affect your vision. • Avoid wearing contact lenses during treatment with BLENREP unless directed by your eye specialist. <p>See “What are the possible side effects of BLENREP?” for more information about serious side effects.</p>
<p>What are the possible side effects of BLENREP?</p>

BLNREP can cause serious side effects, including:

- **See Eye Problems in “What is the most important information I should know about BLNREP?”**
- **Decrease in platelets (thrombocytopenia)** is common with BLNREP, and can also be serious. Platelets are a type of blood cell that help your blood to clot. Your healthcare provider will check your blood cell counts before you start treatment with BLNREP and during treatment. Tell your healthcare provider if you have bleeding or bruising during treatment with BLNREP.
- **Infusion reactions** are common with BLNREP, and can also be serious. Tell your healthcare provider or nurse right away if you get any of the following signs or symptoms of an infusion reaction while receiving BLNREP:

○ chills or shaking	○ dizziness
○ redness of your face (flushing)	○ feel like passing out
○ itching or rash	○ tiredness
○ shortness of breath, cough, or wheezing	○ fever
○ swelling of your lips, tongue, throat, or face	○ feel like your heart is racing (palpitations)
- **The most common side effects of BLNREP include** vision or eye changes such as findings on eye exam (keratopathy), decreased vision or blurred vision, nausea, low blood cell counts, fever, infusion-related reactions, tiredness, and changes in kidney or liver function blood tests.

These are not all the possible side effects of BLNREP.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Reviewer's Comments: *Concur with labeling from an ophthalmology perspective.*

Summary Conclusions: From an ophthalmic perspective, I concur with the accelerated approval of BLNREP (belantamab mafodotin) for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

Wiley A. Chambers, M.D.,
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
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Internal Consult

****Pre-decisional Agency Information****

Please Note: The following review is for DRM only and should not be used to provide comments to the sponsor.

To: Kate Oswell, Health Communications Analyst
Division of Risk Management (DRM)
Office of Surveillance and Epidemiology (OSE)

From: Adesola Adejuwon, Regulatory Review Officer, OPDP

CC: Kevin Wright, Team Leader, OPDP
Neil Vora, Safety Regulatory Project Manager, OSE
Naomi Boston, Team Leader, DRM
Till Olickal, Risk Management Analyst, DRM
Doris Auth, Associate Director, DRM
Jina Kwak, OPDP
Michael Wade, OPDP
CDER-OPDP-RPM

Date: July 29, 2020

Re: BLA 761158
BLENREP™ (belantamab mafodotin-blmf) for injection, for intravenous use
(Blenrep)
Comments on Draft Risk Evaluation and Mitigation Strategies (REMS)
Materials

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for Blenrep:

- Healthcare Provider (HCP) REMS Materials:
 - BLENREP REMS [REDACTED] (b) (4)
 - BLENREP REMS Dear Healthcare Provider Letter (Hard Copy Version)
 - BLENREP REMS Dear Healthcare Provider Letter (Email Version)
 - BLENREP REMS Dear Professional Society Letter
 - BLENREP REMS Fact Sheet
 - BLENREP REMS Healthcare Setting Enrollment Form
 - BLENREP REMS Prescriber Enrollment Form
 - BLENREP REMS Program Overview
 - BLENREP REMS Prescriber Knowledge Assessment
 - BLENREP REMS [REDACTED] (b) (4) Checklist
 - BLENREP REMS Professional Consult Request Form
 - BLENREP REMS Healthcare Setting Training
 - BLENREP REMS Patient Status Form
- Direct-to-Consumer (Patient) REMS Materials:
 - BLENREP REMS Patient Enrollment Form
 - BLENREP REMS Patient Guide
- BLENREP REMS Website

The version of the draft REMS materials used in this review were sent from DRM by Kate Oswell via email on July 14, 2020 and on July 17, 2020. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for BLENREP.

General Comment

Please remind Glaxo-Smith-Kline that REMS materials are not appropriate for use in a promotional manner.

Hard copy mock-ups, such as the proposed website document, often fail to account for factors of production that could affect the effective communication of important information and sources of additional information in the final electronic materials (e.g., active links, corresponding text, branding). Therefore, OPDP cannot provide final comments on the proposed website unless we review the final version in its entirety (i.e., www.BLENREPREMS.com). Furthermore, we remind the sponsor that the REMS specific website should not be the sole source of approved REMS materials.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see “Specific Comment[s]” below):

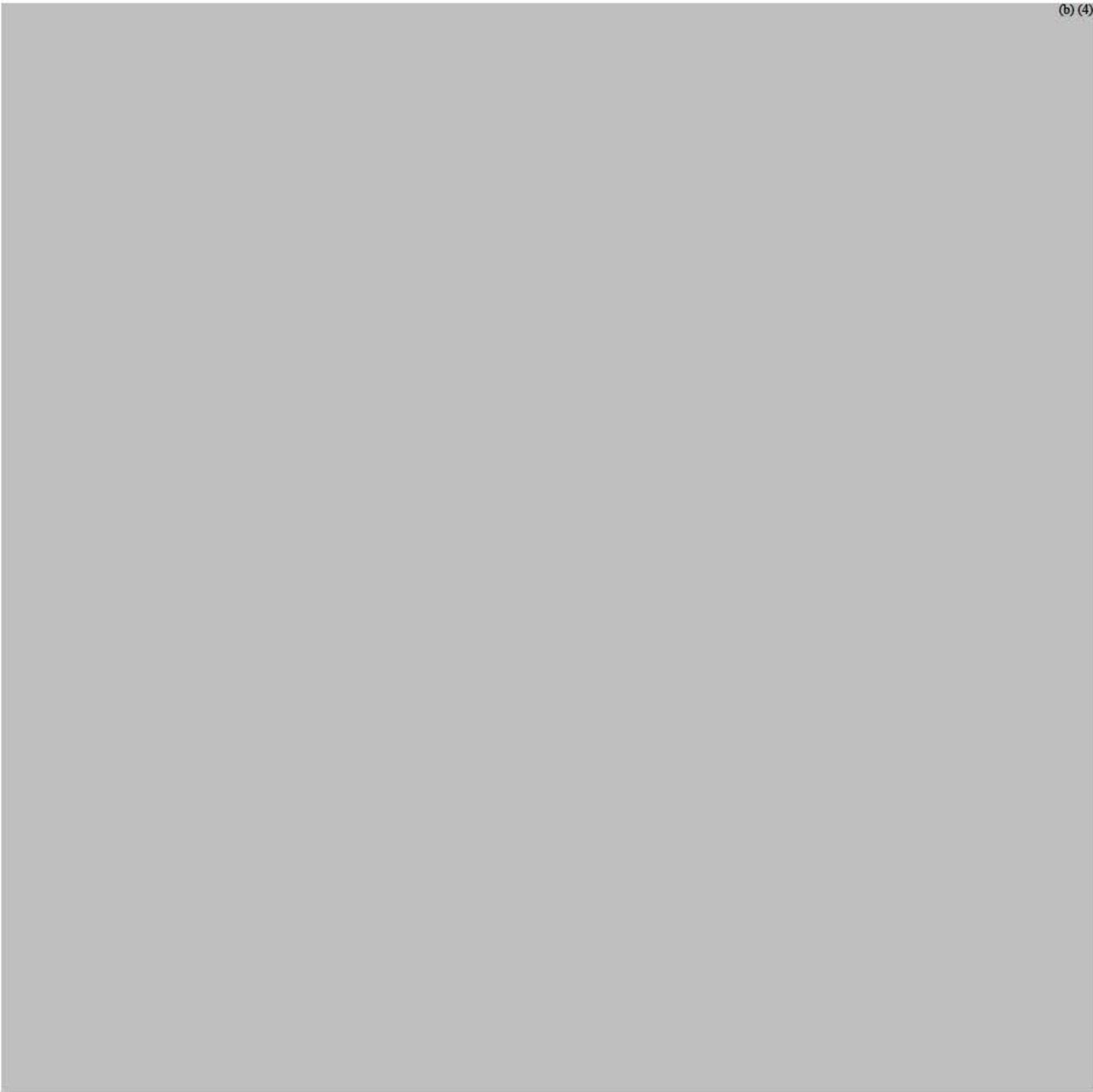
- BLENREP REMS [REDACTED] (b) (4)
- BLENREP REMS Dear Healthcare Provider Letter (Hard Copy Version)
- BLENREP REMS Dear Healthcare Provider Letter (Email Version)
- BLENREP REMS Dear Professional Society Letter
- BLENREP REMS Fact Sheet
- BLENREP REMS Healthcare Setting Enrollment Form
- BLENREP REMS Prescriber Enrollment Form
- BLENREP REMS Program Overview
- BLENREP REMS Prescriber Knowledge Assessment
- BLENREP REMS [REDACTED] Checklist (b) (4)
- BLENREP REMS Professional Consult Request Form
- BLENREP REMS Healthcare Setting Training
- BLENREP REMS Patient Status Form
- BLENREP REMS Patient Enrollment Form
- BLENREP REMS Patient Guide
- BLENREP REMS Website

Specific Comments

OPDP considers the following statements promotional in tone and recommends revising or deleting them from the REMS pieces.

(b) (4)





BLNREP REMS Dear Healthcare Provider Letter (Hard Copy and Email Version)

- Page one of the BLNREP REMS Dear Healthcare Provider Letter includes the following statement: (b) (4)

(b) (4)

- **Risk**

- (b) (4)

According to the BOXED WARNING: OCULAR TOXICITY section of the draft PI, it states: “Withhold BLNREP until improvement and resume or permanently discontinue based on severity” (underlined emphasis added). Therefore, OPDP recommends revising

this presentation to include material information, consistent with the draft PI.

BLNREP REMS Dear Professional Society Letter

- Page one of the BLNREP REMS Dear Professional Society Letter includes the statement: (b) (4)

- **Risk**

- (b) (4)

According to the BOXED WARNING: OCULAR TOXICITY section of the draft PI, it states: “Withhold BLNREP until improvement and resume or permanently discontinue based on severity” (b) (4). Therefore, OPDP recommends revising this presentation to include material information, consistent with the draft PI.

BLNREP REMS Fact Sheet

- Page one of the BLNREP REMS Fact Sheet includes the following statement: “Manage corneal adverse reactions per the *Prescribing Information* with dose reductions or withhold BLNREP until improvement (b) (4).”

- **Risk**

(b) (4)

According to the BOXED WARNING: OCULAR TOXICITY section of the draft PI, it states: “Withhold BLNREP until improvement and resume or permanently discontinue based on severity” (underlined emphasis added). Therefore, OPDP recommends revising this presentation to include material information.

BLNREP REMS Prescriber Enrollment Form

- Page one the BLNREP REMS Prescriber Enrollment Form includes the following statement: (b) (4)

- **Risk**

- (b) (4)

According to the BOXED WARNING: OCULAR TOXICITY section of the draft PI, it states: “BLNREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss, and symptoms such as blurred vision and dry eyes. . . .” (b) (4)” (underlined emphasis added). Therefore, OPDP recommends revising

this presentation to include material information, consistent with the draft PI.

- Page one of the BLENREP REMS Prescriber Enrollment Form includes the following statement: [REDACTED] (b) (4)
- **Risk**
 - This statement may misleadingly imply [REDACTED] (b) (4)
 - According to the WARNINGS AND PRECAUTIONS, *Ocular Toxicity* subsection of the draft PI, it states: “Withhold BLENREP until improvement and resume or permanently discontinue based on severity.” (underlined emphasis added). Therefore, OPDP recommends revising this statement to mitigate the misleading impression.

BLENREP REMS Program Overview

- Page three of the BLENREP REMS Program Overview includes the following section: “**Boxed Warning for Ocular Toxicity**”
 - **Risk**
 - This section of the program overview omits material information. According to the BOXED WARNING: OCULAR TOXICITY section of the draft PI (in pertinent part), it states: “Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BLENREP REMS Program.” For completeness, consider revising to include this material information.
- Page five of the BLENREP REMS Program Overview includes the following statement: “**Manage corneal adverse reactions per Table 1. Dosage Modifications for Corneal Adverse Reactions per the Keratopathy and Visual Acuity (KVA) Scale** in the Prescribing Information with dose reductions or withhold BLENREP until improvement based on severity” (bolded emphasis original; underlined emphasis added).
 - **Risk**
 - This presentation minimizes risks by omitting material information and may misleadingly suggest that only dose reduction or temporarily withholding the dose of Blenrep is needed, when this may not be the case. According to the BOXED WARNING: OCULAR TOXICITY section of the draft PI, it states: “Withhold BLENREP until improvement and resume or permanently discontinue based on severity” (underlined

emphasis added). Therefore, OPDP recommends revising this presentation to include material information.

BLNREP REMS Professional Consult Request Form

- Page one of the BLNREP REMS Professional Consult Request Form contains the following statement:  (b) (4)

- **Risk**

-  (b) (4)
According to the BOXED WARNING: OCULAR TOXICITY section of the draft PI, it states: “**Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms**” (bolded emphasis original; in pertinent part; underlined emphasis added). Therefore, OPDP recommends revising this presentation to include material information.

- Page five of the BLNREP REMS Professional Consult Request Form contains the following statements (in pertinent part; underlined emphasis added):

 (b) (4)

- **Risk**

- These claims were deleted from section  (b) (4) of the draft PI. We recommend deletion.

- **BLNREP REMS Patient Status Form**

- Pages 2 - 3 of the BLNREP REMS Patient Status Form contain the following statements (in pertinent part; underlined emphasis added):

 (b) (4)

- **Risk**

- These claims were deleted from section  (b) (4) of the draft PI. We recommend deletion.

BLNREP REMS Patient Enrollment Form

- Page two of the BLNREP REMS Patient Enrollment Form includes the following statement: [REDACTED] (b) (4)

- **Risk**

- This statement is misleading [REDACTED] (b) (4)

[REDACTED] According to the **“What is the most importance information I should know about BLNREP?”** section of the draft Medication Guide, it states, “Your healthcare provider will send you to an eye specialist to check your eyes before you start treatment with BLNREP, prior to each dose of BLNREP, and for worsening symptoms of eye problems” (underlined emphasis added). We recommend revising this presentation to mitigate this misleading impression by maintaining consistency with language in the draft Medication Guide.

- Page two of the BLNREP REMS Patient Enrollment Form includes the following statement: [REDACTED] (b) (4)

- **Risk**

- This statement is misleading [REDACTED] (b) (4)

[REDACTED] According to the **“What is the most importance information I should know about BLNREP?”** section of the draft Medication Guide, it states: “Even if your vision seems fine, it is important that you get your eyes checked during treatment with BLNREP because some changes can happen without symptoms and may only be seen on an eye exam” (underlined emphasis added). We recommend revising this presentation to mitigate this misleading impression by maintaining consistency with language in the draft Medication Guide.

- Page two of the BLNREP REMS Patient Enrollment Form includes the following statement: [REDACTED] (b) (4)

- **Risk**

- [REDACTED] (b) (4)

[REDACTED] According to the **“How Will I receive BLNREP?”** section of the draft Medication Guide, it states: “Your healthcare provider may decrease your dose, temporarily stop or completely stop treatment with BLNREP if you have serious side effects” (underlined emphasis added). Therefore, we recommend revising this statement to include material information.

- Page two of the BLENREP REMS Patient Enrollment Form includes the following statement: [REDACTED] (b) (4)

- **Risk**

- This claim is misleading [REDACTED] (b) (4)

Therefore, we recommend deleting this statement.

- Page two of the BLENREP REMS Patient Enrollment Form includes the following statement: [REDACTED] (b) (4)

- **Risk**

- This claim is misleading [REDACTED] (b) (4)

[REDACTED] According to the “**What is the most important information I should know about BLENREP?**” section of the draft Medication Guide, it states: “Avoid wearing contact lenses during treatment with BLENREP unless directed by your eye specialist” Therefore, OPDP recommends deleting this information to mitigate this misleading impression and revising to maintain consistency with language in the draft Medication Guide.

BLENREP REMS Patient Guide

- Page eight of the BLENREP REMS Patient Guide includes the following statement: “Eye Exams are required for treatment with BLENREP. Your doctor will use your eye exam results to make sure that you are receiving the correct dose.”

- **Risk**

- This statement misleadingly minimizes risks by omitting material information and may misleadingly imply that only dose modifications could occur as a result of eye exam results when this may not be the case. According to the “**How Will I receive BLENREP?**” section of the Medication Guide, it states: “Your healthcare provider may decrease your dose, temporarily stop or completely stop treatment with BLENREP if you have serious side effects” (underlined emphasis added). Therefore, we recommend revising this statement to include material information.

BLENREP REMS Website

- [REDACTED] (b) (4)

- **Risk**

-

(b) (4)



We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: July 14, 2020
Requesting Office or Division: Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number: BLA 761158
Product Name and Strength: Blenrep (belantamab mafodotin-blmf) for Injection, 100 mg/vial
Applicant/Sponsor Name: GlaxoSmithKline Intellectual Property Development Ltd. England (GlaxoSmithKline)
OSE RCM #: 2019-2433-3
DMEPA Safety Evaluator: Nicole Iverson, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on July 8, 2020 for Blenrep. We review the revised container label and carton labeling for Blenrep (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Iverson N. Label and Labeling Review for Blenrep (BLA 761158). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 11. RCM No.: 2019-2433-2.

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07/14/2020 08:46:38 AM

HINA S MEHTA
07/14/2020 05:42:43 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: June 11, 2020
Requesting Office or Division: Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number: BLA 761158
Product Name and Strength: Blenrep (belantamab mafodotin-blmf) for Injection, 100 mg/vial
Applicant/Sponsor Name: GlaxoSmithKline Intellectual Property Development Ltd. England (GlaxoSmithKline)
OSE RCM #: 2019-2433-2
DMEPA Safety Evaluator: Nicole Iverson, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label received on April 13, 2020 and revised carton labeling received on June 3, 2020 for Blenrep. We reviewed the revised container label and carton labeling for Blenrep (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. We note the labels and labeling contain the word, (b) (4), which is inconsistent with terminology recommended in labeling for hazardous drugs.

3 RECOMMENDATIONS FOR GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LTD. ENGLAND (GLAXOSMITHKLINE)

We recommend the following be implemented prior to approval of this BLA:

^a Iverson N. Label and Labeling Review for Blenrep (BLA 761158). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); YYYY APR 16. RCM No.: 2019-2433-1.

A. General Comments (Container label and Carton labeling)

1. Revise the word, ^{(b) (4)} to "hazardous" on the labels and labeling to reflect alignment with terminology recommended in labeling for hazardous drugs.
Revise "CAUTION: ^{(b) (4)} Agent" to read "CAUTION: Hazardous Agent".

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HINA S MEHTA
06/11/2020 01:41:38 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: April 20,2020

To: Wanda Nguyen, PharmD, Regulatory Project Manager
Division of Hematologic Malignancies 2 (DHM2)

Stacy Shord, PharmD, BCOP, Associate Director for Labeling, (DHM2)

From: Adesola Adejuwon PharmD, MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kevin Wright, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for BLENREP (belantamab mafodotin-blmf) for injection, for intravenous use

BLA: 761158

In response to DHM2 consult request dated October 4, 2019, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for the original BLA submission for BLENREP (belantamab mafodotin-blmf) for injection, for intravenous use (Blenrep).

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHM2 (Wanda Nguyen) on April 6, 2020 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on April 17, 2020.

Thank you for your consult. If you have any questions, please contact Adesola Adejuwon at (240) 402-5773 or Adesola.Adejuwon@fda.hhs.gov.

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: April 17, 2020

To: Wanda Nguyen, PharmD
Senior Regulatory Project Manager
Division of Hematologic Malignancies 2 (DHM2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Ruth Mayrosh, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Adesola Adejuwon, PharmD, MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): BLENREP (belantamab mafodotin-blmf)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: BLA 761158

Applicant: GlaxoSmithKline Intellectual Property Development Ltd.
England

1 INTRODUCTION

On August 26, 2019, GlaxoSmithKline Intellectual Property Development Ltd. England submitted presubmission material as agreed to with the Agency as part of the Real-Time Oncology Review (RTOR) Pilot for an original Biologics License Application (BLA) 761158 for BLENREP (belantamab mafodotin-blmf) for injection. On December 5, 2019, the Applicant submitted the final submission material for the proposed indication of BLENREP (belantamab mafodotin-blmf) (b) (4) for the treatment of adult patients with relapsed or refractory multiple myeloma (b) (4)

On February 10, 2020, the Applicant submitted revised labeling in response to a teleconference with the Agency on January 28, 2020 to discuss risk management planning for corneal adverse reactions. With this submission, the Applicant proposes a Boxed Warning and the (b) (4) Medication Guide (MG).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematologic Malignancies 2 (DHM2) on December 20, 2019 and October 4, 2019, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for BLENREP (belantamab mafodotin-blmf) for injection.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DHM2 under separate cover.

2 MATERIAL REVIEWED

- Draft BLENREP (belantamab mafodotin-blmf) for injection MG received on February 10, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 7, 2020.
- Draft BLENREP (belantamab mafodotin-blmf) for injection Prescribing Information (PI) received on December 5, 2019, and February 10, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 7, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using

fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: April 16, 2020
Requesting Office or Division: Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number: BLA 761158
Product Name and Strength: Blenrep (belantamab mafodotin-blmf) for Injection, 100 mg/vial
Applicant/Sponsor Name: GlaxoSmithKline Intellectual Property Development Ltd. England (GlaxoSmithKline)
OSE RCM #: 2019-2433-1
DMEPA Safety Evaluator: Nicole Iverson, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on April 13, 2020 for Blenrep. We reviewed the revised container label and carton labeling for Blenrep (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container label is acceptable from a medication error perspective; however the carton labeling is unacceptable from a medication error perspective. As currently presented, the Medication Guide statement lacks prominence and may be easily overlooked. Therefore, we recommend increase the prominence of the Medication Guide statement taking into account all pertinent factors, including typography, layout, contrast and other printing features.

3 RECOMMENDATIONS FOR GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LTD. ENGLAND (GLAXOSMITHKLINE)

^a Iverson N. Label and Labeling Review for Blenrep (BLA 761158). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 03. RCM No.: 2019-2433.

We recommend the following be implemented prior to approval of this BLA:

A. Carton labeling

1. As currently presented, the Medication Guide statement lacks prominence and may be easily overlooked. Therefore, we recommend increase the prominence of the Medication Guide statement taking into account all pertinent factors, including typography, layout, contrast and other printing features.

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CLINICAL INSPECTION SUMMARY

Date	March 9, 2020
From	Anthony Orenca M.D., Ph.D., F.A.C.P., Medical Officer Cynthia Kleppinger, M.D., Acting Team Leader <i>for</i> Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Andrea Baines, M.D., Medical Officer Rachel Ershler, M.D., Medical Officer Bindu Kanapuru, M.D., Clinical Team Leader (Acting) Nicole Gormley, M.D., Director Wanda Nguyen, Project Manager Division of Hematology Malignancy 2 (DHP/OHOP)
BLA	761158
Applicant	GlaxoSmithKline
Drug	Belantamab
NME	Yes
Division Classification	Humanized (IgG1) antibody-drug conjugate (ADC) [monoclonal antibody immunoconjugate]
Proposed Indication	Treatment of multiple myeloma patients with relapse or refractory disease
Consultation Request Date	November 26, 2019 (Priority Review)
Summary Goal Date	March 15, 2020
Action Goal Date	April 2, 2020
PDUFA Date	August 5, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three domestic clinical sites and two foreign contract research organizations (CROs) were inspected in support of BLA 761158.

Regulatory deficiencies were noted at one clinical site, as noted below, but determined to not be significant. The study data derived from these three clinical sites are considered reliable and the study in support of this application appears to have been conducted adequately.

In their limited roles and responsibilities to the submitted clinical trial investigation, the two CROs maintained adequate oversight of the clinical trial.

II. BACKGROUND

Recent multiple myeloma treatment options for relapse and/or refractory disease include hematopoietic stem cell transplant (HSCT), second- and third-generation proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies (mAbs) such as daratumumab. However, most patients likely develop resistance to existing therapies. The sponsor proposes belantamab as an additional option for multiple myeloma patients with relapse or refractory disease.

Belantamab is a humanized (IgG1) antibody-drug conjugate (ADC) which binds to B-cell maturation antigen (BCMA), a target widely expressed on malignant plasma cells in multiple myeloma.

The basis for the regulatory decision-making process for this application consists of a single study, protocol 1856GCCC (205678) entitled "A Phase II, Open Label, Randomized, Two-Arm Study to Investigate the Efficacy and Safety of Two Doses of the Antibody Drug Conjugate GSK 2857916 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 (DREAMM 2)."

Study 205678

Study 205678 was a Phase 2, open-label, two-arm, randomized, multicenter study to evaluate the efficacy and safety of belantamab (GSK2857916) monotherapy at the dose levels of 2.5 mg/kg and 3.4 mg/kg administered intravenously every three weeks in participants with relapsed or refractory multiple myeloma. Participants were treated until disease progression or unacceptable toxicity.

The primary study objective was to evaluate the clinical efficacy of two doses of belantamab (GSK2857916) in participants with relapsed/refractory multiple myeloma.

The primary efficacy endpoint was overall response rate, defined as the percentage of participants with a confirmed partial response (PR) or better (i.e., PR, very good partial response [VGPR], complete response [CR] and stringent complete response [sCR]) according to the 2016 International Myeloma Working Group (IMWG) Response Criteria by Independent Review Committee (IRC).

There were 61 clinical study sites that enrolled patients in the study in eight countries (U.S., Canada, and Western Europe). The first patient was consented on [REDACTED]^{(b) (6)} and subsequently randomized and dosed on [REDACTED]^{(b) (6)}. Study 205678 is currently ongoing. The ninety-day safety and efficacy data cut-off was September 20, 2019.

III. RESULTS (by site)

1. Adam Cohen, M.D., Site #235336

Hospital of the University of Pennsylvania
3400 Civic Center Boulevard
Philadelphia, PA 19104

Inspection dates: January 6 to 10, 2020

The institutional review board (IRB) for this study was (b) (4) IRB.

A total of 21 subjects were screened and 15 subjects were enrolled. Five enrolled study subjects who received treatment discontinued from the study due to disease progression. Five subjects were discontinued for disease progression. Five subjects are currently participating in the ongoing study. Records for all 15 enrolled subjects were assessed.

Source documents were reviewed for study eligibility, informed consent, ethics committee review/approval, monitoring, test article accountability, concomitant medication, delegation of authority, primary efficacy endpoint, and adverse event/serious adverse event reporting. Records review of the enrolled subjects indicated that the eligibility criteria for enrollment were met.

Source documents were verified against the case report forms and sponsor data line listings. The primary efficacy endpoint was verifiable at the study site. The study site data audit verified treatment response assessments and laboratory findings including serum M protein, IgG, IgA, IgM, and serum PLC K/L without any discrepancies noted. There was no under-reporting of adverse events. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

2. Hans Lee M.D., Site #235365

University of Texas MD Anderson Cancer Center
1515 Holcombe Boulevard
Houston, TX 77030

Inspection dates: December 16 to January 10, 2020

The IRB for this study was the University of Texas M.D. Anderson Cancer Center Institutional Review Board.

A total of 17 subjects were screened and 15 subjects were enrolled. Two subjects developed disease progression and discontinued from the study. Thirteen subjects completed treatment.

Three subjects are continuing in the ongoing study. Complete records for six enrolled study subjects were reviewed.

For this inspection, a complete review of regulatory documentation at the study site was performed. The task included overall control and administration of the clinical trial, adherence to the study protocol, the IRB documentation, subject records, financial disclosures, monitoring of the study, and review of informed consent forms.

Source documents were reviewed, including informed consent documentation, protocols and amendments, signed Statement of Investigator, financial disclosure statements, IRB submissions and correspondence, adverse event reporting, clinical source data, study test article accountability, concomitant medications, and sponsor monitoring, and adverse event/serious adverse event reporting.

The primary efficacy endpoint raw data were verifiable. There was no under-reporting of adverse events. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection for not conducting the clinical study in accordance with the investigational plan. Specifically, the protocol required that the study drug be reduced at Grade 2 to 3 ocular toxicity. Of the 15 subjects, eight patients (Subject # [REDACTED]^{(b) (6)}) were improperly dosed during the study; each reported ocular toxicity at Grade 2 or 3 and received their study drug dose at the same dosage at treatment assignment. The protocol requires that the study drug be held and/or reduced at Grade 2/3 toxicities. These protocol deviations were reported in the BLA.

During the initial inspectional meeting with Dr. Lee, he indicated he had discovered several significant protocol deviations that led him to place a voluntary temporary hold on enrollment for the study on 8/6/2019 and engage a subsequent corrective action plan. Dr. Lee provided information and the firm's corrective action plan to the FDA inspector, who observed training records and procedures that indicated the corrective actions were mostly complete and effective. The hold was lifted on 8/22/2019.

On January 28, 2020, Dr. Lee responded to the Form 483 that all patients enrolled on the study were retrospectively evaluated for ocular toxicity grading using the study-specific ocular grading criteria. Participant accrual hold and withdrawal of such hold for all the principal investigator's therapeutic studies were instituted by the MD Anderson Patient Safety and Accreditation Committee. The IRB and sponsor were notified accordingly.

For future clinical trials at the clinical site or with sponsor-related activities, Dr. Lee proposed to enhance faculty support for ocular measurements, and to institute formal scientific ophthalmology review of clinical trial study protocols with high risk ocular toxicity.

Reviewer comment:

As noted earlier, the improper dosing events for the eight study subjects at Dr. Lee's site were reported in the submission to the Agency as protocol deviations. Belantamab ocular-related toxicities have emerged as a drug class effect. The protocol tried to address this potential adverse event with dose reduction. The site did not have adequate staff support to adjust the investigational product dosing, as required by the protocol. We are aware that the review team is actively assessing the nature and spectrum of this immunotherapy-related adverse event, including reducing toxicities and risk mitigation of this adverse event, and addressing drug labeling.

In general, this clinical investigator appeared to be in compliance with Good Clinical Practice except for the regulatory observations noted above. These observations appear unlikely to have a significant impact on overall efficacy.

3. Ashraf Badros M.D., Site #235347

University of Maryland
22 S. Greene Street
Baltimore, MD 21201

Inspection dates: December 11 to 13, 2019

The IRB of record was (b) (4)

A total of 18 subjects were screened and 10 patients were enrolled. Six subjects completed treatment. Three study subjects discontinued from the study (two patient deaths due to disease progression and a single patient withdrew further consent to participate). One patient is still participating in the ongoing study. Complete study records for four enrolled study subjects were evaluated.

For this inspection, a complete review of regulatory documentation at the study site was performed. The records reviewed included medical records, regulatory binder documents, delegation logs and signature logs, training logs, source data worksheets, informed consent forms, monitoring follow-up reports, and pharmacy records.

Source documents for all enrolled subjects were verified against the case report forms and sponsor subject data line listings for eligibility, adverse events, and serious adverse event reporting. The primary efficacy endpoint raw data were verifiable. There was no under-reporting of adverse events.

There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

4. (b) (4) / **Contract Research Organization (CRO)**
(b) (4)

Inspection dates: (b) (4)

(b) (4) was contracted to be the Statistical Data Analysis Center (SDAC) responsible for creating and analyzing the statistical analysis datasets and tables, figures and listings for the unblinded interim analysis (IA) data sent to the Independent Data Monitoring Committee (IDMC). The CRO responsibilities were confined to a restricted role as SDAC for the interim analysis. GSK conducted the primary data analysis for the submitted application.

The CRO inspection covered their practices and procedures related to all contracted activities and the statistical analysis plan. A review of the CRO quality oversight, communications, and activities indicated they functioned as an independent, unblinded team when creating and executing the interim analysis deliverables.

(b) (4) conducted their deliverables on GSK provided laptops and systems and all study documentation was archived to GSK's Analysis Platform named HARP. Other than contractual agreements, all records are stored on the GSK systems.

A Form FDA 483 was not issued at the end of the study inspection. In general, the CRO appeared to be in compliance with Good Clinical Practice. CRO oversight appeared to be adequate.

5. (b) (4) **Contract Research Organization (CRO)**
(b) (4)

Inspection dates: (b) (4)

The CRO's role in the study was data management for data queries only. The CRO had no part in the interim analysis. The firm only ensured the CRFs had data suitable and consistent with the protocol requirements.

In assessing the adequacy of CRO data management, no issues were observed. A challenge to the system found that the firm was unable to change data, only queries and their resolution could be entered into the system (InForm).

No significant issues were observed regarding the firm's limited role in the clinical trial.

A Form FDA 483 was not issued at the end of the study inspection. In general, the CRO appeared to be in compliance with Good Clinical Practice.

{See appended electronic signature page}

Anthony Orenca, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Cynthia Kleppinger, M.D., *for*
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 3, 2020
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761158
Product Name, Dosage Form, and Strength:	Blenrep (belantamab mafodotin-xxxx) for Injection, 100 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	GlaxoSmithKline Intellectual Property Development Ltd. England (GlaxoSmithKline)
FDA Received Date:	November 14, 2019, December 5, 2019, and February 10, 2020
OSE RCM #:	2019-2433
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for BLA 761158 Blenrep (belantamab mafodotin-xxxx) for Injection, 100 mg/vial, this review evaluates the proposed container label, carton labeling, Prescribing Information (PI) and Medication Guide for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

GlaxoSmithKline Intellectual Property Development Ltd. England (GlaxoSmithKline) submitted a 351 (a) application to obtain marketing approval of Blenrep for Injection. Blenrep is proposed (b) (4) for the treatment of adult patients with relapsed or refractory multiple myeloma (b) (4)

We performed a risk assessment of the proposed container label, carton labeling, Medication Guide and PI for Blenrep (belantamab mafodotin-xxxx) for Injection to determine whether there are significant concerns in terms of safety related to preventable medication errors. We identified areas of the proposed label and labeling that could be revised to improve clarity and readability of important information. For the Division, we note that the PI lacks clarity in the reconstitution instructions, dilution instructions, and storage information. In addition, the PI uses as placeholder for the conditionally accepted proprietary name, Blenrep. We note the Medication Guide contains an abbreviation for the route of administration and the active ingredient, "belantamab mafodotin" is missing the suffix placeholder. For the Applicant, we note the labels and labeling have a placeholder for the conditionally accepted proprietary

name, Blenrep and the Medication Guide Statement is missing. We also note the administration and storage information lack prominence on the labels and labeling. These factors may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed PI that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for GlaxoSmithKline to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Highlights of Prescribing Information

1. The dosage information as presented in the Dosage and Administration section lacks clarity due to the layout in which the information is presented. Lack of clarity may lead to underdose or overdose medication errors. Revise the statements for clarity, (b) (4) to "The recommended dosage is 2.5 mg/kg as an intravenous infusion over 30 minutes once every 3 weeks."
2. The product has complex preparation instructions and it is important to alert healthcare providers that additional important information is in the Full Prescribing Information. Therefore, we recommend including a bullet stating, "See Full Prescribing Information for instructions on preparation and administration. (2.5)"

B. Prescribing Information

1. General comments
 - a. Replace all presentations of the word, "TRADENAME", with the conditionally accepted name, Blenrep.
2. Dosage and Administration Section
 - a. Section (b) (4)
 - i. The Prescribing Information advises healthcare professionals to (b) (4) Therefore, we recommend replacing the statement, (b) (4)

(b) (4) with "Reconstitute and further dilute BLENREP prior to intravenous infusion." because the usual practice of healthcare professionals is to compound intravenous medications aseptically.

- ii. The reconstitution instructions lack clarity, which may lead to product preparation errors. Therefore we recommend:
 - a. Revise the statement under 2.5 to read, "Calculate the dose and the number of BLENREP vials needed based on the patient's actual body weight. More than one vial may be needed for a full dose"
 - b. Revise the statement, (b) (4) to "Reconstitute each 100 mg (b) (4) with 2 mL of Sterile Water for Injection, USP, to obtain a final concentration of 50 mg/mL."
 - c. To mitigate the risk of administration of a deteriorated product, include the statement, "If the reconstituted solution is not used immediately store refrigerated 36°F to 46°F (2°C to 8°C) for up to 4 hours in the original container. Discard if (b) (4) Do not freeze."

- iii. The dilution instructions lack clarity, which may lead to product preparation errors. Therefore we recommend:
 - a. Combine and revise the first and second bullets under the administration subheading as, "Withdraw the calculated volume of Blenrep from the appropriate number of vials and dilute in a 250 mL infusion bag of 0.9% Sodium Chloride Injection, USP to a final concentration of 0.2 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion. *Do not shake.*"
 - b. To mitigate the risk of administration of a deteriorated product, include the statement, "If the diluted BLENREP infusion solution is not used immediately, store refrigerated 36°F to 46°F (2°C to 8°C) not exceed 24 hours taking into account the expected infusion time. Once removed from refrigeration, administer the diluted BLENREP infusion solution within 6 hours"

3. Dosage Forms and Strengths Section

- a. Revise the statement, (b) (4) To "For injection: 100 mg of belantamab mafodotin-xxxx lyophilized powder in a single-dose vial for reconstitution and further dilution."

4. How Supplied/Storage and Handling Section

- a. Revise the statement from, [REDACTED] (b) (4) [REDACTED] to "Store refrigerated at 36°F to 46°F (2°C to 8°C)."

C. Medication Guide

1. Replace all presentations of the word, "TRADENAME", with the conditionally accepted name, Blenrep.
2. The route of administration is presented using the abbreviation "IV". The route of administration should be described without an abbreviation. Thus, we recommend deleting the abbreviation "IV".
3. In the section, "What are the ingredients in TRADENAME?", the active ingredient, "belantamab mafodotin" is missing the suffix placeholder, "-xxxx". Therefore, we recommend that you revise the active ingredient to appear as "belantamab mafodotin-xxxx".

4.2 RECOMMENDATIONS FOR GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LTD. ENGLAND (GLAXOSMITHKLINE)

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)

1. Replace all presentations of the word, "TRADENAME", with the conditionally accepted name, Blenrep.
2. We note the inclusion of a Medication Guide as part of the labeling submission; however, the Medication Guide statement is missing from the principal display panel of the container label and carton labeling. Per 21 CFR 208.24(d), the label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner. Ensure the Medication Guide statement appears in accordance with 21 CFR 208.24(d).
3. As currently presented, the route of administration statement, "For intravenous infusion after reconstitution and dilution." lacks prominence. Consider the use of different font type or size, bolding, or other means to achieve increased prominence.
4. The Rx Only statement appears prominent in bold font on the principal display panel. Decrease the prominence by debolding the Rx Only statement.
5. The format for the expiration date is not defined. Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors. Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year,

month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward be used to separate the portions of the expiration date.

6. Revise the statement, (b) (4) to "Dosage: See Prescribing Information."
7. Revise and bold the statement from, (b) (4) to "Store refrigerated at 36°F to 46°F (2°C to 8°C)."
We recommend this to increase prominence of this important information and minimize the risk of the storage information being overlooked.

B. Container Label

1. (b) (4) we recommend including the statement in bold red font on the side panel of the container label, "CAUTION: (b) (4) Agent".
2. The discard statement "Discard unused portion" is not present next to the package type term, "Single-dose vial". Inclusion of this discard statement helps minimize the risk of the entire contents of the vial being given as a single dose. Revise the statement "Single-Dose Vial" to read as "Single-Dose Vial. Discard Unused Portion".
3. As currently presented, the location of lot number and expiration date is not clearly defined on the container label. Please confirm the inclusion and location of the lot number and expiration date [refer to 21 CFR 610.60(a)].

C. Carton Labeling

1. (b) (4) we recommend including the statement in bold red font on the principal display panel of the carton labeling, "CAUTION: (b) (4) Agent".
2. The principal display panel of the carton labeling looks cluttered making it difficult to view important information. To decrease visual clutter consider removing the duplicate the statement, (b) (4) as it is not needed.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Blenrep received on December 5, 2019 from GlaxoSmithKline Intellectual Property Development Ltd. England (GlaxoSmithKline).

Table 2. Relevant Product Information for Blenrep	
Initial Approval Date	N/A
Nonproprietary Name	belantamab mafodotin-xxxx
Indication	(b) (4) for the treatment of adult patients with relapsed or refractory multiple myeloma (b) (4)
Route of Administration	Intravenous infusion
Dosage Form	for Injection
Strength	100 mg/vial
Dose and Frequency	(b) (4)
How Supplied	Blenrep is supplied in a carton containing one 100-mg single-dose vial.
Storage	Store (b) (4) at 36°F to 46°F (2°C to 8°C).

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 17, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Blenrep. We did not identify and previous reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Blenrep labels and labeling submitted by GlaxoSmithKline Intellectual Property Development Ltd. England (GlaxoSmithKline).

- Container label received on November 14, 2019
- Carton labeling received on November 14, 2019
- Prescribing Information and Medication Guide (Image not shown) received on February 10, 2020 available from <\\cdsesub1\evsprod\bla761158\0025\m1\us\114-labeling\1141-draft\draft-annotated.pdf>

G.2 Label and Labeling Images

Container label



Carton labeling

^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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**Interdisciplinary Review Team for Cardiac Safety Studies
QT Consultation Review**

Submission	BLA 761158
Submission Number	009
Submission Date	11/14/2019
Date Consult Received	11/18/2019
Drug Name	Belantamab mafodotin (GSK2857916)
Indication	(b)(4) treatment of adult patients with relapsed and refractory multiple myeloma (b)(4)
Therapeutic dose	2.5 mg/kg once every 3 weeks (Q3W) as a 30-min intravenous (IV) infusion
Clinical Division	DHM2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 9/4/2019 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND-119333 dated 08/24/2018 in DARRTS ([link](#));
- Sponsor's concentration-QTc report (Submission 0009, [link](#));
- Sponsor's study report 205678 (Submission 0010, [link](#));
- Sponsor's study report 117259 (Submission 0003, [link](#));
- Sponsor's proposed labelling (Submission 0009, [link](#)).

1 SUMMARY

No large QTc prolongation effect (i.e., >20 msec) of belantamab mafodotin was observed in this QT assessment.

The effect of belantamab mafodotin was evaluated in Study 205678. The highest dose that was evaluated was 3.4 mg/kg Q3W by IV infusion, which covers the therapeutic exposure. The data were analyzed using the by-timepoint analysis as the primary analysis, which did not suggest that belantamab mafodotin is associated with large mean increases in the QTc interval (refer to section 4.3) – see Table 1 for overall results. The findings of this analysis are further supported by the available nonclinical data (section 3.1.2) and exposure-response analysis (section 4.5).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

Actual Treatment	Time (Cycle, Day, Hour)	Δ QTcF (msec)	90.0% CI (msec)
2.50 mg/kg IV over 30 min q3w	Cycle 3 Day 1, 0.5 h	6.3	(-0.1, 12.7)

3.40 mg/kg IV over 30 min q3w	Cycle 6 Day 1, predose	5.2	(-1.4, 11.9)
3.40 mg/kg (lyophilized) IV over 30 min q3w	Cycle 2 Day 1, 0.5 h	5.4	(0.7, 10.2)

For further details on the FDA analysis please see section 4.

In this QT assessment, mean C_{max} values (concentration at 24 hours postdose) of the small molecule payload, cys-mcMMAF, in the 3.4 mg/kg group receiving the liquid formulation or the lyophilized formulation are 1040.3 pg/mL or 1015.7 pg/mL (assay PKC), respectively. Based on the sponsor's population PK analyses, the predicted C_{max} in a typical patient at the therapeutic dose is 920 pg/mL. Therefore, the QT assessment provides coverage for the therapeutic dose.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

There were a few subjects with QTc outliers in studies BMA117159 and 205678 -- see section 3.2.4 and section 4.4.1. Without a control arm to provide a background incidence of QTc outliers in the patient population, it's difficult to attribute these outliers directly to belantamab mafodotin treatment.

No dedicated clinical studies were conducted to assess the effect of intrinsic or extrinsic factors on the systemic exposure of cys-mcMMAF. The sponsor's population PK analyses suggested that age, body weight, gender, race, mild or moderate renal impairment, and mild hepatic impairment would not be expected to substantially increase the exposure of cys-mcMMAF. The sponsor claimed that cys-mcMMAF are unlikely to be a victim of a drug-drug interaction with inhibitors or inducers of cytochromes (CYP) P450 or most drug transporters. We defer the adequacy of these statements to the clinical pharmacology review team.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to Submission 0009 ([link](#)) from the IRT. Our changes are highlighted ([addition](#), ~~deletion~~). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

<p>12.2 Pharmacodynamics</p> <p><u>Cardiac Electrophysiology</u></p> <div style="background-color: #cccccc; height: 40px; width: 100%;"></div> <div style="text-align: right; font-size: small;">(b) (4)</div>

We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.

(b) (4)

3 SPONSOR’S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

(b) (4)

The sponsor was recommended to either demonstrate low systemic exposure of cys-mcMMAF, or to collect additional ECG data and incorporate central reading of ECG data.

In the current submission, the sponsor provided a concentration-QTc analysis report based on Study 205678. 95 and 99 patients received the 2.5 and 3.4 mg/kg Q3W treatment, respectively, using the frozen liquid formulation. An additional 25 patients received the 3.4 mg/kg Q3W doses using the lyophilized formulation. Additional triplicate ECG were included in a subgroup of patients at 24 h ± 2h after the start of infusion on Day 1 of Cycle 1 and Cycle 3; and on Day 4 (±1 day) and on any day from Day 8 to Day 15 in Cycle 1 and Cycle 3. All ECG data was derived by manual central overread. Overall, the studied doses, ECG sampling schedule, and sample size appear adequate to evaluate whether belantamab mafodotin treatment is associated with large mean increase in the QT/QTc interval at the proposed therapeutic dose (2.5 mg/kg Q3W).

ECG data in Study BMA117159 was collected at predose and EOI only and were subject to local machine overread. These data were included in the reviewer’s categorical analysis, but not the by-timepoint analysis or concentration-QTc analysis.

3.1.2 Nonclinical Safety Pharmacology Assessments

The in vitro effects of cys-mcMMAF (SGD-1362) on ionic currents in voltage-clamped human embryonic kidney cells (HEK293) that stably express the human ether-à-go-go-related gene (hERG) was determined at 10 and 100 µM. Cys-mcMMAF slightly inhibited hERG current at 10 and 100 µM, but this inhibition was not statistically significant when compared to vehicle control. The IC50 of cys-mcMMAF on hERG current was not calculated but was estimated to be greater than 100 µM.

Reviewer's comments: The mean C_{max} of cys-mcMMAF is predicted to be 0.92 ng/mL at the proposed therapeutic dose. The ratio between hERG IC50 (>100 uM) and total C_{max} is >10,000-fold.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The sponsor's primary analysis is based on concentrations-QTc analyses.

Reviewer's Comments: The statistical reviewer cannot find sponsor's by-timepoint analyses in the submitted reports. In the reviewer's by-timepoint analysis, the largest upper bounds of 90% CI for $\Delta QTcF$ exceeded 10 msec at doses 2.5 mg/kg and 3.4 mg/kg IV over 30 mins q3w. Please see section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

Reviewer's Comments: In reviewer's categorical analysis, 5 subjects had $QTcF > 500$ msec and 6 subjects had $\Delta QTcF > 60$ msec. Please see section 3.2.4 for sponsor's and section 4.4 for reviewer's additional details.

3.2.3 Exposure-Response Analysis

The sponsor conducted linear regression analyses to estimate the rate of change in $\Delta QTc/\Delta QTcF$ with increasing concentrations of belantamab mafodotin, total mAb, and cys-mcMMAF, using data from Study 205678. The upper bound of the 90% confidence interval of the predicted $\Delta QTcF$ was less than 10 msec for all three moieties.

Reviewer's comment: Because of the large molecular size, belantamab mafodotin and total mAb are expected to have a low risk of direct interaction with cardiac ion channels. Even though the PK/ECG sampling schedule included T_{max} of cys-mcMMAF, the next available time point after T_{max} is too distant to detect potential hysteresis (4 days vs 1 day). Therefore, the reviewers used by-timepoint analysis as the primary analysis and conduct concentration-QTc analysis as the secondary analysis using cys-mcMMAF concentration as the dependent variable.

3.2.4 Cardiac Safety Analysis

Study BMA117159

In Part 1, no trend toward a dose-related increase in QTcF was identified in any of the dose cohorts. Two subjects had increase from baseline QTc >60 msec.

- Subject (b)(6), who received the 0.24 mg/kg dose, had a QTcF value of 554 msec on Day 22 (baseline of 431 msec). This was the EoT visit by reason of physician decision due to disease symptoms and clinical progression.

- Subject (b) (6), who was administered the 3.40 mg/kg dose, experienced a QTcF of 504 msec on Day 8 of the study (Source: Listing 30.0140); QTcF values were <60 msec change from baseline during the remainder of the study (Source: Listing 30.0690).

In Part 2, two subjects had a worst QTcF increase of >60 msec, but only 1 subject exceeded 500 msec. Subject (b) (6) who had a baseline QTcF of 420 msec, experienced QTcF prolongation of 515 msec on Cycle 1 Day 8 of the study, which was confounded by an increased heart rate, but did not have any subsequent values of concern during the study.

Study 205678

There were 6 and 8 participants for whom worst ECG findings were recorded as clinically significant in the 2.5mg/kg and 3.4 mg/kg cohorts, respectively. Further queries with the investigators revealed that of the 14 participants, 1 participant in the 2.5 mg/kg cohort and 2 participants in the 3.4 mg/kg cohort had clinically significant worst case post baseline ECG findings. These participants are briefly described below.

- Participant (b) (6) (2.5mg/kg) had an SAE noted in relation to the ECG Change (Preferred terms: Electrocardiogram T-wave inversion and Mitral Valve disease).
- Participant (b) (6) (3.4 mg/kg) had a history of Grade 1 sinus bradycardia and Grade 1 prolonged QT interval. At W1D4, the ECG showed QTc Prolongation.
- Participant (b) (6) (3.4 mg/kg) had an AE of Grade 1 QTcF prolongation.

There were 1 and 2 participants who had increases to Grade 2 for QTc (Table 90). These participants are briefly described below:

- Participant (b) (6) (2.5 mg/kg cohort) had a QTcB of 504 msec on Day 2 (corresponding QTcF was 461 msec). This participant also had Grade 1 tachycardia on Day 2 that resolved in 2 days with no change in dosing.
- Participant (b) (6) (3.4 mg/kg cohort) had QTcB values of 510 msec pre-dose on Day 1, 511 msec on Day 43 and 502 msec on Day 65 (corresponding QTcF values were 448 msec pre-dose on Day 1, 469 msec on Day 43 and 478 msec on Day 65). There were no relevant AEs associated with this increase.
- Participant (b) (6) (3.4 mg/kg cohort) had QTcF of 477 msec on D1 at the end of infusion, from a baseline of 494 msec. This participant also had Grade 1 IRR on Day 1 that resolved in 1 day with no change in dosing.

There was 1 participant (3.4 mg/kg cohort) who had Grade 3 QTcF values (≥ 501 msec) during the study: Participant (b) (6) had Grade 2 QTcF (491 msec) at baseline and a Grade 3 QTcF of 504 msec on Day 85 for Cycle 4. The participant continued treatment with no change due to this assessment. All subsequent QTcF assessments were Grade 2.

Table 90 Worst-case Increases in Grade for QTcF (Safety Population)

Category ^a	GSK2857916	
	2.5 mg/kg (N=95)	3.4 mg/kg (N=99)
Any Grade Increase, n (%)	13 (14)	14 (14)
Increase to Grade 2	1 (1)	2 (2)
Increase to Grade 3	0	1 (1)

Source: Table 3.0600

Note: Manually calculated QTcF values have been used where machine-read values are not available

a. Grade 0 (<450), Grade 1 (450-480), Grade 2 (481-500), Grade 3 (≥501).

Reviewer’s comment: *The sponsor’s table 90 uses both QTcB and QTcF.*

Worst increases of QTcF of >60 msec occurred in 2 and 0 participants, although none of the participants met the QTc stopping criteria.

- Participant ^{(b)(6)} (2.5 mg/kg dose) had an increase of 65 msec in QTcF on Day 64 from a Cycle 1 Day 1 predose average of 378 msec. No AEs were associated with this increase, but the participant discontinued treatment due to progressive disease.
- Participant ^{(b)(6)} (2.5 mg/kg dose) had an increase to 470 msec in QTcF on Day 1 from a Cycle 1 Day 1 predose average of 406 msec, and no AEs were associated with this increase. Subsequent changes from baseline ranged from 31 msec to 51 msec.

Reviewer’s comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., significant ventricular arrhythmias or sudden cardiac death) occurred in these studies.*

4 REVIEWERS’ ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 bpm) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Waveforms from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not applicable because the aim is to exclude large mean effect.

4.3 BY-TIME ANALYSIS

By-time analyses are based on pivotal Study 205678 with 2.5 mg/kg and 3.4 mg/kg IV, without a placebo nor a positive control. Data with a sample size less than 20 were not analyzed.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for Study 205678 by visit (cycle, day and time). The largest upper bounds of the 2-sided 90% CI on the ΔQTc by visit are shown in Table 2.

Figure 1: Mean and 90% CI of ΔQTcF Time Course (unadjusted CIs).

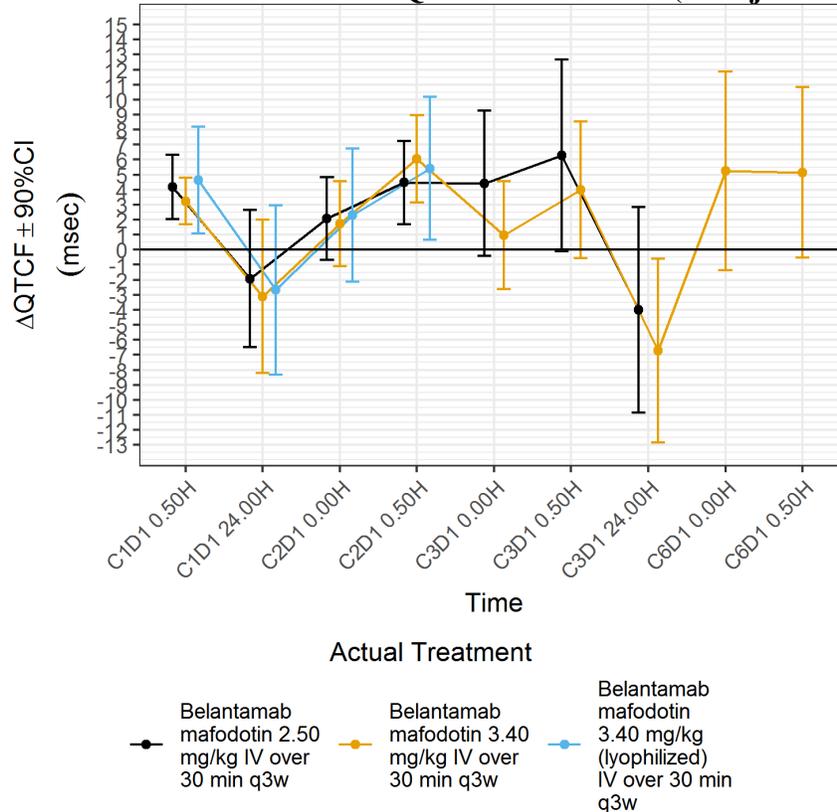


Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQTcF

Actual Treatment	Visit (Cycle & Day)	N	Time (hours)	ΔQTcF (msec)	90.0% CI (msec)
2.50 mg/kg IV over 30 min q3w	Cycle 3 Day 1	30	0.5	6.3	(-0.1, 12.7)
3.40 mg/kg IV over 30 min q3w	Cycle 6 Day 1	26	0	5.2	(-1.4, 11.9)
3.40 mg/kg (lyophilized) IV over 30 min q3w	Cycle 2 Day 1	22	0.5	5.4	(0.7, 10.2)

4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of Δ HR for belantamab mafodotin. The largest upper bounds of the 2-sided 90% CI on the Δ HR by visit are shown in Table 3.

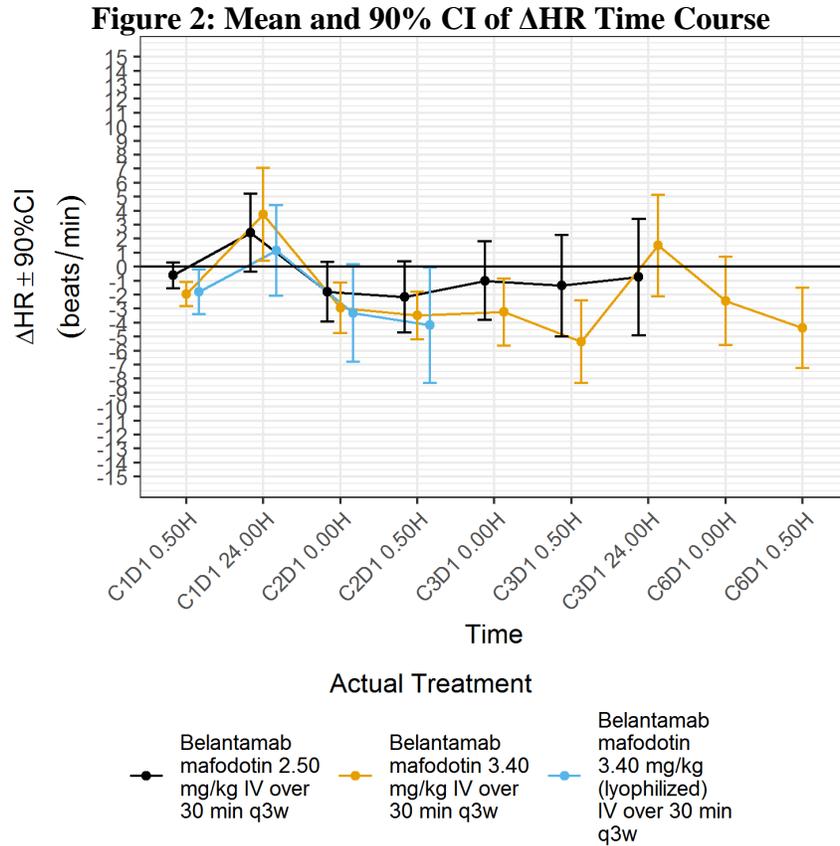


Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Δ HR

Actual Treatment	Visit (Cycle & Day)	N	Time (hours)	Δ HR (beats/min)	90.0% CI (beats/min)
2.50 mg/kg IV over 30 min q3w	Cycle 1 Day 1	31	24	2.4	(-0.4 to 5.2)
3.40 mg/kg IV over 30 min q3w	Cycle 1 Day 1	22	24	3.7	(0.4 to 7.1)
3.40 mg/kg (lyophilized) IV over 30 min q3w	Cycle 1 Day 1	22	24	1.2	(-2.1 to 4.4)

4.3.3 PR

Figure 3 displays the time profile of Δ PR for belantamab mafodotin. The largest upper bounds of the 2-sided 90% CI on the Δ PR by visit are shown in Table 5.

Figure 3: Mean and 90% CI of Δ PR Time Course

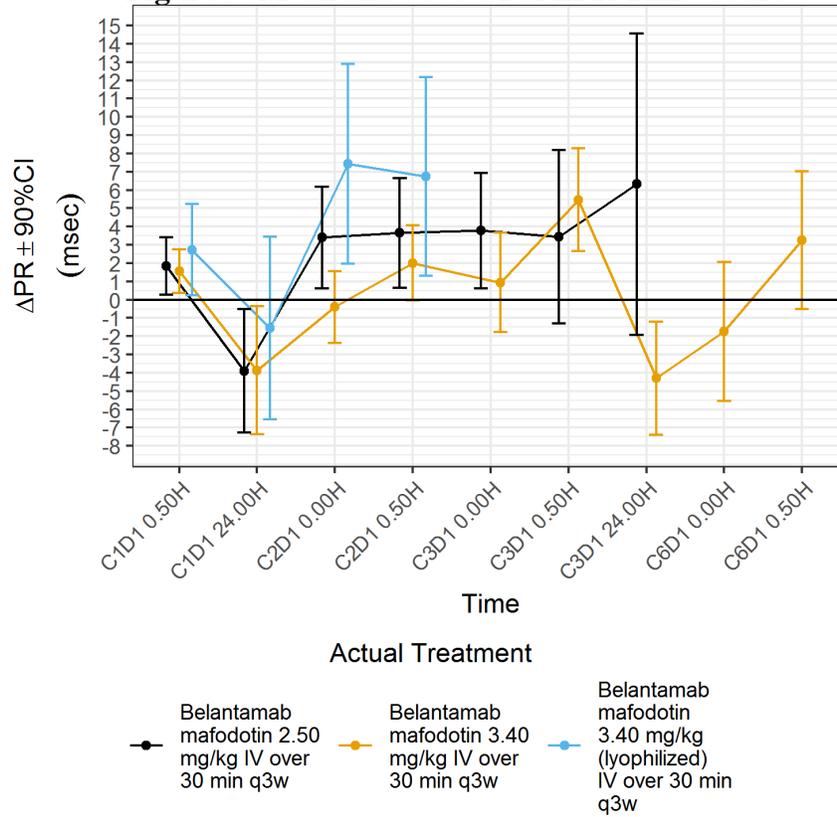


Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Δ PR

Actual Treatment	Visit (Cycle & Day)	N	Time (hours)	Δ PR (beats/min)	90.0% CI (beats/min)
2.50 mg/kg IV over 30 min q3w	Cycle 1 Day 1	31	24	2.4	(-0.4 to 5.2)
3.40 mg/kg IV over 30 min q3w	Cycle 1 Day 1	22	24	3.7	(0.4 to 7.1)
3.40 mg/kg (lyophilized) IV over 30 min q3w	Cycle 1 Day 1	22	24	1.2	(-2.1 to 4.4)

4.3.4 QRS

Figure 4 displays the time profile of Δ QRS for belantamab mafodotin. The largest upper bounds of the 2-sided 90% CI on the Δ QRS by visit are shown in Table 5.

Figure 4: Mean and 90% CI of Δ QRS Time Course

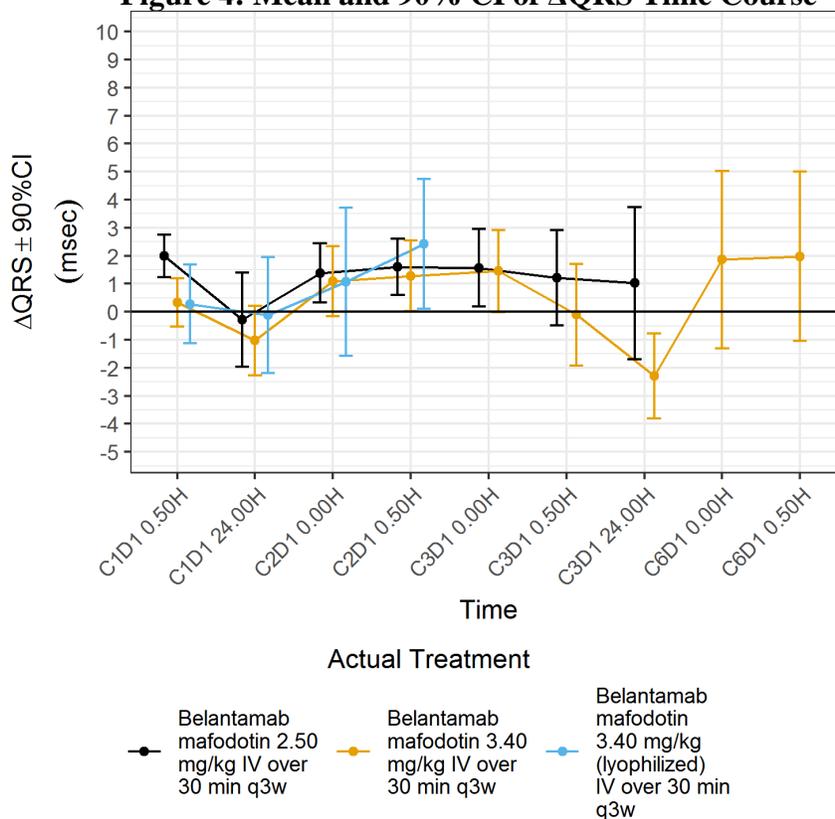


Table 5: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Δ QRS

Actual Treatment	Visit (Cycle & Day)	N	Time (hours)	Δ QRS (msec)	90.0% CI (msec)
2.50 mg/kg IV over 30 min q3w	Cycle 3 Day 1	25	24	1.0	(-1.7 to 3.7)
3.40 mg/kg IV over 30 min q3w	Cycle 6 Day 1	26	0	1.9	(-1.3 to 5.0)
3.40 mg/kg (lyophilized) IV over 30 min q3w	Cycle 2 day 1	22	0.5	2.4	(0.1 to 4.7)

4.4 CATEGORICAL ANALYSIS

The categorical analysis pooled all doses level for Studies 205678 and BMA117159.

4.4.1 QTc

Table 6 lists the number of subjects as well as the number of observations whose QTc values were ≤ 450 msec, between 450 and 480 msec, between 480 and 500 msec and > 500 msec. Five subjects had QTcF values above 500 msec (see section 3.2.4 for details).

Table 6: Categorical Analysis for QTc

Study Identifier	Total (N)		Value ≤ 450 msec		450 msec < Value ≤ 480 msec		480 msec < Value ≤ 500 msec		Value > 500 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
205678	217	2043	175 (80.6%)	1868 (91.4%)	34 (15.7%)	152 (7.4%)	6 (2.8%)	20 (1.0%)	2 (0.9%)	3 (0.1%)
BMA117159	79	1144	64 (81.0%)	1112 (97.2%)	11 (13.9%)	28 (2.4%)	1 (1.3%)	1 (0.1%)	3 (3.8%)	3 (0.3%)

Table 7 lists the categorical analysis results for ΔQTc (≤ 30 msec, between 30 and 60 and > 60 msec). Six subjects with $\Delta QTcF$ above 60 msec.

Table 7: Categorical Analysis for $\Delta QTcF$

Study Identifier	Total (N)		Value ≤ 30 msec		30 msec < Value ≤ 60 msec		Value > 60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
205678	217	2043	190 (87.6%)	1936 (94.8%)	25 (11.5%)	102 (5.0%)	2 (0.9%)	5 (0.2%)
BMA117159	79	1144	63 (79.7%)	1094 (95.6%)	12 (15.2%)	45 (3.9%)	4 (5.1%)	5 (0.4%)

Table 8 lists the categorical analysis results for HR (≤ 100 bpm and > 100 bpm). Sixty subjects experienced HR > 100 bpm. Twenty-one subjects experienced HR > 100 beats/min with a 25% increase from the baseline.

Table 8: Categorical Analysis for HR

Study Identifier	Total (N)		Value ≤ 100 beats/min		Value > 100 beats/min & ≤ 25%		Value > 100 beats/min & > 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
205678	218	2051	175 (80.3%)	1934 (94.3%)	27 (12.4%)	88 (4.3%)	16 (7.3%)	29 (1.4%)
BMA117159	79	1155	62 (78.5%)	1096 (94.9%)	12 (15.1%)	50 (4.3%)	5 (6.3%)	9 (0.8%)

4.4.2 PR

Table 9 lists the categorical analysis results for PR (≤ 220 msec and > 220 msec with and without 25% increase over baseline). Two subjects experienced PR > 220 msec with a 25% increase from the baseline.

Table 9: Categorical Analysis for PR

Study Identifier	Total (N)		Value ≤ 220 msec		Value > 220 msec & ≤ 25%		Value > 220 msec & > 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
205678	216	2031	197 (91.2%)	1934 (95.2%)	17 (7.9%)	88 (4.3%)	2 (0.9%)	9 (0.4%)
BMA117159	79	1153	71 (89.9%)	1132 (98.2%)	8 (10.1%)	21 (1.8%)	0 (0%)	0 (0%)

4.4.3 QRS

Table 10 lists the categorical analysis results for QRS (≤ 120 msec and > 120 msec with and without 25% increase over baseline). 3 subjects experienced QRS > 120 msec with a 25% increase from the baseline.

Table 10: Categorical Analysis for QRS

Study Identifier	Total (N)		Value ≤ 120 msec		Value > 120 msec & ≤ 25%		Value > 120 msec & > 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
205678	218	2049	193 (88.5%)	1852 (90.4%)	23 (10.6%)	194 (9.5%)	2 (0.9%)	3 (0.1%)
BMA117159	79	1155	74 (93.7%)	1105 (95.7%)	4 (5.1%)	49 (4.2%)	1 (1.3%)	1 (0.1%)

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK in study 205678.

Two assays (PKB and PKC) have been used to quantify cys-mcMMAF concentrations in the belantamab mafodotin clinical trials. PKC was developed when the possibility of over-estimation of cys-mcMMAF concentrations using assay PKB was identified. When the samples from study 205678 (approximately 2100 samples) were re-analyzed using assay PKC, a linear regression analysis was used to describe the relationship between the results of the two assays: $PKB = 1.486 * PKC - 8.36$, $R^2 = 0.972$. The reviewers used results from the newer assay (PKC) in the concentration-QTc analysis.

4.5.1 QTc

Prior to evaluating the relationship between drug-concentration and QTc using a linear model, the three key assumptions of the model needs to be evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTc and 3) presence of non-linear relationship. Figure 2 shows the time-course of ΔHR , which shows an absence of significant ΔHR changes. Figure 5 evaluates the time-course of drug-concentration; only time points with more than 15 sample size were included in the plot. Because there is no close time point after the Tmax of cys-mcMMAF, the plot cannot be used to support an evaluation of potential hysteresis. Figure 6 shows the relationship between drug concentration and ΔQTc and supports the use of a linear model.

As an exploratory analysis, the linear model ($\Delta QTcF \sim \text{intercept} + \text{CONC} + \text{adjusted_baseline}$, with random effect on the intercept) was applied to the data and the

goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provide in Table 11.

Figure 5: Time course of drug concentration (top) and QTc (bottom)

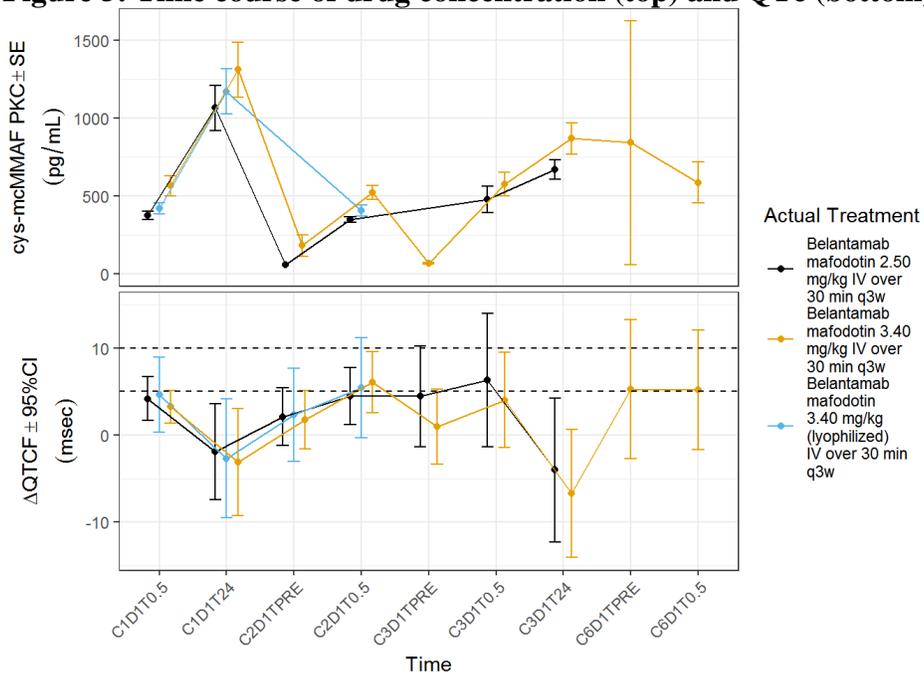


Figure 6: Assessment of linearity of concentration-QTc relationship

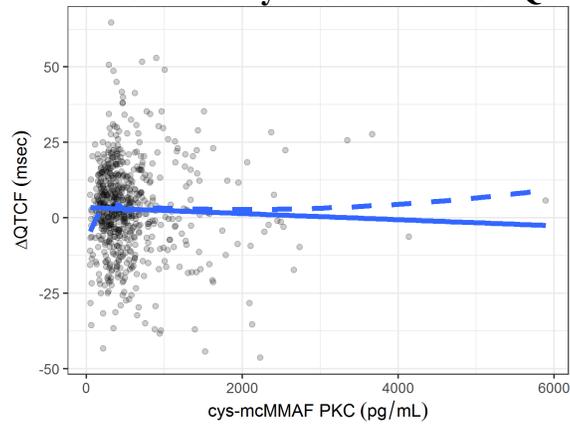


Figure 7: Goodness-of-fit plot for QTc

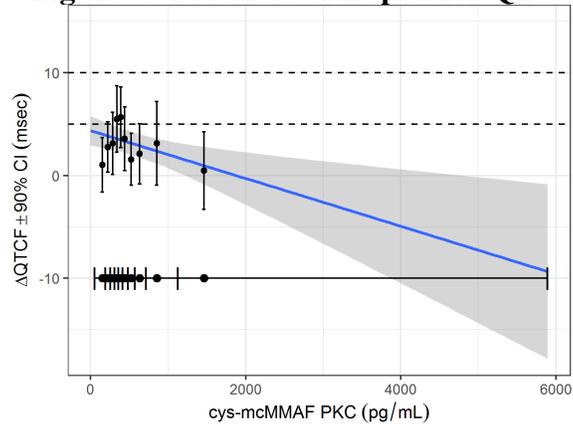


Table 11: Predictions from concentration-QTc model

Actual Treatment	cys-mcMMAF PKC (pg/mL)*	ΔQTcF (msec)	90.0% CI (msec)
2.50 mg/kg IV over 30 min q3w	850.0	2.4	(1.2 to 3.6)
3.40 mg/kg IV over 30 min q3w	1,040.3	2.0	(0.6 to 3.3)
3.40 mg/kg (lyophilized) IV over 30 min q3w	1,015.7	2.0	(0.7 to 3.4)

* geometric mean C_{max} of PK samples at 24-hour postdose.

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/s/

NAN ZHENG
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