TITLE PAGE

Protocol Title: A Phase 2, Randomized, Parallel, Open-Label Study to Investigate the Safety, Efficacy, and Pharmacokinetics of Various Dosing Regimens of Single-Agent Belantamab Mafodotin (GSK2857916) in Participants with Relapsed or Refractory Multiple Myeloma (DREAMM-14)

Protocol Number: 209628 / Amendment 03

Compound Number: GSK2857916

Brief Title:

Study to Investigate Alternative Dosing Regimens of Belantamab Mafodotin in Participants with Relapsed or Refractory Multiple Myeloma (DREAMM-14)

Study Phase: Phase 2

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

SPONSOR SIGNATORY:

Sumita Roy-Ghanta, MD

Group Senior Medical Director Clinical Development Lead
Belantamab Mafodotin Program

Approval Date: 25 Jun 2024

Regulatory Agency Identifying Numbers:

Registry	**ID**
IND	119333
EU CT number	2023-508213-16-00

Protocol/Protocol Amendment 3 Investigator Agreement

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with GCP and all applicable regulatory requirements.
- That I will comply with the terms of the clinical study site agreement.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To cooperate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.

Study identifier	209628
Abbreviated title	DREAMM-14
EU CT number	2023-508213-16-00
Approval date	25 Jun 2024
Title	A Phase 2, Randomized, Parallel, Open-Label Study to Investigate the Safety, Efficacy, and Pharmacokinetics of Various Dosing Regimens of Single-Agent Belantamab Mafodotin (GSK2857916) in Participants with Relapsed or Refractory Multiple Myeloma (DREAMM-14)
Investigator name	
Signature	
Date of signature (DD Month YYYY)	

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 03	*25 Jun 2024*	*TMF-19107833*
Amendment 02 GBR-1	*20-December-2022*	*TMF-15222732*
Amendment 02	*19-December-2022*	*TMF-14902500*
Amendment 01 GBR-1	*04-May-2022*	*TMF-14578074*
Amendment 01 FRA-1	*27-January-2022*	*TMF-14396610*
Amendment 01	*21-January-2022*	*TMF-14343018*
Original Protocol (00)	*14-September-2021*	*TMF-13844035*

Amendment 03 (25 Jun 2024)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

This protocol amendment 03 is a global amendment to address editorial changes to align with the new Sponsor's standard protocol template and ways of working. Flexibility regarding the post-analysis continued treatment (PACT) period was incorporated into the language. Additionally, updates were made to allow flexibility for the end of treatment (EOT) visits, ocular examinations, short term use of steroids and sample collection windows. Safety information was also updated following the DREAMM-2 study completion. The third parties and subcontractors' appendix is now a separate document. A description and rationale for all changes is provided in the table that follows.

Section # and name	Description of change	Brief rationale
Section 1.1 Synopsis	Added flexible language for PACT	To allow flexibility for participants to move into PACT period after study completion
Section 1.3 Schedule of Activities (Table 1)	Included additional details for the EOT Visit definition	Clarification of the EOT Visit definition
	Updated footnote 9	Clarification of the scope of the ocular assessments following EOT
Section 1.3 Schedule of Activities (Table 4)	Updated sample collection window	Alignment with visit windows
Section 2.2.3 Clinical Experience with Belantamab Mafodotin relevant for DREAMM-14	Heading text update	Clarification as to why only DREAMM-1 and DREAMM-2 data are included
	Content update following completion of DREAMM-2 study	Added clinical experience with belantamab mafotodin
Section 2.3.1 Risk Assessment	Updated numbers in table of risk assessment for thrombocytopenia	Added clinical experience with belantamab mafotodin from study 205678
Section 4.1 Overall Design Section 4.6 End of Study Definition/Study Completion	Added flexible language for PACT	To allow flexibility for participants to move into PACT period after study completion
Section 4.5 Participant Completion	Removed “If a participant has been in follow-up for 2 years at the final OS analysis (see Section 4.6) or if the participant dies during the study treatment or follow-up period, that participant is considered to have completed the study. The cause of death should be documented in the electronic Case Report Form (eCRF).” wording	To align with PACT language
Section 4.6 End of Study Definition/Study Completion	Added “and PFS , as well as selected safety data” for the final analysis	Update in scope of final analysis
Section 5 Study Population	Subheaders were added for the inclusion and exclusion criteria	Editorial changes to align with the Sponsor’s standard protocol
Section 6.6.1 Continued Access to Study Treatment After the Final Data Cutoff	Added flexible language for PACT	To allow flexibility for participants to move into PACT period after study completion

Section # and name	Description of change	Brief rationale
prior to End of the Study		
Section 6.8.2 Prohibited Medications and Non-Drug Therapies	Added exception to the use of steroid for adverse event or emergency situations	To allow flexibility considering the sick patient population and short term use of steroids intravenously
	Updated the anti-HIV drugs sentence	Clarification for study conduct
Section 7.2 Participant Discontinuation/Withdrawal from the clinical study	Added language on use of public sources for vital status information collection	Clarification for study conduct
Section 8.3.5 Ocular Examinations	Updated the text on ophthalmic medical follow-up after EOT	Clarification of the scope of the ocular assessments following EOT
Section 8.4.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Added flexible language for a managed access program/drug supply program	To allow flexibility for participants to continue receiving treatment via a managed access program/drug supply program after study completion
	Updated the ocular exam schedule after end of PACT treatment wordings	Program-level updates
Section 8.4.4 Adverse Events of Special Interest	Section was moved up	Editorial changes to align with the Sponsor's standard protocol
Section 8.4.5 Regulatory reporting requirements for SAEs/AESIs	Added Table 13 Timeframes for submitting SAE, pregnancy and other events reports to GSK	Table added to align with the Sponsor's standard protocol template and ways of working
Section 8.4.8 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Serious Adverse Events	Reference to DRE CRF pages was removed	Not applicable for this study
Section 8.9 Immunogenicity Assessments	Removal of "A final ADA sample will be drawn at the EOT visit" sentence	To align with Schedule of Activities
	Added language that sample collection may be terminated early	Allow flexibility
Section 9.4.5 Pharmacokinetic Analyses	"Clinical Pharmacoketics" was updated to "Clinical Pharmacology"	Correction of GSK department name

Section # and name	Description of change	Brief rationale
Section 10.10.3 Informed Consent Process	Added text regarding collection of pregnancy for both maternal and paternal exposure	To align with the Sponsor's standard protocol
Section 10.10.5 Committees Structure	Added paragraph on Safety Review Team	To align with the Sponsor's standard protocol
Third Parties and Subcontractors Appendix	Appendix was removed from Protocol Amendment 3	To align with the Sponsor's standard protocol template and ways of working, a separate document has been created
Section 10.20 Appendix 20: Abbreviations, and Trademarks and Definitions of Terms	Updated to include definitions of terms table	To align with the Sponsor's standard protocol template and ways of working
Throughout the document	Editiorial and document formatting changes	Editorial changes to align with the new Sponsor's standard protocol template and ways of working

Abbreviations: ADA: anti drug antibody; AESI: adverse event of special interest; eCRF: electronic Case Report Form; EOT: End of Treatment; HIV: human immunodeficiency virus; OS: overall survival; PACT: Post Analysis Continued Treatment; PFS: progression free survival; SAE: serious adverse event

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 2, Randomized, Parallel, Open-Label Study to Investigate the Safety, Efficacy, and Pharmacokinetics of Various Dosing Regimens of Single-Agent Belantamab Mafodotin (GSK2857916) in Participants with Relapsed or Refractory Multiple Myeloma (DREAMM-14)

Brief Title:

Study to Investigate Alternative Dosing Regimens of Belantamab Mafodotin in Participants with Relapsed or Refractory Multiple Myeloma (DREAMM-14)

Rationale:

Belantamab mafodotin (GSK2857916) is a B-cell maturation antigen (BCMA)-directed antibody-drug conjugate (ADC) that is conjugated to a microtubule disrupting agent, monomethyl auristatin F (MMAF) with antitumor activity in multiple myeloma (MM) cells. Belantamab mafodotin mediates the killing of tumor cells through MMAF-induced apoptosis as well as by tumor cell lysis through antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). Clinically, single-agent belantamab mafodotin has demonstrated efficacy in participants with relapsed or refractory multiple myeloma (RRMM) who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

Efficacy has been demonstrated at 2.5 mg/kg dose of belantamab mafodotin, administered as an IV infusion once every 3 weeks (Q3W) until progressive disease (PD) or unacceptable toxicity. The Phase 2, open-label, randomized study investigating the efficacy and safety of belantamab mafodotin in participants with RRMM (DREAMM-2) [Lonial, 2020] met its primary endpoint for overall response rate (ORR) of 31% (n=97, 97.5% confidence interval [CI]: 20.8%, 42.6%). DREAMM-2 patient-reported outcomes (PROs) demonstrated that participants treated with belantamab mafodotin at the dose of 2.5 mg/kg generally maintained their health-related quality of life (HRQoL) and physical functioning while on treatment. Although vision-related- activities can be limited during episodes of clinically significant ocular PRO changes, these changes are temporary and do not adversely impact overall HRQoL and physical functioning [Popat, 2020].

Although belantamab mafodotin has demonstrated efficacy in this population, ocular toxicity is common and expected, having been reported in other MMAF-containing ADCs [Parrozzani, 2020]. Belantamab mafodotin administered at the dose of 2.5 mg/kg Q3W can cause changes in the corneal epithelium resulting in changes in vision. Keratopathy (defined as corneal examination findings of microcyst-like- keratopathy, which were mapped to the preferred term keratopathy per Medical Dictionary for Regulatory Activities [MedDRA]) was the most frequent ocular adverse event (AE) in the DREAMM-2 study (71% of participants, with 44% Grade 3 and 1% Grade 4)

[Lonial, 2020]. The corneal changes often result in visual acuity changes, with 54% [51 out of 95] of participants experiencing best corrected visual acuity (BCVA) changes of any grade and 31% [29 out of 95] of Grade 3 to 4 [Farooq, 2020]. These ocular toxicities resulted in high rates of dose delays (47% [45 out of 95] dose delays due to keratopathy) and dose reductions (23% [22 out of 95] dose reductions due to keratopathy).

Alternative dosing regimens of single-agent belantamab mafodotin will be explored in Study 209628 to determine if an improved overall benefit/risk profile can be achieved by modifying the belantamab mafodotin dose, schedule, or both.

In addition to investigating alternative dosing schedules to mitigate the risk of corneal toxicity (Arms A to D), Study 209628 will also assess the use of ocular symptoms (patient-reported symptoms using the Ocular Surface Disease Index [OSDI]) and visual acuity assessments (Snellen chart or equivalent) to inform dose modification decisions and assess potential impact on the frequency of ocular examinations conducted by an eye care specialist on safety and efficacy for the participant (Arm E).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To examine the corneal events associated with single-agent belantamab mafodotin using alternative dosing regimens in participants with RRMM in Arms B to D compared to Arm A	Incidence rate of Grade ≥2 corneal events according to the KVA scale
Secondary	
To further evaluate the ocular safety and tolerability of single-agent belantamab mafodotin in all arms	• Cumulative event rate of corneal events to Week 16 (KVA scale) • Incidence rate of corneal events by grade (KVA scale) • Exposure-adjusted incidence rate of corneal events by grade (KVA scale) • Median duration of dose delay • Percentage of participants requiring dose reductions, dose delays, and study treatment discontinuation due to corneal events (KVA scale) • Cumulative incidence of corneal events by grade (KVA scale) • Toxicity Index by assessment/visit • Duration of corneal events (KVA scale) • Percentage of time on study with corneal events (KVA scale) • Change in BCVA (ΔlogMAR)

Objectives	Endpoints
To evaluate the efficacy of single-agent belantamab mafodotin in all arms	• ORR, defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR, and sCR) • Percentage of participants with a confirmed VGPR or better (i.e., VGPR, CR, and sCR) • TTR is defined as the time between the date of randomization and the first documented evidence of response (PR or better), among participants who achieve a response (i.e., confirmed PR or better) • DoR in responders, defined as the time from first documented evidence of PR or better until PD or death due to any cause • TTP, defined as the time from randomization until the earliest date of documented PD or death due to PD • PFS, defined as the time from randomization until the earliest date of documented PD or death due to any cause • OS, defined as the time from randomization until the date of death due to any cause ***Note:*** *All efficacy endpoints are based on the 2016 IMWG Response Criteria*
To evaluate the overall safety and tolerability of single-agent belantamab mafodotin in all arms	• Instance of AEs (including corneal events) (CTCAE Version 5.0) and changes in laboratory parameters • Percentage of participants requiring dose reductions, dose delays, and study treatment discontinuation due to any AEs (CTCAE Version 5.0)
To assess the pharmacokinetics of single-agent belantamab mafodotin in all arms	Plasma belantamab mafodotin pharmacokinetic parameters, as data permit
To assess anti-drug antibodies against single-agent belantamab mafodotin in all arms	Incidence and titers of ADAs against belantamab mafodotin at each ADA time point

Abbreviations: AE=adverse event; BCVA=best corrected visual acuity; CR=complete response; CTCAE=Common Terminology Criteria for Adverse Events; ΔlogMAR=change in logarithm of the minimum angle of resolution; DoR=duration of response; FACT-GP5=Functional Assessment of Cancer Therapy – General; IMWG=International Myeloma Working Group; KVA=keratopathy visual acuity; ORR=overall response rate; OS=overall survival; OSDI=Ocular Surface Disease Index; PD=progressive disease; PFS=progression-free survival; PR=partial response; PRO-CTCAE=Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; RRMM=relapsed or refractory multiple myeloma; stringent complete response; TTP=time to progression; TTR=time to response; VGPR=very good partial response.

Overall Design:

Study 209628 (DREAMM-14) is a Phase 2, randomized, parallel, open-label, study of belantamab mafodotin administered as a single-agent to participants with RRMM. The study has 5 arms: Arm A, a control arm (2.5 mg/kg Q3W); Arms B through D, 3 arms with dosing alternatives; and Arm E, a fifth exploratory arm to evaluate the feasibility of dosing 1.9 mg/kg every 6 weeks (Q6W) with dose modifications based on ocular symptoms, visual acuity assessments, and corneal findings. All enrolling study sites will participate in Arms A to D; site participation in Arm E is optional and based on site interest and ability.

Participants in Arm A will use the DREAMM-2 established 2.5 mg/kg Q3W dosing regimen. Participants in Arm C will receive a starting dose at 2.5 mg/kg belantamab mafodotin, but dosing will occur at Q6W intervals. Participants in Arms B, D, and E will start at a reduced dose of belantamab mafodotin (1.9 mg/kg) and continue dosing at Q3W (Arm B) and Q6W (Arms D and E) intervals. Each dosing regimen has 1 allowed dose reduction: from 2.5 mg/kg to 1.9 mg/kg in Arms A and C and from 1.9 mg/kg to 1.4 mg/kg in Arms B, D, and E.

Participants in all arms will have Q3W ophthalmic examination and monitoring. All ophthalmic examinations will be performed by a qualified eye care specialist.

All arms except Arm E will follow dose modification due to corneal events as per the keratopathy visual acuity (KVA) scale. In contrast, Arm E will use a symptom-based dose modification approach before each dose, in the oncologist's office; specifically, ocular symptoms and visual acuity assessments using the OSDI and Snellen chart or equivalent, respectively (in addition to corneal examination findings according to the KVA scale), will be used to inform dose modification decisions. ***Note:*** *Although not determining dose modification decisions, corneal events (corneal findings and BCVA) graded per the KVA scale will still be recorded for all participants in Arm E throughout the study.*

Participants in all arms will be treated until PD (confirmed by 2016 IMWG response criteria [Kumar, 2016]), unacceptable toxicity, or death. The study consists of a screening/baseline period, a treatment period, and a post-treatment follow-up period. The primary analysis will be performed at least 9 months after the first response of the last responder (i.e., partial response [PR], very good partial response [VGPR], complete response [CR], and stringent complete response [sCR]) or 12 months after the last participant is randomized into Arms A to D, whichever comes first.

Brief Summary:

The purpose of the study is to explore whether alternative dosing regimens with lower dose intensity of single-agent belantamab mafodotin can improve the benefit/risk profile (i.e., can reduce the risk of corneal events without a clinically meaningful decrease in efficacy) in participants with RRMM compared to the DREAMM-2 established 2.5 mg/kg Q3W dosing regimen. Study details include:

- Study Duration: Approximately 28 months

- Treatment Duration: Until PD, unacceptable toxicity, or death
- Visit Frequency: Q3W

Number of Participants:

Approximately 180 participants will be evaluated in this study, with approximately 40 participants in treatment Arms A to D and 20 in Arm E.

Study Treatment Groups and Duration:

Five treatment arms are planned. Single-agent belantamab mafodotin will be administered at doses and schedules as follows:

- Arm A: 2.5 mg/kg Q3W (control; dose reduction to 1.9 mg/kg allowed)
- Arm B: 1.9 mg/kg Q3W (dose reduction to 1.4 mg/kg allowed)
- Arm C: 2.5 mg/kg Q6W (dose reduction to 1.9 mg/kg allowed)
- Arm D: 1.9 mg/kg Q6W (dose reduction to 1.4 mg/kg allowed)
- Arm E: 1.9 mg/kg Q6W with dose modifications based on ocular symptoms (patient-reported symptoms using the OSDI), visual acuity assessments (Snellen chart or equivalent), and corneal findings (dose reduction to 1.4 mg/kg allowed)

For Arms A and C, the lowest dose level to be studied in each arm is 1.9 mg/kg and for Arms B and D, the lowest dose level to be studied is 1.4 mg/kg (as per dose reduction guidelines).

Participants will be randomized 2:2:2:2:1 into Arms A to E in parallel (at sites participating in optional Arm E) **or** 1:1:1:1 into Arms A to D in parallel (at sites **not** participating in optional Arm E). All participants will be stratified by both the International Staging System (ISS) for MM (I vs II vs III) and the number of prior lines of anti-myeloma therapy (3 vs ≥4). ***Note:*** *For Arm E, in which dose modification decisions are informed by the results of the OSDI questionnaire, the OSDI must be available in the appropriate language in order for a participant to be randomized into this arm. If the OSDI is not available, the participant will be randomized into Arms A to D (1:1:1:1).*

The dose of study treatment will be based on actual body weight calculated at baseline and may be modified to manage toxicities according to protocol guidelines.

An interim analysis is planned when approximately 15 participants each in Arms A to D have been enrolled and have received 2 doses of study treatment with 1 disease assessment following the second dose or confirmed PD per IMWG [Kumar, 2016] or death. Any arm in Arms B to D with ≤2 responders will be discontinued from further enrollment and arms with ≥3 responders will continue enrollment. Enrollment will continue as analysis is being performed. If Arm D is stopped due to futility, Arm E will also be stopped. If Arms B, C, D, or E are stopped due to futility, participants will be given the opportunity to switch to 2.5 mg/kg Q3W (Arm A/control regimen), provided the participant has not experienced PD; the data collected from participants after switching will not be included in the primary analysis and may be analyzed separately.

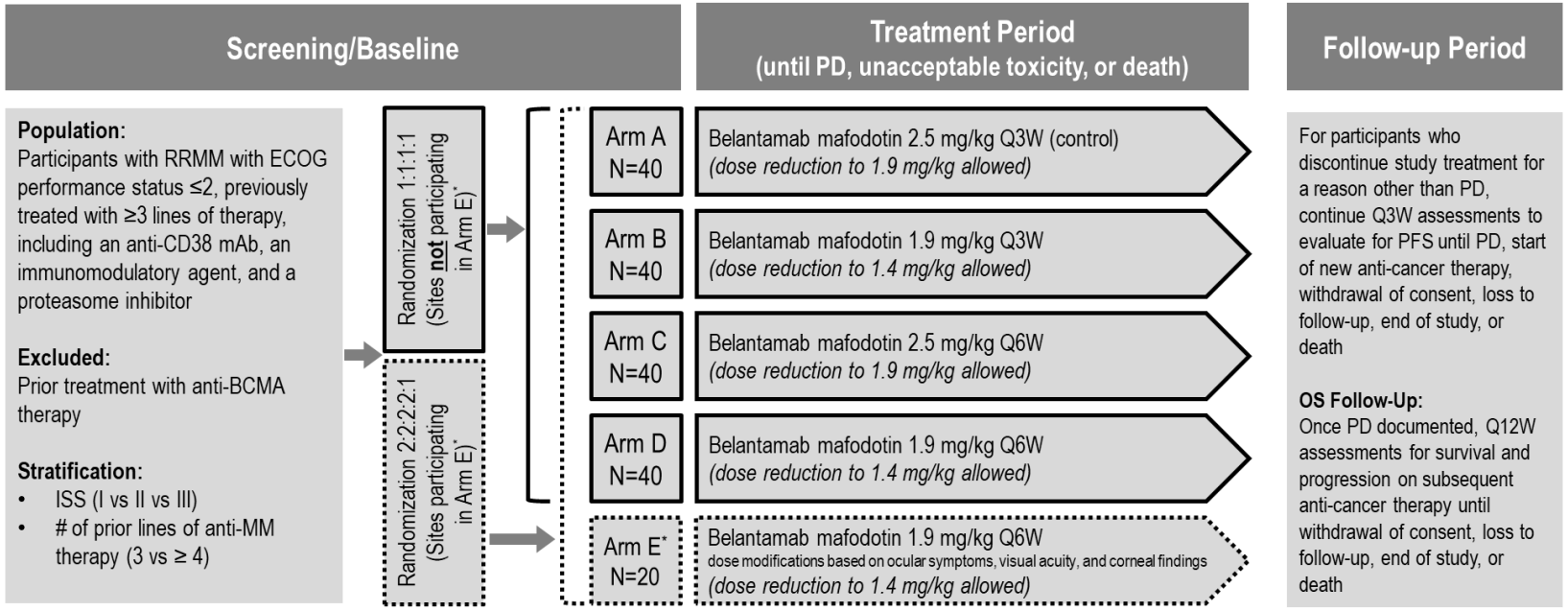
The end of study is defined when the last patient had their last visit (last subject last dose plus 70 days of AE reporting period) or 15 months after last participant first dose (LSFD), whichever comes last.

Following 15 months post-LSFD, DREAMM-14 may move into PACT and/or a managed access program/drug supply program, to allow patients who are still receiving benefit from belantamab mafodotin to continue receiving treatment. For PACT, the collection of new data for all recruited participants who no longer receive study treatment will stop entirely and the clinical study database will be closed. A participant is considered to have completed the study if they have completed all periods of the study including the last visit. Participants in survival follow-up will be considered to have completed the study. Those participants still benefiting from study treatment in the opinion of their treating physician may continue to receive study treatment in the PACT phase and only serious adverse events (SAEs), AEs leading to treatment discontinuation, overdose, pregnancy cases, and pre-specified ocular data will be reported directly to GSK.

Data Monitoring/Other Committee: An Independent Data Monitoring Committee (IDMC) consisting of at least 2 physicians and 1 statistician will review safety and efficacy data as defined in the IDMC Charter.

1.2. Schema

Figure 1 DREAMM-14 Study Schema



Abbreviations: BCMA=B-cell maturation antigen; ECOG=Eastern Cooperative Oncology Group; ISS=International Staging System; mAb=monoclonal antibody; MM=multiple myeloma; OS=overall survival; PD=progressive disease; PFS=progression-free survival; Q12W=every 12 weeks; Q3W=every 3 weeks; Q6W=every 6 weeks; RRMM=relapsed or refractory multiple myeloma.

* All enrolling study sites will participate in Arms A to D; site participation in Arm E is optional and based on site interest and ability.

1.3. Schedule of Activities (SoA)

All assessments planned for participants in Study 209628 are shown in the time and events tables as follows:

- Table 1: Screening, On-Treatment, End of Treatment, and Follow-Up Assessments
- Table 2: Additional Assessments for Participants with Hepatitis B Virus
- Table 3: Additional Assessments for Participants with Hepatitis C Virus
- Table 4: Collection Schedule for Pharmacokinetic, Soluble B-Cell Maturation Antigen, and Anti-Drug Antibody Samples

The details of these assessments are provided in footnotes to the tables and further details are provided in Section 8.

All assessments and visits are expected to be conducted in-person at the appropriate study site or provider office. However, should the need for decentralized and remote assessment approaches arise (e.g., a pandemic) details for implementing these services are provided in Section 10.4.

- The timing of planned study assessments may change during the course of the study based on emerging data/in-stream data review (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing of time points for any planned study assessments as the result of emerging pharmacokinetic/pharmacodynamic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment.
- The competent authority and ethics committee will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the Informed Consent Form. The changes will be approved by the competent authority and the ethics committee before implementation.

Table 1 Schedule of Activities: Screening, On-Treatment, End of Treatment, and Follow-Up Assessments – ALL ARMS

- All screening assessments must be performed within 28 days before the first dose.
- **EOT Visit** will either occur within 30 days after last dose or within 30 days of the last Q3W visit, whichever comes last. All EOT visits must occur before the start of any new anti-myeloma therapy. AEs and SAEs will be collected up to at least 70 days after the last dose of belantamab mafodotin, either via phone or a follow-up visit. Participants who have ocular symptoms at EOT will be followed up for ocular exams (Section 8.3.5) and OSDI questionnaire. After discontinuation of study treatment, the participant should continue disease assessments as per the SoA. Every effort should be made to confirm progressive disease per the IMWG criteria prior to initiating a new anti-myeloma therapy.
- **PFS Assessments:** For participants who discontinue study treatment for a reason other than PD, assessments for PFS will continue to be performed at Q3W (±3 days) from the last on-treatment Q3W assessment visit (as shown in the **ALL ARMS Q3W** regardless of dosing column) until confirmed PD, start of a new anti-myeloma therapy, withdrawal of consent, loss to follow-up, end of the study, or death, whichever occurs first. Once a participant experiences PD, move to the OS follow-up schedule.
- **OS Follow-Up:** All participants who permanently discontinue study treatment and have experienced PD, or have started new anti-myeloma therapy will remain in the study and will be followed for survival and subsequent anti-myeloma therapy by chart review, telephone call, or any form of communication Q12W (±14 days) from the last Q3W assessment visit until withdrawal of consent, loss to follow-up, end of the study, or death, whichever occurs first. A participant does not need to come in for a visit unless they are being followed for changes in vision (see Table 8 for exceptions) that are present at EOT. Record the participant's survival status and whether subsequent anti-myeloma therapy was given.
- **PACT Phase:** Participants who continue to receive study treatment during the PACT phase will be monitored and receive follow-up care in accordance with standard local clinical practice. Assessments will revert to the standard of care at a patient's particular study site and only SAEs, AEs leading to discontinuation of study treatment, overdoses, and pregnancy cases [and pre-specified ocular data], will be reported directly to the Sponsor via paper forms (see Section 8.4 and refer to the Study Reference Manual (SRM)). For participant discontinuing treatment in the PACT phase, no end of treatment visit is required.

Time:	Screening (-28 days)	C1D1	ALL ARMS Q3W ±3 days regardless of dosing (includes PFS assessments)	Arms A & B Dosing Visit Q3W ±3 days	Arms C, D, & E Dosing Visit Q6W ±3 days	EOT Visit*	OS Follow-Up (Q12W; ±14 days)
Day (D)	**From D-28**	**D1**	**D22, D43, etc.**	**D22, D43, etc.**	**D43, D85 etc.**		
Cycle (C)		**C1D1**		**C2D1, C3D1 etc.**	**C2D1, C3D1 etc.**		
Study Assessments							
Informed consent[1]	X						
Demographics	X						
Medical history, disease history, and characteristics (includes substance abuse and family history of premature cardiovascular disease)	X						
Prior anti-myeloma therapy (including radiation and transplants)	X						
Inclusion/exclusion criteria	X						
Optional genetics consent[2]	X						
Concomitant medications[3]	Ongoing						
Safety Assessments							
Physical examination	X	X		X[4]	X[4]	X	
Vital signs (BP, HR, and temperature)[5]	X	X		X[4]	X[4]	X	
12-lead ECG[6]	X						
ECOG performance status	X	X	X			X	
Ocular examination[7]	X		X[8,9]			X	X[9]
Visual acuity[10]		**Arm E** only			**Arm E** only		
Hematology[11]	X	X[12]	X			X	
Clinical chemistry[11]	X	X[12]	X			X	
Urinalysis (dipstick) **or** spot urine (ACR)[11, 13]	X	X[12]	Q6W from W7			X	
eGFR[11,14]	X	X[12]		X	X	X	
HBsAg, HBcAb, HCAb, HBV DNA, HCV RNA[11,15]	X						
Pregnancy test (WOCBP only)[11]	X[16]	X[16]		X[4, 17]	X[4, 17]	X[18]	
AEs/SAEs[19]		Ongoing					

Time:	Screening (-28 days)	C1D1	ALL ARMS Q3W ±3 days regardless of dosing (includes PFS assessments)	Arms A & B Dosing Visit Q3W ±3 days	Arms C, D, & E Dosing Visit Q6W ±3 days	EOT Visit*	OS Follow-Up (Q12W; ±14 days)
Day (D)	**From D-28**	**D1**	**D22, D43, etc.**	**D22, D43, etc.**	**D43, D85 etc.**		
Cycle (C)		**C1D1**		**C2D1, C3D1 etc.**	**C2D1, C3D1 etc.**		
Disease Evaluation Assessments: [20] For participants who are discontinuing study treatment due to PD, confirmation based on laboratory assessments must be performed from a different sample collection (serum/urine) preferably **before** institution of any new anti-myeloma therapy and, if possible, within 14 days of the date of the initial assessment showing unconfirmed progressive disease.							
β2 microglobulin[11]	X						
UPEP (on 24 h urine collection)[11]	X	X[12]	X			X	
Urine immunofixation[11]	X		X[21]			X[21]	
SPEP[11]	X	X[12]	X			X	
Serum immunofixation[11]	X		X[21]			X[21]	
Serum kappa, lambda FLC, FLC ratio[11]	X	X[12]	X			X	
IgG, IgM, IgA[11]	X		X			X	
IgD/E, if applicable[11, 22]	X		X			X	
Calcium corrected for albumin (serum)[11]	X		X			X	
Response assessment[23]			X			X	
BM Aspirate/Biopsy Assessments[11]							
BM (biopsy and/or aspirate) for disease assessment (percentage of malignant plasma cells)	X[24]		X[25]				
BM aspirate for FISH testing[26]							
BM (biopsy and/or aspirate) for BCMA expression and biomarker research[27]							
BM biopsy to assess sCR by IHC			X[28]				
Imaging Assessments							
Skeletal survey[29]	X		As clinically indicated[30]				
EMD assessment[31]	X		X (Q12W)			X	
Study Treatment							
Premedication (as needed)		X		X	X		
Belantamab mafodotin		X		X[32]	X[32]		

Time:	Screening (-28 days)	C1D1	ALL ARMS Q3W ±3 days regardless of dosing (includes PFS assessments)	Arms A & B Dosing Visit Q3W ±3 days	Arms C, D, & E Dosing Visit Q6W ±3 days	EOT Visit*	OS Follow-Up (Q12W; ±14 days)
Day (D)	**From D-28**	**D1**	**D22, D43, etc.**	**D22, D43, etc.**	**D43, D85 etc.**		
Cycle (C)		**C1D1**		**C2D1, C3D1 etc.**	**C2D1, C3D1 etc.**		
Supportive Care							
Cooling eye masks[33]		X		X	X		
Preservative-free artificial tears[33]		X	Daily until EOT				
PK and ADA Assessments[11]							
PK[34]		X		X[4]	X[4]		
Immunogenicity (ADA)[35]		X		X[4]	X[4]		
Biomarker Assessments[11]							
sBCMA (serum)[36]		X		X[4]	X[4]		
TBNK panel (whole blood)[37]		X	X				
Health Outcomes Assessments							
PRO-CTCAE		X	X[38]			X	
OSDI[39]		X	X[40]			X[40]	X[40]
FACT-GP5		X	X[38]			X	
EORTC-QLQ-C30		X	X[38]			X	
EORTC-QLQ-MY20		X	X[38]			X	
PGIS[41]		X	Q6W			X	
PGIC[41]			Q6W			X	
Post-PD Status							
Survival status[42]							X
Subsequent anti-myeloma therapy[43]						X	X

Abbreviations: ACR=albumin/creatinine ratio; ADA=anti-drug antibody; AE=adverse event; AESI=adverse event of special interest; BCMA=B-cell maturation antigen; BM=bone marrow; BP=blood pressure; C=Cycle; CR=complete response; CT=computed tomography; D=Day; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eGFR=estimated glomerular filtration rate; EMD=extramedullary disease; EOI=end of infusion; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module; EORTC-QLQ-MY20=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma Module; EOT=end of treatment; FACT-GP5=Functional Assessment of Cancer Therapy – General Population; FISH=florescence in-situ hybridization; FLC=free light chain; FSH=follicle-stimulating hormone; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCAb; hepatitis C antibody HCV=hepatitis C virus; HR=heart rate; ICF=Informed Consent Form; Ig=immunoglobulin; IHC=immunohistochemistry; IMWG=International Myeloma Working

Group; MDRD=Modified Diet in Renal Disease; MRI=magnetic resonance imaging; OS=overall survival; OSDI=Ocular Surface Disease Index; PD=progressive disease; PET=positron emission tomography; PFS=progression-free survival; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PK=pharmacokinetics; PRO-CTCAE=Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; Q12W=every 12 weeks; Q3W=every 3 weeks; Q6W=every 6 weeks; QTcF=QT interval corrected using Fridericia's formula; RNA=ribonucleic acid; SAE=serious adverse event; sBCMA=soluble B-cell maturation antigen; sCR=stringent complete response; SOI=start of infusion; SPD=sum of the products of the perpendicular diameters; SPEP=serum protein electrophoresis; SRM=Study Reference Manual; TBNK=T, B, and natural killer cells; UPEP=urine protein electrophoresis; US=United States; W=week; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential.

* EOT Visit will either occur within 30 days after last dose or within 30 days of the last Q3W visit, whichever comes last. All EOT visits must occur before the start of any new anti-myeloma therapy.

1. The ICF must be signed before any study-specific assessments are performed.
2. Informed consent for optional genetics research must be obtained before collecting the sample. The sample will be collected at the first opportunity after a participant has met all eligibility requirements or on C1D1 before infusion.
3. Concomitant medications administered after EOT should only be recorded for SAEs/AESIs as defined in Section 8.4.
4. If no treatment is administered at C2 or later cycles, the following assessments do not need to be done, unless clinically indicated or at EOT visit: physical examination, vital signs, and pregnancy test. For dose-related time points (up to C12D1), if a participant is not dosed do not collect associated PK, ADA, and sBCMA samples.In the case of liver events, PK and sBCMA samples must be collected.
5. On C1D1 (first infusion) dosing day, vital signs must be assessed at pre-dose (within 30 minutes before the SOI), within 15 minutes after EOI, and 1 hour post-EOI. On subsequent dosing days, vital signs must be assessed at pre-dose (within 30 minutes before the SOI) and within 15 minutes after EOI. On days where vital sign time points align with blood sampling time points, vital signs should be assessed before blood samples are drawn. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.
6. Single ECG at screening, unless QTcF is prolonged, in which case triplicate ECGs are required; to be performed after at least 5 minutes of rest.
7. See Section 8.3.5.1 for list of ocular examination procedures. All ocular examinations will be performed by a qualified eye care specialist such as an ophthalmologist or optometrist (Section 10.1).
8. On-treatment ocular examinations should occur Q3W irrespective of dosing. When dosing, ocular examinations must be performed within 5 days before dosing. If the participant is not being dosed, ocular examinations may be performed within ±3 days of the Q3W visit. If a participant develops vision changes or other ocular symptoms, the participant should be promptly evaluated by a qualified eye care specialist such as an ophthalmologist or optometrist (as defined in Section 10.1). In case of persistent ocular examination findings, newly developed ocular symptoms, or vision changes, the participants will have further exams until resolution (to Grade 1 or baseline), or more frequently as clinically indicated by the qualified eye care specialist such as an ophthalmologist or optometrist.
9. Participants with corneal events (KVA Grade 2 or higher) at EOT will be followed by a qualified eyecare specialist until full resolution of ophthalmic changes (KVA Grade 1 or better), start of new anti-myeloma therapy or up to 1 year, whichever occurs first. If the participant is in PFS follow-up, ocular assessments must be performed Q3W ±3 days. If the participant is in OS follow-up, ocular assessments must be performed Q12W ±14 days. Additional ocular examinations can be performed at the discretion of the eye care specialist and/or investigator.
10. For participants in Arm E only, visual acuity will be assessed at the oncologist's office before dosing.
11. See Section 10.13 for a comprehensive list of laboratory tests that must be collected for all participants and if analyzed locally or centrally.
12. Assessment does not need to be repeated on C1D1 if corresponding screening assessment was completed within 72 hours before the first dose. Thereafter, hematology and clinical chemistry should be performed and reviewed within 72 hours prior to dosing.

13. ACR (spot urine preferably from first void). Urine dipstick for protein may be used to assess for presence of urine protein. ACR must be collected at screening and thereafter to be done in any participant with urine dipstick result of ≥2+ (during study treatment), or with positive protein if urine dipstick protein quantification is not available. ACR will be performed at a local laboratory. If local testing is not available, then central testing will be performed.
14. eGFR as calculated by MDRD formula (see Section 10.5).
15. See eligibility criteria (Section 5). HBV DNA testing must be done to determine participant eligibility only if HBsAg+ or HBcAb+. HCV RNA testing must be done to determine participant eligibility only if HCAb+.
16. Serum testing at screening and C1D1. The first test should be performed within 10 to 14 days before the first dose and the second test should be performed within 24 hours before the first dose. For questionable cases (child-bearing status), FSH and estradiol (as needed in WONCPB potential only) should be performed at local laboratory (see Section 8.3.7).
17. CXD1 pregnancy tests may be either serum or urine and each pregnancy test must be performed within 72 hours before dosing.
18. Final pregnancy test (serum or urine) must be performed in WOCBP within 70 days after the last dose. Follow-up pregnancy assessment by telephone for WOCBP should be performed 4 months after the last dose of study treatment.
19. AEs/SAEs will be collected up to at least 70 days after the last dose of study treatment. All SAEs related to study participation (e.g., protocol-mandated procedures, tests, or change in existing therapy) are to be collected from consent through OS follow-up. All AEs/SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (see Section 8.4).
20. Disease evaluation (except imaging and skeletal survey) will be performed Q3W (± 3 days) even if treatment is not administered. For participants who are discontinuing study treatment due to PD, the confirmation of PD is based on two central laboratory assessments performed from a different sample collection performed either on the same day or, if possible, within 14 days of the original date of PD, preferably before institution of any new anti-myeloma therapy. This may be performed at the EOT visit.
21. Serum/urine immunofixation will be performed each time that M protein is not quantifiable by SPEP (0 g/dL) or UPEP (0 mg/24hr).
22. Only required for participants with IgD/E myeloma.
23. To be assessed based on disease laboratory tests and imaging (if applicable) as outlined in this table. Response assessment is based on IMWG criteria [Kumar, 2016].
24. Portion of the aspirate collected for disease assessment will be used for FISH testing. Any remaining biopsy and/or aspirate sample from disease assessments (depending on institutional practice) should be retained for biomarker research.
25. For flow cytometry or IHC analysis at the time of suspected CR for confirmation of plasma cells <5% (always) or at time of suspected PD (only if not evident otherwise). BM must be collected as per institutional practice; however, a BM core biopsy is preferred. To be tested locally.
26. FISH testing to be performed locally at least for: t(4;14), t(14;16), amp(1q), del(1p), and del(17p13). If participant is known to have tested positive for t(4;14) or t(14/16),on previous tests, FISH for those translocations does not need to be repeated, regardless of when the previous tests were performed. For amp(1q), del(1p), and del(17p13), FISH results from samples taken within 60 days before the first dose are acceptable. The results of this test are not required for participants to start D1. If testing cannot be performed at a local laboratory the samples can be sent to the central laboratory.
27. BM collection should be performed per institutional practice.
28. In participants achieving a CR, BM biopsy to confirm sCR by IHC (kappa/lambda ratio). This will be collected for all participants and should be analyzed locally (if not available, central testing can be used).
29. Imaging of bones for lytic lesions by a method aligned with the institutional guidance (e.g., X-ray, CT, or MRI). The same modality used at screening must be used throughout study.
30. Only if clinically indicated or if worsening clinical symptoms suggest skeletal PD. Imaging is not required if the PD is evident otherwise. The same modality used at screening must be used throughout study. Imaging of bones for lytic lesions by a method aligned with the institutional guidance (e.g., X-ray, CT, or MRI).
31. Imaging (i.e., CT, MRI, or PET-CT) is only required for participants with EMD, per local guidance, Q12W ±1 week from the date of randomization (e.g., W13, W25, W37, etc.) through 1 year and then as clinically indicated. The same modality used at screening must be used throughout the study. Selected target lesion must be measured and followed

over time. Plasmacytoma measurements should be taken from the CT portion of the PET-CT, or MRI scans, or dedicated CT scans, where applicable. For participants with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor burden will be determined by the SPD of the measured lesions. All imaging scans must be retained at the investigative site as source documents. See Section 8.2 for more information on imaging, EMD measurement and follow-up, and PD due to EMD. Also see the SRM for additional information.

32. Belantamab mafodotin administration on D1 of C2 to CX, ±3 days. All scheduled cycle visits must be calculated from C1D1. See Section 6.1.1 for dosing schedule for Arms A to E and Section 6.5 in case a dose is delayed.
33. Cooling eye masks may be applied to both eyes for as long as tolerated, up to 4 hours. Preservative-free artificial tears should be used 4 to 8 times a day in each eye, beginning from C1D1 until EOT. Allow 5 to 10 minutes between administration of artificial tears and steroid eye drops, if administered together. In the event of ocular symptoms (i.e., dry eyes), the use of artificial tears may be increased up to every 2 hours. See Section 6.8.1 for more detail on supportive care information.
34. PK samples are required for all participants according to the schedules for PK sample collection in each treatment arm (Table 4).
35. Blood samples for ADA measurement in serum will be collected before the start of the infusion on dosing days at selected doses in each treatment arm (Table 4).
36. sBCMA (serum): Collect sBCMA samples at the same PK time points as specified in Table 4.
37. TBNK samples to be collected pre-dose on C1D1. All other timepoints, samples may be collected at any time during Q3W assessment.
38. Collected only while a participant remains on treatment.
39. Collected for all participants in all arms. For Arm E only: OSDI will contribute to determination of dose modification decisions (Go/No-Go) for participants (see Section 6.5).
40. Participants with no corneal events at the EOT ocular assessment will have no further OSDI collection. Participants with corneal events (see Table 8 for exceptions) at the EOT ocular assessment will have OSDI collected Q12W until resolution or baseline, with the final OSDI collected at the Q12W visit after resolution or return to baseline, or for up to 12 months, whichever occurs first.
41. Complete every 6 weeks from W7 (W7, W13, W19, W25, etc.) during treatment and at EOT. PGIC is not administered at C1D1.
42. Survival status may be obtained via a telephone call.
43. Information on subsequent anti-myeloma therapies and response to these therapies to be collected at any time after EOT visit.

Table 2 Additional Assessments for Participants with HBV

***Note**: The assessments listed in this table apply **only** to participants (those in screening and those already enrolled) who have a history of HBV; all assessments must be done as needed **in addition** to the required assessments for all participants listed in Table 1.*			
HBV Assessments	**During Screening/ Before Starting Treatment**	**During Treatment**	**EOT**
HBV-related liver imaging[1]	X	X	X
HBV DNA testing[2]	X	X	X
Prevention of HBV reactivation[3]	X	X	X

Abbreviations: DNA=deoxyribonucleic acid; EOT=end of treatment; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; LFT=liver function test.

1. For participants who test positive for HBsAg, conduct liver imaging (specific test per standard of care at local institution) to rule out/identify cirrhosis, focal hepatic lesions, and/or biliary abnormalities at baseline. Repeat liver imaging 1 year after starting treatment with belantamab mafodotin and twice yearly thereafter for as long as a participant remains on study treatment or as clinically indicated.
2. Conduct HBV DNA testing before the start of treatment with belantamab mafodotin and every 12 weeks thereafter, if LFT elevations that fulfill liver event monitoring or stopping criteria (Section 7.1.1 and Section 10.6) occur, or if there is any clinical suspicion of hepatitis reactivation.
3. For participants who test positive for HBsAg, appropriate antiviral therapy (e.g., tenofovir or entecavir) per local guidance should be started before beginning treatment with belantamab mafodotin, continue through to completion of treatment with belantamab mafodotin, and should not be stopped unless advised by a local hepatology or virology services.

Table 3 Additional Assessments for Participants with HCV

***Note**: The assessments listed in this table apply **only** to participants (those in screening and those already enrolled) who have a history of HCV; all assessments must be done as needed **in addition** to the required assessments for all participants listed in Table 1.*			
HCV Assessments	**During Screening/ Before Starting Treatment**	**During Treatment**	**After Treatment**
HCV RNA testing[1]	X	X	
Therapy for active HCV[2]	X		

Abbreviations: HCV=hepatitis C virus; LFT=liver function test; RNA=ribonucleic acid.

1. Conduct HCV RNA testing before the start of treatment with belantamab mafodotin and every 12 weeks thereafter, if LFT elevations that fulfill liver event monitoring or stopping criteria (Section 7.1.1 and Section 10.6) occur, or if there is any clinical suspicion of hepatitis reactivation.
2. Antiviral therapy should be given to participants with HCV before enrollment using an 8 (to 12) week course with curative intent per local guidance. Before enrollment, participants must have a negative HCV RNA test result after a washout period of ≥4 weeks after antiviral therapy.

Table 4 Collection Schedule for PK, sBCMA, and ADA Samples – ALL ARMS

Dose Number/Visit	Day	Arm A: 2.5 mg/kg Q3W Arm B: 1.9 mg/kg Q3W			Arm C: 2.5 mg/kg Q6W Arm D: 1.9 mg/kg Q6W Arm E: 1.9 mg/kg Q6W (symptom-based dose modification)			Window
		PK[1]	sBCMA[2]	ADA[3]	PK[1]	sBCMA[2]	ADA[3]	
1	1	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Within 0-30 mins prior to SOI
		EOI	EOI		EOI	EOI		Within 0-30 mins after EOI
		SOI + 2 h	SOI + 2 h		SOI + 2 h	SOI + 2 h		Within ±15 minutes
	2	SOI + 24 h	SOI + 24 h		SOI + 24 h	SOI + 24 h		Within ±2 hours
	4	Anytime	Anytime		Anytime	Anytime		Within ±24 hours
	8-15	Anytime	Anytime		Anytime	Anytime		1 sample anytime between Day 8-15 in the cycle, inclusive.
	22	If next dose delayed	If next dose delayed		Anytime	Anytime		Within ***72*** hours
	43				If next dose delayed	If next dose delayed		Within ***72*** hours
2	1	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Within 0-30 mins prior to SOI
		EOI	EOI		EOI	EOI		Within 0-30 mins after EOI
3	1	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Within 0-30 mins prior to SOI
		EOI	EOI		EOI	EOI		Within 0-30 mins after EOI
4	1	Pre-dose	Pre-dose		Pre-dose	Pre-dose		Within 0-30 mins prior to SOI
6	1	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	
9	1	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	
12	1	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	

Abbreviations: ADA=anti-drug antibody; AE=adverse event; cys-mcMMAF=cysteine-maleimidocaproyl monomethyl auristatin F; EOI=end of infusion; EOT=end of treatment; mAb=monoclonal antibody; PK=pharmacokinetics; Q3W=every 3 weeks; Q6W=every 6 weeks; sBCMA=soluble B-cell maturation antigen; SOI=start of infusion.

1. Plasma sample for belantamab mafodotin and cys-mcMMAF at each time point
2. Serum sample for sBCMA at each time point
   Serum sample for ADA at each time point

2. INTRODUCTION

2.1. Study Rationale

Belantamab mafodotin (GSK2857916) is a B-cell maturation antigen (BCMA)-directed antibody-drug conjugate (ADC) that is conjugated to a microtubule disrupting agent, monomethyl auristatin F (MMAF) with antitumor activity in multiple myeloma (MM) cells. Belantamab mafodotin mediates the killing of tumor cells through MMAF-induced apoptosis as well as by tumor cell lysis through antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). Clinically, single-agent belantamab mafodotin has demonstrated efficacy in participants with relapsed or refractory multiple myeloma (RRMM) who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

Efficacy has been demonstrated at 2.5 mg/kg dose of belantamab mafodotin , administered as an IV infusion once every 3 weeks (Q3W) until progressive disease (PD) or unacceptable toxicity. The Phase 2, open-label, randomized study investigating the efficacy and safety of belantamab mafodotin in participants with RRMM (DREAMM-2) [Lonial, 2020] met its primary endpoint for overall response rate (ORR) of 31% (n=97, 97.5% confidence interval [CI]: 20.8%, 42.6%). DREAMM-2 patient-reported outcomes (PROs) demonstrated that participants treated with belantamab mafodotin at the dose of 2.5 mg/kg generally maintained their health-related quality of life (HRQoL) and physical functioning while on treatment. Although vision-related activities can be limited during episodes of clinically significant ocular PRO changes, these changes are temporary and do not adversely impact overall HRQoL and physical functioning [Popat, 2020].

Although belantamab mafodotin has demonstrated efficacy in this population, ocular toxicity is common and expected, having been reported in other MMAF-containing ADCs [Parrozzani, 2020]. Belantamab mafodotin administered at the dose of 2.5 mg/kg Q3W can cause changes in the corneal epithelium resulting in changes in vision. Keratopathy (defined as corneal examination findings of microcyst-like keratopathy, which were mapped to the preferred term keratopathy per Medical Dictionary for Regulatory Activities [MedDRA]) was the most frequent ocular AE in the DREAMM-2 study (71% of participants, with 44% Grade 3 and 1% Grade 4) [Lonial, 2020]. The corneal changes often result in visual acuity changes, with 54% [51 out of 95] of participants experiencing best corrected visual acuity (BCVA) changes of any grade and 31% [29 out of 95] of Grade 3 to 4 [Farooq, 2020]. These ocular toxicities resulted in high rates of dose delays (47% [45 out of 95] dose delays due to keratopathy) and dose reductions (23% [22 out of 95] dose reductions due to keratopathy).

Alternative dosing regimens of single-agent belantamab mafodotin will be explored in Study 209628 to determine if an improved overall benefit/risk profile can be achieved by modifying the belantamab mafodotin dose, schedule, or both.

In addition to investigating alternative dosing schedules to mitigate the risk of ocular toxicity (Arms A to D), Study 209628 will also assess the use of ocular symptoms (patient-reported symptoms using the Ocular Surface Disease Index [OSDI]) and visual acuity assessments (Snellen chart or equivalent) to inform dose modification decisions and assess potential impact on the frequency of ocular examinations conducted by an eye care specialist on safety and efficacy for the participant (Arm E).

2.2. Background

2.2.1. Multiple Myeloma

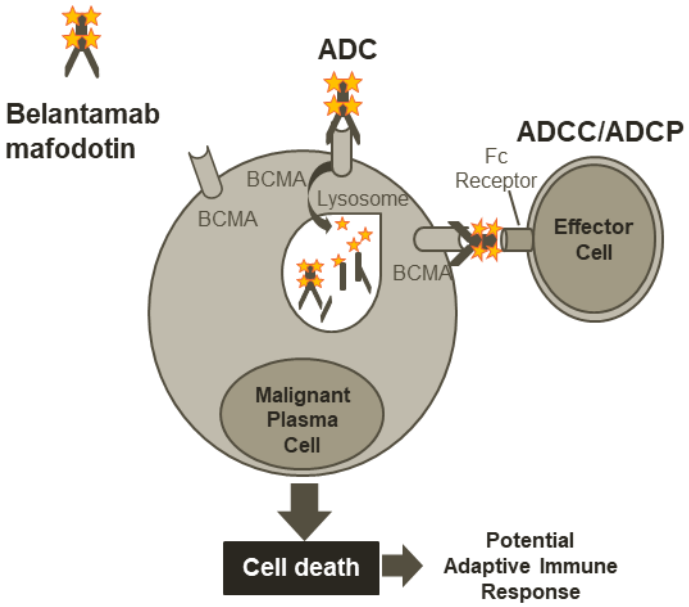
MM is an incurable malignancy and accounts for 1% of all cancers and for 10% of all hematologic malignancies [Moreau, 2017]. Worldwide, approximately 103,000 new cases are diagnosed annually, and an estimated 32,270 new cases and 12,830 deaths will have occurred in the US in 2020 Siegel, 2020].

Treatment of symptomatic or active MM includes autologous stem cell transplant and different combinations of drugs having different mechanisms of action: corticosteroids, alkylating agents (e.g., melphalan, cyclophosphamide), anthracyclines, proteasome inhibitors (e.g., bortezomib, carfilzomib, ixazomib), histone deacetylase inhibitors (e.g., panobinostat), immunomodulatory drugs (e.g., thalidomide, lenalidomide, pomalidomide), nuclear export inhibitors (e.g., selinexor) and monoclonal antibodies (mAbs) (e.g., daratumumab, isatuximab, elotuzumab) [Pinto, 2020; Rajkumar, 2020]. Although almost 100% of patients will respond to first-line therapy, most of them will experience eventual PD and require further treatment. Duration of response (DoR) and response rates decline dramatically in every subsequent line of therapy for this malignancy. In addition, despite significant advances in these treatment options, most patients with MM will ultimately develop resistance to existing therapies and die of relapse. Therefore, there is a high unmet medical need for new treatment options that can help improve clinical outcomes and overcome resistance to existing drugs for patients with MM who have progressed on existing therapies.

2.2.2. Antibody-Drug Conjugate Belantamab Mafodotin

Belantamab mafodotin binds to BCMA and kills MM cells via a multi-modal mechanism including release of cytotoxic cysteine-maleimidocaproyl monomethyl auristatin F (cys-mcMMAF) inside BCMA-expressing MM cells, thereby inducing apoptosis, enhancing ADCC and ADCP, and inducing immunogenic cell death (Figure 2) [Oca, 2019; Tai, 2014]. Exposure of dendritic cells to tumor cells undergoing immunogenic cell death is expected to result in an antigen-specific T-cell response, enhancing the immunogenic response against MM.

Figure 2 Belantamab Mafodotin Mechanism of Action



Abbreviations: ADC=antibody-drug conjugate; ADCC/ADCP=antibody-dependent cell-mediated cytotoxicity/antibody-dependent cellular phagocytosis; BCMA=B-cell maturation antigen.

2.2.3. Clinical Experience with Belantamab Mafodotin relevant for DREAMM-14

2.2.3.1. Clinical Studies

Single-agent belantamab mafodotin has demonstrated positive clinical activity with a well-defined and manageable safety profile in heavily pre-treated participants with RRMM (Q3W schedule via IV administration) in the first time in human (FTIH) study BMA117159 (DREAMM-1; NCT02064387) and the pivotal Phase 1 Study 205678 (DREAMM-2; NCT03525678).

FTIH Study BMA117159/DREAMM-1

In the FTIH DREAMM-1 study, which consisted of a dose escalation period (Part 1, n=38) and a dose expansion period (Part 2, n=35), as of the primary analysis data cutoff date of 31 August 2018, a total of 73 participants with RRMM received at least 1 dose of belantamab mafodotin [Trudel, 2019] (see also the current version of the Belantamab Mafodotin Investigator's Brochure).

As of the efficacy data cutoff date of 31 August 2018, a total of 35 participants were treated at the 3.4 mg/kg dose in Part 2 of the DREAMM-1 study. Participants were heavily pre-treated: 57% of participants had 5 or more prior lines of therapy. The ORR was 60% (95% CI: 42.1%, 76.1%) and was comprised of partial response (PR): 6%; very good partial response (VGPR): 40%; complete response (CR): 9%; and stringent complete response (sCR): 6%. The median DoR was 14.3 months (95% CI: 10.6 months, not reached [NR]). The median progression-free survival (PFS) in this population was 12.0 months (95% CI: 3.1 months, not estimable [NE]). For participants with prior

daratumumab treatment and refractory to both immunomodulatory drugs and proteasome inhibitors (n=5/13), the confirmed ORR was 39% (95% CI: 13.9%, 68.4%) and median PFS was 6.2 months (95% CI: 0.7 months, 7.9 months) [Trudel, 2019].

Phase 2 Study 205678/DREAMM-2

The Phase 2 Study 205678/DREAMM-2 ***evaluated*** the same 2 single-agent IV doses (2.5 and 3.4 mg/kg) of belantamab mafodotin administered Q3W until PD in participants who have failed at least 3 prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and who are refractory to an immunomodulatory drug and a proteasome inhibitor. A total of 194 participants received frozen drug product in the main cohort and 24 participants received 3.4 mg/kg lyophilized drug product. Primary analysis data from this study indicated no new safety signals and the profile of AEs was similar to the experience in the DREAMM-1 study for both arms. Both dose levels, 2.5 and 3.4 mg/kg, were shown to have a positive benefit/risk profile [Li, 2017; Lonial, 2020].

The final analysis of the study (data cut-off date: 31-Mar-2022) confirmed the efficacy and safety results of the primary analysis. The ORR was 32% (97.5% CI: 21.7,43.6) in the 2.5 mg/kg cohort and 35% (97.5% CI: 24.8, 47.0) in the 3.4 mg/kg cohort. More than half of responders (58% and 69%) had a response of VGPR or better. The median DoR was 12.5 months (95% CI: 4.2, 19.3) in the 2.5 mg/kg cohort and 6.2 months (95% CI: 4.8,18.7) at 3.4 mg/kg cohort. The median PFS was 2.8 months (95% CI: 1.6, 3.6) and 3.9 months (95% CI: 2.0, 5.8), respectively. The median OS was 15.3 months (95% CI: 9.9, 18.9) in the 2.5 mg/kg cohort and 14.0 months (95% CI: 10.0, 18.1) in the 3.4 mg/kg cohort.

Key safety data of the DREAMM-2 study include the following (data for 2.5 mg/kg cohort are presented first, followed by the 3.4 mg/kg cohort): Serious adverse events (SAE) occurred in 45% and 54% of participants, of which 15% and 21% were related to study treatment. SAE in >3% of participants in either cohort included pneumonia (7% and 14%), pyrexia (7% and 5%), and hypercalcemia (4% and none). Fatal SAEs related to study treatment occurred in 1% and 2% of participants, including sepsis (1%), cardiac arrest (1%), and lung infection (1%). Grade 3 or 4 AEs related to study treatment were reported in 58% and 64% of the participants. The most common treatment-related Grade 2 AEs reported were keratopathy (59% and 64%), thrombocytopenia (14% and 27%), vision blurred (13% and 18%), infusion-related reaction (13% and 5%), anemia (6% and 10%), and neutropenia (4% and 10%). The most common AEs (≥25%) were keratopathy, thrombocytopenia, anemia, nausea, vision blurred, and pyrexia. Infusion-related reactions of any Grade occurred in 21% and 16% of participants, including Grade 3 in 3% and 1%.

Permanent discontinuation due to AEs occurred in 12% of participants in both cohorts of which 9% and 5% were considered treatment-related. Keratopathy (3% in both cohorts) was the most frequent AE resulting in permanent discontinuation. Dose interruptions due to an AE occurred in 54% and 62% of participants. Dose reductions due to an AE occurred in 36% and 44% of participants. AEs which required a dose reduction in >3% of patients included keratopathy (28% and 30%) and thrombocytopenia (4% and 11%). The most common Grade 3 or 4 (≥10%) laboratory abnormalities were decreases of

lymphocytes, platelet count, hemoglobin, neutrophils, and leukocytes, and increases in gamma glutamyl transferase values.

2.2.3.2. Safety

Single-agent belantamab mafodotin was demonstrated to have a manageable safety profile in heavily pre-treated participants with RRMM. Safety data for single-agent belantamab mafodotin were pooled (data as of 20 September 2019) for the DREAMM-2 study and supportive FTIH study DREAMM-1 by treatment cohorts of 2.5 mg/kg and 3.4 mg/kg.

The most common AEs in both treatment cohorts were keratopathy (corneal epithelium changes observed on ophthalmic examination), thrombocytopenia, and anemia. The incidence of AEs, including Grade 3 to 4 AEs was comparable between belantamab mafodotin 2.5 mg/kg and 3.4 mg/kg cohorts. AEs leading to dose delays and dose reductions were less frequent in the 2.5 mg/kg cohort compared to the 3.4 mg/kg cohort (51% and 32% compared to 67% and 52%, respectively). AEs leading to permanent treatment discontinuation occurred in 10% and 11% of participants in the 2.5 and 3.4 mg/kg cohorts, respectively. More participants in the 3.4 mg/kg cohort experienced serious adverse events (SAEs) (50%) and fatal SAEs (6%) compared with the 2.5 mg/kg cohort (41% and 3%, respectively).

Single-agent belantamab mafodotin 2.5 mg/kg was selected as the recommended dose based on comparable efficacy with a more favorable safety profile (i.e., lower incidence of thrombocytopenia and neutropenia and less frequent dose delays or reductions) compared with the 3.4 mg/kg dose.

Adverse Events of Special Interest

Adverse events of special interest (AESIs) for belantamab mafodotin are corneal events, thrombocytopenia, and infusion-related reactions (IRRs), and are described as follows.

Corneal Events

Corneal events, reported in most cases as keratopathy, blurred vision, and dry eye events, are the most frequently reported AEs with belantamab mafodotin.

In the DREAMM-2 final analysis report (data as of 31 March 2022), events in the Eye disorders System Organ Class occurred in 98% of participants treated with belantamab mafodotin 2.5 mg/kg (n=95). The most common ocular AEs were keratopathy (changes in corneal epithelium identified on eye exam, with or without symptoms, 71%), blurred vision (23%), and dry eye (15%). Belantamab mafodotin can cause keratopathy with or without vision impairment. In the safety population treated with belantamab mafodotin 2.5 mg/kg (n=95), median time to onset for the first occurrence of a keratopathy event was 28 days.

Dose modifications, specifically dose delays, appear to be the most important mitigation strategy. Concomitant use of preservative-free artificial tear drops might also be beneficial, although they are not expected to prevent the occurrence of the epitheliopathy.

Participants with a history of dry eye symptoms prior to starting belantamab mafodotin were more likely to develop keratopathy compared with participants without such history. Therefore, active management of dry eye symptoms prior to and during treatment is recommended (i.e., administration of preservative-free artificial tears). Permanent treatment discontinuations due to corneal events were rare and occurred in <5% of participants.

The ocular sub-study of DREAMM-2 provided no evidence that corticosteroid eye drops are beneficial in preventing or mitigating corneal events.

Thrombocytopenia

In the DREAMM-2 final analysis report (data as of 31 March 2022), thrombocytopenic events (thrombocytopenia and platelet count decreased) occurred in 38% participants treated with belantamab mafodotin 2.5 mg/kg; severity ranging between Grade 1 and 4. Grade 3 or higher events occurred in 22% of participants, and 1% overall were considered SAEs. The median time-to-onset of the first thrombocytopenic event was 25.5 days and the median time to resolution was 21.5 days.

Most participants had a decrease from baseline in their platelet counts during the study. In general, participants who initiated treatment with lower platelet numbers tended to continue to have thrombocytopenia while on treatment with belantamab mafodotin.

Infusion-Related Reactions

IRRs are expected for biologic agents. The majority of IRRs were non-serious and Grade 1 or Grade 2 in severity. In DREAMM-2, IRRs occurred in 21% of participants receiving belantamab mafodotin 2.5 mg/kg. Symptoms of IRRs have included chills, asthenia, hypertension, lethargy, pyrexia, nausea, diarrhea, tachycardia, hypotension, and vomiting. Most IRRs occurred with the first infusion and few participants experienced IRRs with subsequent infusions.

Although not protocol-mandated, pre-medications for IRR prophylaxis (including paracetamol, antihistamines, and steroids) were administered to 26% to 27% of participants. One participant (2.5 mg/kg cohort) discontinued treatment due to IRRs (Grade 3 IRRs at first and second infusion).

2.2.3.3. Pharmacokinetics and Pharmacodynamics in Humans

The pharmacokinetics and pharmacodynamics of belantamab mafodotin (ADC, including complex with soluble BCMA [sBCMA]), total mAb (including complex), and cys-mcMMAF were investigated in 291 participants with RRMM after IV administration at doses from 0.03 to 4.6 mg/kg Q3W in Study BMA117159 (n=73) and at doses of 2.5 or 3.4 mg/kg Q3W in Study 205678 (n=218).

Maximum concentrations (Cmax) of belantamab mafodotin and total mAb were observed at or shortly after the end of infusion, while cys-mcMMAF Cmax values were generally observed on Day 2. On a molar basis, plasma concentrations of cys-mcMMAF were <1%

of belantamab mafodotin concentrations. There was limited accumulation (less than 2-fold) of belantamab mafodotin or cys-mcMMAF during subsequent cycles.

Belantamab mafodotin pharmacokinetics were well described by a linear, two-compartment population model, with a time-varying decrease in clearance (CL) in a population pharmacokinetic analysis. At Cycle 1, belantamab mafodotin had a systemic CL of 0.92 L/day, steady-state volume of distribution (Vss) of 10.8 L, and an elimination half-life of 12 days in participants with RRMM in Study 205678. Over time, CL was reduced by 28%, resulting in an elimination half-life of 14 days. The time to 50% change in CL was approximately 50 days.

No clinically significant differences in the pharmacokinetics of belantamab mafodotin or cys-mcMMAF were observed based on age (34 to 89 years), sex, race (African American/Black and White), body weight (42 to 130 kg), mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 ml/min/1.73m^2) or mild hepatic impairment (National Cancer Institute-Organ Dysfunction Working Group classification). Higher serum levels of β_2-microglobulin, immunoglobulin G (IgG), and sBCMA and lower levels of albumin are associated with more advanced MM or a higher MM disease burden. Higher baseline IgG and sBCMA levels and lower baseline albumin levels were associated with higher belantamab mafodotin CL leading to lower average concentration and concentration at the end of the dosing interval (Ctau) of belantamab mafodotin. Higher baseline IgG and sBCMA levels were associated with higher cys-mcMMAF central volume of distribution, leading to lower cys-mcMMAF Cmax.

In non-clinical studies, cys-mcMMAF had limited metabolic CL. In vitro data suggested that belantamab mafodotin and cys-mcMMAF are unlikely to perpetrate a drug-drug interaction or to be a victim of a drug-drug interaction with inhibitors or inducers of cytochromes P450. Cys-mcMMAF was an in vitro substrate of organic anion transporting polypeptides (OATP)1B1 and OATP1B3, multidrug resistance associated proteins (MRP)1, MRP2, and MRP3, a borderline substrate of bile salt export pump, and a possible substrate of P-glycoprotein (P-gp). After the administration of belantamab mafodotin to participants with RRMM, only intact cys-mcMMAF was detected in pooled human urine, with no evidence of other MMAF-related urinary metabolites.

Free sBCMA levels were measured in Study BMA117159 and Study 205678. All participants exhibited reductions in free sBCMA concentration at end of infusion compared to baseline at Cycle 1, with a return to near-baseline level by 7 days after dosing, reflecting binding of belantamab mafodotin to sBCMA. Maximum decreases ranged from 2 to 97%, which were qualitatively dose-dependent, with larger reductions in free sBCMA at higher doses.

Exposure-response analyses performed for Study 205678 and/or Study BMA117159 found that ocular safety endpoints were most strongly associated with belantamab mafodotin exposure, while efficacy endpoints had a weaker association with belantamab mafodotin exposure. Both safety and efficacy endpoints were associated with participant characteristics. Belantamab mafodotin Ctau was associated with probability of corneal events and keratopathy, and cys-mcMMAF Cmax was associated with probability of thrombocytopenia. Probability of occurrence of dry eye, blurred vision, neutropenia, and

IRR were not associated with an exposure measure. In addition, the results of the analysis of concentration against corrected QT interval (QTc) demonstrated that belantamab mafodotin or cys-mcMMAF did not have a significant effect on cardiac repolarization.

Additional information related to belantamab mafodotin clinical pharmacokinetics, pharmacodynamics, and exposure-response relationships can be found in the current version of the Investigator's Brochure.

2.3. Benefit/Risk Assessment

The following section will address the benefit/risk assessment for this study and the population to be enrolled. More detailed information about the known and expected benefits and risks and reasonably expected AEs of belantamab mafodotin may be found in the current versions of the Investigator's Brochure and the local approved product label, where applicable.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Treatment (belantamab mafodotin)		
Keratopathy (changes to the corneal epithelium, potentially resulting in vision changes)	Changes in ***the*** corneal epithelium on ocular examination have been frequently observed with belantamab mafodotin and ***were*** most commonly associated with keratopathy (changes in the corneal epithelium upon examination), blurred vision, dry eyes, photophobia and changes in visual acuity. Participants with a history of dry eye were more prone to develop changes in the corneal epithelium. Based on available follow-up data, vision returned to, or near, baseline in most cases.	• Active monitoring of the corneal epithelium and visual acuity as outlined in the SoA (Section 1.3) • Evaluation and management by an eye care professional. • Dose modification guidelines are outlined in Section 6.5
Thrombocytopenia	Belantamab mafodotin may cause transient thrombocytopenia in some participants which, for most cases, recovered between doses. In study 205678, which included participants treated with belantamab mafodotin 2.5 mg/kg, thrombocytopenia was noted in ***38***% of participants and ranged between Grade 1 to 4 in severity.	• Routine monitoring of hematologic panels as outlined in the SoA (Section 1.3) • Supportive therapy per local medical practice (e.g., platelet transfusion) • Dose modification guidelines are outlined in Section 6.5.3
Nephrotoxicity	Nonclinical safety experiments have demonstrated primary glomerular injury and tubular degeneration/regeneration (in rat and monkey). These morphologic changes were accompanied by large molecular weight proteinuria (albuminuria) and enzymuria. Single-cell necrosis of the kidney and bladder urothelium was also noted in the chronic study. The renal changes were dose-dependent and reversible. Severe tubular degeneration/regeneration and marked glomerulonephritis as a result of immune complex disease associated with ADA led to the early euthanasia of 1 monkey following 5 weekly doses of 10 mg/kg. Increased ACR (albuminuria) has been reported in participants receiving belantamab mafodotin not indicative of disease progression and, in such cases, appropriate monitoring and dose modification should be considered.	• Kidney function monitoring including albumin/creatinine ratio (ACR) • Education of participants on the need to maintain adequate urinary output • Dose modification guidelines for increased serum creatinine and urinary albumin/creatinine ratio are outlined in Section 6.5.3

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Increased Infections due to immunosuppression or neutropenia	In nonclinical studies, belantamab mafodotin has been associated with decrease in immunoglobulins in monkeys, at all doses. An increase in immunoglobulins was seen in rats (rats are not an antigen-specific species for belantamab mafodotin). Immunosuppression is frequently associated with an increased risk of infection. Serious and nonserious infections have been reported in belantamab mafodotin studies, including respiratory infections, pneumonia, and sepsis. Neutropenic events, including febrile neutropenia have been observed with belantamab mafodotin.	• Participants with an active infection are excluded. • Monitoring for infections and immediate treatment of immunosuppression according to standard practice. • Routine monitoring of hematologic panels as outlined in the SoA (Section 1.3). • Supportive therapy per local medical practice (e.g., growth factors). • Prophylactic antibiotics, per local institutional guidance, in participants with Grade 3-4 neutropenia. • Immediate hospitalization of participants with febrile neutropenia. • Dose modification guidelines are outlined in Section 6.5.3
Infusion-related Reactions (IRRs)	IRRs were reported in participants treated with belantamab mafodotin. Most IRRs were Grade 1-2 and were manageable with medical treatment.	• Close monitoring for signs of IRR • Consider premedication for IRR in participants at risk • If an IRR occurs, follow the guidance in Section 6.5.3
Pneumonitis	Nonclinical safety experiments have demonstrated the presence of progressive microscopic changes in the lungs (prominent alveolar macrophages associated with eosinophilic material; mixed perivascular/neutrophilic inflammation) in rats at all doses tested. Cases of pneumonitis, including fatal events, have been observed with belantamab mafodotin although a causal association has not been established.	• Monitoring for clinical signs and symptoms related to pulmonary toxicity. If a participant experiences new or worsening pulmonary symptoms, (e.g., cough, dyspnea) without obvious etiology, further diagnostic tests and management should be performed and further treatment with belantamab mafodotin delayed are detailed in Section 6.5.3. • An overall benefit/risk assessment should be considered for the participant prior to continuing belantamab mafodotin treatment. • Further diagnostic tests and management will be implemented immediately in cases of suspected pneumonitis as described in Section 6.5.3.

Abbreviations: ACR=albumin/creatinine ratio; ADA=anti-drug antibody; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BCMA=B-cell maturation antigen; cys-mcMMAF=cysteine-maleimidocaproyl monomethyl auristatin F; CK=creatine kinase; CT=computed tomography; IRR=infusion-related reaction; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PET=positron emission tomography; RRMM=relapsed or refractory multiple myeloma; SoA=Schedule of Activities; ULN-upper limit of normal.
Note: Refer to the current version of the Belantamab Mafodotin Investigator's Brochure for further information.

2.3.2. Benefit Assessment

Efficacy has been demonstrated at 2.5 mg/kg belantamab mafodotin administered as an IV infusion Q3W until PD or unacceptable toxicity.

Data from Study DREAMM-1, a Phase 1, FTIH, open-label, dose-escalation plus dose-expansion study of belantamab mafodotin 20 mg/mL in participants with RRMM, demonstrated substantial clinical efficacy at the dose of 3.40 mg/kg administered IV Q3W, with promising and clinically meaningful tumor response rates (see Section 2.2.3).

The data from the DREAMM-2 study further demonstrated that belantamab mafodotin has significant clinical activity in participants with heavily pre-treated MM. In this study, both dose levels evaluated, 2.5 and 3.4 mg/kg, had a positive benefit/risk profile (see Section 2.2.3).

Clinical responses were also observed in participants with dose interruptions and reductions for toxicities, hence belantamab mafodotin demonstrated remarkable clinical benefit and favorable efficacy response in participants with lower doses and/or longer dose intervals.

Based on this profile, it is reasonable to hypothesize that this study may identify an alternative belantamab mafodotin dosing regimen that reduces the risk of corneal events without jeopardizing efficacy, to improve the overall benefit/risk profile in treated participants. If any of the investigational arms are stopped due to futility at the interim analysis and participants are still on treatment, participants will be given the opportunity to switch to 2.5 mg/kg Q3W (Arm A/control regimen) with dose modifications based on the keratopathy visual acuity (KVA) scale, which has already demonstrated benefit.

2.3.3. Overall Benefit/Risk Conclusion

Considering the measures to minimize risks to participants in this study, the potential risks identified in association with belantamab mafodotin administered at alternative doses are justified by the anticipated benefits that may be afforded to participants with RRMM.

3. OBJECTIVES AND ENDPOINTS AND ESTIMANDS

Objectives and Endpoints

Objectives	Endpoints
Primary	
To examine the corneal events associated with single-agent belantamab mafodotin using alternative dosing regimens in participants with RRMM in Arms B to D compared to Arm A	Incidence rate of Grade ≥2 corneal events according to the KVA scale (see Table 8)
Secondary	
To further evaluate the corneal safety and tolerability of single-agent belantamab mafodotin in all arms	• Cumulative event rate of corneal events to Week 16 (KVA scale) • Incidence rate of corneal events by grade (KVA scale) • Exposure-adjusted incidence rate of corneal events by grade (KVA scale) • Median duration of dose delay • Percentage of participants requiring dose reductions, dose delays, and study treatment discontinuation due to corneal events (KVA scale) • Cumulative incidence of corneal events by grade (KVA scale) • Toxicity Index by assessment/visit • Duration of corneal events (KVA scale) • Percentage of time on study with corneal events (KVA scale) • Change in BCVA (ΔlogMAR)

Objectives	Endpoints
To evaluate the efficacy of single-agent belantamab mafodotin in all arms	• ORR, defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR, and sCR) • Percentage of participants with a confirmed VGPR or better (i.e., VGPR, CR, and sCR) • TTR is defined as the time between the date of randomization and the first documented evidence of response (PR or better), among participants who achieve a response (i.e., confirmed PR or better) • DoR in responders, defined as the time from first documented evidence of PR or better until PD or death due to any cause • TTP, defined as the time from randomization until the earliest date of documented PD or death due to PD • PFS, defined as the time from randomization until the earliest date of documented PD or death due to any cause • OS, defined as the time from randomization until the date of death due to any cause ***Note:*** *All efficacy endpoints are based on the 2016 IMWG Response Criteria [Kumar, 2016]*
To evaluate the overall safety and tolerability of single-agent belantamab mafodotin in all arms	• Instance of AEs (including ocular AEs) (CTCAE Version 5.0) and changes in laboratory parameters • Percentage of participants requiring dose reductions, dose delays, and study treatment discontinuation due to any AEs (CTCAE Version 5.0)
To assess the pharmacokinetics of single-agent belantamab mafodotin in all arms	Plasma belantamab mafodotin pharmacokinetic parameters, as data permit
To assess anti-drug antibodies against single-agent belantamab mafodotin in all arms	Incidence and titers of ADAs against belantamab mafodotin at each ADA time point
Exploratory	
To assess the pharmacokinetics of cys-mcMMAF in all arms	Plasma cys-mcMMAF pharmacokinetic parameters, as data permit
To evaluate the toxicity over time of single-agent belantamab mafodotin in all arms	Longitudinal ToxT AUC, as data permit
To explore exposure-response relationships between belantamab mafodotin and cys-mcMMAF exposure and clinical endpoints for efficacy and safety in all arms	Explore relationships between belantamab mafodotin exposure (e.g., Cmax, Cavg, or Ctau) and clinical endpoints (e.g., response, ocular toxicity), if data permit
To explore the relationship between biological characteristics and clinical response in all arms	Tumor- and blood-based analyses of DNA, RNA, and protein changes including, but not limited to, baseline and on-treatment sBCMA, BCMA expression on myeloma cells, and peripheral immune cell numbers and phenotypes

Objectives	Endpoints
To evaluate the safety and tolerability of single-agent belantamab mafodotin with dose modifications based on ocular symptoms, visual acuity assessments based on self-reported symptomatic AEs, and corneal findings (Arm E only)	• Changes from baseline in pre-specified symptomatic AEs and impacts as measured by the PRO-CTCAE • Changes from baseline and proportion of participants with within-participant meaningful change in self-reported ocular symptoms and related impacts as measured by OSDI • Level of overall bother/tolerability as measured by the single item FACT-GP5
To evaluate and compare changes in symptoms and HRQoL in all arms	• Frequency and severity/intensity of symptomatic AEs as measured by the PRO-CTCAE • Changes from baseline and within-participant meaningful change in self-reported ocular symptoms and related impacts as measured by the OSDI • Level of overall bother/tolerability as measured by the single-item FACT-GP5 • Change from baseline in HRQoL as measured by the EORTC-QLQ-C30 and EORTC-QLQ-MY20 • Global cancer symptoms severity and change as measured by the PGIS/PGIC
To evaluate the feasibility of dosing modifications based on ocular symptoms, visual acuity assessments, and corneal findings (Arm E) compared to dosing modifications based on KVA scale (Arm A).	The incidence of keratopathy (all grades), visual acuity changes, ocular symptoms, related impacts based on OSDI, and corneal findings in the symptom-based dose modification arm will be compared to the selected standard dose modification control arm.
To evaluate in silico individualized dosing by ISS stage or other disease characteristics at baseline using virtual treatment arms	Efficacy and safety endpoints will be calculated for virtual treatment arms created by combination of participants selected from the study treatment arms based on disease characteristics (e.g., ISS stage)
To investigate the relationship between host genetic variation and the study treatment in all arms	Effect of host genetic variation on response to study treatment including, but not limited to, belantamab mafodotin

Abbreviations: ADA=anti-drug antibody; AE=adverse event; AUC=area under the curve; BCVA=best corrected visual acuity; BCMA=B-cell maturation antigen; Cavg=average concentration; Cmax=maximum concentration; CR=complete response; Ctau=concentration at the end of the dosing interval; CTCAE=Common Terminology Criteria for Adverse Events; cys-mcMMAF=cysteine-maleimidocaproyl monomethyl auristatin F; ΔlogMAR=change in logarithm of the minimum angle of resolution; DNA=deoxyribonucleic acid; DoR=duration of response; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module; EORTC-QLQ-MY20=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma Module; FACT-GP5=Functional Assessment of Cancer Therapy – General; HRQoL=health-related quality of life; IMWG=International Myeloma Working Group; KVA=keratopathy visual acuity; MRD=minimal residual disease; NGS=next generation sequencing; ORR=overall response rate; OS=overall survival; OSDI=Ocular Surface Disease Index; PD=progressive disease; PFS=progression-free survival; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PR=partial response; PRO-CTCAE=Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; RNA=ribonucleic acid; RRMM=relapsed or refractory multiple myeloma; sCR=stringent complete response; sBCMA=soluble B-cell maturation antigen; ToxT=toxicity over time; TTP=time to progression; TTR=time to response; VGPR=very good partial response.

Primary Estimand

The primary clinical question of interest is: What is the impact on the incidence of Grade ≥2 corneal events when belantamab mafodotin is administered at alternate dose regimens relative to the DREAMM-2 established 2.5 mg/kg Q3W dosing regimen?

The estimand is described by the following attributes:

- Population: Participants with RRMM who have received 3 or more lines of prior therapy
- Endpoint: Incidence rate of Grade ≥2 corneal events according to the KVA scale
- Treatment condition: Different dosing regimen compared to control
- Intercurrent event: Not applicable
- Summary measure: Estimates of incidence rate of Grade ≥2 corneal events (KVA scale)
- Rationale: Alternative dosing regimens of single agent belantamab mafodotin will be explored in Study 209628 to determine if an improved overall benefit/risk profile can be achieved by modifying the belantamab mafodotin dose, schedule, or both.

4. STUDY DESIGN

4.1. Overall Design

Study 209628 (DREAMM-14) is a Phase 2, randomized, parallel, open-label, study of belantamab mafodotin administered as a single-agent to participants with RRMM. The study has 5 arms: Arm A, a control arm (2.5 mg/kg Q3W); Arms B through D, 3 arms with dosing alternatives; and Arm E, a fifth exploratory arm to evaluate the feasibility of dosing 1.9 mg/kg every 6 weeks (Q6W) based on ocular symptoms (patient-reported symptoms using the OSDI), visual acuity assessments (Snellen chart or equivalent), and corneal findings (KVA scale). All enrolling study sites will participate in Arms A to D; site participation in Arm E is optional and based on site interest and ability.

The treatment arms are as follows and a study schema is provided in Section 1.2.

- **Arm A: 2.5 mg/kg Q3W**
  - Rationale for Arm A: control
  - Dose modification for corneal events: see Section 6.5.1 (dose reduction to 1.9 mg/kg allowed)
- **Arm B: 1.9 mg/kg Q3W**
  - Rationale for Arm B dosing: see Section 4.3
  - Dose modification for corneal events: see Section 6.5.1 (dose reduction to 1.4 mg/kg allowed)
- **Arm C: 2.5 mg/kg Q6W**
  - Rationale for Arm C dosing: see Section 4.3
  - Dose modification for corneal events: see Section 6.5.1 (dose reduction to 1.9 mg/kg allowed)
- **Arm D: 1.9 mg/kg Q6W**
  - Rationale for Arm D dosing: see Section 4.3
  - Dose modification for corneal events: see Section 6.5.1 (dose reduction to 1.4 mg/kg allowed)
- **Arm E: 1.9 mg/kg Q6W with dose modifications based on ocular symptoms, visual acuity assessments, and corneal findings**
  - Rationale for Arm E dosing: see Section 4.4
  - Dose modification for corneal events: see Section 6.5.2 (dose reduction to 1.4 mg/kg allowed)

Participants in Arm A will use the DREAMM-2 established 2.5 mg/kg Q3W dosing regimen. Participants in Arm C will receive a starting dose at 2.5 mg/kg belantamab mafodotin, but dosing will occur at Q6W intervals. Participants in Arms B, D, and E will start at a reduced dose of belantamab mafodotin (1.9 mg/kg) and continue dosing at Q3W (Arm B) and Q6W intervals (Arms D and E). Each dosing regimen has 1 allowed dose reduction: from 2.5 mg/kg to 1.9 mg/kg in Arms A and C, E and from 1.9 mg/kg to 1.4 mg/kg in Arms B, D, and E.

Participants in all arms will have Q3W ophthalmic examination and monitoring (see Section 8.3.5.1). All ophthalmic examinations will be performed by a qualified eye care specialist (as defined in Section 10.1).

All arms except Arm E will follow dose modification due to corneal events as per the KVA scale (see Table 8). In contrast, Arm E will use a symptom-based dose modification approach before each dose, in the oncologist's office; specifically, ocular symptoms and visual acuity assessments using the OSDI and Snellen chart or equivalent, respectively (in addition to corneal examination findings according to the KVA scale), will be used to inform dose modification decisions (see Table 9). ***Note:*** *Although not determining dose modification decisions, corneal events (corneal findings and BCVA) graded per the KVA scale will still be recorded for all participants in Arm E throughout the study.*

Participants in all arms will be treated until PD (confirmed by 2016 IMWG response criteria [Kumar, 2016]), unacceptable toxicity, or death. The study consists of a screening/baseline period, a treatment period, and a post-treatment follow-up period. The primary analysis will be performed at least 9 months after the first response of the last responder (i.e., PR, VGPR, CR, and sCR) or 12 months after the last participant is randomized into Arms A to D, whichever comes first. The study duration is anticipated to be approximately 28 months.

Following 15 months after LSFD, DREAMM-14 study may move into PACT and/or a managed access program/drug supply program, to allow patients who are still receiving benefit from belantamab mafodotin to continue receiving treatment. For PACT, the collection of new data for all recruited participants who no longer receive study treatment will stop entirely and the clinical study database will be closed. A participant is considered to have completed the study if they have completed all periods of the study including the last visit. Those participants still benefiting from study treatment in the opinion of their treating physician may continue to receive study treatment in the PACT phase, and only serious adverse events (SAEs), AEs leading to treatment discontinuation, overdose, and pregnancy cases, and pre-specified ocular data will be reported directly to GSK.

The study will end when the last patient had their last visit (last subject last dose plus 70 days of AE reporting period or 15 months after LSFD, whichever comes last***)***.

4.2. Scientific Rationale for Study Design

The study objectives and endpoints will generate data to explore alternative dosing regimens of single-agent belantamab mafodotin and determine if an improved overall benefit/risk profile can be achieved by modifying the belantamab mafodotin dose, schedule, or both.

The primary endpoint, incidence of Grade ≥2 corneal events based on the KVA scale, was selected to demonstrate clinically relevant changes in ocular toxicity associated with belantamab mafodotin and takes into account not only the incidence rate of ocular toxicity but also the severity of the ocular toxicity.

Because ocular toxicity caused by belantamab mafodotin is multifactorial and complex, a range of secondary endpoints was selected to better understand and describe the different aspects of the toxicity, including features that are of clinical and participant interest, such as severity of the ocular toxicity, the duration of the event, the recurrence of events, and how this impacts vision-related activities.

4.2.1. Participant Input into Study Design

The perspective of participants was sought in the final design of this study. The sponsor's Oncology Patient Council was asked to comment on the justification for the alternate arms and to provide input on the outcomes that are most important to them.

4.3. Justification for Selected Doses and Schedules

The control arm will use belantamab mafodotin at the dosing regimen of 2.5 mg/kg IV Q3W, which has demonstrated efficacy with an ORR of 31% (97.5% CI: 20.8%, 42.6%) in heavily pre-treated participants with RRMM in the pivotal DREAMM-2 study [Lonial, 2020]. The present study, 209628 (DREAMM-14), will enroll the same population as enrolled in DREAMM-2 study. The overall objective is to explore whether alternative dosing regimens with lower dose intensity of single-agent belantamab mafodotin can improve the benefit/risk profile (i.e., can reduce the risk of corneal events without a clinically meaningful decrease in efficacy).

A longitudinal mathematical model of the time-course of corneal events (KVA scale) was developed based on data from DREAMM-2 and a longitudinal model of the time-course of efficacy (serum M protein) was developed based on data from the participants who were followed for efficacy by serum M protein in the FTIH study BMA117159 (DREAMM-1) and DREAMM-2. These models were combined with the population pharmacokinetic model to simulate efficacy and safety data over time for each candidate dosing regimen. Both studies that provided the data for the model development studied one planned dosing schedule, Q3W, with most participants receiving a starting dose of 2.5 mg/kg or higher; therefore, some of the simulated regimens are outside the data used for model development.

The candidate dosing regimens were diverse in terms of individual dose levels (from 0.83 to 2.5 mg/kg) and dosing intervals (from once weekly to every 9 weeks [Q9W]). The maximum planned dose intensity was 2.5 mg/kg Q3W. The simulations incorporated adaptive dose modifications due to corneal events in accordance with the prescribing information and treatment discontinuation due to PD based on the International Myeloma Working Group (IMWG) response criterion for serum M protein. The simulations used the same participants (DREAMM-2, n=218) for each dosing regimen to facilitate comparison of the results.

The results of the simulations were evaluated by assessing predicted reductions in corneal events endpoints based on simulated Q3W assessment visits (e.g., probability of Grade ≥2 or Grade ≥3 events on the KVA scale, proportion of time on study with Grade ≥2 events on the KVA scale), and corresponding predicted changes in efficacy (ORR, ≥VGPR). In addition, cumulative doses (planned as well as predicted in the simulations) were summarized.

Alternative dosing regimens, all with lowered dose intensity, showed a simultaneous loss of efficacy with reduction of corneal events. More frequent dosing at a lower dose with the same planned cycle dose (e.g., 0.83 mg/kg once weekly or 1.25 mg/kg on Days 1 and 8 of a three-week cycle) led to a larger relative reduction in efficacy compared to the relative reduction in corneal events and was therefore not pursued. Higher individual doses early in the dosing regimen appeared to be better from a benefit/risk perspective (e.g., initiating treatment at 2.5 or 1.9 mg/kg compared to 1.25 or 0.9 mg/kg). Longer dosing intervals early in a dosing regimen (e.g., Q9W) resulted in more early discontinuations due to PD.

Three candidate regimens were selected for evaluation in this study:

- Arm B: 1.9 mg/kg Q3W
- Arm C: 2.5 mg/kg Q6W
- Arm D: 1.9 mg/kg Q6W

Each dosing regimen has 1 allowed dose reduction: from 2.5 mg/kg to 1.9 mg/kg in Arms A and C and from 1.9 mg/kg to 1.4 mg/kg in Arms B, D, and E.

These investigational regimens were selected to include regimens that were predicted to have varying levels of reduction in corneal toxicity (rate of Grade ≥3 corneal toxicity [KVA scale]) with associated predicted reductions in ORR. In addition, they incorporate diversity in dosing approaches (e.g., lower dose at treatment initiation, longer dosing interval). Arms B and D investigate a lower initial dose (1.9 mg/kg) compared to the control arm and allow reduction to 1.4 mg/kg. Arms C and D investigate a longer dosing interval (Q6W) compared to the control arm.

Based on the planned dosing regimens, Arms B, C, and D will deliver 76%, 50%, and 38%, respectively, of the cumulative dose in the control Arm A. However, Arms B, C, and D are predicted to deliver approximately 83%, 70%, and 57%, respectively, of the cumulative dose in Arm A, based on the predicted median cumulative doses for the 4 treatment arms at 12, 24, and 36 weeks after initiation of treatment. The latter is based on simulations which incorporate dose delays and reductions for ocular toxicity (KVA scale) and treatment discontinuation for PD.

Thus, the study will investigate dosing regimens with reduced dose intensity to explore the impact of starting dose, frequency, and the combination of changing both starting dose and frequency and is expected to generate a dataset to facilitate more definitive analyses of dose and exposure factors associated with efficacy and corneal events.

4.4. Rationale for the Investigation of Symptom-Based Dose Modifications (Arm E)

Arm E of this study will assess the feasibility of "symptom-based dose modifications" where dose modification decisions of belantamab mafodotin will be determined based on ocular symptoms (patient-reported symptoms using the OSDI), visual acuity assessments (Snellen chart or equivalent), and corneal findings (KVA scale). The dosing regimen for Arm E is 1.9 mg/kg Q6W (i.e., the same as Arm D), and a standard ocular examination will be performed by an eye care specialist (Section 8.3.5.1).

Based on analyses conducted to support the interpretation of the OSDI in the context of ocular AEs associated with belantamab mafodotin, the OSDI has suggested content validity to cover the symptoms that participants frequently reported throughout qualitative interviews, moderate correlation with the KVA scale, is responsive to corneal events, and suggests an ability to distinguish between changes in grading of the KVA scale, on average. Scores for the OSDI range from 0 to 100, with higher scores meaning worse symptoms or functioning. Thresholds for meaningful change in participants with RRMM receiving BLENREP have been evaluated, with a deterioration of 8.3 for Ocular Symptoms and 16.7 for Vision-Related Functioning determined to be a meaningful change [Eliason, 2020; Popat, 2020].

The Snellen chart is an established tool for the assessment of visual acuity and is widely used in primary care, pediatric, and eye care specialist offices. Feedback from the GSK Oncology and Ophthalmology council has indicated that, with appropriate training, the oncology clinic staff will be capable of assessing visual acuity using a Snellen chart or equivalent. BCVA requires additional equipment that typically resides within an eye care specialist's clinic, not the oncologist's office. Therefore, to make this visual acuity assessment suitable for the oncologist clinic setting, visual acuity instead of BCVA will be used for the symptom-based dose modification decision assessment.

Justification for exploring the feasibility of symptom-based dose modification in this study is based on the following observations:

The original ocular monitoring plan set forth in the early belantamab mafodotin FTIH studies DREAMM-1 and DREAMM-2 was established due to the safety concern inherent with MMAF-containing ADCs; thus, a conservative and rigorous safety monitoring schedule was implemented (baseline and Q3W full eye examinations by an eye care specialist, including a slit lamp examination, to evaluate the corneal epithelium and BCVA assessment).

Key findings from the pooled safety population (n=218) in DREAMM-2 have demonstrated that keratopathy is common (76%) and mostly Grade ≤3 (7% Grade 1, 22% Grade 2, 45% Grade 3, and 0.5% Grade 4). 40% of events had resolved by the end of treatment (EOT) at the 13-month data cut, (29% with dose modification), while 52% of cases had ongoing keratopathy (15% still on treatment, 8% in follow-up, and 28% lost to follow-up or died). Nine cases of corneal epithelial erosion and ulceration have been observed across the belantamab mafodotin program and occurred after a mean of 10 cycles (range: 2 to 28 cycles).

A recent analysis of 773 eye examinations in DREAMM-2 evaluating the association of corneal epithelium changes (keratopathy) with BCVA changes showed that Grade 3 to 4 keratopathy was associated with minimal or no BCVA changes (Grade ≤1 in only 12.5% [97/773] of evaluations). When patient-reported ocular symptoms were also considered, Grade 3 to 4 keratopathy was associated with Grade ≤1 BCVA changes or ocular symptoms in only 7.5% (58/773) of evaluations. Mild or no (Grade ≤2) keratopathy was associated with Grade ≤1 BCVA changes in 59.5% (460/773) of evaluations, or in 38.8% (300/773) of evaluations if also no ocular symptoms were reported [Terpos, 2021]. Overall, Grade 3 to 4 keratopathy was found in 24.9% (193/773) of evaluations, whereas Grade 2 to 4 BCVA changes or ocular symptoms occurred more frequently in 53.7% (415/773) of evaluations. Consequently, these findings suggest that

BCVA changes and ocular symptoms could be used as a valid alternative for belantamab mafodotin dose modification decisions and, with that, potentially reduce the frequency of a full examination by an eye care specialist. Furthermore, because BCVA changes or ocular symptoms occur more frequently than Grade 3 to 4 keratopathy, a symptom-based dose modification approach could be nimbler and, with that, mitigate the occurrence of Grade 4 keratopathy. This approach would alleviate burden on participants and the healthcare system. The safety of such a symptom-based dose modifications approach will be tested prospectively in Arm E of this study.

In Arm E, participants will complete a symptom-based inquiry using the OSDI [Miller, 2010] (see Section 8.10.1.2) to assess ocular symptoms and functioning and the oncology clinic will conduct a Snellen chart or equivalent assessment to measure visual acuity, both within the oncologist's office and before dosing. In parallel, the eye care specialist will perform the same eye examination as in the control arm (Section 8.3.5.1) Q3W. The results from the OSDI and the visual acuity assessment will be used to determine the dosing decision (Go or No-Go criteria; see Table 9); however, to ensure safety is not compromised while testing the novel approach, if the eye examination raises concerns (see Section 6.5.2), dosing will be withheld and consideration for restarting at a lower dose once resolved to Grade ≤1, will subsequently be made.

Data from Arm E may warrant further exploration of the utility of symptom-based dose modifications of single-agent belantamab mafodotin.

4.5. Participant Completion

A participant will be considered to have withdrawn from the study if the participant has not died and is lost to follow-up, has withdrawn consent, at the investigator's discretion is no longer being followed, or if the study is closed/terminated.

4.6. End of Study Definition/Study Completion

The primary analysis is planned to be performed at least 9 months after the first response of the last responder (i.e., PR, VGPR, CR, and sCR) or 12 months after the last participant is randomized into Arms A to D, whichever comes first. After the primary analysis, the study will continue, and participants will remain on-treatment and continue to be followed-up. A final analysis which includes updated OS and PFS, as well as selected safety data, will be performed.

The final analysis will occur 15 months from LSFD and the DREAMM-14 study may move into PACT and/or a managed access program/drug supply program. For PACT, the collection of new data for all recruited participants who no longer receive study treatment will stop entirely and the clinical study database will be closed. As a part of PACT, participants may continue to receive belantamab mafodotin if they are gaining clinical benefit as assessed by the investigator until they meet any protocol-defined treatment discontinuation criteria. Although the clinical study database will be closed at the time of the final data cutoff, the study remains open until all participants discontinue study treatment and complete the 70-day safety follow-up and the end of study definition is reached. Only SAEs, overdose, and pregnancy cases, and prespecified ocular data will be reported directly to the GSK.

Dispensing of study treatment following 15 months after LSFD may utilize a manual resupply option, and drug accountability assessment will be performed at the site. All participants will be monitored and receive follow-up care in accordance with standard local clinical practice. For participants who do continue to receive belantamab mafodotin beyond the time of the final data cut-off, investigators will continue to report all SAEs, overdose, and pregnancy cases up to 70 days after last dose of study treatment, and pre-specified ocular data (see SRM) will be reported until resolution unless the event is considered by the investigator to be unlikely to resolve or the participant is lost to follow-up, in accordance with Section 8.4.1. Additionally, any SAE and pre-specified ocular event that is ongoing at the time of the final data cut-off must be followed up to resolution unless the event is considered by the investigator unlikely to resolve or the participant is lost to follow-up.

The end of study is defined when the last participant had their last visit (last participant last dose plus 70 days of SAE reporting period) or 15 months after LSFD, whichever comes last. A participant is considered to have completed the study if they have completed all periods of the study including the last visit. GSK retains the right to request additional information for any participant with ongoing AE(s)/SAE(s)/ocular events at the end of the study, if judged necessary.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

5.1.1. Age

1. Participant must be 18 years of age inclusive (or the legal age of consent in the jurisdiction in which the study is taking place; see Section 10.7) at the time of signing the Informed Consent Form (ICF).

5.1.2. Type of Participant and Disease Characteristics

2. Participant has Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (see Section 10.8).
3. Participant has a histologically or cytologically confirmed diagnosis of MM as defined by IMWG criteria [Rajkumar, 2016], and
   a. Has undergone stem cell transplant or is considered transplant ineligible, and
   b. Has failed at least 3 prior lines of anti-myeloma therapies, including an anti-CD38 antibody (e.g., daratumumab) alone or in combination, and is refractory to an immunomodulatory agent (e.g., lenalidomide, pomalidomide) and a proteasome inhibitor (e.g., bortezomib, ixazomib, carfilzomib).

Note: See Section *10.3 for guidelines for the determination of the number of prior lines of therapy in multiple myeloma.*

Note: *Refractory myeloma is defined as disease that is nonresponsive while on primary or salvage therapy or progresses within 60 days of last therapy. Non-responsive disease is defined as either failure to achieve at least minimal response or development of PD while on therapy [Rajkumar, 2011].*

Note: *Failed myeloma therapy is inclusive of refractory myeloma therapy or therapy stopped due to unacceptable toxicity.*

4. Participant has measurable disease with at least one of the **following** criteria:
   a. Serum M protein ≥0.5 g/dL (≥5 g/L), **or**
   b. Urine M protein ≥200 mg/24h, **or**
   c. Serum free light chain (FLC) assay: Involved FLC level ≥5 mg/dL (≥50 mg/L) **and** an abnormal serum FLC ratio (<0.26 or >1.65)
5. Participants with a history of autologous stem cell transplant are eligible for study participation provided the following eligibility criteria are met:
   a. Transplant was >100 days before study enrollment, **and**
   b. Participant has no active infection(s), **and**
   c. Participant meets the remainder of the eligibility criteria outlined in this protocol.
6. All prior treatment-related toxicities (defined by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version 5.0) must be Grade ≤1 at the time of enrollment, except for alopecia and Grade 2 peripheral neuropathy.
7. Life expectancy of at least 6 months, in the opinion of the investigator.

5.1.3. Sex and Contraceptive/Barrier Requirements

8. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Female Participants

A female participant is eligible to participate if she is not pregnant or breastfeeding and at least one of the following conditions apply:

- Is not a woman of childbearing potential (WOCBP) as defined in Section 10.9, **or**
- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency (as described in Section 10.9) during the treatment period and for at least 4 months after the

last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.

A WOCBP must have a negative highly sensitive serum pregnancy test (as required by local regulations) within 72 hours before the first dose (Cycle 1 Day 1) of study treatment (see Section 8.3.7).

Additional requirements for pregnancy testing during and after study treatment are provided in Section 8.3.7 and the Schedule of Activities (SoA) (Section 1.3).

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

b. Male Participants

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Male participants are eligible to participate if they agree to the following conditions from the time of first dose of study treatment until 6 months after the last dose of study treatment to allow for clearance of any altered sperm:

- Refrain from donating sperm**, plus either:**
  - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent, **or**
  - Must agree to use contraception/barrier as follows: Agree to use a male condom, even if they have undergone a successful vasectomy, with female partner use of an additional highly effective contraceptive method with a failure rate of <1% per year as described in Section 10.9, when having sexual intercourse with a WOCBP (including pregnant females).

5.1.4. Informed Consent

9. Participant is capable of giving signed informed consent as described in Section 10.10 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.1.5. Other Inclusions

10. Participant meets country-specific inclusion criteria described in Section 10.7, if applicable.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

5.2.1. Medical Conditions

1. Participant has symptomatic amyloidosis, active POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes), or active plasma cell leukemia at the time of screening.
2. Participant currently has corneal epithelial disease, except nonconfluent superficial punctate keratitis (SPK).
3. Participant has evidence of active mucosal or internal bleeding.
4. Participant has presence of an active renal condition (infection, requirement for dialysis, or any other condition that could affect participant's safety). Participants with isolated proteinuria resulting from MM are eligible, provided they fulfill adequate organ function inclusion criteria (Exclusion Criteria 24).
5. Participant has any serious and/or unstable pre-existing medical condition, psychiatric disorder, or other conditions (including laboratory abnormalities) that could interfere with the participant's safety, obtaining informed consent, or compliance with the study procedures.
6. Participant has malignancies other than the disease under study are excluded, except for any other malignancy from which the participant has been disease-free for >2 years and, in the opinion of the principal investigator and GSK Medical Director, will not affect the evaluation of the effects of the study treatment on the currently targeted malignancy (MM). Participants with curatively treated non-melanoma skin cancer may be enrolled without a 2-year restriction.
7. Participant has evidence of cardiovascular risk including any of the following criteria:
    a. Evidence of current clinically significant untreated arrhythmias, including clinically significant electrocardiogram (ECG) abnormalities including second degree (Mobitz Type II) or third degree atrioventricular block, **or**
    b. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting 3 months before screening, **or**
    c. Class III or IV heart failure as defined by the New York Heart Association functional classification system (see Section 10.11).
    d. Uncontrolled hypertension.
8. Participant is a pregnant or lactating female.
9. Participant has an active infection requiring antibiotic, antiviral, or antifungal therapy.
10. Participant has known human immunodeficiency virus (HIV) infection, unless the participant can meet all of the following criteria:
    a. Established anti-retroviral therapy (ART) for ≥4 weeks and HIV viral load <400 copies/mL, **and**

b. CD4+ T cell (CD4+) counts ≥350 cells/μL, **and**

c. No history of acquired immunodeficiency syndrome-defining opportunistic infections within the last 12 months.

Note: *Consideration must be given to ART and prophylactic antimicrobials that may have a drug-drug interaction and/or overlapping toxicities with belantamab mafodotin or other combination products as relevant (Section 6.8.2).*

5.2.2. Liver Safety

11. Participants with hepatitis B virus (HBV) will be excluded unless the criteria in can Table 5 be met.

Table 5 Criteria for Determining HBV Status

Serology	Screening	During Study Treatment
HBcAb+, HBsAg-	• HBV DNA undetectable	• Monitoring per protocol (Section 1.3) • Antiviral therapy started if HBV DNA becomes detectable
HBsAg+ at screening or ≤3 months before the first dose of study treatment	• HBV DNA undetectable • Highly effective antiviral therapy started ≥4 weeks before the first dose of study treatment • Baseline imaging per protocol (Section 1.3) • Participants with cirrhosis are excluded	• Antiviral therapy maintained throughout study treatment • Monitoring and management per protocol (Section 1.3)

Abbreviations: DNA=deoxyribonucleic acid; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus.
Note: Presence of HBsAb indicating previous vaccination will not exclude a participant.

12. Participants with a positive hepatitis C antibody test result or a positive hepatitis C virus (HCV) ribonucleic acid (RNA) test result at screening or ≤3 months before the first dose of study treatment will be excluded unless the participant can meet ***one of*** the following criteria:

    d. Negative HCV RNA test result

    e. Successful antiviral therapy (usually 8 weeks duration), followed by a negative HCV RNA test result after a washout period of □4 weeks.

13. Participant has cirrhosis or current unstable liver or biliary disease per investigator assessment, defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice.

Note: *Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) is acceptable if a participant otherwise meets entry criteria.*

14. Participant has alanine aminotransferase (ALT) >2.5× upper limit of normal (ULN).

15. Participants has total bilirubin >1.5×ULN (isolated total bilirubin >1.5×ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

5.2.3. Prior/Concomitant Therapy

16. Participant has received systemic anti-myeloma therapy within ≤14 days or 5 half-lives, whichever is shorter, before the first dose of study treatment.
17. Participant has received plasmapheresis □7 days before the first dose of study treatment.
18. Participant has received systemic therapy with high dose steroids (equivalent to □60 mg prednisone daily for ≥4 days) administered to treat MM or non-MM disease within ≤14 days before the first dose of study treatment.
19. Participant has received a prior allogenic stem cell transplant.

    Note: *Participants who have undergone syngeneic transplant will be allowed, only if there is no history of graft versus host disease.*

20. Participant has used an investigational drug ≤14 days or 5 half-lives, whichever is shorter, before the first dose of study treatment **or** has received therapy with a monoclonal antibody ≤30 days before the first dose of study treatment, whichever is shorter.

    Note: *Use of monoclonal antibodies for serious conditions unrelated to multiple myeloma, such as COVID, may be permitted after consultation with the GSK Medical Director.*

21. Participant has received prior treatment with an anti-BCMA targeted therapy or has a known immediate or delayed hypersensitivity or idiosyncratic reaction to drugs chemically related to belantamab mafodotin, or any of the components of the study treatment.
22. Participant has received prior treatment with an antibody-drug conjugate.
23. Participant has received any major surgery ≤4 weeks before the first dose of study treatment. An exception may be allowed for bone stabilizing surgery after consultation with the GSK Medical Director.

5.2.4. Diagnostic Assessments

24. Participants has inadequate bone marrow reserve or organ functions as demonstrated by any of the following criteria:
    a. Absolute neutrophil count $<1.0\times10^9$/L
    b. Hemoglobin <8 g/dL
    c. Platelet count $<50\times10^9$/L
    d. Spot urine (albumin/creatinine ratio) >500 mg/g (56 mg/mmol)
    e. eGFR <30 mL/min/1.73 m^2 (as calculated by Modified Diet in Renal Disease equation, see Section 10.5)

    Note: *Laboratory results obtained during screening must be used to determine eligibility criteria. In situations where laboratory results are outside the permitted*

range, the investigator may re-test the participant and the subsequent within range screening result may be used to confirm eligibility.

Note: *Supportive care as needed, including transfusion of blood products or growth factors, before or during the study* ***is*** *allowed.*

5.3. Lifestyle Considerations

Contact lenses are prohibited for participants while they are receiving belantamab mafodotin treatment. Contact lens use may be restarted after the last dose of study treatment once a qualified eye care specialist (see Section 10.1) confirms there are no other contraindications. For Arms A to E, the use of bandage contact lenses is permitted during study treatment as directed by the treating eye care specialist.

No other lifestyle restrictions are required for participants in this study.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details (including previous treatment with the [redacted] as a reason for screen failure), eligibility criteria, any protocol deviations, and any SAEs.

Individuals identified as screen failures may be rescreened if the failure was based on elements of eligibility that may change, e.g., laboratory test results. Rescreening of a participant more than once requires discussion with the GSK Medical Director. Rescreened participants must be assigned a new unique participant number that is different from the initial number.

5.5. Criteria for Temporarily Delaying Enrollment, Randomization, or Administration of Study Treatment

Not applicable.

6. STUDY TREATMENT AND CONCOMITANT THERAPY

Study treatment is defined as any investigational treatment intended to be administered to a study participant according to the study protocol.

6.1. Study Treatments Administered

A summary of the identity and characteristics of the individual components of study treatment are included in the following sections.

6.1.1. Belantamab Mafodotin

Belantamab mafodotin will be administered intravenously over approximately 30-60 minutes at different doses in each of the 5 study arms as shown in Table 6. The dose to be administered is based on actual body weight measurement on Cycle 1 Day 1 before dosing. For subsequent dosing, if the change in body weight is ≤10% from Cycle 1 Day 1 (before dosing), the dose does not need to be recalculated. However, if the change of body weight is >10% (i.e., increased or decreased) from baseline, then the dose needs to be recalculated based on this new weight; which will become the new baseline for weight comparison at subsequent visits. The dose may be reduced to address toxicity according to protocol guidelines (Section 6.5).

Table 6 Study Arms and Treatment Administered (Belantamab Mafodotin)

Arm Name	A	B	C	D, E
Treatment Name on Label	GSK2857916 for injection, 100 mg			
Type	Biologic/drug (antibody-drug conjugate)			
Dose Formulation	Lyophilized powder in single-use vial for reconstitution			
Unit Dose Strength	100 mg/vial			
Dosage Levels	2.5 mg/kg[a] Q3W	1.9 mg/kg[b] Q3W	2.5 mg/kg[a] Q6W	1.9 mg/kg[b] Q6W
Route of Administration/ Duration	IV infusion over at least 30-60 minutes[c, d]			
Use	Control	Experimental	Experimental	Experimental
AxMP, IMP, or NIMP	IMP	IMP	IMP	IMP
Manufacturer/ Sourcing	Manufactured and provided centrally by the sponsor (GlaxoSmithKline)			
Packaging and Labeling	Study treatment will be provided as a lyophilized powder in a single vial. Each vial will be labeled as per country requirements.			
Dosing Instructions	• Reconstitute belantamab mafodotin lyophilized powder 100 mg/vial with 2.0 mL of sterile water for injection before use • Dilute belantamab mafodotin in normal 0.9% saline to the appropriate concentration for the dose. Doses of belantamab mafodotin are to be administered as an IV infusion via an infusion pump • See the current version of the Belantamab Mafodotin Investigator's Brochure for compatible administration materials			
Current Aliases	Belantamab mafodotin, BLENREP™			

Abbreviations: AxMP=auxiliary medicinal product; IMP=investigational medicinal product; NIMP=non-investigational medicinal product; Q3W=every 3 weeks; Q6W=every 6 weeks.

a. Dose reduction allowed to 1.9 mg/kg.
b. Dose reduction allowed to 1.4 mg/kg.
c. Infusions may be prolonged in the event of an infusion reaction. If multiple participants experience clinically significant infusion reactions, the infusion rate may be slowed for all future administrations of study treatment for all participants. Should this global change in infusion rate be required, it will be communicated to the sites in writing.

d. Premedication (e.g., systemic corticosteroids) is not required unless deemed medically necessary by the investigator, in which case it should be administered according to institutional recommendations.

6.2. Preparation, Handling, Storage, and Accountability

See the Pharmacy Manual and product label for further guidance on administration of belantamab mafodotin.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply**,** ***prepare*****,** or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

Precaution will be taken to avoid direct contact with the study treatment. A Material Safety Data Sheet describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure**,** ***site personnel are to*** notify the monitor, GSK Medical Director, and/or GSK study contact.

6.3. Assignment to study intervention

Methods to minimize bias in this clinical study include randomization and stratification as described in Table 7.

Table 7 Methods to Minimize Bias

Type of Study	• Open-label
Central randomization via IRT system	• This is an open-label study; therefore, no blinding of treatment identity is needed. However, to ensure study integrity, steps will be taken to restrict sponsor access to key information while the study is ongoing and prevent data aggregation, except for where specified in the protocol (i.e., IDMC, see Section 9.5.1). • Upon completion of all the required screening assessments, eligible participants will be centrally randomized using a central IRT system, RAMOS NG, by the investigator or authorized site staff. • RAMOS NG allows study sites to register and randomize participants and also records stratification information. Randomization list will be done centrally using a randomization schedule generated by the GSK Clinical Statistics Department in RandALL NG, which will assign participants in **either** a 2:2:2:2:1 ratio to Arms A to E in parallel (at sites participating in optional Arm E) **or** a 1:1:1:1 ratio to Arms A to D in parallel (at sites **not** participating in optional Arm E). ***Note:*** *For Arm E, in which dose modification decisions are informed by the results of the OSDI questionnaire, the OSDI must be available in the appropriate language in order for a participant to be randomized into this arm. If the OSDI is not available, the participant will be randomized into Arms A to D (1:1:1:1).*
Stratification	1. ISS for MM (I vs II vs III) (see Section 10.2) 2. Number of prior lines of anti-MM therapy (3 vs ≥4) (see Section 10.3)

Abbreviations: GSK=GlaxoSmithKline; IRT=Interactive Response Technology; IDMC=Independent Data Monitoring Committee; ISS=International Staging System; MM=multiple myeloma.

6.4. Study Treatment Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

6.5. Dose Modification (Dose Reductions and Dose Delays)

Arms A and C will use 2.5 mg/kg as the belantamab mafodotin starting dose, with one permitted dose reduction to 1.9 mg/kg. Arms B, D, and E will use 1.9 mg/kg as the belantamab mafodotin starting dose, with one permitted dose reduction to 1.4 mg/kg. See Section 4.3 for the rationale for the doses and schedules investigated in this study.

If the participant cannot tolerate the drug after the allowed dose reduction of belantamab mafodotin, he or she must discontinue treatment for lack of tolerability.

In case of full resolution of symptoms which lead to dose reduction and after discussing with the GSK Medical Director, further treatment at the previous dose level may be considered by the investigator.

If a dose is delayed, the participant should wait for the next scheduled dose to resume treatment. The reason for any dose delay must be documented in the participant's eCRF and clinic record. In individual cases where in the judgment of the investigator waiting a full cycle to resume treatment after delay (skipping dose) related to toxicity which has resolved would be detrimental to the participant's health and exceptional circumstances, the principal investigator should contact the GSK Medical Director to discuss an earlier restart. An earlier restart may be considered only for participants who have recovered from toxicity to Grade ≤1. The dosing with belantamab mafodotin cannot occur more frequently than every 21 days (±3-day window). In cases of dose delay, efficacy, safety, and ocular assessments must remain every 3 weeks in line with initial schedule from C1D1, which may result in 2 separate visits (1 for dosing, 1 for Q3 weekly assessments); thereafter, every effort should be made to eventually align subsequent dosing and Q3 weekly visits to the original dosing schedule (C1D1) using the visit windows. Evaluations associated with a dose would be entered into the eCRF under the next scheduled cycle.

Resuming treatment with belantamab mafodotin will be possible with or without dose reduction after the toxicity has resolved to Grade 1 or less.

6.5.1. Dose Modification for Corneal Events (Arms A to D)

Corneal toxicity in Arms A to D will be graded using the KVA scale in Table 8. Dose modification guidelines as per Table 8 will be followed accordingly.

Note: *For Arm E, while the KVA scale will* ***not*** *be used for dose modification decisions, the KVA grade* ***will be determined*** *based on the eye care specialist assessment to allow endpoint analysis.*

Table 8 KVA Scale and Dose Modification Guidelines for Corneal Toxicities for Belantamab Mafodotin Treatment for Arms A to D

Grade	Corneal Findings[a]	Change in Snellen-Equivalent BCVA[b, c]	Recommended Dosage Modifications
0	Clear cornea	First visit or no change from baseline	Start or continue belantamab mafodotin at current dose
1	Mild (nonconfluent) SPK	Visual acuity has decreased not more than 0.1 logMAR units from baseline	Start or continue belantamab mafodotin at current dose
2	Presence of peripheral confluent SPK, patchy microcyst-like deposits, peripheral subepithelial haze, or peripheral stromal opacity	Visual acuity has decreased more than 0.1 logMAR units, but not more than 0.3 logMAR units[d], from baseline and is equal to or better than 1.0 logMAR (20/200)	Withhold belantamab mafodotin until both corneal findings and visual acuity improve to Grade 1 or better and then resume at the same dose

Grade	Corneal Findings[a]	Change in Snellen-Equivalent BCVA[b, c]	Recommended Dosage Modifications
3	Presence of central confluent SPK, diffuse (confluent) microcyst-like deposits, central subepithelial haze, or central stromal opacity	Visual acuity has decreased more than 0.3 logMAR units[d] from baseline and is equal to or better than 1.0 logMAR (20/200)	Withhold belantamab mafodotin until both corneal findings and visual acuity improve to Grade 1 or better and then resume at a reduced dose
4	Corneal ulcer[e]	Visual acuity is worse than 1.0 logMAR (20/200)	**Arms A-C:** Consider permanent discontinuation of belantamab mafodotin. If continuing treatment, withhold belantamab mafodotin until both corneal findings and visual acuity improve to Grade 1 or better and then resume at a reduced dose **Arm D:** Permanently discontinue belantamab mafodotin[f]

Abbreviations: BCVA=best corrected visual acuity; KVA=keratopathy visual acuity; logMAR=logarithm of the minimum angle of resolution; SPK=superficial punctate keratitis.

a. Certain corneal findings are not considered to be related to treatment with belantamab mafodotin and are excluded from the KVA scale and dose modification criteria. These findings include the following: cataracts, macular degeneration, ocular traumatic events, retinal conditions (e.g., retinal hemorrhage, retinal vein thrombosis), and other findings that may arise as a result of pre-existing conditions.
b. Snellen-equivalent BCVA is recommended to be tested on a visual acuity chart which has an approximately equal number of letters per line and equal spacing between lines.
c. If visual acuity is worse than 1.0 logMAR (20/200) in each eye before to the first administration of belantamab mafodotin, recommended dosage modifications should be based on the corneal findings in the worst eye, not on visual acuity.
d. A 0.3 logMAR unit change is a halving of the visual angle (e.g., 20/20 to 20/40) or (20/50 to 20/100), etc.
e. Includes other corneal epithelial defects such as corneal erosions.
f. Investigators who believe that further treatment of a participant with belantamab mafodotin is warranted (i.e., no other treatment options) may submit a request to the GSK Medical Director for the participant to resume study treatment after corneal findings and visual acuity improve to Grade 1 or better. GSK will review the details of the participant's clinical status and ocular findings. If the GSK Medical Director and study team agree that further treatment with belantamab mafodotin is appropriate, the case will be escalated through the standard GSK medical governance process. If continued treatment is approved by GSK, treatment with belantamab mafodotin will be continued according to the dose modification guidelines; if not approved, the participant will be permanently discontinued from study treatment.

6.5.2. Dose Modifications Based on Ocular Symptoms, Visual Acuity Assessments, and Corneal Findings (Arm E)

To determine dosing decisions for participants in Arm E, the oncology clinic will perform, on the date of or up to 3 days before dosing, a symptom-based inquiry using the OSDI to assess ocular symptoms and impacts on vision-related activities and visual acuity assessment using a Snellen chart or equivalent. The dosing decision (Go – Criteria A, or No-Go – Criteria B; Table 9) will be based on these results, however, if any of the following conditions are identified during the ocular examination (conducted by eye care specialist), then dosing will be withheld and consideration for restarting at a lower dose once resolved to "Criteria A" will subsequently be made:

- Epithelial erosions **and/or**
- Ulceration **and/or**
- Significant sub-epithelial haze **and/or**
- Perforation

Table 9 Dose Modification Guidelines for Belantamab Mafodotin Treatment for Arm E based on OSDI, Visual Acuity, and Corneal Findings

	Clinical Visual Symptoms OSDI, Visual Acuity[a], and Corneal Findings	Belantamab Mafodotin Dose Modification[b]
Criteria A	**Conducted in Oncologist's Office:** • OSDI Q1-5 if < "Half of the time" at baseline: ≤1 category worsening • OSDI Q1-5 if ≥ "Half of the time" at baseline: no worsening • OSDI Q6-9 < "All of the time" • Visual acuity has decreased ≤0.1 logMAR units from baseline[c] **Conducted by Eye Care Specialist:** • No corneal findings of Grade ≥2 according to the KVA scale	Continue treatment at the same dose
Criteria B[e]	**Conducted in Oncologist's Office:** • OSDI Q1-5 if < "Half of the time" at baseline: ≥2 category worsening • OSDI Q1-5 if ≥ "Half of the time" at baseline: any worsening • OSDI Q6-9 = "All of the time" (unless participant baseline is "All of the time") • Visual acuity has decreased >0.1 logMAR units from baseline[c] **Conducted by Eye Care Specialist:** • Corneal findings of Grade ≥2 according to the KVA scale	Hold treatment until resolves to Criteria A, then resume treatment at 1.4 mg/kg Q6W[d] **For corneal findings of Grade 4 according to the KVA scale:** Permanently discontinue treatment[e]

Abbreviations: KVA=keratopathy visual acuity; logMAR= logarithm of the minimum angle of resolution; OSDI=Ocular Surface Disease Index; Q6W=every 6 weeks.

Note: OSDI baseline is defined as C1D1. OSDI categories include: "None of the time", "Some of the time", "Half of the time", "Most of the time", "All of the time".

a. If visual acuity baseline changes (e.g., due to cataract surgery) then the new visual acuity baseline has to be used for subsequent assessment.
b. Dose modification should be based on the most severe grade. If eyes differ in severity, the dose modification guideline should be applied based on the more severe eye.
c. Visual acuity will be assessed in both eyes with and without pinhole (i.e., 4 readings). If the reading in one eye differs with and without pinhole, the better value for that eye will be used. The findings from the eye with the largest visual acuity change from baseline will be used in the dosing decision. Note: A 0.3 logMAR unit change is a halving of the visual angle (e.g., 20/20 to 20/40); or (20/50 to 20/100), etc.
d. If any criteria are met, where "ANY" refers to each item in each bullet, i.e., each question (Q1 through Q9) should be assessed separately.
e. Investigators who believe that further treatment of a participant with belantamab mafodotin is warranted (i.e., no other treatment options) may submit a request to the GSK Medical Director for the participant to resume study treatment after corneal findings and visual acuity improve to Grade 1 or better. GSK will review the details of the participant's clinical status and ocular findings. If the GSK Medical Director and study team agree that further treatment with belantamab mafodotin is appropriate, the case will be escalated through the standard GSK medical governance process. If continued treatment is approved by GSK, treatment with belantamab mafodotin will be continued according to the dose modification guidelines; if not approved, the participant will be permanently discontinued from study treatment.

6.5.3. Dose Modification for Treatment-Related Non-Ocular Adverse Events (All Arms)

For all other non-ocular belantamab mafodotin-related toxicities Table 10 and Table 11 will be followed, with Arms A and C (starting dose 2.5 mg/kg) reducing to 1.9 mg/kg and Arms B, D, and E (starting dose 1.9 mg/kg) reducing to 1.4 mg/kg.

Table 10 Dose Modification Guidelines for Belantamab Mafodotin-Related AEs

Toxicity	Grade/ Description of Toxicity	Recommendations
Serum creatinine Graded according to NCI-CTCAE criteria	Grade 2 >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	• Repeat within 48 hours if elevation cannot be explained by concomitant sepsis, TLS, other severe condition with fever or dehydration. • If confirmed: withhold belantamab mafodotin, initiate treatment and monitoring as clinically indicated, and follow for resolution. • Discuss any further treatment with belantamab mafodotin with GSK Medical Director
	Grade 3 >3.0 x baseline; >3.0 - 6.0 x ULN Or Grade 4 >6.0 x ULN	• Provide appropriate medical treatment • If drug related, permanently discontinue treatment with belantamab mafodotin • If due to another cause (such as sepsis, or dehydration), withhold treatment with belantamab mafodotin. Upon recovery to Grade 1, restart treatment at the same dose level.

Toxicity	Grade/ Description of Toxicity	Recommendations
Spot urine (ACR)	>2000 mg/g (or 224 mg/mmol)	• Re-test (at least 7 days apart). • If not confirmed: continue treatment with belantamab mafodotin at current dose • If confirmed on re-test and no clear evidence of PD: ○ Withhold treatment with belantamab mafodotin ○ Repeat testing within 4 weeks ○ If spot urine <2000 mg/g (224 mg/mmol): may restart treatment with belantamab mafodotin with a dose reduction ○ If spot urine remains >2000 mg/g (224 mg/mmol) after 4 weeks: consider permanently discontinuing belantamab mafodotin, provide treatment as clinically indicated, and follow for resolution.
Urine dipstick	2+	• May continue treatment with belantamab mafodotin • Confirm by quantitative assessment using ACR (spot urine from first void) • If ACR >2000 mg/g at the next cycle, follow guidance for spot urine.
	≥3+	• Withhold treatment with belantamab mafodotin and follow for resolution • Perform quantitative assessment using ACR (spot urine from first void)
Thrombocytopenia (on days of dosing)	Grade 3	• **No bleeding**: continue treatment with belantamab mafodotin with 1 dose level reduction; consider reverting to previous dose once thrombocytopenia recovers to Grade ≤2 • **With bleeding**: withhold treatment with belantamab mafodotin and restart treatment after resolution with 1 dose level reduction • Consider additional supportive medical treatment (e.g., transfusion), as clinically indicated and per local practice
	Grade 4	• Withhold treatment with belantamab mafodotin; consider restarting with 1 dose level reduction after resolution or transfused to Grade ≤3, only if there is no active bleeding at time of restart • If thrombocytopenia is considered disease-related, is not accompanied by bleeding, and recovers with transfusion to >25x10^9/L, continuing treatment with belantamab mafodotin with 1 dose level reduction may be considered after discussion with the GSK Medical Director

Toxicity	Grade/ Description of Toxicity	Recommendations
Febrile neutropenia (graded according to NCI-CTCAE)	Grades 3-4 (defined as: single temperature of 38.3°C or sustained temperature of 38°C for >1 h **and** ANC <1.0x10^9/L)	• Withhold the treatment with belantamab mafodotin and immediately hospitalize participant with appropriate management, per local institutional guidance • Consider additional supportive medical treatment per local practice (e.g., growth factors) • Upon resolution, consider a dose reduction of belantamab mafodotin if neutropenia was drug-related
Neutropenia without fever (graded according to NCI-CTCAE)	Grade ≥3 (defined as ANC <1.0x10^9/L)	• If noted on Day 1 of any cycle, withhold treatment with belantamab mafodotin • Restart treatment with belantamab mafodotin at current dose once neutropenia resolves to Grade ≤2 (ANC ≥1.0x10^9/L) on Day 1 of the subsequent cycle • Administer prophylactic antibiotics, per physician discretion and local institutional guidance; consider providing growth factors. • Local guidance must be followed for hematologic monitoring, if more conservative than the protocol SoA specifications. • In cases of frequent, recurrent neutropenia (ANC <1.0x10^9/L), consider dose reduction of belantamab mafodotin by 1 level
IRR[a]	Grade 2	• Stop the infusion, provide appropriate medical treatment, and continue infusion at half the original infusion rate after resolution to Grade 0-1
	Grade 3	• Further treatment with belantamab mafodotin must be discussed with GSK Medical Director. • Treatment continuation only allowed after resolution to Grade ≤1 and with pre-medication and extension of infusion time to 2-4 h • Any future infusion must be pre-medicated
	Grade 4	• Permanently discontinue treatment with belantamab mafodotin
Pneumonitis	Grade 2	• Withhold treatment with belantamab mafodotin • Upon resolution, restart treatment with 1 dose level reduction • If participant is already at the lowest dose level, then rechallenge with the same dose must be discussed with the GSK Medical Director

Toxicity	Grade/ Description of Toxicity	Recommendations
	Grades 3-4	• Permanently discontinue treatment with belantamab mafodotin

Abbreviations: ACR=albumin/creatinine ratio; AE=adverse event; ANC=absolute neutrophil count; GSK=GlaxoSmithKline; IRR=infusion-related reaction; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PD=progressive disease; SoA=Schedule of Activities; ULN=upper limit of normal.

a. If symptoms resolve within 1 hour of stopping infusion, the infusion may be restarted at half of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise, treatment with belantamab mafodotin must be held until symptoms resolve and the participant must be pre-medicated for the next scheduled dose.

Table 11 General Dose Modification and Management Guidelines for Belantamab Mafodotin-Related AEs Not Otherwise Specified[a]

Severity	Management	Follow-Up
Grade 1	• Administer symptomatic treatment as appropriate • Continue treatment with belantamab mafodotin[a]	• Provide close follow-up to evaluate for increased severity • No dose modification necessary
Grade 2	• Administer symptomatic treatment as appropriate • Investigate etiology • Consider consulting subspecialist and/or a diagnostic procedure	*Symptoms resolved in ≤7 days:* • Continue treatment with belantamab mafodotin at the current dose after resolution *Symptoms ongoing >7 days or worsening*: • Withhold treatment with belantamab mafodotin[b] or consider dose reduction • If resolution takes >3 weeks, consult GSK Medical Director • If symptoms continue or worsen to Grade 3-4, see below
Grade 3	• Provide appropriate medical treatment • Consider Consulting subspecialist	• Delay treatment until resolution to Grade ≤1 • Consider dose reduction • Consider consultation with GSK Medical Director • **Exception**: Participants who develop Grade 3 toxicities which respond to standard medical treatment and resolve to Grade ≤1 within 48 h may continue treatment at current or reduced dose
Grade 4	• Provide appropriate medical treatment • Consider consulting subspecialist • Discuss with GSK medical director	• Withhold treatment with belantamab mafodotin • Further treatment with belantamab mafodotin only allowed on individual basis if, in discussion with GSK Medical Director, it is agreed that benefits outweigh the risks for a given participant

Abbreviations: AE=adverse event; GSK=GlaxoSmithKline.

a. Treatment-related decisions can be made based on local laboratory results if central laboratory results are not available or are delayed.

b. In case a dose is delayed, the participant should wait for the next scheduled dose to resume treatment.

6.5.4. Management of and Dose Modification for Participants with Hepatitis B Virus

- Cases of HBV are required to be managed by local hepatology or infectious disease services. If no subspecialist support is available, consultation with the GSK Medical Director is required before enrolling participants with positive HBV titers into the study.
- Participants with HBV should be monitored according to the SoA (Section 1.3).
- For participants who experience clinically significant elevations in liver chemistry, follow the liver event monitoring and stopping criteria (Section 7.1.1 and Section 10.6) and immediately evaluate the etiology, including HBV deoxyribonucleic acid (DNA) testing.

Dose modification guidelines for participants with a history of HBV who experience a reactivation of the virus (detectable HBV DNA levels) while on study treatment are provided in Table 12.

Table 12 Dose Modification Guidelines for HBV Reactivation

Toxicity	Grade/Description of Toxicity	Recommendations
HBV reactivation	Detectable HBV DNA	• **Immediately (≤1 week) consult with local specialist(s) for case review and to start or modify HBV therapy and monitoring** • **Withhold treatment with belantamab mafodotin** • **Promptly contact the GSK Medical Director. Further** treatment with belantamab mafodotin **is only allowed if agreed** by the **GSK Medical Director**. • Follow liver event monitoring and stopping criteria per protocol for elevation in liver function tests (Section 7.1.1 and Section 10.6).

Abbreviations: DNA=deoxyribonucleic acid; GSK=GlaxoSmithKline; HBV=hepatitis B virus.

6.6. Continued Access to Study Treatment after the End of the Study

Study participants who continue to benefit from study intervention beyond the final data cutoff will continue to have access to study intervention until the EOS as defined in Section 4.6. There is no planned intervention following the EOS.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

Refer to the SoA (Table 1) for follow-up assessments of participants who are to be followed for disease progression and survival after they permanently discontinue from

study treatment until the final data cutoff date and to Section 4.6 for follow-up assessments from the final data cutoff date to the EOS.

6.6.1. Continued Access to Study Treatment After the Final Data Cutoff prior to End of the Study

Participants receiving belantamab mafodotin following 15 months after LSFD, (i.e., after the final data cut-off; see Section 4.6) may continue to receive belantamab mafodotin, if in the opinion of their treating physician, they are continuing to derive clinical benefit from continued treatment. Study treatment will continue until a study discontinuation criterion (see Section 7), as assessed by the investigator, has been met.

DREAMM-14 study may move into a PACT phase where the study remains open only to provide continued access to treatment for study participants who are continuing to derive clinical benefit, and/or will continue to receive treatment via a managed access program/drug supply program.

Participants who continue study treatment in the PACT phase receive care in accordance with local standard clinical practice, and will continue to be monitored for all SAEs, AEs leading to treatment discontinuation, overdoses and pregnancy cases and pre-specified ocular data while receiving belantamab mafodotin in the PACT phase. Information relating to participant care will be recorded on participant medical records, with the exception of SAEs, AEs leading to treatment discontinuation, overdoses and pregnancy cases and pre-specified ocular data that must continue to be reported to GSK for aggregate safety reporting but will not be reported as a part of this study. Investigators will report all SAEs, AEs leading to treatment discontinuation, overdoses, and pregnancy cases until 70 days after a participant receives their last dose of study drug in accordance with Section 8.4. Pre-specified ocular data will be reported until resolution, unless the event is considered by the investigator to be unlikely to resolve or the participant is lost to follow-up. After the final data cut-off, recording and follow-up of SAEs, AEs leading to treatment discontinuation, overdoses, pregnancy cases, and pre-specified ocular data will be done via paper forms (see SRM for details). Additionally, drug accountability data will also be collected at the site and assessments will revert to the standard of care at a participant's particular site.

6.7. Treatment of Overdose

There is no specific information on overdose of belantamab mafodotin. GSK does not recommend specific treatment for an overdose of belantamab mafodotin. In the event of an overdose (defined as administration of more than the protocol-specified dose) of belantamab mafodotin, the investigator should:

- Contact the GSK Medical Director immediately.
- Evaluate the participant to determine, in consultation with the GSK Medical Director, if possible, whether study intervention should be interrupted or whether the dose should be reduced.

- Closely monitor the participant for AEs, SAEs, and laboratory abnormalities until they are resolved and belantamab mafodotin concentrations are predicted to be within the anticipated range in absence of the overdose
- Obtain an additional pharmacokinetic and serum sBCMA sample as soon as the overdose situation is recognized and contact the GSK Medical Director for further guidance with regards to additional sample collection (determined on a case-by-case basis)
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF

Decisions regarding belantamab mafodotin or administration of standard of care agents after an overdose will be made by the investigator in consultation with the GSK Medical Director based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

Participants should receive full supportive care during the study, including transfusions of blood products, growth factors, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, as appropriate.

While on study, a participant who is diagnosed with an unrelated malignancy that can be addressed by local therapy can remain on study, study treatment may be resumed after discussion with the GSK Medical Director. The participant should continue to be followed for disease progression of multiple myeloma as per the SoA.

Participants will be instructed to inform the investigator before starting any new medications from the time of first dose of study treatment until the EOT visit. Any concomitant medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded in the eCRF along with the following details:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The GSK Medical Director should be contacted if there are any questions regarding concomitant or prior therapy.

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by GSK and stored in the study file. The SRM will be updated to include this information. Any such changes will be communicated to the investigative sites in the form of a letter.

6.8.1. Ocular Supportive Care: Guidelines and Prophylactic Measures

Ocular adverse events, which commonly manifest as superficial microcystic keratopathy, have been observed with ADCs, including those conjugated to MMAF.

Further information regarding corneal events associated with belantamab mafodotin is found in Section 2.1 and Section 2.3.1; prophylactic measures are included in this section. See the SoA (Section 1.3) for guidance on required monitoring for corneal toxicity.

Study sites must establish a close collaboration with a qualified eye care specialist such as an ophthalmologist or optometrist (for qualifications see Section 10.1) who will be responsible for assessing participants while they are on-study and managing participants who develop ocular symptoms or vision changes (see Table 8 for exceptions). Management of such participants must be performed in close communication with the GSK Medical Director and the site's qualified eye care specialist. Participants will be assessed by a qualified eye care specialist such as an ophthalmologist or optometrist at screening/baseline in all arms.

6.8.1.1. Eye Drops and Cooling Eye Masks

Preservative-Free Artificial Tears

Participants in Arms A to E will receive preservative-free lubricant eyedrops to be used 4 to 8 times a day in each eye, starting on Day 1 of belantamab mafodotin until EOT. In the event of ocular symptoms (i.e., dry eyes), the use of artificial tears may be increased up to every 2 hours.

Steroid Eye Drops

Corticosteroid eye drops are not required as prophylaxis but participants in Arms A to E may use these therapeutically if clinically indicated per discretion of an eye care specialist. Allow 5 to 10 minutes between administration of artificial tears and steroid eye drops, if administered together. If steroid eye drops are deemed medically necessary and prescribed, intraocular pressure must be monitored if used for >7 days.

A qualified eye care specialist (see Section 10.1) consult is required for all participants who develop signs or symptoms of corneal events or require steroid eye drops for >7 days.

Cooling Eye Masks

While not yet clinically demonstrated, it is theoretically possible the application of a cooling eye mask during belantamab mafodotin administration, and in the first few hours after infusion, may decrease ocular side effects. Cooling eye masks may be applied to both eyes for as long as tolerated, up to 4 hours.

6.8.2. Prohibited Medications and Non-Drug Therapies

Chronic treatment with oral steroids is prohibited while a participant is on study. However, short-term (≤7 days) use of oral ***or intravenous*** steroids is allowed on study to manage acute complications related to study treatment (e.g., as prophylaxis and/or treatment of an IRR) or to treat exacerbations of chronic conditions ***or to manage an AE***. Use of inhaled steroids is allowed on study to treat exacerbations of asthma or chronic

obstructive pulmonary disease. Chronic low-dose replacement therapy (≤10 mg/day prednisolone) is allowed on study for participants with adrenal insufficiency.

Administration of live or live-attenuated vaccines is contraindicated 30 days before the first dose of study treatment and while receiving study treatment. Use of live or live-attenuated vaccines is further contraindicated for at least 70 days after the last dose of belantamab mafodotin. Killed or inactivated vaccines may be administered, however, the response to such vaccines cannot be predicted.

Other prohibited therapies include the following:

- Plasmapheresis: prohibited ≤7 days before the first dose of study treatment through the end of study
- Any other approved or investigational anti-myeloma therapy not specified in this protocol (including but not limited to immunomodulatory and anti-neoplastic drugs or proteasome inhibitors). This is inclusive of all medications with activity against multiple myeloma and medications used for other indications that have anti-myeloma properties.
- Any investigational agents other than belantamab mafodotin

Caution should be exercised when belantamab mafodotin is combined with strong inhibitors of P-gp.

Drugs that are OATP1B1/1B3 inhibitors, including the following anti-HIV and antimicrobial drugs, are prohibited unless considered medically necessary:

- Anti-HIV drugs: atazanavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
- Anti-hepatitis C virus drugs: simeprevir, telaprevir
- Antibiotics: clarithromycin, erythromycin, rifampin/rifampicin
- Antifungals: itraconazole
- Others: cyclosporine, eltrombopag, gemfibrozil

  Whenever possible, preferred alternative anti-HIV drugs and antimicrobials should be prescribed to participants who require these therapies.

See the SRM for more detailed information and a full list of prohibited concomitant medications.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole is detailed in Section 10.10.9.

7.1. Discontinuation of Study Treatment

Participants will receive study treatment until confirmed disease progression per IMWG criteria [Kumar, 2016], unacceptable toxicity (including meeting stopping criteria for liver chemistry defined in Section 7.1.1), or death.

Study treatment must be permanently discontinued for any of the following reasons:

- Disease progression, as defined by IMWG criteria [Kumar, 2016], or unacceptable toxicity
- Participant has met any of the protocol-defined safety stopping criteria
- Pregnancy

In addition, study treatment may be permanently discontinued for any of the following reasons:

- Deviation(s) from the protocol
- Request of the participant or proxy (withdrawal of consent by participant or proxy)
- Investigator's discretion
- Participant is lost to follow-up
- All or part of the study is closed or terminated

The primary reason study treatment was permanently discontinued must be documented in the participant's medical records and eCRF.

If the participant voluntarily discontinues from treatment due to toxicity, AE must be recorded as the primary reason for permanent discontinuation on the eCRF.

Once a participant has permanently discontinued from study treatment, the participant will continue to be followed until the end of study.

All participants who permanently discontinue from study treatment for any reason other than confirmed progression or death will be followed up for PFS as specified in the SoA (see Section 1.3).

Before discontinuing study treatment strictly due to disease progression, sites should contact the GSK Medical Director to confirm progression meets IMWG criteria [Kumar, 2016]. The GSK Medical Director will review the central laboratory results as well as imaging results (if applicable) to confirm progressive disease as per IMWG criteria. If progressive disease criteria are not met, the investigator retains the decision to determine if treatment should be discontinued. However, the reason for treatment

discontinuation should only be documented as disease progression if IMWG criteria for confirmed progressive disease are met.

Note: Confirmation for progressive disease require two consecutive central laboratory assessments if there is no known evidence of radiographic PD; or an imaging assessment confirming new bone lesions, definite progression of existing, or development of new, extramedullary plasmacytomas (as per IMWG criteria [Kumar, 2016]) if radiographic studies were performed.

Once a participant has permanently discontinued study treatment, the participant will not be allowed to restart study treatment.

All participants who discontinue from study treatment will have safety assessments at the time of discontinuation and EOT follow-up according to the SoA (Section 1.3).

Post-Treatment Follow-Up

All participants who permanently discontinue study treatment in the absence of PD will remain in the study and will be followed for progression according to the protocol schedule until one of the following occurs (whichever comes first):

- PD according to IMWG criteria
- New anti-myeloma therapy initiated
- Withdrawal of consent
- Loss to follow-up
- End of study (as described in Section 4.6.)
- Death

OS Follow-Up

All participants who permanently discontinue study treatment and have experienced PD or have started new anti-myeloma therapy will remain in the study and will be followed for survival and subsequent anti-myeloma therapy until one of the following occurs (whichever comes first):

- Withdrawal of consent
- Loss to follow-up
- End of study (as described in Section 4.6)
- Death

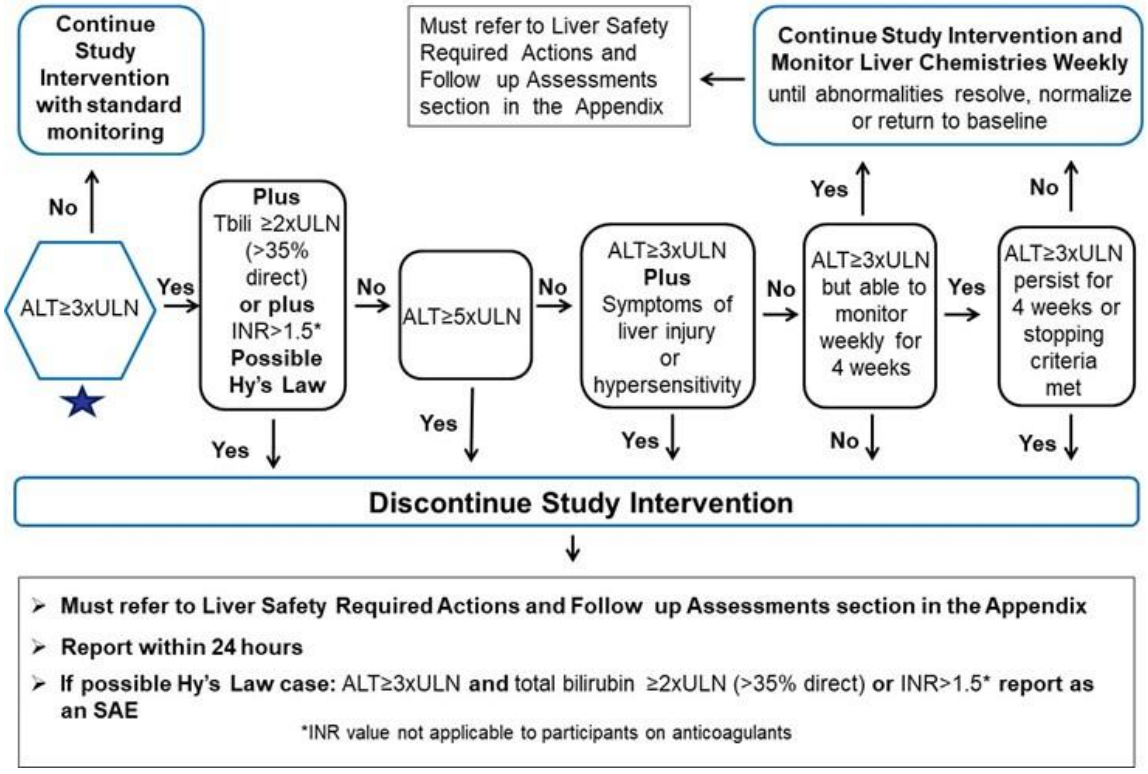
7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study treatment for abnormal liver tests is required when **either** of the following situations occur:

- A participant meets one of the conditions outlined in the liver chemistry stopping and increased monitoring algorithm (Figure 3), **or**
- In the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the investigator believes that it is in the best interest of the participant.

Figure 3 Liver Chemistry Stopping and Increased Monitoring Algorithm



Abbreviations: ALT=alanine aminotransferase; INR=international normalized ratio; SAE=serious adverse event; tbili=total bilirubin; ULN=upper limit of normal.

Refer to Section 10.6 for required liver safety actions, ***monitoring,*** and follow-up ***to assess the causality of liver events*** and to Section 10.12 for required process for study treatment restart/rechallenge if considered for a participant.

Participants who do not meet protocol-specified liver event stopping criteria but meet protocol-defined increased monitoring criteria may continue to receive study intervention with increased (i.e., weekly) liver chemistry monitoring. Refer to Section 10.6 for details regarding required increased monitoring of liver chemistry with continued study intervention.

7.1.2. Corneal Event Stopping Criteria

For participants in Arms A to D, dose modifications and stopping criteria for corneal events should be based on grading corneal events according to the KVA scale for corneal

toxicities (see Table 8). For participants in Arm E, refer to Section 6.5.2 (dose modifications) and Section 9.2.2 (safety stopping rule for unacceptable ocular toxicity).

Participants who develop Grade 4 corneal events according to the KVA scale must be discussed in detail with the treating qualified eye care specialist (as defined in Section 10.1), the GSK Medical Director, and, possibly, a third party ophthalmologist in order to determine whether the participant can be allowed to restart treatment with belantamab mafodotin or whether belantamab mafodotin should be permanently discontinued (Table 8). The decision will be documented in study files, together with individual assessment of benefit/risk.

7.1.3. Infusion-Related Reaction Management and Stopping Criteria

Premedication is not required before infusion unless deemed medically appropriate by the investigator after evaluation of IRRs. Premedication should be considered in any participant who experienced an IRR at the first or any subsequent infusion with belantamab mafodotin.

For full details regarding the management of IRRs during infusion with belantamab mafodotin, see Table 10. For IRRs of any grade/severity, immediately interrupt the belantamab mafodotin infusion and manage symptoms. Once reaction symptoms resolve, resume the infusion at a reduced rate. Premedication may be required with subsequent infusions.

A participant that experiences a Grade 4 IRR associated with belantamab mafodotin should be permanently withdrawn from the study.

7.1.4. Allergic and Anaphylactic Reaction Stopping Criteria

All participants will be monitored carefully for evidence of allergic response. A participant that exhibits signs or symptoms of severe hypersensitivity or anaphylaxis will receive appropriate medical treatment and must permanently discontinue study treatment.

7.1.5. Rechallenge

If a participant meets liver chemistry stopping criteria, do not restart/rechallenge the participant with study treatment unless **all** of the following criteria are met:

- GSK approval **is granted**, **and**
- Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) approval is obtained, if required, **and**
- Separate consent for study treatment restart/rechallenge is signed by the participant and the participant is informed of any associated risks.
- Refer to Section 10.12 for details on the restart/rechallenge process.

If GSK approval to restart/rechallenge the participant with study treatment **is not granted**, then the participant must permanently discontinue study treatment and may continue in the study for protocol-specified follow-up assessments.

7.2. Participant Discontinuation/Withdrawal from the *clinical* Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.
- At the time of discontinuing from the study, a discontinuation (EOT) visit should be conducted (Section 1.3). for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- After a participant withdraws or discontinues from the study, site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study treatment. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information. Upon the retrieval of vital status, site personnel will be responsible of entering data in EDC.
- The participant will be permanently discontinued from the study treatment and the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Withdrawn participants who have received at least 1 dose of study treatment will not be replaced.

The primary reason for participant withdrawal from the study will be documented in the eCRF based on what is described in Section 7.1.

- Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.14).

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if ***they*** repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study treatment. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and general procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Participants who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of "screen failure".
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure**s** met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Demographic and baseline assessments will include year of birth, sex, race, and ethnicity.
- Medical/medication/family history will be assessed as related to the eligibility criteria listed in Section 5.
- Survival follow-up can be conducted by chart review, telephone call, or any other form of communication as laid out in the SoA.
- Visit windows:
    - Baseline disease assessments must be completed ≤28 days before the date of randomization unless otherwise specified.
    - Screening assessments performed within the permitted time do not need to be repeated on Cycle 1 Day 1 unless otherwise specified.
    - Safety laboratory assessments completed within 72 hours of first dose do not need to be repeated on Cycle 1 Day 1.
    - Imaging must be completed ≤28 days before the date of randomization.
    - On-study Q3W and Q6W assessments have a ±3-day window.
    - After Cycle 1 Day 1, on-study ocular examinations should be performed ≤5 days before dosing. If the participant is not being dosed, ocular examinations may be performed within ±3 days of the Q3W visit.
    - EOT visits have +30 day window.
    - OS follow-up visits have a ±14-day window.

8.2. Efficacy Assessments

The following efficacy endpoints will be evaluated in all participants in the study:

- ORR, defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR, and sCR)
- Percentage of participants with a confirmed VGPR or better (i.e., VGPR, CR, and sCR)
- Time to response (TTR), defined as the time between the date of randomization and the first documented evidence of response (PR or better), among participants who achieve a response (i.e., confirmed PR or better)
- DoR in responders, defined as the time from first documented evidence of PR or better until PD or death due to any cause
- Time to progression (TTP), defined as the time from randomization until the earliest date of documented PD or death due to PD
- PFS, defined as the time from randomization until the earliest date of documented PD or death due to any cause
- OS, defined as the time from randomization until the date of death due to any cause

Efficacy assessments and/or diagnostic criteria will be evaluated during treatment by current practice guidelines for the management of RRMM [Anderson, 2016; Kumar, 2016; Moreau, 2017; Rajkumar, 2016]. These may include:

- Laboratory tests
  - Urine protein electrophoresis (on 24 hour urine collection) and urine immunofixation for urine M protein assessment
  - Serum protein electrophoresis and serum immunofixation for Serum M protein assessment
  - Serum kappa, lambda FLC, FLC ratio
  - IgG, IgM, IgA
  - IgD, IgE (only in participants with IgD/E myeloma)
  - Calcium corrected for albumin
- Bone marrow (BM) aspirate and/or biopsy at screening and to confirm CR/sCR. Additional BM testing if CR is achieved: biopsy for immunohistochemistry to confirm sCR.
- Skeletal survey at screening as clinically indicated
- Imaging for extramedullary disease (EMD) (in participants with EMD) and skeletal survey
- Physical examination (as indicated for palpable/superficial lesions)

All efficacy assessments must be performed on a calendar schedule and must not be affected by dose interruptions/delays. For post-baseline assessments, a window of ±3 days is permitted to allow for flexible scheduling.

For participants who are discontinuing study treatment due to PD, the confirmation of PD is based on two central laboratory assessments (by 2016 IMWG response criteria [Kumar, 2016]) performed from a **different blood collection** either on the same day or, if possible, within 14 days of the original date of suspected PD, preferably before institution of any new anti-myeloma therapy. If the last imaging assessment was ≥8 weeks before the participant's discontinuation from study treatment and PD has not been documented, a new disease assessment must be obtained at the time of discontinuation. For participants with PD due to EMD, confirmatory scans are not required. The laboratory parameters do not need to be repeated if the EMD is the only site of progression.

8.2.1. Response Evaluation

Clinical response assessments for RRMM will be evaluated as defined by 2016 IMWG response criteria [Kumar, 2016], as data permits, and assessed by the investigator.

8.3. Safety Assessments

Study safety assessments and their timing are summarized in the SoA (Section 1.3).

8.3.1. Physical Examinations

- A complete physical examination will include assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded. (***Note:*** *Body weight at Cycle 1 Day 1 [before dosing] will be used for dose calculation of belantamab mafodotin. See Section 6.1.1 for guidance on belantamab mafodotin dosing if weight change is observed after C1D1).*
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

Vital sign measurements to be measured after 5 minutes rest and will include systolic and diastolic blood pressure, heart rate, and temperature.

On Cycle 1 Day 1 (first infusion) dosing day, vital signs must be assessed at pre-dose (within 30 minutes before the start of infusion), within 15 minutes after end of infusion, and 1 hour post-end of infusion. On subsequent dosing days, vital signs must be assessed at pre-dose (within 30 minutes before the start of infusion) and within 15 minutes after end of infusion.

On days where vital sign time points align with blood sampling time points, vital signs should be assessed before blood samples are drawn.

On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

In general, participants must also be monitored for at least 1 hour after the completion of the infusion of belantamab mafodotin and may be discharged if considered clinically stable and all other study procedures have been completed.

In case of IRRs monitoring will be performed with higher frequency (as clinically indicated).

8.3.3. Electrocardiograms

A 12-lead ECG is obtained at screening. The ECG machine should automatically calculate the heart rate and measure PR, QRS, QT, and QTc intervals according to Fridericia's formula. No further ECGs are required, but, if obtained as part of medical care, a 12-lead ECG should be performed by qualified personnel at the site after the participant has at least a 5-minute rest.

8.3.4. Eastern Cooperative Oncology Group Performance Status

The participant's performance status will be assessed using the ECOG scale (see Section 10.8).

8.3.5. Ocular Examinations

Study sites must establish a close collaboration with a qualified eye care specialist such as an ophthalmologist or optometrist (for qualifications see Section 10.1) who will be responsible for assessing participants while they are on-study and managing participants who develop ocular symptoms or vision changes (see Table 8 for exceptions). Management of such participants must be performed in close communication with the GSK Medical Director and the site's qualified eye care specialist. Participants will be assessed by a qualified eye care specialist such as an ophthalmologist or optometrist at screening/baseline in all arms.

On-treatment ocular exams are to be performed Q3W, up to 5 days before dosing, from Cycle 2 onwards. If the participant is not being dosed, ocular examinations may be performed within ±3 days of the Q3W visit. If a participant develops vision changes or other ocular symptoms, the participant should be promptly evaluated by a qualified eye care specialist such as an ophthalmologist or optometrist (as defined in Section 10.1). In case of persistent ocular examination findings, newly developed ocular symptoms, or vision changes, the participants will have further exams until resolution (to Grade 1 or baseline), or more frequently as clinically indicated by the qualified eye care specialist.

If steroid eye drops are deemed medically necessary and prescribed, intraocular pressure must be monitored if used for >7 days.

Participants with corneal events per the KVA scale (Grade 2 or higher) at the EOT visit will be followed by a qualified eye care specialist until full resolution of ophthalmic changes (Grade 1 or better) or start a new anti-myeloma therapy, or up to 1 year (whichever comes first).

If the participant is in PFS follow-up, ocular assessments must be performed Q3W ±3 days. If participant is in OS follow-up, ocular assessments must be performed Q12W ±14 days. Additional examinations can be performed at the discretion of the eye care specialist and/or investigator.

8.3.5.1. Ocular Examinations and Procedures (Eye Care Specialist's Office, ALL Arms)

A full **screening/baseline** ophthalmic examination for **all participants** (Arms A to E) must include the following assessments for both eyes (OU):

1. Best corrected visual acuity (BCVA)
2. Documentation of manifest refraction and the method used to obtain BCVA
3. Current glasses prescription (if applicable)
4. Anterior segment (slit lamp) examination with focus on the cornea and lens, including fluorescein staining of the cornea
5. Tonometry (intraocular pressure measurement)
6. Dilated funduscopic examination

The **on-treatment and follow-up** ophthalmic examinations for **all participants** (Arms A to E) should include the following assessments for OU and will occur according to the SoA (Section 1.3):

1. BCVA
2. Documentation of manifest refraction and the method used to obtain BCVA
3. Anterior segment (slit lamp) examination with focus on the cornea and lens, including fluorescein staining of the cornea
4. Intraocular pressure measurement (if clinically indicated)
5. Dilated fundoscopic examination (if clinically indicated)

The **EOT and last follow-up** ophthalmic examination, if required, should match the screening/baseline examination.

Additional examinations should be performed at the discretion of the qualified eye care specialist.

8.3.5.2. Ocular Examinations and Procedures (Oncologist's Office, Arm E ONLY)

After ocular assessments by an eye care specialist (see Section 8.3.5.1), participants in Arm E will also undergo a visual acuity assessment in the oncologist's office (according to the SoA [Section 1.3]), in order to determine dose modification decisions per Section 6.5.2.

8.3.6. Clinical Safety Laboratory Tests

- See Section 10.13 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 70 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or GSK Medical Director.
    - In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to Section 10.14.1 and Section 10.14.2).
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory tests, as defined in Section 10.13, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).
- Local laboratory results may be used to make decisions regarding treatment or management of AEs. If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., AE/SAE or dose modification), then the results must be recorded.
- Details for the preparation and shipment of samples for central laboratory assessments are provided in the Laboratory Manual. Also refer to the Laboratory Manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.
- Before administration of the first dose of study treatment, results of laboratory assessments should be reviewed. Any laboratory test with a value outside the normal range may be repeated (before the first dose) at the discretion of the investigator.

8.3.7. Pregnancy Testing

- Refer to Section 5.1 for pregnancy testing entry criteria.
- Serum pregnancy testing should be performed at screening in WOCBP, only. The first test should be performed within 10 to 14 days before the first dose and the second test should be performed within 24 hours before the first dose. For

questionable cases (child-bearing status), follicle-stimulating hormone and estradiol (as needed in WONCPB potential only) should be performed at local laboratory.

- Pregnancy testing after screening and Cycle 1 Day 1 may be either urine or serum (as required by local regulations) and must be performed with 72 hours before dosing.
- Final pregnancy testing may be either urine or serum (as required by local regulations) and must be performed in WOCBP within 70 days after the last dose. Follow-up pregnancy assessment by telephone for WOCBP should be performed 4 months after the last dose of study treatment.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.8. Suicidal Ideation and Behavior Risk Monitoring

Not applicable.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE or SAE can be found in Section 10.14.1 and Section 10.14.2, respectively.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following-up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (see Section 7.1). This includes events reported by the participant.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.14.4 and Section 10.14.5.

8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

- All AEs and SAEs will be collected from the start of study treatment until at least 70 days after discontinuation of study treatment, regardless of initiation of a new anti-myeloma therapy or transfer to hospice, at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) will be recorded from the time a participant consents to participate in the study up to and including any follow-up.

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.14. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 13.
- Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, the investigator must record it in the medical records per the local country requirements. If the investigator considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- After the final data cutoff, participants still deriving clinical benefit in the opinion of their treating physician may continue to receive belantamab mafodotin in the PACT phase and/or will continue to receive treatment via a managed access program/drug supply program.

For participants in the PACT phase of the study, GSK will continue to collect safety information including SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases and pre-specified ocular data via paper forms which will be reported directly to GSK (see SRM for details). SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases will be reported during the PACT treatment period and for up to 70 days after last dose and pre-specified ocular data will be reported until resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up. Additionally, any SAEs that are ongoing at the time of the final data cutoff must be followed up to resolution unless the event is considered by the investigator unlikely to resolve, or the patient is lost to follow-up. Updates to these events will also occur via paper forms directly to GSK (see SRM for details). GSK retains the right to request additional information for any patient with ongoing AE(s)/SAE(s)/ocular events at EOS, if judged necessary.

Ocular Follow-Up:
For participants who continue to receive belantamab mafodotin as part of PACT:

- Ocular exam schedule during PACT treatment:
  - Participants without ocular (including corneal) examinations findings, symptoms, or vision changes when entering the PACT phase will be required to have an ocular assessment at least every 12 weeks, or as clinically indicated, until the end of treatment.
  - For participants who at the time of entering PACT have ocular (including corneal) examinations findings, symptoms or vision changes (or develop these during PACT treatment), the ocular assessment will occur every three weeks

(and prior to the next belantamab mafodotin infusion if dosing), until resolution (KVA Grade 1 or baseline). After resolution, the ocular exam assessment frequency reduces to at least every 12 weeks, or as clinically indicated, until the end of treatment.

- Ocular exam schedule after end of PACT treatment:
  - It is advised that participants with treatment-related ocular examination findings at the end of the study continue to have ocular assessments as standard of care until resolution. Note that patients who continue to receive belantamab mafodotin via commercial source of a managed access program/drug supply program should follow ocular examination guidance provided by the source/program from which they are receiving belantamab mafodotin.
  - For participants without ocular (including corneal) examination findings, symptoms, or vision changes at the end of PACT treatment no further ocular exams are required.

For participants who stopped belantamab mafodotin prior to PACT but have ongoing ocular events at the time of final study data cutoff/start of PACT:

- Participants with treatment-related ocular (including corneal) examination findings, symptoms, or vision changes at the start of PACT have ocular assessments at least every 12 weeks for up to 12 months from the end of treatment or until resolution (KVA Grade 1 or baseline), or withdrawal of consent, whichever comes first.

8.4.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-AESIs (as defined in Section 8.4.4), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.14.4.

8.4.4. Adverse Events of Special Interest

AESIs for belantamab mafodotin are corneal events, thrombocytopenia, and IRRs. Severity of corneal events will be graded using the KVA scale (provided in Table 8). Severity of thrombocytopenia and IRRs will be graded using NCI-CTCAE Version 5.0. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment are provided in Section 6.5.

8.4.5. Regulatory reporting requirements for SAEs/*AESIs*

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- For SAEs/AESIs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

Table 13 Timeframes for submitting SAE, pregnancy and other events reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours* ‡	Paper/electronic AEs Report	24 hours*	Paper/electronic AEs Report
Pregnancies	24 hours*	Paper pregnancy notification report/electronic pregnancy report	24 hours *	Paper pregnancy follow-up report/electronic pregnancy report
AESIs	24 hours** ‡	Paper/electronic AEs Report	24 hours*	Paper/electronic AEs Report

AE = adverse event; AESI = adverse event of special interest; eCRF = electronic case report form; DRE = disease-related event; PRE = population related event; SRT = Safety Review Team.

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.

**Timeframe allowed once the investigator determines that the event meets the protocol definition of an AESI

‡ Paper AEs Report will be dated and signed by the investigator (or designee). For each SAE/AESI, the investigator(s) must document in the medical notes that they have reviewed the SAE/AESI and have provided an assessment of causality.

8.4.6. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and for 4 months after the last dose of study treatment. Details of all pregnancies in female partners of male participants will be collected after the start of study treatment and for 6 months after the last dose of study treatment.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the pregnancy

(first obtain the necessary signed informed consent from the female partner if the pregnancy occurs in the female partner of a male participant). While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The pregnant participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the pregnant participant /pregnant female partner and the neonate for 6 to 8 weeks after delivery and the information will be forwarded to the sponsor. See Table 13 for reporting timeframes.
- Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the investigator will be reported to the sponsor as described in Section 8.4.5. While the investigator is not obligated to actively seek this information in former female study participants/female partners of male participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study must discontinue study treatment.

8.4.7. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.14.3 and for all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific CV section of the CRF within 1 week of receipt of a CV Event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported. Record deaths due to the disease under study in the Death eCRF. Record deaths due to reasons other than the disease under study in the standard Death Details eCRF.

CCI

[redacted]

8.4.9. Medical device deficiencies

Not applicable.

8.5. Pharmacokinetics

8.5.1. Blood Sample Collection for Pharmacokinetics

Blood samples for pharmacokinetic analysis of belantamab mafodotin (ADC) and cys-mcMMAF will be collected for all participants at the time points indicated in the SoA (Section 1.3). Alterations may be made to the sampling schedule based on the results from analyses of emerging data. Such alterations, if made, will not require a protocol amendment and will be documented in the laboratory manual.

Each pharmacokinetic sample should be collected as close as possible to the planned time relative to the administration of the drug being measured on pharmacokinetic sampling days. The actual date and time of each blood sample collection will be recorded. Details on pharmacokinetic blood sample collection including blood volumes, processing, storage, and shipping procedures are provided in the SRM.

sBCMA samples should be collected at all pharmacokinetic time points as close as possible to the belantamab mafodotin pharmacokinetic sample.

All pharmacokinetic, sBCMA, and ADA samples once collected can be analyzed if the sample date and time have been recorded.

Pharmacokinetic and accompanying sBCMA sample collection may be terminated when sufficient data have been collected.

8.5.2. Pharmacokinetic Sample Analysis

Plasma pharmacokinetic sample analysis will be performed under the control of GSK. Concentrations of belantamab mafodotin and cys-mcMMAF will be determined in plasma samples using the currently approved bioanalytical methodology. The bioanalytical site will be detailed in the relevant sample processing documents (e.g., Central Laboratory Worksheet [CLW]) and raw data will be archived at the bioanalytical site for the specified portion of the retention period before being returned to the GSK archives for the reminder of the retention period.

8.6. Genetics

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Information regarding genetic research is included in Section 10.15. In approving the clinical protocol, the IRB/IEC and, where required, the applicable regulatory agency, are also approving the genetic research described unless otherwise indicated. Where required by regulatory authorities, approval of the genetic assessments can occur after approval is obtained for the rest of the study. In that case, written approval will indicate that approval of the genetic assessments is being deferred and the study, except for genetic assessments, can be initiated. If genetic assessments are not approved, they will not be conducted.

8.7. Biomarkers/Translational Research

Biomarker research is part of this study and will involve peripheral blood (serum and plasma), BM, and tumor biopsies. sBCMA and BCMA expression in tumor cells will be analyzed and the relationship of these biomarkers relative to response to belantamab mafodotin will be assessed. Additionally, any blood, serum, plasma, and BM samples collected during this study may be used to measure novel biomarkers to identify factors associated with the biological and clinical responses to belantamab mafodotin. If relevant, this approach may be extended to include the identification of biomarkers associated with AEs. Unless stated otherwise, these investigations may be performed irrespective of whether a response to belantamab mafodotin is observed. The novel biomarkers may involve DNA analysis, RNA analysis, cell analysis (T, B, and natural killer cells flow panel), and/or protein analysis.

Samples will be collected at the time points indicated in the SoA (Section 1.3). The sample collection strategy may be adjusted on the basis of emerging data from this study or other studies involving belantamab mafodotin in order to ensure optimal evaluation of any potential biomarkers. Additionally, novel biomarkers may also be incorporated, as data warrant. These analyses may include but not be limited to:

- BCMA expression by immunohistochemistry and/or DNA/RNA analysis performed on BM biopsies and/or aspirates
- Measurements of the serum levels of sBCMA
- Soluble factors
- Parallel blood analyses that may evaluate effects on natural killer or other immune cell populations

8.7.1. Soluble B-Cell Maturation Antigen

The BCMA receptor undergoes gamma-secretase mediated cleavage, leading to release of the BCMA extracellular domain as sBCMA into circulation [Laurent, 2015].

sBCMA will be measured in all treatment arms of this study.

sBCMA samples should be collected at all pharmacokinetic time points for all participants, according the SoA (Section 1.3).

Serum sBCMA sample analysis will be performed under the control of GSK using the currently approved analytical methodology. The bioanalytical site will be detailed in the relevant sample processing documents (e.g., CLW) and raw data will be archived at the analytical site for the specified portion of the retention period before being returned to the GSK archives for the reminder of the retention period.

8.7.2. Tumor Biomarker Analysis

While BCMA expression is present in all MM cells, there is some cell to cell variability and differences in membranous and cytosolic localization patterns. Therefore, it is important to determine if there is any association between the expression levels of BCMA on MM cells and clinical responses. BM samples will be collected during this study at the time points indicated in the SoA (Section 1.3).

BCMA expression analysis to be performed preferably on a BM biopsy sample. Any remaining aspirate and/or biopsy sample will be used for biomarker research (which may include immune cell characterization and/or profiling and/or DNA/RNA analyses).

8.7.3. RNA Transcriptome Research

RNA expression studies may be conducted using RNA sequencing, quantitative reverse transcriptase-polymerase chain reaction and/or alternative equivalent technologies which can facilitate the simultaneous measurement of the relative abundances of RNA species resulting in an RNA expression profile for BM or other samples. The RNAs assayed may be those involved with the following:

1. The pathogenesis of MM
2. The absorption, distribution, metabolism, or excretion of belantamab mafodotin
3. The participant's response to belantamab mafodotin.

In addition, continuing research may identify other proteins or regulatory RNAs that may be involved in the response to belantamab mafodotin or the pathogenesis of MM. The RNAs that code for these proteins and/or regulatory RNAs may also be studied. This would enable the evaluation of changes in RNA expression profiles that may correlate with biological responses relating to MM and the action of belantamab mafodotin.

The samples may also be used to confirm findings by application of alternative technologies.

8.8. T, B, and Natural Killer Cells

Whole blood will be collected and analyzed by flow cytometry for percentage and absolute counts of monocytes, T, B, and natural killer cells, as well as the expression of activation markers on these cell types to help inform on participant immune status.

8.9. Immunogenicity Assessments

Serum samples for the analysis of anti-belantamab mafodotin antibodies will be collected before each belantamab mafodotin infusion (at dose 1, 2, 4, 6, 9 and 12, see Table 4). These samples will be tested by the sponsor or sponsor's designee.

Anti-belantamab mafodotin antibody samples will be tested for anti-belantamab mafodotin antibodies using a tiered-testing scheme consisting of validated screening, confirmation, and titration assays. Briefly, all samples will be tested in the screening assay. Samples that screen positive are considered potentially positive and will be tested for specificity in a confirmation assay. Finally, titer values will be obtained for confirmed positive samples using a titration assay. The sample results (e.g., positive or negative) and titer values (positive samples only) will be reported. Samples that test positive for anti-belantamab mafodotin antibodies may be further characterized in a validated neutralizing antibody assay to determine the neutralizing activity of the antibodies.

The detection and characterization of antibodies to belantamab mafodotin will be performed using validated assays. The anti-belantamab mafodotin antibody assay was designed to detect antibodies to belantamab mafodotin, the unconjugated monoclonal antibody, and the linker-payload portion of belantamab mafodotin. Anti-belantamab mafodotin antibody samples will be disposed 3 months after final approved results are provided to the clinical study team or its designee or upon documented study termination.

Immunogenicity sample analysis will be performed under the control of GSK, using the currently approved analytical methodology. The analytical site will be detailed in the relevant sample processing documents (e.g., CLW) and raw data will be archived at the analytical site for the specified portion of the retention period before being returned to the GSK archives for the reminder of the retention period.

Sample collection for immunogenicity (ADA) assessment may be terminated when sufficient data have been collected.

8.10. Patient-Reported Outcomes

PROs should be done at the start of the visit before any assessments and before any results are discussed. All participants will complete the self-administered version of each questionnaire, unless their vision or other factors prevents them from being able to complete the questionnaire on their own. Participants who are not able to complete the questionnaire on their own (e.g., vision problems) and so require assistance, should have the PROs administered to them in an interview-administered format. If the interviewer-administered format is used, the questionnaires should be read to the participants verbatim, and participant responses should be recorded directly without any interpretation. For any additional assessments conducted via telephone (either during

participation in the treatment period or during follow-up), the interview-administered format should be used.

The questionnaires will be administered to participants in different regions based on the availability of translated versions. For Arm E, in which dose modification decisions are informed by the results of the OSDI questionnaire, the OSDI must be available in the appropriate language in order for a participant to be randomized into this arm.

8.10.1. Treatment and Tolerability-Related Patient-Reported Outcomes

Three treatment-related PRO questionnaires will be performed in this study. More details about all participant questionnaires can be found in the SRM.

8.10.1.1. Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

The PRO-CTCAE is a PRO measure developed to evaluate symptomatic toxicity in participants in oncology clinical studies [Basch, 2014]. The PRO-CTCAE was designed to be used as a companion to the CTCAE, the standard lexicon for AE reporting in oncology studies. The PRO-CTCAE includes an item library of 124 items representing 78 symptomatic toxicities drawn from the CTCAE. The PRO-CTCAE provides a systematic yet flexible tool for descriptive reporting of symptomatic treatment side effects in oncology clinical studies. Up to 3 attributes are asked depending upon the relevance to the question, including frequency, severity, and interference with usual or daily activities. The recall period is “over the past 7 days”. In the present study, a selection of items from the PRO-CTCAE version 1.0 item library will be administered to participants. These items are mouth sores, problems tasting food, decreased appetite, nausea, vomiting, constipation, diarrhea, pain in abdomen, shortness of breath, cough, itchy skin, hives, numbness/tingling in hands or feet, blurry vision, flashing lights, floaters, watery eyes, fatigue/lack of energy, pain/burning with urination, bruising, chills, and nosebleeds.

8.10.1.2. Ocular Surface Disease Index (OSDI)

The OSDI is a 12-item questionnaire designed to assess both the frequency of dry eye symptoms and their impact on vision-related functioning [Dougherty, 2011; Schiffman, 2000]. The OSDI has demonstrated good reliability, validity, sensitivity, and specificity, and can be used as a complement to other clinical and participative measures of dry eye disease by providing a quantifiable assessment of dry eye symptom frequency and the impact of these symptoms on vision related functioning. The OSDI includes a Total Score and 3 domain scores of Ocular Symptoms (sensitivity to light, gritty eyes, painful or sore eyes, blurred vision, poor vision), Vision-Related Functioning (reading, driving at night, working on computer/ATM, watching TV) and Environmental Triggers (windy conditions, dry areas, air conditioning), with a recall period of “the last week”. The response options are based on frequency: “none of the time”, “some of the time”, “half of the time”, “most of the time”, and “all of the time”.

8.10.1.3. Functional Assessment of Cancer Therapy – General Population (FACT-GP5)

The FACT-G (now in version 4) is a 27-item compilation of general questions divided into 4 primary quality of life domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being [Cella, 1993]. It is considered appropriate for use with participants with any form of cancer and has also been used and validated in other chronic illness condition (for example, HIV/AIDS and multiple sclerosis) and in the general population (using a slightly modified version).

The FACT-GP5 item is a single item from the FACT-G, which assesses how bothersome the side effects of treatment are for participants with cancer. The recall period is the past 7 days, and the item has a 5 category response scale ranging from "0=Not at all" to "4=Very much". This item is being included to assess the overall tolerability of treatment from the participant's perspective.

8.10.2. Health-Related Quality of Life

Three HRQoL assessments will be performed in this study. More details about all participant questionnaires can be found in the SRM.

8.10.2.1. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-Item Core Module (EORTC-QLQ-C30)

The EORTC-QLQ-C30 is a 30-item questionnaire containing both single- and multi-item measures [Aaronson, 1993]. These include 5 functional scales (Physical, Role, Cognitive, Emotional, and Social Functioning), 3 symptom scales (Fatigue, Pain, and Nausea/Vomiting), a Global Health Status/quality of life scale, and 6 single items (Constipation, Diarrhea, Insomnia, Dyspnea, Appetite Loss, and Financial Difficulties). Scores for each scale and single-item measure are averaged and transformed linearly to a score ranging from 0 to 100. A high score for functional scales and for Global Health Status/quality of life represent better functioning ability or HRQoL, whereas a high score for symptom scales and single items represents significant symptomatology [Proskorovsky, 2014].

8.10.2.2. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma Module (EORTC-QLQ-MY20)

The EORTC-QLQ-MY20 is a supplement to the EORTC-QLQ-C30 instrument used in people with MM [Aaronson, 1993; Cocks, 2007]. The module comprises 20 questions that address four myeloma-specific HRQoL domains: Disease Symptoms, Side Effects of Treatment, Future Perspective, and Body Image. Three of the four QLQ-MY20 domains are multi-item scales: Disease Symptoms (includes bone aches or pain, back pain, hip pain, arm or shoulder pain, chest pain, and pain increasing with activity); Side Effects of Treatment (includes drowsiness, thirst, feeling ill, dry mouth, hair loss, upset by hair loss, tingling hands or feet, restlessness/agitation, acid indigestion/heartburn, and burning or sore eyes); and Future Perspective (includes worry about death and health in the future,

and thinking about illness). The Body Image scale is a single-item scale that addresses physical attractiveness.

As with the EORTC-QLQ-C30, EORTC-QLQ-MY20 domain scores are averaged and transformed linearly to a score ranging from 0 to 100. A high score for Disease Symptoms represents a high level of symptomatology or problems [Proskorovsky, 2014].

8.10.2.3. Patient Global Impression Items

The Patient Global Impression of Severity (PGIS) assesses global impression of symptoms severity at baseline and subsequent time points. The second question, the Patient Global Impression of Change (PGIC) serves to rate the global change in symptoms at subsequent time points. In addition to evaluating symptom severity and change, these questions serve as anchors to establish thresholds of clinically meaningful change for the questionnaires in the study [Guy, 1976].

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

The primary focus of this study will be on identifying a dosing regimen with the potential to minimize the risk of ocular toxicity without a qualitatively clinically meaningful impact on efficacy, based upon the safety, clinical activity, and pharmacokinetic profiles.

9.1. Statistical Hypothesis

No formal hypothesis testing will be performed in this study.

9.2. Sample Size Considerations

Approximately 40 participants will be enrolled into Arms A [control], B, C, and D, each, and approximately 20 participants will be enrolled into Arm E (N=180). The sample size and associated operating characteristics were evaluated via simulations.

An interim analysis is planned when approximately 15 participants each in Arms A to D have been enrolled and have received 2 doses of study treatment with 1 disease assessment following the second dose or confirmed PD per IMWG [Kumar, 2016] or death. Any arm in Arms B to D with ≤2 responders will be discontinued from further enrollment and arms with ≥3 responders will continue enrollment (see Section 9.5).Enrollment will continue as analysis is being performed. If Arm D is stopped due to futility, Arm E will also be stopped. If Arms B, C, D, or E are stopped due to futility, participants will be given the opportunity to switch to 2.5 mg/kg Q3W (Arm A/control regimen), provided the participant has not experienced PD; the data collected from participants after switching will not be included in the primary analysis and may be analyzed separately.

***Note**: Enrolled means a participant's, or their legally authorized representative's, agreement to participate in a clinical study after completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but who do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn before participating in any study activity after screening.*

9.2.1. Sample Size Assumptions: Primary Endpoint

Based on the Grade ≥2 incidence rate observed in the 95 participants in the 2.5 mg/kg Q3W arm of the DREAMM-2 study (based on the 20 September 2019 data cutoff date), the prior of the incidence rate in Arm A is assumed to follow a Beta (6.32, 3.68) distribution with a mean of 63.2% and an effective sample size of 10, which is down-weighted so that the prior is informative yet data to be collected in this study will still dominate the conclusion. The prior of those of Arms B to D are assumed to follow a Beta (0.41, 0.59) distribution with a mean of 41%, which corresponds to a 35% relative reduction from the incidence rate of 63.2%, and an effective sample size of 1.

The primary analysis will be performed at least 9 months after the first response of the last responder (i.e., PR, VGPR, CR, and sCR) or 12 months after the last participant is randomized into Arms A to D whichever comes first.

The operating characteristics in Table 14 are summarized based on 40 participants per arm. The acceptance criterion is the posterior probability of the difference in incidence rates between the control and test arm being >0.17 is >0.7. The difference of 0.17 is chosen such that there is a reasonable chance of identifying an arm with improved safety in this study and the probability of falsely identifying an arm is well controlled. When the true incidence rates of Grade ≥2 are 63% and 40% in the control and test arms respectively, the probability of meeting acceptance criterion is 80%. When the true differences in incidence rates are 0, the probability of meeting acceptance criterion is within 4%, suggesting that the probability of falsely identifying an arm that is not actually safer than the control is very well controlled. In general, when there are 40 participants per arm, the simulation has shown good operating characteristics. For the primary analysis, the arm that meets the interim threshold based on efficacy and has the highest posterior probability of meeting the acceptance criterion for safety will be identified. The lower 95% CI of the difference in incidence rates between the identified arm and control Arm A will need to be >2.5% in order for the identified arm to be declared to show an improved toxicity profile compared with that of the control arm.

Table 14 Study Safety Operating Characteristics

Incidence rate of Grade ≥2 corneal event (KVA scale)		Probability of identifying an arm that meets acceptance criterion: *P (incidence rate of control – incidence rate of test arm >0.17) >0.7*
Control Arm	Test Arm	
0.5	0.1	>0.99
0.5	0.2	0.95
0.5	0.3	0.67
0.5	0.35	0.42
0.5	0.4	0.23
0.5	0.45	0.1
0.5	0.5	0.04
0.632	0.1	>0.99
0.632	0.2	>0.99
0.632	0.3	0.97
0.632	0.35	0.92
0.632	0.4	0.8
0.632	0.45	0.56
0.632	0.5	0.37
0.632	0.55	0.18
0.632	0.6	0.08
0.632	0.632	0.03
0.7	0.1	>0.99
0.7	0.2	>0.99
0.7	0.3	0.99
0.7	0.35	0.99
0.7	0.4	0.94

Incidence rate of Grade ≥2 corneal event (KVA scale)		Probability of identifying an arm that meets acceptance criterion: *P (incidence rate of control – incidence rate of test arm >0.17) >0.7*
Control Arm	Test Arm	
0.7	0.45	0.84
0.7	0.5	0.68
0.7	0.55	0.42
0.7	0.6	0.23
0.7	0.632	0.16
0.7	0.7	0.03

Abbreviations: KVA=keratopathy visual acuity.

9.2.2. Safety Stopping Rule for Arm E

Unacceptable toxicity is defined as the rate of Grade 4 corneal events (KVA scale) being significantly (1-sided alpha of 0.025) higher than 5%. Continuous monitoring will be conducted once 5 participants are dosed in Arm E. The observed number of participants who experience Grade 4 corneal events (KVA scale) will be compared against the safety stopping rule in Table 15. Enrollment may stop for Arm E if the safety stopping rule is met based on the totality of the safety data. For example, if 2 out of 5 participants experience Grade 4 corneal events (KVA scale), enrollment for the arm may stop after review of all safety data. Operating characteristics for the stopping rule are provided in Section 10.16.

If Arm E is stopped due to safety, and participants are still on treatment, they will be given the opportunity to switch to Arm A in which they will receive study treatment at 2.5 mg/kg Q3W dosing regimen with dose modification now based on the KVA scale instead of on ocular symptoms and visual acuity assessments.

Table 15 Safety Stopping Rule for Arm E

Number of Participants Dosed	Stop if Number of Participants with Grade 4 Corneal Events (KVA Scale) is:	Observed Rate
5	≥2	0.4
6-13	≥3	0.23-0.5
14-20	≥4	0.2-0.29

Abbreviations: KVA=keratopathy visual acuity.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

For purposes of analysis, the following study populations are defined (Table 16):

Table 16 Definitions of Study Analysis Populations

Population	Description
All Screened	The All Screened Population will consist of all participants who sign the ICF to participate in the clinical study. Participants in this population will be used for screen failure summary.
ITT	The ITT Population will consist of all randomized participants, whether or not randomized treatment was administered. This population will be based on the treatment to which the participant was randomized and will be the primary population for the analysis of efficacy data. Any participant who receives a treatment randomization number will be considered to have been randomized.
Safety	All randomized participants who receive at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.
PK	The PK Population will consist of those participants in the Safety Population from whom at least 1 post-treatment PK sample has been obtained and analyzed. This population will be the primary population for PK analyses.
Evaluable population (IA only)	The Evaluable Population for the interim analysis will consist of all participants who have received 2 doses of study treatment and have completed 1 disease assessment after the second dose, or confirmed PD or death. This population will be the primary population for futility assessment at Interim analysis only.

Abbreviations: IA=interim analysis; ICF=Informed Consent Form; ITT=Intent-to-Treat; PK=pharmacokinetic.

9.4. Key Elements of Statistical Analysis Plan

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the Statistical Analysis Plan (SAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the SAP and final clinical study report (CSR).

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative, data from all participating centers will be pooled before analysis.

All data up to the time of study completion/withdrawal from study/treatment switching will be included in the analysis, regardless of duration of treatment.

As the duration of treatment for a given participant will depend on efficacy and tolerability, the duration of follow-up will vary between participants. Consequently, there will be no imputation for missing data.

Demographic and baseline characteristics will be summarized.

All statistical analyses will be performed by GSK (the sponsor) or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the clinical activity and safety data is outlined below. Statistical analyses will be performed

for each treatment arm separately and the alternative regimens in Arm B to D will be compared to Arm A to decide whether a regimen has shown improved safety based on the acceptance criterion.

9.4.1. Dosing Based on Baseline Disease Characteristics – Virtual Treatment Arm

Approaches for individualized dosing will be investigated by combining participants from different treatment arms based on specific selection criteria to create a virtual "treatment arm" for the resulting dosing approach. Each virtual treatment arm can then be summarized for corneal toxicity and efficacy and compared to the treatment Arms A to D. Examples include the following:

- International Staging System (ISS) stage-based dosing:
  - Arm B (1.9 mg/kg Q3W) for ISS I and II and Arm A (2.5 mg/kg Q3W) for ISS III.

    Combine the ISS I/II participants at the 1.9 mg/kg Q3W dose from Arm B and the ISS III participants at 2.5 mg/kg Q3W from Arm A to create an ISS stage-based dosing treatment arm of 1.9 mg/kg Q3W in ISS I/II and 2.5 mg/kg Q3W in ISS III.
  - Arm C (2.5 mg/kg Q6W) for ISS I, Arm B (1.9 mg/kg Q3W) for ISS II, and Arm A (2.5 mg/kg Q3W) for ISS III.

Other similar analyses possibly also involving other disease characteristics at baseline may be included in the SAP, and specific details will be provided in the SAP.

9.4.2. General Considerations

Descriptive statistics for safety, efficacy, and pharmacokinetic data will be generated to summarize the information for each dosing regimen. Demographics, baseline characteristics, and efficacy will be summarized using the Intent-to-Treat (ITT) Population. AEs, clinical laboratory parameters, and vital signs will be summarized using the Safety Population. Pharmacokinetic parameter values will be summarized using the Pharmacokinetic (PK) Population. Appropriate subgroup analyses may be performed if data permit.

9.4.3. Safety Analyses

All safety analyses will be performed on the Safety Population. All serially collected safety endpoints (e.g., laboratory tests, vital signs, ECGs) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a "worst-case" analysis. Complete details of the safety analyses will be provided in the SAP.

Table 17 Statistical Analysis Methods: Safety

Endpoint	Statistical Analysis Methods
Primary	Incidence rate of Grade ≥2 corneal events according to the KVA scale is the primary endpoint. It is calculated as the percentage of participants with Grade ≥2 corneal events assessed by KVA scale.
Secondary	• Cumulative event rate of corneal events to Week 16 (KVA scale) is defined as the percentage of corneal events of each grade out of all the events up to Week 16. • Incidence rate of corneal events by grade (KVA scale) is defined as the percentage of participants with corneal events by grade according to the KVA scale in the respective treatment group. • The exposure-adjusted incidence rate is defined as the number of participants with corneal events divided by the total exposure time among participants in the respective treatment group at risk of an initial occurrence of the event. • Median duration of dose delay is defined as the median duration in time of all the dose delays in the respective treatment group. • Percentage of participants requiring dose reduction is defined as the percentage of participants that require dose reduction out of all the participants in the respective treatment group. • Percentage of participants requiring dose delay is defined as the percentage of participants that require dose delay out of all the participants in the respective treatment group. • Percentage of participants requiring study treatment discontinuation is defined as the percentage of participants that require study treatment discontinuation out of all the participants in the respective treatment group. Cumulative incidence of corneal events by grade (KVA scale) is calculated as the number of new events divided by the total number of individuals in the population at risk for a specific time interval. Assuming that the times experiencing the event of interest are: t_1, t_{j-1}, and t_j, the overall event (both events of interest and competing risk events) free rate up to, but not including time t_j, will be obtained from the Kaplan-Meier estimates and is denoted by $S(t_j)$. • A participant's toxicity index score is defined as a function of the ordered toxicity grades, where the toxicity grades are represented in descending order by the sequence. The maximum toxicity grade is the integer part of the final score: $$TI = \Sigma_{i=1}^{n} \frac{X_i}{\prod_{j=1}^{i-1}(1+X_j)}$$ • Duration of corneal events (KVA scale) for each participant is defined as the sum of all the corneal events. • Percentage of time on study with corneal events (KVA scale) is defined as the percentage of time that a participant has corneal events out of the total time that a participant is on the study. • Change in BCVA (ΔlogMAR) is defined as the change of logMAR compared with baseline or the first visit after the cataract surgery.
Exploratory	Exploratory analyses will be described in the SAP.

Abbreviations: AE=adverse event; (Δ)logMAR=(change in) logarithm of the minimum angle of resolution; KVA=keratopathy visual acuity; SAP=Statistical Analysis Plan.

9.4.3.1. Extent of Exposure

The number of participants administered study treatment will be summarized according to the duration of therapy.

9.4.3.2. Adverse Events

AEs will be coded using the standard MedDRA and grouped by SOC. Severity of corneal events will be graded using the KVA scale (Table 8). Severity of all other AEs will be graded by the investigator according to the NCI-CTCAE Version 5.0.

Events will be summarized by frequency and proportion of total participants, SOC, and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, ocular AEs, SAEs, and AEs leading to discontinuation of study treatment. AEs, if listed in the NCI-CTCAE Version 5.0, will be summarized by the maximum grade. Otherwise, the AEs will be summarized by maximum intensity.

Characteristics (e.g., number of occurrences, action taken, grade, etc.) of the following AEs of special interest will be summarized separately: corneal events, thrombocytopenia, and IRRs.

The incidence of deaths and the primary cause of death will be summarized.

9.4.3.3. Clinical Laboratory Evaluations

The evaluation of clinical laboratory tests will focus on selected laboratory analytes from the hematology and blood chemistry panel.

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE Version 5.0. Laboratory test results outside the reference ranges that do not have an associated NCI-CTCAE criterion will be summarized using proportions. Further details will be provided in the SAP.

Descriptive statistics (mean, standard deviation, median, range) will be used to summarize observed laboratory values and change from baseline in observed value at each scheduled visit or worst-case postbaseline, as appropriate.

9.4.3.4. Immunogenicity

For each participant, the results and titers of anti-belantamab mafodotin binding antibodies will be listed for each assessment time point. The frequency and percentage of participants with positive and negative results will be summarized for each assessment time and overall for each participant by treatment arm and for all treatment arms combined. Detailed information will be included in the SAP.

9.4.3.5. Other Safety Measures

Data for vital signs and ECGs will be summarized based on pre-determined criteria identified to be of potential clinical concern. For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum.

For categorical variables, the summaries will include frequencies and corresponding percentages. Further details will be provided in the SAP.

9.4.4. Efficacy Analyses

Analysis of efficacy endpoints will be based on investigator-assessed confirmed response and dates according to IMWG criteria [Kumar, 2016] with the ITT Population unless otherwise specified. The analytical methods planned for each endpoint are described in Table 18.

The number and percentage of participants with the best confirmed response in the following response categories will be summarized by treatment arm: sCR, CR, VGPR, PR, overall response (sCR+CR+VGPR+PR), minimal response (MR), stable disease (SD), PD, and not evaluable. The corresponding exact 95% CI for ORR will also be provided. Participants with unknown or missing responses will be treated as non-responders, i.e., these participants will be included in the denominator when calculating percentages of response.

Table 18 Statistical Analytical Methods: Efficacy

Endpoint	Description
Secondary	• ORR defined as percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR and sCR), according to the 2016 IMWG response criteria [Kumar, 2016]. • DoR is defined as the time from first documented evidence of PR or better until the earliest date of PD or death due to any cause among participants who achieve a response (i.e., confirmed PR or better) as assessed by the investigator per IMWG criteria [Kumar, 2016]. Responders without PD will be censored at the censoring time point for TTP. • Distribution of DoR will be summarized using the Kaplan-Meier method by treatment arm. The median, 25th, and 75th percentiles of DoR will be estimated and corresponding 95% Cis will be estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982]. • TTR is defined as the time between the date of randomization and the first documented evidence of response (PR or better), among participants who achieve a response (i.e., confirmed PR or better) as assessed by the investigator per IMWG criteria [Kumar, 2016]. • TTR will be summarized descriptively by treatment arm using medians and quartiles in the subset of participants with a confirmed response of PR or better as the best overall response. Sensitivity analysis will be conducted using investigator-assessed responses. • TTP is defined as the time from randomization until the earliest date of PD as assessed by the investigator per IMWG criteria [Kumar, 2016]], or death due to PD. Determination of dates of TTP event and dates for censoring will be described in the SAP. • TTP analysis will be conducted using a similar approach as for the PFS analysis. • PFS, defined as the time from randomization until the earliest date of documented PD as assessed by the investigator per IMWG criteria [Kumar, 2016] or death due to any cause. PFS will be summarized by arm, and median, first, and third quartiles of PFS will be estimated using the Kaplan-Meier method. • OS, defined as the interval of time from randomization to the date of death due to any cause. Participants who are alive will be censored at the date of last contact. OS will be summarized by arm, and median, first, and third quartiles of OS will be estimated using the Kaplan-Meier method.
Exploratory	Exploratory analyses will be described in the SAP.

Abbreviations: CR=confirmed response; IMWG=International Myeloma Working Group; ORR=overall response rate; OS=overall survival; PD=progressive disease; PFS=progression-free survival; PR=partial response; SAP=Statistical Analysis Plan; sCR=stringent complete response; TTP=time to progression; TTR=time to response; VGPR=very good partial response.

9.4.5. Pharmacokinetic Analyses

9.4.5.1. Pharmacokinetic Data Analyses

Pharmacokinetic analyses will be the responsibility of Clinical ***Pharmacology*** Modelling and Simulation, GSK. Population pharmacokinetic methods will be used for pharmacokinetic analyses.

Plasma belantamab mafodotin concentration-time data may be combined with data from other studies and analyzed using a population pharmacokinetic approach. The initial

analysis will use the then-current population pharmacokinetic model to generate post-hoc belantamab mafodotin pharmacokinetic parameter estimates. Based on the individual *post-hoc* parameter values, dosing information, and sample collection times, belantamab mafodotin plasma concentrations at the time of sample collection will be predicted for each participant. Model evaluation will consist of comparison of model-predicted and observed concentrations. If necessary, model estimation will be performed. Results of this analysis may be provided in a separate report.

CPMS analysts may be provided with population PK and PK/PD datasets for population PK and PK/PD model refinement before database lock.

9.4.5.2. Statistical Analysis of Pharmacokinetic Data

Statistical analyses of the pharmacokinetic data will be the responsibility of Clinical Pharmacology Modeling and Simulation (CPMS), GSK.

Linear and semi-logarithmic individual concentration-time profiles and mean and median profiles (when appropriate) will be plotted for belantamab mafodotin and cys-mcMMAF. Concentrations of belantamab mafodotin and cys-mcMMAF will be listed for each participant and summarized (when appropriate) by planned time point and treatment arm.

Pharmacokinetic parameters will be listed and summarized descriptively (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV%, and 95% CI of log-transformed parameters) by cycle and treatment arm for each analyte.

9.4.6. Pharmacokinetic/Pharmacodynamic Analyses

If deemed appropriate and if data permit, exposure-response relationships between belantamab mafodotin exposure and clinical activity and/or toxicity may be explored using population methods. If data permit, the effects of covariates may be explored. Data may be combined with data from other studies and results of this analysis may be provided in a separate report.

9.4.7. Biomarker/Translational Research Analyses

BCMA expression in BM samples and sBCMA levels in circulation obtained pre-dose will be quantified and reviewed/analyzed for a potential relationship to response. Post-dose measurements of sBCMA will be evaluated for dynamic changes during and after treatment. If data permit, additional exploratory analyses may be performed for novel biomarkers. Data for these exploratory analyses that are received after database freeze will not constitute a database unfreeze and, if warranted, the results of these analyses will be provided in a separate report.

Full details of analysis approaches will be provided in the SAP.

9.4.8. Patient-Reported Outcomes Analyses

Group-level descriptive statistics and evaluation of within-participant meaningful change will be used to summarize scores derived from different questionnaires and change from baseline at each scheduled visit. Additional details of these analyses will be provided in the SAP.

9.5. Interim Analysis

An interim analysis is planned when approximately 15 participants each in Arms A to D have received 2 doses of study treatment with 1 disease assessment following the second dose or confirmed PD per IMWG [Kumar, 2016] or death.

Table 19 displays the probability of stopping an arm early at interim analysis according to different true response rates of the experimental regimens (Arms B to D). The interim analysis threshold of ≤2 responders provides reasonable protection of study participants from an ineffective treatment.

Table 19 Arm Stopping Probability at Interim Analysis by True Response Rate

True Response Rate	Probability of Arm Stopping at ≤2 Responders
0.31	0.11
0.25	0.24
0.2	0.4
0.15	0.6

If Arm D is stopped due to futility, Arm E will also be stopped. If Arms B, C, D, or E are stopped due to futility, and participants are still on treatment, they will be given the opportunity to switch to 2.5 mg/kg Q3W (Arm A/control regimen) with dose modifications based on the KVA scale.

Available data from Arm E will be provided at the time of the interim analysis.

Additional interim analyses may also be conducted as deemed necessary for decision making by the Independent Data Monitoring Committee (IDMC).

The SAP will describe the planned interim analyses in greater detail.

9.5.1. Independent Data Monitoring Committee

An IDMC consisting of at least 2 physicians and 1 statistician will review safety and efficacy data as defined in the IDMC Charter. Additional details, including the list of outputs supporting decision making at the interim analysis, will be provided in the IDMC Charter.

The first IDMC review meeting is planned when approximately 15 participant each in Arms A to D have received 2 doses of study treatment with 1 disease assessment after the second dose, or confirmed PD per IMWG [Kumar, 2016] or death. Other IDMC review

meetings will be planned on an ad-hoc basis based on any safety signals. Additional details will be provided in the IDMC Charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Eye Care Specialist's Qualifications and Requirements

For examiners with a degree in ophthalmology or optometry, those involved in eye evaluations in the protocol must be able to provide comprehensive eye care to participants, ranging from routine check-ups to treatment and ongoing management of visual disease. This includes, at a minimum, the ability to perform the following activities:

- Comprehensive eye examination
- Visual acuity with manual refraction examination and analysis of results
- Anterior segment (slit lamp) examination and analysis of results
- Intraocular pressure measurement
- Dilated fundoscopic examination
- Diagnosis and treatment of ocular issues and diseases such as keratopathy or glaucoma

10.2. Appendix 2: International Staging System for Multiple Myeloma

The International Staging System (ISS) for multiple myeloma will be used to stratify participants into this study; the staging guidelines are as follows:

Stage	Criteria
I	Serum β2-microglobulin <3.5 mg/L, serum albumin ≥3.5 g/dL
II	Not Stage I or III
III	Serum β2-microglobulin ≥5.5 mg/L

Source: Greipp, 2005.

10.3. Appendix 3: Guidelines for the Determination of the Number of Prior Lines of Therapy in Multiple Myeloma

The number of prior lines of anti-multiple myeloma therapy will be used to stratify participants into this study and should be determined according to the guidelines by Rajkumar et al [Rajkumar, 2015] as follows:

Definition of Line of Therapy

- A line of therapy consists of the following:
- ≥1 complete cycle of a single agent or
- A regimen consisting of a combination of several drugs or
- A planned sequential therapy of various regimens (e.g., 3 to 6 cycles of initial therapy with bortezomib-dexamethasone [VD] followed by stem cell transplantation [SCT], consolidation, and lenalidomide maintenance is considered 1 line).

New Line of Therapy

A treatment is considered a new line of therapy if any 1 of the following 3 conditions are met:

1. **If a line of therapy is discontinued for any reason and a different therapy is started, it should be considered a new line of therapy.**

   Note: *A regimen/line is considered to have been discontinued if all the drugs in that given regimen have been stopped. A line is not considered to have been discontinued if some of the drugs of the regimen, but not all, have been discontinued.*

- For example, toxicity with lenalidomide plus low-dose dexamethasone (RD) as pre-transplant induction, and therefore treatment is switched to bortezomib, cyclophosphamide, and dexamethasone (VCD). In that case, RD is counted as line 1 and VCD (and subsequent planned SCT) as line 2.

2. **Unplanned addition or substitution of 1 or more drugs (or combination of drugs) in an existing regimen due to any reason is considered a new line of therapy.**

- For example, RD as initial therapy, and, due to inadequate response, bortezomib is added (RVD); counted as 2 lines. In that case, enter RD as line 1 and RVD as line 2.

3. **In patients undergoing >1 SCT (except in the case of a planned tandem SCT with a predefined interval [such as 3 months]), each SCT (autologous or allogeneic) should be considered a new line of therapy regardless of whether the conditioning regimen used is the same or different.**

- For example, post-transplant observation without maintenance, and then, due to paraprotein rise 6 months later, lenalidomide is started, which is not planned maintenance; hence, lenalidomide will be considered as a new line.

Interruptions and Dose Modifications:

1. If a regimen is interrupted or discontinued for any reason and the same drug or combination is restarted without any other intervening regimen, then it should be counted as a single line.

- For example, RD as initial therapy for 2 years, then stopped due to plateau phase (or any other cause), and then restarted 6 months later due to progression: this should be counted as 1 line.

2. If a regimen is interrupted or discontinued for any reason, and then restarted at a later time point but 1 or more other regimens were administered in between, or the regimen is modified through the addition of 1 or more agents, then it should be counted as 2 lines

- For example: RVD followed by progression at some point, and then VCD is used; then, RVD is used again as a salvage strategy: this is counted as 3 lines. Enter RVD as line 1, VCD as line 2, and then RVD as line 3.

3. Modification of the dosing of the same regimen should not be considered a new line of therapy.

10.4. Appendix 4: Decentralized and Remote Assessment Approaches

Decentralized Ophthalmologic Examinations

Where applicable country and local regulations and infrastructure allow, protocol-required eye examinations may be done at a specified alternative eye care specialist clinic. Activities that may be done as part of decentralized eye examinations must follow the schedule provided in the SoA (Section 1.3) and include the following:

- Visual acuity by near-chart visual acuity or pinhole
- Slit lamp examination
- Tonometry (intraocular pressure measurement)
- Ophthalmoscopy

The participant should be informed of any potential risks associated with decentralized ophthalmologic examinations and sign a revised ICF, if required. IRBs/IECs should be informed and/or approve of this change in approach and the process documented in study files.

Remote Patient-Reported Outcomes Administration

Where applicable country and local regulations and infrastructure allow, remote patient-reported outcome (PRO) administration may be permitted. Remote PRO administration is defined as administration of protocol PROs by a qualified third party over the telephone. The remote PRO administrator will use the versions of the PROs designed for verbal administration. The remote PRO administrator will have access to the electronic PRO portal for the study and input participant responses as the interview is being conducted.

The participant should be informed of any potential risks associated with the remote PRO administration and sign a revised ICF if required. IRBs/IECs should be informed and/or approve of this change in approach and the process documented in study files.

10.5. Appendix 5: Modified Diet in Renal Disease Formula

The Modified Diet in Renal Disease (MDRD) formula for calculating the estimated glomerular filtration rate (eGFR) is as follows:

$$eGFR = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

eGFR is expressed in mL/min/1.73 m^2, serum creatinine is expressed in mg/dL, and age is expressed in years.

The following website will auto-calculate the creatinine clearance:

http://nephron.org/cgi-bin/MDRD_GFR/cgi

10.6. Appendix 6: Liver Safety Required Actions and Follow-Up Assessments

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Liver chemistry stopping criteria and required follow-up assessments are as follows:

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥5xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥3xULN <u>and</u> total bilirubin ≥2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥3xULN <u>and</u> INR>1.5</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥3xULN <u>and</u> cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions, Monitoring, and Follow-Up Assessments</th></tr>
<tr><th>Actions</th><th>Follow-Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event form and complete SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow-up assessments as described in the Follow-Up Assessments column
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING)
<u>MONITORING:</u>
If ALT≥3xULN <u>and</u> total bilirubin ≥2xULN or INR>1.5:
• Repeat liver chemistries (include ALT, AST, ALP, total bilirubin, and INR) and perform liver event follow-up assessments within 24 hours
• Monitor participants twice weekly until liver chemistries resolve, stabilize, or return to within baseline
• A specialist or hepatology consultation is recommended
For all other criteria (bilirubin <2xULN and INR≤1.5):
• Repeat liver chemistries (include ALT, AST, ALP, total bilirubin, and INR) and perform liver</td><td>• Viral hepatitis serology[4]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend
• Blood sample for PK analysis and a blood sample for sBCMA, obtained within 70 days after last dose of belantamab mafodotin[5]
• Serum CPK, LDH, GGT, GLDH, and serum albumin
• Fractionate bilirubin, if total bilirubin ≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs, or other over-the-counter medications
• Record alcohol use on the liver event alcohol intake report form
If ALT≥3xULN <u>and</u> total bilirubin ≥2xULN or INR>1.5 obtain the following in addition to the assessments listed above:
• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal</td></tr>
</table>

event follow-up assessments **within 24 to 72 hours** • Monitor participants weekly until liver chemistries resolve, stabilize, or return to within baseline **RESTART/RECHALLENGE:** • **Restart/rechallenge is allowed per protocol, but do not resume study treatment unless GSK approval is granted**. If restart/rechallenge **is not granted**, permanently discontinue study treatment and continue participant in the study for any protocol-specified follow-up assessments. Refer to restart/rechallenge guidelines in Section 10.12.	antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins) • Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g., where the participant has been resident in the clinical unit throughout) • Liver imaging (ultrasound, MRI, or CT) to evaluate liver disease (complete liver imaging form) • Liver biopsy may be considered and discussed with local specialist if available, for instance: ○ In participants when serology raises the possibility of autoimmune hepatitis ○ In participants when suspected drug-induced liver injury progressor or fails to resolve on withdrawal of study treatment ○ In participants with acute or chronic atypical presentation • If liver biopsy conducted, complete liver biopsy form

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=serum creatine phosphokinase; CT=computed tomography; DNA=deoxyribonucleic acid; eCRF=electronic Case Report Form; GGT=gamma glutamyl transferase; GLDH=glutamate dehydrogenase; GSK=GlaxoSmithKline; Ig=immunoglobulin; INR=international normalized ratio; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PK=pharmacokinetic(s); RNA=ribonucleic acid; SAE=serious adverse event; sBCMA=soluble B-cell maturation antigen; SRM=Study Reference Manual; ULN=upper limit of normal.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN **and** total bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR>1.5, which may indicate severe liver injury (possible "Hy's law"), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; the INR threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash, or eosinophilia)
4. Includes: Hepatitis A IgM antibody; hepatitis B surface antigen, and hepatitis B core antibody (IgM); hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody. If hepatitis delta antibody assay cannot be performed, it can be replaced with polymerase chain reaction of hepatitis D RNA virus (where needed) [Le Gal, 2005].
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment before the blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated **or** a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the laboratory manual.

Oncology liver chemistry increased monitoring criteria with continued therapy are as follows:

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Treatment – Liver Monitoring Event	
Criteria	**Actions**
• ALT ≥3xULN **but** <5xULN **and** total bilirubin <2xULN or INR ≤1.5, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the GSK Medical Director **within 24 hours** of learning of the abnormality to discuss participant safety • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, ALP, total bilirubin, and INR) until they resolve, stabilize, or return to within baseline • If, at any time, participant meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN, total bilirubin <2xULN, and INR ≤1.5, monitor participants twice monthly until liver chemistries resolve or return to within baseline

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GSK=GlaxoSmithKline; INR=international normalized ratio; ULN=upper limit of normal.

10.7. Appendix 7: Country-Specific Requirements

France

- Additional inclusion criterion for participants in France: A participant is eligible to be included in the study only if they are either affiliated to or a beneficiary of a social security category.
- Additional inclusion criterion for participants in France: Only participants who have failed at least 4 prior lines of anti-myeloma therapies will be included in the study.

South Korea

- Modified inclusion criterion 1 for participants in South Korea: In South Korea, a participant must be over 19 years of age inclusive at the time of signing the informed consent.

Taiwan

- Modified inclusion criterion 1 for participants in Taiwan: In Taiwan, a participant must be at least 20 years of age at the time of signing the informed consent.

Thailand

- Modified inclusion criterion 1 for participants in Thailand: In Thailand, a participant must be at least 20 years of age at the time of signing the informed consent.

10.8. Appendix 8: Eastern Cooperative Oncology Group (ECOG) Performance Status

Performance Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken, 1982.

10.9. Appendix 9: Contraceptive and Barrier Guidance

Contraceptive and barrier guidance for participants is provided in this appendix.

10.9.1. Definitions

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. After menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Note:

- A post-menopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with >1 FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal, highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

      For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

      Note: *Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.*

      If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Pre-menopausal female with permanent infertility due to **one** of the following procedures (for the purpose of this study):
   a. Documented hysterectomy
   b. Documented bilateral salpingectomy
   c. Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

   ***Note**: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.*

2. Postmenopausal female

   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

   - A high FSH level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

10.9.2. Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
IUD
IUS[c]
Bilateral tubal occlusion
Azoospermic partner (vasectomized or due to a medical cause) • Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. ***Note**: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.*
Highly Effective Methods[b] That Are User-Dependent
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • Oral • Intravaginal • Transdermal • Injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • Oral • Injectable
Sexual abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Abbreviations: CTFG=Clinical Trial Facilitation Group; IUD=intrauterine device; IUS= Intrauterine hormone-releasing system; LAM=lactational amenorrhea method.

Note: Periodic abstinence (calendar, symptom-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with CTFG guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

10.10. Appendix 10: Regulatory, Ethical, and Study Oversight Considerations

10.10.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following considerations:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations.
- The protocol, protocol amendments, Informed Consent Form (ICF), Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval before implementation of changes made to the study design, as per national requirements, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval before initiation, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following actions:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of serious adverse events or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.10.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.10.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- Sample testing will be done in accordance with the recorded consent of the individual participant.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about belantamab mafodotin or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have belantamab mafodotin approved for medical use or approved for payment coverage.

The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorized designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

In case of unexpected pregnancy, participant must be informed that PI such as date of birth and sex of the baby will be collected as part of safety follow-up. Consent for collection of information about the baby may be obtained from the participant and/or their partner per local regulations.

If partners of male participants become pregnant during the study, consent will need to be obtained or notification given per local regulation to the partner before collecting their PI such as, last menstrual period and year of birth, or the PI such as date of birth and sex of their baby as part of safety follow-up.

10.10.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.10.5. Committees Structure

An Independent Data Monitoring Committee (IDMC) consisting of at least 2 physicians and 1 statistician will review safety and efficacy data as defined in the IDMC Charter. Additional details, including the list of outputs supporting decision making at the interim analysis, will be provided in the IDMC Charter.

The first IDMC review meeting is planned when approximately 15 participants each in Arms A to D have received 2 doses of study treatment with 1 disease assessment following the second dose, or confirmed PD per IMWG [Kumar, 2016] or death. Other IDMC review meetings will be planned on an adhoc basis based on any safety signals. Additional details will be provided in the IDMC Charter.

Available data from Arm E will be provided at the time of the IDMC.

An SRT is in place for each GSK product. It comprises a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.

10.10.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the CSR. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their participants received. The investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or

improve participant care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.

- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.

10.10.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic Case Reports Forms (eCRFs) unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the Case Report Form Completion Guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL Plan to identify systematic issues that can impact participant rights, safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. In the event of a conflict between this protocol and the fully executed clinical study agreement, the protocol shall prevail with respect to records retention.

Additional information regarding remote data management and monitoring are provided in Section 10.17.

10.10.8. Source Documents

- For this study, there will be source data recorded directly into the eCRF (i.e., no prior written or electronic record of data is available).
- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the SRM.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.10.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study's first participant's first visit (FSFV) occurs (i.e., the date the first participant is screened).

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to the following:

For study termination:

- Discontinuation of further study treatment development.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.10.10. Publication Policy

GSK seeks to publish medically or scientifically significant results in searchable peer-reviewed scientific literature within 18 months from LSLV. GSK follows International Committee of Medical Journal Editors standards for authorship and uses good publications practices to guide publications.

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.11. Appendix 11: New York Heart Association Classification

The New York Heart Association Functional Classification: Class I, II, III, or IV Heart Failure [Dolgin, 1994] provides a simple way of classifying the extent of heart failure. It places participants in 1 of 4 categories based on the level of limitation experienced during physical activity as follows:

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

10.12. Appendix 12: Liver Safety Drug Restart or Rechallenge Guidelines

- If participant meets liver chemistry stopping criteria, do not restart/rechallenge participant with study treatment unless all of the following criteria are met:
- GlaxoSmithKline (GSK) approval is granted (see following description), and
- Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the participant and the participant is informed of any associated risks.

If GSK approval to restart/rechallenge participant with study treatment **is <u>not</u> granted**, then the participant must permanently discontinue study treatment and may continue in the study for protocol-specified follow-up assessments.

Rechallenge After Liver Stopping Events that are Possibly Related to Study Treatment

After drug-induced liver injury (DILI), **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies** [Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane re-administered within 1 month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include the following:

- Hypersensitivity with initial liver injury (e.g., fever, rash, eosinophilia) [Andrade, 2009]
- Jaundice or bilirubin >2xupper limit of normal (ULN) with initial liver injury (direct bilirubin >35% of total)
- Ongoing severe liver injury defined by ALT >3xULN, bilirubin >2xULN (direct bilirubin >35% of total), or international normalized ratio >1.5
- Serious adverse event or fatality has earlier been observed with drug rechallenges [Hunt, 2010; Papay, 2009]
- Evidence of drug-related non-clinical liability (e.g., reactive metabolites, mitochondrial impairment) [Hunt, 2010].

Rechallenge refers to resuming study treatment after DILI. Because of the risks associated with rechallenge after DILI, this should only be considered for a participant for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit/risk assessment of rechallenge is considered to be favorable.

Approval by GSK for rechallenge with study treatment can be considered when the following criteria are met:

- Principal investigator requests consideration of rechallenge with study treatment for a participant who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available
- IRB/IEC approval for rechallenge with study treatment must be obtained, as required

If the rechallenge is approved by GSK in writing:

- The participant must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death
- The participant must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study file.
- Study treatment must be administered at the dose specified by GSK
- Participants approved by GSK for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol
- If, after study treatment rechallenge, the participant meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued
- GSK Medical Director and the IRB/IEC must be informed of the participant's outcome after study treatment rechallenge
- GSK must be notified of any adverse events, as per Section 8.4 and Section 10.14

Restart After Transient Resolving Liver Stopping Events Not Related to Study Treatment

Restart refers to resuming study treatment after liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g., biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, restart is not permitted following a liver stopping event when the underlying cause was alcohol-related hepatitis.

Approval by GSK for study treatment restart can be considered when the following criteria are met:

- Principal investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension, and liver chemistries have improved to normal or are within 1.5×baseline and ALT <3×ULN)
- Possible study treatment-induced liver injury has been excluded by the principal investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study treatment has an identified genetic marker associated with liver injury (e.g., lapatinib,

abacavir, amoxicillin/clavulanate), the presence of the marker should be excluded. If study treatment-related liver injury cannot be excluded, the guidance on rechallenge will apply (Section 7.1.5)

- There is no evidence of alcohol-related hepatitis
- IRB/IEC approval of study treatment restart must be obtained, as required

If restart of study treatment is approved by GSK in writing:

- The participant must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death
- The participant must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study file.
- Study treatment must be administered at the dose specified by GSK
- Participants approved by GSK for restart of study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol
- If a participant meets protocol-defined liver chemistry stopping criteria after study treatment restart, the study treatment should be permanently discontinued
- GSK Medical Director and the IRB/IEC must be informed of the participant's outcome after study treatment restart
- GSK must be notified of any adverse events, as per Section 8.4 and Section 10.14

10.13. Appendix 13: Clinical Laboratory Tests

A list of clinical laboratory tests required during the study is included in Table 20. See the SoA (Section 1.3) for the timing and frequency.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

Table 20 Protocol-Required Clinical Laboratory Tests

Hematology[1,2]			
• Platelet count • RBC count • WBC count (absolute)	• Hemoglobin • Hematocrit	RBC Indices: • MCV • MCH • MCHC	Automated WBC Differential (%) or Absolute: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Clinical Chemistry[1,2]			
• BUN • Creatinine • Glucose • Sodium • Magnesium	• Potassium • Chloride • Carbon dioxide (CO_2 or bicarbonate) [3] • Calcium • Phosphorous	• AST • ALT • GGT • ALP • CK	• Total and direct bilirubin • Uric acid • Albumin • Total protein • LDH
Urine Tests			

• Urinalysis[1,2]
  ○ Specific gravity, pH, glucose, protein, blood, and ketones by dipstick
  ○ Microscopic examination (if blood or protein is detected by dipstick)
• Spot urine (ACR)[4,5]			

Other Laboratory Tests			
• eGFR[1] • HBsAg[5]; HBcAb[5], HCAb[1], HBV DNA[5] (see note), HCV RNA[5] (see note) ***Note:*** *HBV DNA testing must be done to determine participant eligibility if HBsAg+ or HBcAb+* ***Note:*** *HCV RNA testing must be done to determine participant eligibility if HCAb+* • Pregnancy test (urine or serum)[1];FSH[1], and estradiol[1] (as needed in WONCBP only)			
Disease Evaluation Laboratory Tests[6]			
• β2-microglobulin • UPEP (on 24 h urine collection), urine immunofixation (urine M protein calculation) • SPEP; serum immunofixation (serum M protein calculation) • Serum kappa, lambda FLC, FLC ratio • IgG, IgM, IgA, IgD/IgE[7] • Calcium corrected for albumin (serum)			

Bone Marrow Aspiration/Biopsy
• BM aspirate and/or biopsy for disease assessments (screening, CR, and PD [only if PD not evident otherwise])[1] • BM aspirate for FISH testing[5,8] • BM aspirate and/or biopsy for BCMA expression and biomarker research[6] • BM biopsy to confirm sCR (by IHC)[5]
PK and ADA[6]
• Samples for belantamab mafodotin PK analysis (cys-MMAF and ADC) • Samples for anti-belantamab mafodotin antibody analysis (immunogenicity)
Biomarker Measurements[6]
• sBCMA (serum) • TBNK panel (whole blood)
Optional Laboratory Tests
• Genetic Sample[9]

Abbreviations: ACR=albumin/creatinine ratio; ADA=anti-drug antibody; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BCMA-B-cell maturation antigen; BM=bone marrow; BUN=blood urea nitrogen; CK=creatine kinase; CO_2=carbon dioxide; eGFR=estimated glomerular filtration rate; FISH=fluorescence-in-situ hybridization; FLC=free light chain; FSH=follicle-stimulating hormone; GGT=gamma-glutamyl transferase; HBsAg=hepatitis B surface antigen; HBcAb=hepatitis B core antibody; HCAb=hepatitis C antibody; HCV=hepatitis C virus; Ig=immunoglobulin; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PD=progressive disease; PK=pharmacokinetic(s); RBC=red blood cell; sBCMA=soluble B-cell maturation antigen; sCR=stringent complete response; SPEP=serum protein electrophoresis; TBNK=T, B, and natural killer cells; UPEP=urine protein electrophoresis; WBC=white blood cell; WONCBP=women of nonchildbearing potential.

1. To be performed at local laboratory.
2. Hematology, clinical chemistry, and urinalysis should be performed and reviewed 72 hours prior to dosing.
3. Performed only if considered local standard of care.
4. ACR (spot urine preferably from first void). Urine dipstick for protein may be used to assess for presence of urine protein. ACR must be collected at screening and thereafter to be done in any participant with urine dipstick result of ≥2+ (during study treatment), or with positive protein if urine dipstick protein quantification is not available. ACR will be performed at a local laboratory. If local testing is not available, then central testing will be performed.
5. If not available locally, can be performed centrally.
6. To be performed at central laboratory.
7. Only for participants with IgD/E myeloma.
8. FISH testing at least for: t(4;14), t(14;16), amp(1q), del(1p) and del(17p13). If participant is known to have tested positive for t(4;14) or t(14/16) on previous tests regardless of time frame, FISH for these translocations does not need to be repeated. FISH results for amp(1q), del(1p) and del(17p13) from samples taken within 60 days before the first dose are acceptable.
9. Informed consent for optional sub-studies (e.g., genetic research) must be obtained once the participant meets all eligibility criteria before collecting a sample.

10.14. Appendix 14: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.14.1. Definition of Adverse Event

AE Definition
• An adverse event (AE) is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. ***Note:*** *An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.*
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected treatment-treatment interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.14.2. Definition of Serious Adverse Event

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the following criteria:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which, hypothetically, might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions, but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Possible Hy's law case: alanine aminotransferase ≥3x upper limit of normal (ULN) **and** total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio >1.5 must be reported as an SAE. • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of treatment dependency or treatment abuse.

10.14.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the electronic Case Report Form (eCRF) for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

10.14.4. Recording and Follow-Up of Adverse Events and Serious Adverse Events

Recording of AEs and SAEs
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory results, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information. • It is not acceptable for the investigator to send photocopies of the participant's medical records to GlaxoSmithKline (GSK) in lieu of completion of the GSK required form. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories: • Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. • Moderate: Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. • Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Assessment of Causality
The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. • A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.** • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.
Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.14.5. Reporting of Serious Adverse Events to GlaxoSmithKline

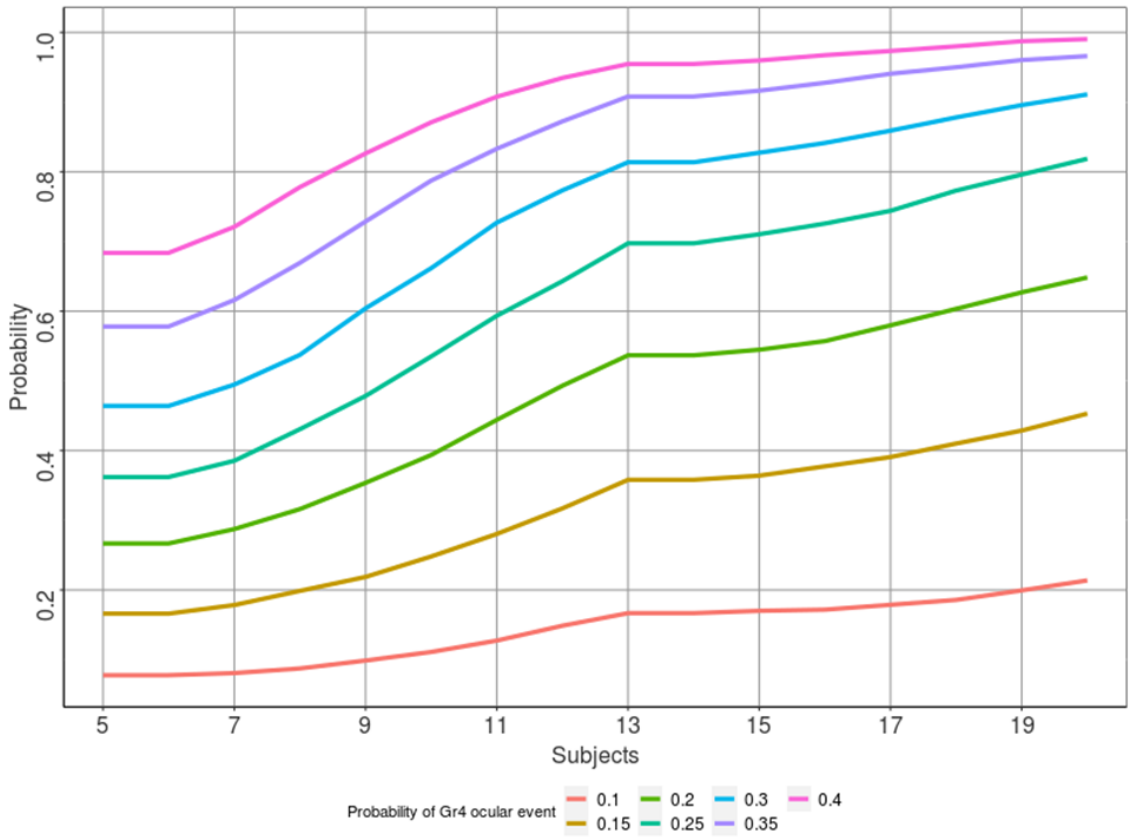
SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the GSK Medical Director/SAE Coordinator by telephone. • Contacts for SAE reporting can be found in the Study Reference Manual (SRM).
SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the GSK Medical Director/SAE Coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

10.15. Appendix 15: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study treatment, susceptibility, severity, and progression of disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for deoxyribonucleic acid (DNA) analysis.
- DNA samples will be used for research related to belantamab mafodotin or MM and related diseases. They may also be used to develop tests/assays (including diagnostic tests) related to belantamab mafodotin or study treatments of this drug class, and MM. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analyzed for relationships between genetic variants in the host and response to belantamab mafodotin. A detailed description of any planned analyses will be documented in a Statistical Analysis Plan (SAP) before initiation of analyses. Planned analyses and results of genetic investigations will be reported either as part of the clinical SAP and CSR, or in a separate genetics SAP and report, as appropriate.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to belantamab mafodotin or study interventions of this class. The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on belantamab mafodotin (or study treatments of this class) or MM continues, but no longer than 15 years after the last participant's last visit or other period as per local requirements.

10.16. Appendix 16: Operating Characteristics of the Safety Stopping Rule for Arm E



10.17. Appendix 17: Data Management/Monitoring

Source Data Verification/Source Document Review (SDV/SDR)

During periods in which on-site monitoring is not permitted, GlaxoSmithKline (GSK) will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution and in accordance with local law and regulatory guidance documents.

Remote SDV/SDR will be proposed to study sites to meet a participant and/or critical data quality need, e.g., to assess participant safety or to ensure data integrity. The study specific monitoring plan will be updated in accordance with remote monitoring practices adopted for the country/study. The Informed Consent Form will be updated in line with local regulations to permit remote monitoring practices. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.

Electronic Case Report Form Final or Interim Sign-Off Process

The principal investigator is responsible for ensuring that the data within the electronic Case Report Form (eCRF) casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 and 4.9.2). The principal investigator may sign/re-sign the eCRF from any computer/location by accessing the electronic data capture platform) using his/her unique eCRF login credentials.

Essential Document Sign-Off Process

If an investigator is unable to print and sign essential documents such as Protocol/Amendment signature page, then Email approval can be accepted by replying to the relevant email that is sent by GSK. Note that unblinding procedures remain the same as those documented in the protocol and other study-related documents.

10.18. Appendix 18: Progression-Free Survival Event and Censoring Rules

Situation	Date of Event (Progression/Death) or Censored[a]	Event (Progression/Death) or Censored
No adequate baseline assessments and the participant has not died (if the participant has died, follow the rules for death indicated at the bottom of the table)	Randomization	Censored
No post-baseline assessments and the participant has not died (if the participant has died, follow the rules for death indicated at the bottom of the table)	Randomization	Censored
PD documented between scheduled visits and progression documented without extended loss-to-follow-up time[e]	Date of assessment of PD[b] (1) min (Date of next scheduled visit, date of death)	Event (1) Event
With post-baseline assessment but no PD (or death)	Date of last "adequate" assessment of response[c]	Censored
No adequate post-baseline assessment before start of new anti-myeloma therapy	Randomization	Censored
With adequate post-baseline assessment and new anti-myeloma therapy started (before documented PD).[d]	Date of last "adequate" assessment of response[c] (on or before starting anti-myeloma therapy) (1) Date of starting new anti-myeloma therapy	Censored (1) Event
Death before first scheduled assessment (or death at baseline or without any adequate assessments)	Date of death	Event
Death between adequate assessment visits	Date of death	Event

Situation	Date of Event (Progression/Death) or Censored[a]	Event (Progression/Death) or Censored
Death or PD after missing 2 or more scheduled assessments	Date of last "adequate" assessment of response[b] (before missed assessments): since disease assessment is every 3 weeks, a window of 49 days (6 weeks + 7-day window) will be used to determine whether there is extended time without adequate assessment. If the time difference between PD or death and last adequate disease assessment is more than 49 days, PFS will be censored at the last adequate disease assessment before PD or death. (1) Date of death or progression	Censored (1) Event
(1) Treatment discontinuation due to clinical PD before PD or death	(1) Date of treatment discontinuation	(1) Event

Abbreviations: CR=complete response; FLC=free light chain; MR=minimal response; PD=progressive disease; PEP=protein electrophoresis; PFS=progression-free survival; PR=partial response; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response.

Note: (1) Rules to be applied for PFS sensitivity analysis.

a. Event or censored are based on confirmed responses.
b. The earliest of (i) Date of serum/urine PEP test (if progression is based on increase in serum or urine M protein); or (ii) Date of radiological assessment of extramedullary disease (if progression is based on increase in the size of existing plasmacytoma or appearance of new soft tissue plasmacytoma, or (iii) Date of last radiological assessment of bone lesions (if progression is based on increase in the size of existing bone lesions or appearance of new bone lesions), or (iv) Date of laboratory test for FLC (if progression is based on increase of difference between involved and uninvolved FLCs).
c. An adequate assessment is defined as an assessment where the response is sCR, CR, PR, VGPR, MR, or SD.
d. If PD and new anti-myeloma therapy occur on the same day, assume the progression was documented first (e.g., the outcome is progression and the date is the date of the assessment of progression).
e. Extended loss-to-follow-up time = 6 weeks + 7 day window = 49 day window; Without extended loss-to-follow-up time is defined as: $\leq$ 49 days; after an extended loss-to-follow-up time is defined as: >49 days.

10.19. Appendix 19: Visual Acuity Conversion

Snellen	Snellen (Metric)	logMAR	Decimal
No light perception[a]	No light perception	4.0	No light perception
Light perception[a]	Light perception	3.9	Light perception
Hand motion[b], or 20/20,000	Hand motion, or 60/6,000	3.0	0.001
Counts fingers[c], or 20/2,000	Counts fingers, or 60/600	2.0	0.01
20/800	6/240	1.6	0.025
20/640	6/200	1.5	0.03
20/500	6/150	1.4	0.04
20/400	6/120	1.3	0.05
20/320	6/96	1.2	0.06
20/250	6/76	1.1	0.08
20/200	6/60	1.0	0.10
20/160	6/48	0.9	0.13
20/150	6/45	0.9[d]	0.13
20/125	6/38	0.8	0.16
20/100	6/30	0.7	0.20
20/80	6/24	0.6	0.25
20/70	6/21	0.5[d]	0.29
20/63	6/20	0.5	0.32
20/60	6/18	0.5[d]	0.33
20/50	6/15	0.4	0.40
20/40	6/12	0.3	0.50
20/32	6/10	0.2	0.63
20/30	6/9	0.2[d]	0.67
20/25	6/7.5	0.1	0.80
20/20	6/6	0.0	1.00
20/16	6/5	-0.1	1.25
20/15	6/4.5	-0.1[d]	1.33
20/12.5	6/3.5	-0.2	1.6
20/10	6/3	-0.3	2.0

Source: Adapted from Holladay, 2004

Abbreviation: logMAR=logarithm of the minimum angle of resolution.

a. "Light perception" or "no light perception" do not have corresponding Snellen or decimal values
b. Hand motion at 2 feet
c. Counting fingers at 2 feet
d. Values that are not in logMAR steps such as 20/150 are included because of their common appearance in older visual acuity charts. Values are rounded to the nearest decimal to keep measures to a single decimal place.

10.20. Appendix 20: Abbreviations,Trademarks and Definitions of Terms

ACR	albumin/creatinine ratio
ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADCC	antibody dependent cellular cytotoxicity
ADCP	antibody dependent cellular phagocytosis
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ART	anti-retroviral therapy
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AxMP	auxiliary medicinal product
BCMA	B-cell maturation antigen
BCVA	best corrected visual acuity
BM	bone marrow
BP	blood pressure
Cavg	average concentration
cfDNA	circulating plasma cell-free DNA
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL	clearance
CLW	Central Laboratory Worksheet
Cmax	maximum concentration
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CSR	Clinical Study Report
CT	computed tomography
Ctau	concentration at the end of the dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CV	cardiovascular
cys-mcMMAF	cysteine-maleimidocaproyl monomethyl auristatin F
ΔlogMAR	change in logarithm of the minimum angle of resolution
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DoR	duration of response
DRE	disease-related event
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EMD	extramedullary disease
EOI	end of infusion

EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-Item Core Module
EORTC-QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma Module
EOT	end of treatment
FACT-GP5	Functional Assessment of Cancer Therapy – General Population
FDA	Food and Drug Administration
FISH	fluorescence-in-situ hybridization
FLC	free light chain
FSFV	first participant's first visit
FSH	follicle-stimulating hormone
FTIH	first time in human
GCP	good clinical practice
GGT	gamma glutamyl transferase
GSK	GlaxoSmithKline
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCAb	hepatitis C antibody
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRQoL	health-related quality of life
HRT	hormone replacement therapy
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IMP	investigational medicinal product
IMWG	International Myeloma Working Group
INR	international normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	interactive response technology
ISS	International Staging System
ITT	Intent-to-Treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
KVA	keratopathy visual acuity
LAM	lactational amenorrhea method
LDH	lactate dehydrogenase
LFT	liver function test
LSFD	time the last participant receives their first dose of study treatment
mAb	monoclonal antibody
MDRD	Modified Diet in Renal Disease

MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MMAF	monomethyl auristatin F
MR	minimal response
MRI	magnetic resonance imaging
MRP	multidrug resistance associated proteins
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not estimable
NGS	next generation sequencing
NIMP	non-investigational medicinal product
NR	not reached
OATP	organic anion transporting polypeptide
ORR	overall response rate
OS	overall survival
OSDI	Ocular Surface Disease Index
OU	both eyes
P-gp	P-glycoprotein
PACT	Post Analysis Continued Treatment
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
POEMS	polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes
PR	partial response
PRO	patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
Q3W	every 3 weeks
Q6W	every 6 weeks
Q9W	every 9 weeks
Q12W	every 12 weeks
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
QTL	quality tolerance limit
RD	lenalidomide plus low-dose dexamethasone
RVD	lenalidomide plus low-dose dexamethasone and bortezomib
RNA	ribonucleic acid
RRMM	relapsed or refractory multiple myeloma
SAE	serious adverse event
SAP	Statistical Analysis Plan
sBCMA	soluble B-cell maturation antigen
sCR	stringent complete response
SCT	stem cell transplantation
SD	stable disease
SDV/SDR	Source Data Verification/Source Document Review
SoA	Schedule of Activities
SOC	system organ class

SOI	start of infusion
SPEP	serum protein electrophoresis
SPK	superficial punctate keratitis
SRM	Study Reference Manual
TBNK	T, B, and natural killer cells
SUSAR	suspected unexpected serious adverse reactions
tmax	time taken to reach maximum concentration
ToxT	toxicity over time
TTP	time to progression
TTR	time to response
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States
V	volume of distribution
VCD	bortezomib, cyclophosphamide, and dexamethasone
VD	bortezomib-dexamethasone
VGPR	very good partial response
Vss	volume of distribution at steady-state
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
BLENREP

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA
RandALL NG

Term	Definition
Caregiver	A 'caregiver' is someone who: lives in the close surroundings of a participant and has a continuous caring role or has substantial periods of contact with a participant and is engaged in their daily health care (e.g., a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home). In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol specified procedures.
Combination product	Combination product comprises any combination of: drug device biological product. Each drug, device, and biological product included in a combination product is a constituent part.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria
Essential documents	Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced

Term	Definition
Investigational Product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form
IMP	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual(s) or party(ies) to perform those study-related duties and functions.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention vaccine[s]/product[s]/control). Synonym: subject
Randomization	Process of random attribution of intervention to participants to reduce selection bias
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Standard of Care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries
Study intervention	Term used throughout the clinical study to cover all types of investigational and non-investigational products, including medical devices and vaccines, intended to be administered to the study participants during the study conduct. Procedures conducted to manage participants or to collect data are excluded from the usage of this term.
Study monitor	An individual assigned by the sponsor and responsible for ensuring proper conduct of clinical studies at 1 or more investigational sites
SUSAR	In a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., IB for an unapproved IMP). All ADRs that are both serious and unexpected are subject to expedited reporting.

10.21. Appendix 21: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Summary of Previous Amendments

Amendment 02 (19-Dec-2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment: Amendment 02 is a global protocol amendment to align with program-level updates, removing the assessments of clinical responses by proprietary algorithm and only to be evaluated by the investigator as defined by 2016 International Myeloma Working Group (IMWG) response criteria [Kumar, 2016]. Other program-level updates include removal of all minimal residual disease (MRD), total plasma monoclonal antibody and cfDNA assessments, and end of treatment collection of pharmacokinetic, anti-drug antibody, and serum B-Cell maturation antigen (sBCMA) samples to reduce participant burden. In addition, distinct definitions for the end of data collection for the final clinical study report and the end of study timepoints, including implementation of the PACT period in the study have been included. Risk assessment and alignment with updated risks in belantamab mafodotin Investigator's Brochure v10 has been amended in the protocol.

Study-level changes that have been incorporated to include the addition of a defined evaluable population for the planned interim analysis, including an update to the interim analysis definition. To allow flexibility for participants with at least 3 prior lines to enroll in the study, the amended protocol removes the 20% limit for participants who have received 3 prior lines of therapy. Safety terminology has been updated, with 'corneal events' replacing 'ocular AEs' for the primary and secondary endpoints based on the keratopathy visual acuity (KVA) scale.

Furthermore, additional clarifications have also been provided. A description and rationale for all changes is provided in the table that follows.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Protocol Synopsis; Section 1.3 Schedule of Activities Section 3 Objectives and Endpoints and Estimands; Section 4.1 Overall Design; Section 4.2 Scientific Rationale for Study Design; Section 4.3 Justification for Selected Doses and Schedules Section 4.4 Rationale for the Investigation of Symptom-based Dose Modifications (Arm E) Section 6.5.1 Dose Modification for Corneal Events (Arms A to D) Section 9.2.1 Sample Size Assumptions: Primary Endpoint Section 9.4.1 Dosing based on Baseline Disease Characteristics – Virtual Treatment Arm Section 9.4.3 Safety Analyses	Update of primary and secondary endpoints to specify terminology with 'corneal events' replacing 'ocular AEs'.	Alignment with program-level updates
Section 1.1 Protocol Synopsis; Section 3 Objectives and Endpoints and Estimands; Section 8.4.1 Blood Sample Collection for Pharmacokinetics Section 8.4.2 Pharmacokinetic Sample Analysis Section 8.8 Immunogenicity Assessments	Removed the assessment of total plasma monoclonal antibody concentration.	The immunogenicity assay no longer requires total monoclonal antibody concentration values for interpretation.
Section 1.1 Protocol Synopsis; Section 6.3 Measures to Minimize Bias: Randomization	Removed enrollment target of having 20% of participants who have received 3 prior lines of therapy	To allow flexibility for participants with at least 3 prior lines to enroll in the study
Section 1.1 Synopsis Section 9.3.1 Analysis Populations Section 9.5 Interim Analysis Section 9.5.1 Independent Data Monitoring Committee Section 10.10.5 Committees Structure	Clarification provided related to the Evaluable Population for planned interim analyses to occur after 15 participants each in Arms A to D have received 2 doses of study treatment with 1 disease assessment following the second dose, or confirmed progressive disease (PD) per IMWG [Kumar, 2016], or death.	Clarification for data analyses including update for the interim analysis definition

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 4.1 Overall Design	Additional content to the overall study has been added which includes post analysis continued treatment (PACT) implementation and End of Study definition. Included distinct definitions for end of data collection timepoint for the final clinical study report (CSR) and End of Study timepoint.	Clarification on End of Study and PACT definitions.
Section 1.1 Synopsis Section 2.1 Study Rationale Section 2.3.2 Benefit Assessment Section 3 Objectives and Endpoints Section 4.1 Overall Design Section 4.3 Justification for Selected Doses and Schedules Section 9.2.2 Safety Stopping Rule for Arm E	Removal of regulatory approval of belantamab mafodotin	Alignment with program-level updates
Section 1.3 Schedule of Activities Section 7.1 Discontinuation of Study Treatment	Clarification that treatment discontinuation should be undertaken after confirmation of PD per IMWG criteria.	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarify confirmation of PD as per IMWG criteria prior to initiating a new anti-myeloma therapy.	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarification that information related to subsequent anti-myeloma therapies should be collected at any time after end of treatment visit.	Clarification for study conduct
Section 1.3 Schedule of Activities Section 10.13 Appendix 13 Clinical Laboratory Tests	Clarification that laboratory tests should be completed and reviewed 72 hours prior to dosing.	Clarification for study conduct
Section 1.3 Schedule of Activities Section 10.13 Appendix 13 Clinical Laboratory Tests	Clarification that ACR urine sample must be collected at screening.	Clarification for study conduct
Section 1.3 Schedule of Activities Section 8.1 Efficacy Assessments	Clarification that PD must be confirmed by 2 central laboratory assessments.	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarification that serum/urine immunofixation will be performed each time that M-protein is not quantifiable by SPEP (0g/dL) or UPEP (0mg/24hr).	Clarification for study conduct

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Sampling time windows for PK, sBCMA, and ADA assessments have been added to Table 4	Clarification for study conduct
Section 1.3 Schedule of Activities Section 8 Study Assessments and Procedures Section 8.2.5 Ocular Examinations	Clarification on timing of ocular examinations when participant is not receiving a dose of study treatment.	Clarification for study conduct
Section 1.3 Schedule of Activities	Revised to remove the EOT PK, ADA, and sBCMA.	Alignment with program-level updates
Section 1.3 Schedule of Activities Section 3 Objectives and Endpoints Section 8.1 Efficacy Assessment Section 8.1.2 Minimal Residual Disease Assessment Section 10.13 Appendix 13 Clinical Laboratory Tests	Revised to remove samples, exploratory endpoint and assessments related to MRD	Alignment with program-level updates
Section 1.3 Schedule of Activities Section 8.6 Biomarkers/Translational Research Section 8.6.3 Circulating Plasma Cell-Free DNA Analysis Section 10.13 Appendix 13 Clinical Laboratory Tests	Revised to remove samples and analyses related to cfDNA	Collection no longer required due to limited interoperability of cfDNA data and to reduce participant burden
Section 1.3 Schedule of Activities; Section 5.1 Inclusion Criteria Section 5.2 Exclusion Criteria Section 6.8.2 Prohibited Medications and Non-drug therapies Section 7.1 Discontinuation of Study Treatment Section 8.2.5 Ocular Examinations Section 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information Section 10.18 Appendix 18: Progression-Free Survival Event and Censoring Rules	Updated language to refer to anti-cancer therapy and/or anti-MM therapy as anti-myeloma therapy.	Alignment with program-level updates
Section 2.3.1 Risk Assessment	Update to risk assessment and alignment with updated risks in belantamab mafodotin Investigator's Brochure v10.	Alignment with program-level updates

Section # and Name	Description of Change	Brief Rationale
Section 4.6 End of Study Definition	New paragraph added to align with PACT implementation. Included distinct definitions for end of data collection timepoint for the final CSR and End of Study timepoint.	Clarification on End of Study and PACT definitions.
Section 5.1 Inclusion Criteria (Criterion 3)	Added definition of failed myeloma therapy	Clarification for study conduct
Section 5.2 Exclusion Criteria (Criterion 20)	Added clarification that use of monoclonal antibodies for serious conditions are permitted after consultation with the Medical Director.	Clarification for study conduct
Section 6.1.1 Belantamab Mafodotin	Window of intravenous administration has been broadened to 30-60 minutes.	Update for study conduct
Section 6.1.1 Belantamab Mafodotin	Clarification on calculation of belantamab mafodotin dosage based on body weight.	Clarification for study conduct
Section 6.5 Dose Modification (Dose Reductions and Dose Delays)	Clarification of conditions and timing of treatments related to dose delay.	Clarification for study conduct
Section 6.5.3 Dose Modification for Treatment-related Non-ocular Adverse Events (All Arms)	Dose modification guidelines for belantamab mafodotin updated to align with NCI-CTCAE guidelines.	Alignment with program-level updates
Section 6.6 Continued Access to Study Treatment after the End of the Study	Updated the title and language of the section to align with PACT implementation.	Clarification on End of Study and PACT definitions.
Section 6.6.1 Continued Access to Study Treatment after the Final Data Cutoff prior to End of the Study Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Updated language to align with PACT implementation.	Clarification on End of Study and PACT definitions.
Section 6.8 Concomitant Therapy	Guidance added for study participants who may be diagnosed with unrelated malignancy and concomitant therapies.	To define the allowance of local therapy for unrelated malignancies
Section 6.8.2 Prohibited Medications and Non-Drug Therapies	Clarification added to define scope of myeloma therapy.	Clarification for study conduct

Section # and Name	Description of Change	Brief Rationale
Section 8.1.1 Response Evaluation Section 9.4.4 Efficacy Analyses Section 10.18 Progression-Free Survival Event and Censoring	Clinical response assessments for relapsed or refractory multiple myeloma (RRMM) will only be evaluated by the investigator as defined by 2016 IMWG response criteria [Kumar, 2016], as data permits, removing the assessment by proprietary algorithm.	Updated as per regulatory agency feedback on other DREAMM studies
Section 8.2.2 Vital Signs	Removed requirement for semi-supine position while obtaining vital sign measurements	Clarification for study conduct
Section 8.2.5 Ocular Examinations	Clarification on timing of ocular examinations when participant has reached end of treatment.	Clarification for study conduct
Section 8.3.5 Pregnancy	Updated language to indicate the investigator will follow up 6 to 8 weeks after delivery.	To align with updated neonate follow-up in current informed consent form
Section 9.3.1 Analysis Populations	Clarification added on the definition of the PK evaluable population	Clarification for study analysis
Section 9.4.5.1 Pharmacokinetic Data Analysis	Clarification provided related to the planned pharmacokinetic analyses.	Clarification for study conduct
Section 10.7 Appendix 7: Country-Specific Requirements	Limit enrollment to only participants who have failed at least 4 prior lines of anti-myeloma therapies (France-specific).	Regulatory agency requirement (France) incorporated into the global protocol amendment from France-specific protocol amendment.
Section 10.10.7 Appendix 10 Data Quality Assurance	Update to indicate that quality tolerance limits are pre-defined in the Quality tolerance limits (QTL) plan.	Clarification for data quality management
Section 10.10.11 Third Parties and Subcontractors	Listing of third parties and subcontractors supporting this study.	Added for clinical trial transparency
Section 10.13 Appendix 13 Clinical Laboratory Tests	Removed requirement for reticulocyte assessment as a part of clinical laboratory testing. Additional updates related to CO_2 and PK assessments.	To allow for greater flexibility for sites and clarification for study conduct
Section 10.18 Appendix 18: Progression-Free Survival Event and Censoring Rules	Updates to progression-free survival censoring rule, and definitions of adequate assessment and loss-to-follow-up window	Alignment with program-level updates
Section 10.21 Appendix 21 Abbreviations and Trademarks	Updated to include PACT	Standard document practice
Throughout the document	Minor editorial and document formatting changes	Minor, therefore have not been summarized

Abbreviations: BCVA=best corrected visual acuity; CR=Complete response; DoR=Duration of Response; IMWG=International Myeloma Working Group; KVA=keratopathy visual acuity; logMAR= logarithm of the minimum angle of resolution; MRD=minimal residual disease; OS=overall survival; OSDI=Ocular Surface Disease Index; PACT=post analysis continued treatment; PD=progressive disease; PFS=progression-free survival; PR=partial response; PRO-CTCAE=Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QTL=quality tolerance limit; SPEP=serum protein electrophoresis; sCR=stringent Complete Response ; UPEP=urine protein electrophoresis; VGPR=very good partial response.

Amendment 01 (21-Jan-2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment: Amendment 01 is a global protocol amendment to address health authority feedback. Additional clarifications have also been provided. A description and rationale for all changes is provided in the table that follows.

Section # and Name	Description of Change	Brief Rationale
Document headers, Title Page, Sponsor Signatory page, Protocol Amendment Summary of Changes section (new)	Document headers, Title Page, and Sponsor Signatory page were updated according to the Sponsor's template; Protocol Amendment Summary of Changes section was added	Editorial changes to align with the Sponsor's standard protocol template and ways of working
1.1. Synopsis (Objectives and Endpoints) 3. Objectives and Endpoints and Estimands 8.1 Efficacy Assessments 9.4.4 Efficacy Analyses (Table 17)	Updated the definition of DoR to include death due to any cause	Health authority request that death due to any cause should be included in the DoR definition
1.1 Synopsis (Overall Design) 4.1 Overall Design 4.6 End of Study Definition/Study Completion 9.2.1 Sample Size Assumptions: Primary Endpoint	Amended the timing of when the primary analysis will be performed	Health authority recommendation that all subjects have a minimum of 9-12 months follow-up from the onset of first response to allow for an adequate assessment of durability of response and safety

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis (Study Treatment Groups and Duration) 5.1. Inclusion Criteria (criterion 4d)	Removed the measurable disease inclusion criterion for participants with only extramedullary disease (non-irradiated plasmacytoma with ≥1 measurable lesion that has a single diameter of ≥2 cm) and corresponding enrollment cap (≤5%) of these participants	Health authority request as this is not in the IMWG definition of measurable disease
5.2 Exclusion Criteria (criterion 21)	Added hypersensitivity or idiosyncratic reaction to belantamab mafodotin or any study treatment components	Health authority request that these participants are excluded from the study
5.2 Exclusion Criteria (criterion 24)	Changed units of measure of hemoglobin from 10^9/L to g/dL.	Error correction
1.3 Schedule of Activities (OS Follow-Up, footnote 9, and footnote 42) 6.5.1. Dose Modification for Ocular Adverse Events (Arms A to D)/ Table 8 KVA Scale and Dose Modification Guidelines for Corneal Toxicities for Belantamab Mafodotin Treatment for Arms A to D (new footnote a) 6.8.1. Ocular Supportive Care: Guidelines and Prophylactic Measures 7.1.2. Corneal Event Stopping Criteria 8.2.5. Ocular Examinations 9.2.2. Safety Stopping Rule for Arm E/Table 14 Safety Stopping Rule for Arm E	Removed “treatment-related” qualifier when referencing ocular toxicity/corneal findings and provided a list of exceptions to ocular toxicities/corneal findings considered **not** to be related to belantamab mafodotin	Health authority request to provide clarity around ocular toxicity/corneal findings not being monitored in participants as it is expected most events may be related to study treatment

Section # and Name	Description of Change	Brief Rationale
6.5.1. Dose Modification for Ocular Adverse Events (Arms A to D)/Table 8 KVA Scale and Dose Modification Guidelines for Corneal Toxicities for Belantamab Mafodotin Treatment for Arms A to D 6.5.2. Dose Modifications Based on Ocular Symptoms, Visual Acuity Assessments, and Corneal Findings (Arm E)/Table 9 Dose Modification Guidelines for Belantamab Mafodotin Treatment for Arm E based on OSDI, Visual Acuity, and Corneal Findings	Table 8 only: Corrected Grade 2 change in Snellen-Equivalent BCVA to, "…and is **equal to or** better than 1.0 logMAR (20/200)"; Corrected Grade 3 change in Snellen-Equivalent BCVA to, "…and is **equal to or** better than 1.0 logMAR (20/200)"; Corrected Grade 4 change in Snellen-Equivalent BCVA to, "Visual acuity is **worse than** 1.0 logMAR (20/200)." Table 8 only: Added a new footnote (e) to specify that Grade 4 "Corneal ulcer" includes other corneal epithelial defects such as corneal erosions. Table 8 and Table 9: Updated dose modification guidelines to advise permanent discontinuation of belantamab mafodotin in participants receiving the lowest dose and who experience a Grade 4 event according to the KVA scale. However, investigators may submit a request for treatment continuation to be reviewed by the sponsor.	Error correction to align with the belantamab mafodotin label Program update as these severe corneal defects have been observed in other DREAMM studies and to ensure participant safety. Health authority request that these participants be permanently discontinued from study treatment

Section # and Name	Description of Change	Brief Rationale
6.5.2. Dose Modifications Based on Ocular Symptoms, Visual Acuity Assessments, and Corneal Findings (Arm E)/Table 9 Dose Modification Guidelines for Belantamab Mafodotin Treatment for Arm E based on OSDI, Visual Acuity, and Corneal Findings Throughout (including Figure 1 DREAMM-14 Study Schema)	Updated visual acuity criteria from 0.3 to 0.1 logMAR and corneal findings criteria to be based on Grades 2 through 4 according to the KVA scale. Per the above change, updated the protocol wording throughout that Arm E dose modifications that are based on ocular symptoms (patient-reported symptoms using the OSDI), visual acuity assessments (Snellen chart or equivalent)**, and corneal findings (KVA scale)**.	Health authority request to revise the dose modification guidelines for Arm E to hold belantamab mafodotin for Grade ≥2 events according to the KVA scale
7.1 Discontinuation of Study Treatment	Updated the protocol wording to clarify that study treatment discontinuation is mandatory in case of PD, unacceptable toxicity, pregnancy or in case the participant has met any of the protocol-defined safety stopping criteria.	Update per health authority request
8.1.2. Minimal Residual Disease Assessment	Clarified that MRD assessments will be performed using the clonoSEQ assay and that MRD negativity will be assessed using a 10^{-5} sensitivity threshold in participants achieving a response of CR or better. **The MRD negativity rate in participants achieving a response of VGPR or better will be assessed as an additional sensitivity analysis.**	Update per health authority request
8.9.1.1. Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)	Specified what items of the PRO-CTCAE will be assessed	Clarification of the exact PRO-CTCAE items that will be administered in the study per health authority request

Section # and Name	Description of Change	Brief Rationale
9.2.1 Sample Size Assumptions: Primary Endpoint/Table 13 Study Safety Operating Characteristics	Changed acceptance criteria and introduced an additional criterion based on lower 95% CI of the estimates on difference in Grade ≥2 corneal event rates between test and control arms	Update per health authority request
9.4. Key Elements of Statistical Analysis Plan	Removed redundant information regarding statistical comparison of the treatment arms to the control arm	Information already presented in Section 9.2.1. Sample Size Assumptions: Primary Endpoint
9.4.4. Efficacy Analyses/ Table 17 Statistical Analytical Methods: Efficacy	Updated the statistical analysis methods to correctly describe approach for the secondary endpoints of OS and PFS	Correction/clarification per health authority request
10.4. Appendix 4 **Decentralized and Remote Assessment** Approaches (and corresponding wording referencing Section 10.4 in Section 1.3. Schedule of Activities (SoA))	Removed home healthcare and telemedicine measures. Clarified that eye examinations not performed centrally are to be conducted at only a specified alternative eye care specialist clinic, **not in the participant's home**. These visits are considered **decentralized assessments** and **not** home healthcare, telemedicine, or remote eye examinations.	Removed home healthcare and telemedicine measures as they are not considered appropriate for the study at this time. Clarification to study conduct if measures for decentralized eye examinations are followed per health authority request
10.18. Appendix 18: Progression-Free Survival Event and Censoring Rules	In the "Date of Event" column of the "Death or PD after missing 2 or more scheduled assessments" row, corrected, "…since disease assessment is every 4 weeks, a window of 70 days (6 weeks + 3-day window)" to "…since disease assessment is every **3** weeks, a window of **49** days (6 weeks + **7**-day window)" and corrected, "If the time difference between PD/death…is more than **49** days,"	Error correction and alignment with other DREAMM studies

Abbreviations: BCVA=best corrected visual acuity; CR=Complete response; DoR=Duration of Response; IMWG=International Myeloma Working Group; KVA=keratopathy visual acuity; logMAR= logarithm of the minimum angle of resolution; MRD=minimal residual disease; OS=overall survival; OSDI=Ocular Surface Disease Index; PD=progressive disease; PFS=progression-free survival; PR=partial response; PRO-CTCAE= Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; VGPR=very good partial response.

10.22. Appendix 22: French-Specific Requirements

This appendix includes all applicable requirements of French Public Health Code / specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information to the study protocol.

1. Concerning the « SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA»

A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category (French Public Health Code L.1124-1).
It is the investigator's responsibility to ensure and to document (in the source document - subject notes) that the subject is affiliated to or beneficiary of a social security category.

2. Concerning the "STUDY GOVERNANCE CONSIDERATIONS"

- **In section "Regulatory and Ethical Considerations, including the Informed Consent Process" of study protocol**

⇒ Concerning **the process for informing the subject** and/or his/her legally authorized representative, the following text is added:

French Patient Informed Consent is a document which summarizes the main features of the study and allows collection of the subject and/or his/her legally authorized representative written consent. It also contains a reference to the single scientific and ethical regulatory authorisation.

⇒ Concerning **the process for obtaining** subject informed consent:

- When a research involving human being **is carried out on a minor / on an adult in the care of a "tutelle" guardian**, consent is given by their legal representative.

- When research involving human being **is carried out on an adult in the care of a "curatelle" guardian**, consent is given by the subject assisted by his guardian.

When research involving human being is considered for **an adult incapable** of expressing her/his consent and not under a legal protection order, consent is given by a person of trust as defined in article L. 1111-6 and, failing this, by the family, or a person who maintains close and stable links with the subject.

⇒ **Concerning the management of the Patient Informed Consent Forms**, the following text is added:

French Patient Informed Consent Form is in duplicate (triplicate for minor subject).
The first page of the Patient Informed Consent Form is given to the investigator. The copy is kept by the patient or legally authorized representative.

- **NOTIFICATION TO THE HOSPITAL DIRECTOR**

In accordance with Article R.1123-69 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

- **INFORMATION TO THE HOSPITAL PHARMACIST**

In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the IB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial.

- **Ethnic Origin**

In accordance with the data privacy regulation, the ethnic origin, as any personal data, can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

- **TESTING OF BIOLOGICAL SAMPLES**

In accordance with the French Public Health Code – article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

3. Concerning the " DATA MANAGEMENT " the following text is added:

Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacists if applicable, involved in this clinical trial, and data regarding the subjects recruited in this clinical trial (subject number, treatment number, subjects status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GSK or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the data privacy regulation, each of these people aforesaid has a right of access, correction and opposition on their own data through GSK (Clinical Operations Department).

4. Concerning Data Privacy

In accordance with the applicable data privacy regulation, personal data are processed in a manner that ensures appropriate security, including protection against unauthorized or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organizational measures. The processing is whether deemed to be compliant with one of the methodology of reference **(MR-001)** or has been the subject of a request for authorization to the CNIL. The Investigator has, regarding the processing data related to her/him, a right of access, of rectification, erasure and of opposition with GSK in accordance with the legal provisions.

5. Investigational Product Accountability, Reconciliation, and Destruction

In specific situations where institutional practices dictate that the site disposes of and/or destroys IP prior to allowing the "monitor" to verify and document IP accountability, the following applies:

*"During the conduct of the Study, Investigational Product (IP) will be destroyed by the Institution prior to a GSK "**monitor**" conducting final investigational product accountability. Institution agrees that such destruction will comply with Institution's investigational product accountability procedures and will provide GSK with investigational product accountability logs and supporting documentation to verify adherence to 'Bonnes Pratiques Cliniques' (decision dated on the 24th of November 2006).*

11. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-376.

Anderson KC, Alsina M, Atanackovic D, Biermann JS, Chandler JC, Costello C, et al. NCCN Guidelines Insights: Multiple Myeloma, Version 3.2016. J Natl Compr Canc Netw. 2016;14(4):389-400.

Andrade RJ, Robles M and Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8(6):709-714.

Basch E, Reeve BB, Mitchell SA, Clauser SB, Minasian LM, Dueck AC, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst. 2014;106(9).

Brookmeyer R and Crowley J. A confidence interval for the median survival time. Biometrics. 1982;38:29-41.

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993;11(3):570-579.

Cocks K, Cohen D, Wisloff F, Sezer O, Lee S, Hippe E, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-MY20) in assessing the quality of life of patients with multiple myeloma. Eur J Cancer. 2007;43(11):1670-1678.

Dolgin M, Association CCotNYH, Committee NYHAC, Fox AC and Levin RI. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. Little, Brown; 1994.

Dougherty BE, Nichols JJ and Nichols KK. Rasch analysis of the Ocular Surface Disease Index (OSDI). Invest Ophthalmol Vis Sci. 2011;52(12):8630-8635.

Eliason L, Loubert A, Gorsh B, Meunier J, Kleinman D, Sapra S, et al. PCN309 Methodology for Evaluating Meaningful Change Thresholds in Patient-Reported Outcome (PRO) Measures for Corneal Events in Patients with Relapsed/Refractory Multiple Myeloma (RRMM) Receiving Single-Agent Belantamab Mafodotin (BELAMAF). Value in Health. 2020;23:S477.

Farooq AV, Degli Esposti S, Popat R, Thulasi P, Lonial S, Nooka AK, et al. Corneal Epithelial Findings in Patients with Multiple Myeloma Treated with Antibody-Drug Conjugate Belantamab Mafodotin in the Pivotal, Randomized, DREAMM-2 Study. Ophthalmol Ther. 2020;9(4):889-911.

Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Blade J, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23(15):3412-3420.

Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised. Rockville, MD: National Institute of Mental Health; 1976.

Holladay JT. Visual acuity measurements. J Cataract Refract Surg. 2004;30(2):287-290.

Hunt CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: a systematic review. Hepatology. 2010;52(6):2216-2222.

Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e346.

Langat DL, Wheaton DA, Platt JS, Sifers T and Hunt JS. Signaling pathways for B cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL) in human placenta. Am J Pathol. 2008;172(5):1303-1311.

Laurent SA, Hoffmann FS, Kuhn PH, Cheng Q, Chu Y, Schmidt-Supprian M, et al. gamma-Secretase directly sheds the survival receptor BCMA from plasma cells. Nat Commun. 2015;6:7333.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Deny P, et al. Quantification of hepatitis delta virus RNA in serum by consensus real-time PCR indicates different patterns of virological response to interferon therapy in chronically infected patients. J Clin Microbiol. 2005;43(5):2363-2369.

Li X, Wulfsohn MS and Koch GG. Considerations on Testing Secondary Endpoints in Group Sequential Design. Statistics in Biopharmaceutical Research. 2017;9(4):333-337.

Lonial S, Lee HC, Badros A, Trudel S, Nooka AK, Chari A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol. 2020;21(2):207-221.

Miller KL, Walt JG, Mink DR, Satram-Hoang S, Wilson SE, Perry HD, et al. Minimal clinically important difference for the ocular surface disease index. Arch Ophthalmol. 2010;128(1):94-101.

Moreau P, San Miguel J, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv52-iv61.

Oca M, Bhattacharya S, Vitali N, Patel K, Kaczynski H, Shi H, et al. The anti-BCMA Antibody-Drug Conjugate Belantamab Mafodotin (GSK2857916) Drives Immunogenic Cell Death and Immune-Mediated Anti-Tumor Responses, and in Combination with an OX40 Agonist Potentiates in vivo Activity: PF558. HemaSphere. 2019;3:231.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, et al. Drug-induced liver injury following positive drug rechallenge. Regul Toxicol Pharmacol. 2009;54(1):84-90.

Parrozzani R, Lombardi G, Midena E, Leonardi F, Londei D, Padovan M, et al. Corneal side effects induced by EGFR-inhibitor antibody-drug conjugate ABT-414 in patients with recurrent glioblastoma: a prospective clinical and confocal microscopy study. Ther Adv Med Oncol. 2020;12:1758835920907543.

Pinto V, Bergantim R, Caires HR, Seca H, Guimaraes JE and Vasconcelos MH. Multiple Myeloma: Available Therapies and Causes of Drug Resistance. Cancers (Basel). 2020;12(2).

Popat R, Lonial S, Voorhees P, Esposti S, Gupta I, Opalinska J, et al. DREAMM-2: Single-Agent Belantamab Mafodotin (Belamaf) Effects on Patient-Reported Outcome (PRO) Measures in Patients with Relapsed/Refractory Multiple Myeloma (RRMM). 2020;136:27-28.

Proskorovsky I, Lewis P, Williams CD, Jordan K, Kyriakou C, Ishak J, et al. Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. Health Qual Life Outcomes. 2014;12:35.

Rajkumar SV. Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol. 2016;91(7):719-734.

Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691-4695.

Rajkumar SV and Kumar S. Multiple myeloma current treatment algorithms. Blood Cancer J. 2020;10(9):94.

Rajkumar SV, Richardson P and San Miguel JF. Guidelines for determination of the number of prior lines of therapy in multiple myeloma. Blood. 2015;126(7):921-922.

Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD and Reis BL. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol. 2000;118(5):615-621.

Siegel RL, Miller KD and Jemal A. Cancer statistics, 2020. 2020;70(1):7-30.

Tai YT, Mayes PA, Acharya C, Zhong MY, Cea M, Cagnetta A, et al. Novel anti-B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. Blood. 2014;123(20):3128-3138.

Terpos E, Mikhael J, Hajek R, Chari A, Zweegman S, Lee HC, et al. Management of patients with multiple myeloma beyond the clinical-trial setting: understanding the

balance between efficacy, safety and tolerability, and quality of life. Blood Cancer J. 2021;11(2):40.

Trudel S, Lendvai N, Popat R, Voorhees PM, Reeves B, Libby EN, et al. Antibody-drug conjugate, GSK2857916, in relapsed/refractory multiple myeloma: an update on safety and efficacy from dose expansion phase I study. Blood Cancer J. 2019;9(4):37.

Signature Page for 209628 TMF-19107833 v2.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 25-Jun-2024 13:24:19 GMT+0000

Signature Page for TMF-19107833 v2.0