Statistical Analysis Plan

Study ID: 209628

Study Official 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)

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TITLE PAGE

Protocol Title:	A Phase II, 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)
Study Number:	209628
Compound Number:	GSK2857916
Abbreviated Title:	Study to Investigate Alternative Dosing Regimens of Belantamab Mafodotin in Participants with Relapsed or Refractory Multiple Myeloma (DREAMM-14)
Acronym:	DREAMM-14

Sponsor Name:

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1.0	Refer to Document Date	21Jan2022	Not Applicable	Original version
SAP amendment 1	Refer to Document Date	Protocol amendment 02(PA02) 19Dec2022.	**Section 1.1** • Update of primary and secondary endpoints to specify terminology 'corneal events' replacing 'ocular AEs'. • Removed the assessment of total plasma monoclonal antibody concentration • Removed MRD negativity endpoint **Section 1.1.1** • Updated 'Ocular AE' to 'Corneal event'. **Section 1.2** • Removed enrollment target of having 20% of participants who have received 3 prior lines of therapy • Updated 'Approved dose of belantamab mafodotin(2.5 mg/kg) to 'DREAMM-2 established 2.5 mg/kg Q3W dosing regimen' • Updated the interim analysis definition **Section 3** • Added Evaluable population (IA only)	Updated as per PA02

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			Section 4.2, 4.2.1, 4.2.2 , 4.3, 4.3.1, 5.2, Table 8, Table 9 Updated 'Ocular AEs' to ' Corneal event'.	
			Section 4.1.2 • Removed "For ECG analyses, if the latest , non-missing pre dose value is from triplicate, the participant level baseline is defined as the mean of triplicate baseline assessments"	ECG is being collected only at screening.
			Section 4.3 • Added details for the analysis of cumulative incidence of corneal events. Removed "by grade" from the title.	This is competing risk analysis and event of interest is corneal event of Grade 2 or above, so a by grade analysis is not possible.
			Section 4.3 • Updated text to "the baseline for deriving change in logMAR would be reset to the BCVA after the surgery and the visit closest to the next dose administration." From "the baseline for deriving change in logMAR would be reset	Added more details.

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			to the first visit after the surgery".	
			Section 4.3.1 • Updated 'derived response' to 'investigator assessed' response for ORR at interim, primary and final analysis.	Updated as per PA02
			Table 3 • Corrected confirmed response for scenario 11; from NE to SD. **Table 4** • Updated PFS censoring rule	Updated as per PA02
			Section 4.3.2 • Removed "Sensitivity analysis will be conducted using investigator assessed responses for Duration of response ,PFS, and Time to response" as derived response is no longer being used. • Removed ' sensitivity for DoR' as 'death due to PD' is no longer applicable. • Added a PFS sensitivity analysis using alternative censoring rule defined in Table 4.	

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Section 4.4 • Removed MRD rate analysis description	Updated as per PA02
			Section 4.5 • Removed ECG from the worst case analysis.	ECG is being collected only at screening.
			Section 4.5.1 • Added dose modification summary based on Any AE, any AE or mKVA scale event, any non-ocular AE, any non-ocular AE or mKVA scale event. • Added derived dose delay summary in case multiple action can't be entered in data for the first Grade 3 mKVA scale event.	This is to provide a broader overview of reasons leading to dose modification. Derive dose delay numbers in case of first Grade 3 corneal event by mKVA scale , in case data can't capture multiple action taken.
			Section 4.5.2.1 • Removed text 'days for Q3W and 1-42, 43-84, 85-126 , >126 for Q6W'.	Corneal exams are Q3W irrespective of the dosing frequency.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Section 4.5.3.2 • Removed analysis for vital sign and ECG based on potential clinical concern.	ECG is only being collected at baseline
			Section 4.5.3.3 • Removed Electrocardiogram analysis description	ECG is only being collected at baseline
			Section 4.5.3.4 (It's 4.5.3.3 in SAP amend 01) • Added a summary of worst change in logMAR based on line of change for better and worse eye. • Added a summary of microcyst-like deposits by grade. • Removed 'Corneal epithelia defect' from the shift table, as it's not collected in the CRF, • Added a summary for characteristics of defined worsened vision. • Updated definition of 'No change', 'possible worsened vision' and 'definite worsened vision' . For example, Definite worsened vision is defined as >0.3 logMAR change now (as	To align with DREAMM14 mKVA scale

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			per mKVA scale, Grade 3 BCVA is more than 0.3 change in logMAR from baseline), previously it was >=0.3.	
			Section 4.6.1 • Added an age subgroup <65, >=65. • Added Ethnic background subgroup 'Asian Vs other '.	These subgroups are of clinical interest.
			Section 4.6.5 • Added details for model estimation. **Section 4.6.6.1** • Added exposure response for efficacy and safety analysis.	
			Section 4.6.8 • Removed text "For treatment beyond 12 doses, collect samples for ADA analysis before each infusion every 6th dose of belantamab mafodotin (dose 18, 24, 30, and so on, until PD). A final ADA sample will be drawn at the EOT visit."	Updated as per PA02
			Section 4.7, 4.8 • Updated interim analysis definition.	

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			• Updated that ORR will be based on investigator assessed response instead of 'derived response.	
			Section 4.9 • Removed clarification regarding PK population	PA02 includes updated PK population definition, so there's no change to protocol defined analysis.
			Section 4.10 • Added 'post treatment switch analysis'	Protocol suggests not to include data post-treatment switch under primary analysis; hence a separate analysis is proposed for participant switching to Arm A.
			Section 6.1.1 • Added Summary of treatment discontinuation by including any AE, any AE or mKVA scale event, non-ocular AE , non-ocular AE	This is to provide a broader overview of reasons leading to treatment

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			or mKVA and any ocular AE or mKVA scale event **Section 6.1.1.1** • 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.'	discontinuation. This is not applicable anymore, however it's there in PA02. This would be corrected in the next protocol amendment.
			Section 6.1.1.3 • Added final analysis and End of study definition.	Updated as per PA02
			Section 6.1.6 • Removed entire section Study Intervention Compliance	
			Section 6.2.4 • Added "If the participant is not being dosed, ocular examinations may be performed within ± 3 days of the Q3W visit"	Updated as per PA02

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Section 6.3 • Added population pharmacokinetic analyses **Section 6.4** • Added pharmacokinetic/pharmacodynamic analyses	This is an important component towards assessment of improved benefit/risk profile with alternative dosing regimens
SAP amendment 2	Refer to document date	Protocol amendment 3 25 June 2024	**Section 4.6.3** • Added analyses for exploratory arm E	A separate SAP for arm E is no longer applicable and is included within SAP Amendment 02
			Section 4.3 • Added definition for derivation of dose delay before End of Treatment • Added "If site have selected dose reduced on the exposure form, derive dose delay if applicable for Q3W or Q6W cycles"	This is to provide clarity to specific scenarios for dose delay derivation.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Section 6.2 • Added eCOA compliance section.	This is to align with the Sponsor's updated release to the new SAP template with eCOA compliance.
			Section 4.6.3 • Added sensitivity analysis to the following endpoints – o Arm E specific tables (OSDI, VA by oncologists' assessment)	This is added to conduct the analysis excluding patients with significant data quality issues which may impact interpretation of the endpoints.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses and outputs to be included in the Clinical Study Report (CSR) for Protocol 209628 / 02.

This statistical analysis plan (SAP) is intended to describe the efficacy, safety, pharmacokinetic (PK), biomarker, and patient reported outcome (PRO) analysis required for the study. Details of the planned interim analyses, as well as the final analyses, are provided. Additional details with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

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 Relapsed or Refractory Multiple Myeloma compared to the DREAMM-2 established 2.5 mg/kg Q3W dosing regimen.

Table 1 Summary of 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 [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

Objectives	Endpoints
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
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 FACTGP5 • 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

Objectives	Endpoints
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

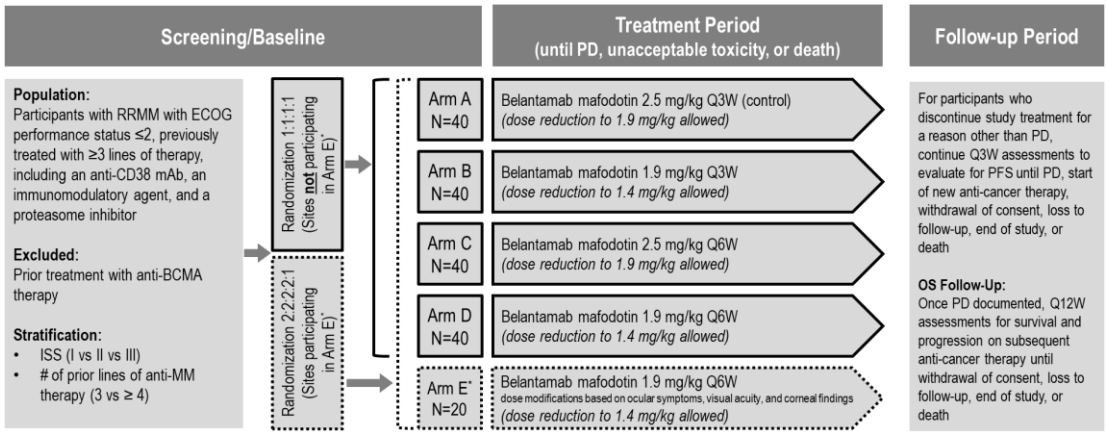
1.1.1. Estimands

The primary clinical question of interest is: what is the impact on the incidence of Grade ≥2 corneal events (KVA) 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.

1.2. Study Design

Overview of Study Design and Key Features	
	
Design Features	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 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 modified keratopathy visual acuity (mKVA) 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 mKVA scale), will be used to inform dose modification decisions. ***Note:*** *Although not determining dose*

Overview of Study Design and Key Features	
	modification decisions, ocular events (corneal findings and BCVA) graded per the mKVA scale will still be recorded for all participants in Arm E throughout the study. The KVA scale used in DREAMM-14 is a modified version of the original KVA scale used in other DREAMM studies. Key differences in the modified KVA scale include the addition of Grade 0, use of logMAR units for visual acuity and additional descriptions of corneal findings. 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 posttreatment 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. Study details include • Study Duration: Approximately 28 months • Treatment Duration: Until PD, unacceptable toxicity, or death • Visit Frequency: Q3W
Study intervention	**m A: 2.5 mg/kg Q3W** (DREAMM-2 established single agent dosing regimen) o Rationale for Arm A: control o Dose modification for ocular events: see Section 6.5.1 of the CSP (dose reduction to 1.9 mg/kg allowed) **m B: 1.9 mg/kg Q3W** o Rationale for Arm B dosing: see Section 4.3 of the CSP o Dose modification for ocular events: see Section 6.5.1 of the CSP (dose reduction to 1.4 mg/kg allowed) **Arm C: 2.5 mg/kg Q6W** o Rationale for Arm C dosing: see Section 4.3 of the CSP o Dose modification for ocular events: see Section 6.5.1 of the CSP (dose reduction to 1.9 mg/kg allowed) **Arm D: 1.9 mg/kg Q6W** o Rationale for Arm D dosing: see Section 4.3 of the CSP o Dose modification for ocular events: see Section 6.5.1 of the CSP (dose reduction to 1.4 mg/kg allowed) **m E: 1.9 mg/kg Q6W with dose modifications based on ocular symptoms, visual acuity, and corneal findings assessments** o Rationale for Arm E dosing: see Section 4.4 of the CSP

Overview of Study Design and Key Features	
	○ Dose modification for ocular events: see Section 6.5.2 of the CSP (dose reduction to 1.4 mg/kg allowed)
Study intervention Assignment	• 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 of the CSP). • 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).* There are two stratification factors- 1.ISS for MM (I vs II vs III) (see Section 10.2 of the CSP) 2.Number of prior lines of anti-MM therapy (3 vs ≥4)
Interim Analysis	An interim analysis is planned when 15 participants each in Arms A to D have been enrolled and have received at least two doses of study treatment with one disease assessment following the second dose, or confirmed PD per IMWG [Kumar, 2016] or death .. Refer Section 4.7 for details.

2. STATISTICAL HYPOTHESES

No formal hypothesis testing will be performed in this study.

2.1. Multiplicity Adjustment

Not applicable.

3. ANALYSIS SETS

Table 2 Study Analysis Sets

Analysis Set	Definition / Criteria	Analyses Evaluated
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.	Study population
Intent-to-Treat (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.	Efficacy
Safety	All randomized participants who receive at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.	Safety
Pharmacokinetic (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.	PK
Evaluable population (IA only)	The Evaluable Population for the interim analysis will consist of all participants who have received two doses of study treatment and have completed one disease assessment after the second dose or confirmed PD or death. This population	Futility at IA

Analysis Set	Definition / Criteria	Analyses Evaluated
	will be the primary population for futility assessment at Interim analysis only	

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

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.

In the case of wrong stratification assigned at the time of randomization, the analyses will be performed based on the data collected in the CRF, not the assigned stratum at randomization.

Confidence intervals will use 95% confidence levels unless otherwise specified.

Data will be listed and summarized according to the GSK reporting standards, where applicable. Subject level data will be available through the Reporting & Analysis Plan Improving Design and Delivery of Outputs Data Viewer (RAPIDO DV) tool. Selected listings will be created in static fashion. See OPS for more details.

In this multicenter global study, enrolment will be presented by country and site. Data from all participating centers will be integrated and no controlling for center-effect will be considered in the statistical analyses. 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 prior to analysis.

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

4.1.2. Baseline Definition

For all endpoints, unless otherwise specified, the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. For participants who did not receive study treatment during the study, baseline will be defined as the latest, non-missing collected value.

For laboratory data, baseline will be the latest non-missing pre-dose value from central laboratory. If no central laboratory value is available, the latest non-missing pre-dose value from local laboratory will be used. For efficacy laboratory tests, only central lab values will be used.

Unless otherwise stated, if baseline data is missing, no derivation will be performed and baseline will be set to missing.

4.2. Primary Endpoints Analyses

The primary endpoint for the study is the incidence rate of Grade ≥2 corneal events according to the KVA scale. This analysis will be performed on the safety population.

4.2.1. Definition of Primary Endpoint

Incidence rate of Grade ≥2 corneal events according to the KVA scale: The percentage of participants with Grade ≥2 corneal events assessed by KVA scale.

The arm that meets the interim threshold based on efficacy (refer Section 4.7) and meets both the following criteria will be declared to show an improved toxicity profile compared to the control arm A-

1. Posterior probability P (incidence rate of control arm – incidence rate of test arm > 0.17) > 0.7. The details on the posterior distribution is provided in Section 4.2.2.
2. The lower 95% CI of the difference in incidence rates between the test arm and the control Arm A should be > 2.5%.

4.2.2. Main analytical approach

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.

Let n1, x1 be the sample size and number of Grade ≥ 2 corneal events in Arm A respectively, and n2, x2 be the sample size and number of Grade ≥ 2 corneal events in the test arm.

Then, the posterior distribution of the incidence rate in Arm A will follow ~ Beta(6.32+x1, 3.68+n1-x1) and posterior distribution of the incidence rate in the test arm will follow ~ Beta(0.41+x2, 0.59+n2-x2)

For each arm of B-D, the testing procedure will be performed as the following:

1. Sample 100000 p1's from Beta(6.32+x1, 3.68+n1-x1)
2. Sample 100000 p2's from Beta(0.41+x2, 0.59+n2-x2)

3. Calculate the probability of $p1-p2 > 0.17$ from the above 100000 simulations.
4. If the above probability is > 0.7, the arm is considered to have met the Bayesian acceptance criterion and continue to step 5; otherwise stop here.
5. Exact 95 % Confidence interval for difference in incidence rate of Grade ≥2 corneal events between control arm and test arm will be calculated.

The arm with the highest posterior probability and having lower 95 % CI > 2.5% will be declared to show an improved toxicity profile compared to the control arm.

A table showing posterior probability and exact 95 % CI , as defined above, will be presented.

Summary of incidence rate of Grade ≥2 corneal events according to the KVA scale by treatment arm will be presented.

Other AE related summaries are defined under Section 4.5.2.

4.3. Secondary Endpoint Analyses and definition

- **Cumulative event rate of corneal events to Week 16 (KVA scale)**

  It's defined as percentage of corneal events of each grade out of all the events up to Week 16.

  A summary of cumulative event rate by treatment arm will be created.

- **Incidence rate of corneal events by grade (KVA scale)**

  It is defined as the percentage of participants with corneal events by grade according to the KVA scale in the respective treatment group.

  A summary of incidence rates of corneal events (KVA scale), and the component of the KVA scale (Corneal exam findings grade and Visual acuity grade) for all subjects at the data cut-off and as landmark analysis at 3 months, 6 months, 9 months, and 12 months by treatment arm will be provided.

- **Exposure adjusted incidence rate of corneal events by grade (KVA scale)**

  It 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. Refer Section 4.3.1 for calculation.

  Exposure adjusted incidence rate analysis will be used to assess the rate of each adverse event of interest per period of exposure. This analysis will be performed for dry eye events, blurred vision events, thrombocytopenic events, and IRR.

- **Median duration of dose delay**

  It is defined as the median duration in time of all the dose delays in the respective treatment group. Duration of delays is defined as period from the expected start date of dose to actual start date of current dose.

Calculation: (actual start date of current dose - expected start date of dose).

For Q3W dosing, Expected start date of dose = actual start date of previous dose + 21.

For Q6W dosing, Expected start date of dose = actual start date of previous dose + 42.

For delays from expected last dose to “End Date”, the analysis will follow the below criteria for considering “End Date” and choose the earliest date of the following –

A. Treatment Discontinuation Date: If this is earliest date or all dates (A)-(E) are the same then consider 30 days for Q3W cycles (following protocol definition of EOT as 30 days from last dose) OR Q6W + 3 days (45 days) for Q6W cycles.

B. Date of Death.

C. Date of decision to discontinue treatment.

D. Start date of new Anti-myeloma therapy.

E. Last contact date

If one of the (B)-(E) is the earliest date, use Q3W + 3 or Q6W + 3 for respective cycles.

If site have selected dose reduced on the exposure form, then also the dose delay will be derived if applicable for Q3W or Q6W cycles similarly.

- **Percentage of participants requiring dose reductions, dose delays, and study treatment discontinuation due to corneal events (KVA scale)**

The percentage of participants that require dose reduction out of all the participants in the respective treatment group.

Percentage of participants requiring dose delay - 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.

Refer Section 4.5.1. Extent of Exposure for planned analysis.

- **Cumulative incidence of corneal events (KVA scale)**

It 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: t1, tj-1, and tj, the overall event (both events of interest and competing risk events) free rate up to, but not including time tj, will be obtained from the Kaplan Meier estimates and is denoted by S(tj).

The probability that the event of interest happens in the time interval (t_{j-1}, t_j) which is denoted by $p(t_j)$, will be estimated by the number of events of interest occurring at time t_j divided by the number of individuals at risk before t_j. The probability of experiencing the event of interest in the time interval (t_{j-1}, t_j) will be estimated by $p(t_j)^* S(t_{j-1})$. The cumulative incidence up to time t_j will be estimated by $\sum_{i=1}^{j} p(t_i) * S(t_{i-1})$. Note that event time here may not be the onset time for Grade 2 event but the onset time of any corneal event for participants with Grade 2 or above corneal events, since only maximum grade is collected for an AE.

Discontinuation of treatment or death without the event of interest will be considered as a competing risk since its occurrence precludes the occurrence of the event of interest. For the purpose of this analysis, the date for treatment discontinuation will use last infusion date + 70 days. 70 days is approximately 5 times half-life of belantamab mafodotin. Participants who are still on treatment but did not have an event of interest will be censored at the last corneal examination date.

- **Toxicity Index by assessment/visit**

  It 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-

$$TI = \Sigma_{i=1}^{n} \frac{X_i}{\prod_{j=1}^{i-1}(1 + X_j)}$$

  Refer Section 4.3.1. Main analytical approach for planned analysis.

- **Duration of corneal events (KVA scale)**

  It is defined for each participant as the sum of duration of all the corneal AEs. The duration is defined as time from onset of any corneal events (KVA scale) of Grade 2 or above to the first time resolution to baseline, Grade 1 or below. It requires at least one day gap between the resolution of all events from first occurrence to the onset of second occurrence.

- **Percentage of time on study with corneal events (KVA scale)**

  It 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.

Time on corneal events is defined as time from onset of any corneal events (KVA scale) of Grade 2 or above to the first-time resolution to baseline, Grade 1 or below. It requires at least one day gap between the resolution of all events from first occurrence to the onset of second occurrence.

Time on study is defined as:

Date of Study Completion or Discontinuation – Date of randomization +1

- **Change in BCVA (ΔlogMAR)**

  Defined as change of logMAR units compared with baseline or the first visit after the cataract surgery. Refer Section 4.5.3.3. Ocular Examinations for planned analysis. If patient had cataract surgery, the baseline for deriving change in logMAR would be reset to the BCVA after the surgery and the visit closest to the next dose administration.

- **Overall Response rate**

  Defined as the 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].

- **Percentage of participants with a confirmed VGPR or better**

  Defined as percentage of participant with confirmed VGPR, CR, and sCR, according to the 2016 IMWG response criteria [Kumar, 2016].

- **Time to Response**

  Defined as the time between the date of randomization and the first documented evidence of response (PR or better), among participants who achieve a response (i.e., confirmed PR or better), according to the 2016 IMWG response criteria [Kumar, 2016].

- **Duration of Response**

  It is defined as the time from first documented evidence of PR or better until PD among responders according to the 2016 IMWG response criteria [Kumar, 2016] or death due to any cause.

- **Time to Progression**

  Defined as the time from randomization until the earliest date of documented PD or death due to PD, according to the 2016 IMWG response criteria [Kumar, 2016]. Responders without PD will be censored at the censoring time point for time to progression (TTP).

- **Progression Free Survival**

  Defined as the time from randomization until the earliest date of documented PD, according to the 2016 IMWG response criteria [Kumar, 2016], or death due to any cause.

- **Overall Survival**

  Defined as the time from randomization until the date of death due to any cause.

4.3.1. Main analytical approach

Exposure adjusted incidence rate of corneal events by grade (KVA scale)

Exposure adjusted incidence rate = (Number of participants with ocular events / Total participant-years)*100

Participant years = Sum of participant duration of dosing in days (across all participants)/365.25,

Participant duration of dosing in days=Event onset date or (last dose date + 70) – first dose date + 1.

For participants with event, first event onset date will be used and for participants without an event, last dose date + 70 will be used. If a participant died or discontinued from study prior to last infusion date + 70 days without the event of interest, the death date or study discontinuation date will replace last infusion date+70. Seventy days is approximately 5 times half-life of belantamab mafodotin.

Toxicity Index (TI)

Let X1, X2…..Xn be the toxicity grades of a subject, rank the toxicity grade of a subject toxicity profile in descending order X1 >=X2 >=…>=Xn,

$$TI = X_1 + \frac{X_2}{1 + X1} + \frac{X_3}{(1 + X_1)(1 + X_2)} + \cdots + \frac{X_n}{(1 + X_1) \ldots (1 + X_{n-1})}$$

(X1 be the maximum toxicity grade for a subject)

Summary statistics for Toxicity Index by treatment arm will be provided. A data listing indicating TI will also be provided.

Overall response rate (ORR)

ORR at interim analysis, primary and final analysis will be analyzed based on the investigator-assessed confirmed responses, using the algorithm specified in

Table 3.The date of the first of the two consecutive assessments will be used as the date of the confirmed response.

Table 3 Response confirmation algorithm

#	Response at the First Time Point	Response at Subsequent Disease Assessment[1]	Confirmed Response at the First Time Point
1	sCR	sCR	sCR
2	sCR	CR	CR
3	CR	sCR/CR	
4	sCR/CR	VGPR	VGPR
5	VGPR	sCR/CR/VGPR	
6	sCR/CR/VGPR	PR	PR
7	PR	sCR/CR/VGPR/PR	
8	sCR/CR/VGPR/PR	MR	MR
9	MR	sCR/CR/VGPR/PR/MR	
10	sCR/CR/VGPR/PR/MR	SD	SD
11	sCR/CR/VGPR/PR/MR	PD (any reason) *OR* No subsequent disease assessment: participant **died or discontinued study or started new anti-cancer therapy** before further adequate disease assessment.	SD
12	PD (due to reasons other than imaging, i.e., plasmacytoma or bone lesion)	PD (any reason) including PD after initiation of new anti-cancer therapy. *OR* No subsequent disease assessment: participant died due to PD before further adequate disease assessment (including death due to PD after initiation of new anti-cancer therapy).	PD
13	PD (due to reasons other than imaging, i.e., plasmacytoma or bone lesion)	sCR/CR/VGPR/PR/MR/SD *OR* No subsequent disease assessment: participant **died due to reasons other than PD** before further adequate disease assessment. *OR* No subsequent disease assessment: participant **discontinued study** before further adequate disease assessment.	NE

#	Response at the First Time Point	Response at Subsequent Disease Assessment[1]	Confirmed Response at the First Time Point
14	sCR/CR/VGPR/PR/MR/PD (due to reasons other than imaging, i.e., plasmacytoma or bone lesion)	No subsequent disease assessment: participant has not died, discontinued from study or (except for PD) started new anti-cancer therapy; but as yet has no further adequate disease assessments.	Unconfirmed (UC) sCR/CR/VGPR/PR/MR/PD. Will be categorized as NE for final ORR analysis. For ORR analysis in IA, the UC response (PR or better) will be counted as responder.
15	SD	Any *OR* No subsequent disease assessment.	SD
16	PD due to imaging (plasmacytoma or bone lesion)	Any *OR* No subsequent disease assessment.	PD
17	NE or missing	Any *OR* No subsequent disease assessment.	NE

[1] Subsequent disease assessment is defined as the next adequate (not missing or NE) disease assessment following the first timepoint before (or on the same date of) start of new anti-cancer therapy except for confirmation of PD, for which PD or death due to PD after new anti-cancer therapy are considered for confirmation of PD. No minimal time interval is required for the subsequent disease assessment, but a different sample is required for confirmation.
[2] SD does not need to be confirmed.
[3] PD due to imaging (i.e., plasmacytoma or bone lesion) does not need to be confirmed.
[4] Where criteria are not mutually exclusive, take the first that applies.

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.

Only the assessments from the start of treatment up to the earlier of confirmed disease progression or the start of new anti-cancer therapy will be considered. Only new systemic anti-cancer drugs taken are considered as anti-cancer therapy (radiotherapy and surgeries are not considered as systemic anti-cancer therapy for the purpose of this analysis).

A waterfall plot showing the maximum percent reduction from baseline in Serum M-protein, or Urine M-protein, or difference between two types of serum free light chain (FLC) [Kappa light chain (Kappa LC) and Lambda light chain (Lambda LC)] for each participant will be produced by treatment arm. Indication of the best overall response will be provided below the plot. Only the assessments from the start of treatment up to the start of new anti-cancer therapy will be considered. Only new systemic anti-cancer drugs

taken are considered as anti-cancer therapy (radiotherapy and surgeries are not considered as systemic anti-cancer therapy for the purpose of this analysis).

The maximum percent reduction will be plotted in the following hierarchical order:

1. Plot Serum M-protein maximum percent reduction from baseline if data is available.
2. If (1) is not feasible, plot Urine M-protein maximum percent reduction from baseline if data is available.
3. If both (1) and (2) are not feasible, plot maximum percent reduction from baseline for difference between two types of Serum FLC if data is available.

Difference between two types of Serum FLC

The percent change from baseline for difference between two types of Serum FLC is defined as:

$$\%\ change\ from\ Baseline = \frac{post\text{-}baseline\ difference - baseline\ difference}{baseline\ difference} \times 100\%$$

To calculate the difference, the "involved" and "non-involved" light chains must be determined at first based on the ratio of non-missing values for Serum Kappa LC protein and Serum Lambda LC protein at baseline.

The detailed algorithm is provided as below:

If the baseline ratio of (Kappa LC/Lambda LC)>1.65, then Kappa LC is defined as involved FLC, and Lambda LC is defined as non-involved FLC. Then

- Difference between involved and uninvolved = $Lambda\ LC - Kappa\ LC$

If the baseline ratio of (kappa/lambda) <0.26, then Lambda light chain is defined as involved FLC, and Kappa light chain is defined as non-involved FLC

- Difference between involved and uninvolved = $Lambda\ LC - Kappa\ LC$

If the baseline ratio of (Kappa LC/Lambda LC) ≤1.65 and ≥0.26, then "involved" and "non-involved" FLC cannot be determined (ratio is normal), and maximum percent reduction from baseline for difference between two types of Serum FLC won't be available.

Percentage of participants with a confirmed VGPR or better (i.e., VGPR, CR, and sCR)

The derivation of confirmed response shall be based on the algorithm specified in

Table 3.The number and percentage of participants with confirmed sCR, CR, VGPR will be summarized by treatment arm. The corresponding 95% CI will also be provided.

Duration of response (DoR)

DoR will be summarized using Kaplan-Meier method by treatment arm for participants with a confirmed PR or better. If there are sufficient number of responders who subsequently progress or die due to any cause, median DoR, first and third quartiles, 95% CI estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982] and probability of maintaining response at 06-month, 09-months and 12-month will be provided. A figure and listing of DoR time will also be provided.

Time to response (TTR)

TTR will be summarized descriptively by treatment arm using median, first and third quartiles and 95% CI, will be estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982] in the subset of participants with a confirmed response of PR or better as the best overall response.

Time to progression (TTP)

TTP will be summarized using Kaplan-Meier method by treatment arm. If there are sufficient number of progressions or death due to PD, median TTP, first and third quartiles and 95% CI, will be estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982].

A summary of the assignments for progression and censoring dates for TTP are specified in Table 4.

Progression-free survival (PFS)

PFS will be summarized using Kaplan-Meier method by dose level. If there is a sufficient number of progressions or deaths, median PFS, first and third quartiles, 6-month , 9-month, 12-month, 15-month and 18-month PFS rate, and 95% CIs will be estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982].

Table 4 Progression-Free Survival Event and Censoring Rules

Situation	Date of Event (Progression/Death) or Censored	Outcome 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

Situation	Date of Event (Progression/Death) or Censored	Outcome Event (Progression/Death) or 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 lost-to-follow-up time[e].	Date of assessment of PD [b] (1) minimum of (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 (prior to documented PD).[d]	Date of last "adequate" assessment of response [c] (on or prior to 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
Death or PD after missing 2 or more scheduled assessments.	Date of last "adequate" assessment of response [b] (prior to 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/death and last adequate disease assessment is more than 49 days, PFS will be	Censored (1) Event

Situation	Date of Event (Progression/Death) or Censored	Outcome Event (Progression/Death) or Censored
	censored at the last adequate disease assessment prior to PD or death. (1) Date of death or progression.	
(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; PEP=protein electrophoresis; PD=progressive disease; 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 is sCR, CR, PR, VGPR, MR, SD.
d. If PD or death and new anti-myeloma therapy occur on the same day assume the progression or death was documented first (e.g., outcome is progression or death and the date is the date of the assessment of progression or death). If anti-cancer therapy is started prior to any adequate assessments, censoring date should be the date of randomization.
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: ≤ 49 days; after an extended loss-to-follow-up time is defined as: >49 days

Adequate baseline assessment is defined as at baseline, a participant has at least one of the following measurements:

- Serum M-protein ≥0.5 g/dL (≥5 g/L) or
- Urine M-protein ≥200 mg/24h or
- Serum FLC assay: Involved FLC level ≥5 mg/dL (≥50 mg/L) and an abnormal serum free light chain ratio (<0.26 or >1.65) or

Refer to Section 6.1.1.2 “Extended Loss to Follow-up or Extended Time without an Adequate Assessment”.

Overall survival (OS)

Participants who withdraw consent from the study or are lost to follow-up will be censored at the time of withdrawal or lost to follow-up. Participants who do not have a death record at the clinical cut-off date for the analysis will be censored at the last known alive date. The last contact date will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

OS will be summarized using the Kaplan-Meier method by treatment arm. For each arm, the Kaplan-Meier estimates for the median OS time, the first and third quartiles will be presented, along with 95% CIs if there are sufficient number of deaths. A graph of survival curves and a listing of survival times will also be provided. In addition, depending on maturity of data, the survival probability at 6, 12 and 18 months with 95% CI will be estimated using Kaplan-Meier method.

4.3.2. Sensitivity Analyses

A PFS sensitivity analysis using alternative censoring rules defined in Table 4 will be performed.

4.4. Exploratory Endpoint Analyses

Patient Reported Outcomes (PRO) Analyses

The below patient reported outcomes domains are included in the study. The domains and items administered for each PRO are described in

Table 5.

Table 5 Summary of PRO domains and items administered

PRO name	Number of items	Domains
PRO-CTCAE	23-35 depending upon skip pattern items	Selected AE items for trial
OSDI	12 items	Ocular Symptoms Vision-Related Functioning Environmental Triggers
EORTC QLQ-C30	30 items	Global health status/QoL Physical functioning Role functioning Emotional functioning Cognitive functioning Social functioning Fatigue Nausea and vomiting Pain Dyspnea Insomnia Appetite loss

PRO name	Number of items	Domains
		Constipation Diarrhea Financial difficulties
EORTC-QLQ-MY20	20 items	Disease Symptoms Future Perspective Body Image Side Effects
PGI-S	Single item	Global symptom severity and change
PGI-C	Single item	
FACT-GP5	Single item	Overall level bother of Side effects

All questionnaires will be scored according to published scoring guidelines or the developer's guidelines if published guidelines are not available. All PRO analyses will be based on the Intent-to-Treat (ITT) analysis set, unless stated otherwise.

Patient reported outcomes (PROs) while on treatment and post-discontinuation will be examined, unless otherwise specified.

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

The Patient Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a patient reported outcome measure developed to evaluate symptomatic toxicity in patients on cancer clinical trials (Basch, 2014). The PRO-CTCAE was designed to be used as a companion to the Common Terminology Criteria for Adverse Events (CTCAE), the standard lexicon for AE reporting in cancer trials. The PRO-CTCAE includes an item library of 124 items representing 78 symptomatic toxicities drawn from the CTCAE. PRO-CTCAE provides a systematic yet flexible tool for descriptive reporting of symptomatic treatment side effects in cancer clinical trials. In the present study, a subset of items selected 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.

The levels and related code values for PRO-CTCAE are shown Table 6

Table 6 PRO-CTCAE classification summary

	Levels and related code values				
Response Scale	**0**	**1**	**2**	**3**	**4**
Frequency	Never	Rarely	Occasionally	Frequently	Almost constantly
Severity	None	Mild	Moderate	Severe	Very severe
Interference	Not at all	A little bit	Somewhat	Quite a bit	Very much

Present/Absent	No	Yes			

For each selected item from the library: Maximum PRO-CTCAE score at post-baseline for each item attribute will be summarized by counts and proportions. Changes from baseline at each scheduled visit for each item will be provided.

A listing of the PRO-CTCAE score will be available through subject-level data via RAPIDO DV for each attribute (Frequency, Severity, Interference, Presence).

Ocular Surface Disease Index

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 includes a Total Score and 3 domain scores of Ocular Symptoms (sensitivity to light, gritty eyes, painful or sore eyes), Vision Related Functioning (blurred vision, poor vision, 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".

For the OSDI, the total score will be calculated as well as scores for the three subscales (Ocular Symptoms: item 1-3; Vision-related Function: item 4-9; and Environmental Triggers: item 10-12).

$$Total\ OSDI\ Score = \frac{Sum\ of\ scores\ for\ all\ questions\ answered \times 100}{Total\ number\ of\ questions\ answered \times 4}.$$

Subscale scores are computed similarly with only the questions from each subscale used to generate its own score. A score of 100 corresponds to complete disability (a response of "All of the time" to all questions answered), while a score of 0 corresponds to no disability (a response of "None of the time" to all questions answered). Therefore, decrease in score from baseline means improvement.

For each of the three sub-scales, the descriptive summary of the actual value and change from baseline at selected time points will be provided. The number and percentage will be provided for total score and each sub scale. Additionally, recovery from first event defined as ≥ threshold decrease (improvement) from the Worst score will be summarized.

Table 7 Meaningful Score Change Thresholds for OSDI

Score	Total score	Ocular Symptoms	Vision-related Function
MCID	14.58	16.67	12.5

Plots of mean change from baseline (including baseline) and 95% CI over time by visit, and at end of study treatment, last follow-up, and worst case post-baseline for Vision related function domain will also be provided.

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

The FACT-GP5 item is a single item from the FACT-G [Cella, 1993], 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".

The number and percentage will be reported for each category of FACT GP5 from 0 = Not at all, 1 = A little bit, 2 = Somewhat, 3 = Quite a bit, 4 = very much, 3+4, Any scale >0, by visit and treatment arm.

European Organization 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].

Descriptive summaries (mean, SD, median, min and max) of the actual value and change from baseline at selected time points will be provided for EORTC QLQ-C30 summary score and each domain score. In addition, the summary of change from baseline of the Fatigue domain score will also be performed by responder status (Responder: best confirmed derive response is ≥PR; non-responder: all other participants who do not achieve a best confirmed response of PR or better). The number and percentage of participants with post-baseline score improved by ≥ 10 points from baseline score will be summarized at selected time points.

Plots of mean change from baseline (including baseline) and 95% confidence interval over time by visit, and at end of study treatment and last follow-up for pain and fatigue domains will also be provided.

European Organization 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.

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].

4.5. (Other) Safety Analyses

All safety analyses will be performed on the Safety Population, unless otherwise specified. All serially collected safety endpoints (e.g., laboratory tests, vital signs 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.

Unless otherwise specified, no “Total” column will be provided for safety outputs.

4.5.1. Extent of Exposure

The number of cycles administered to study treatment will be summarized with mean, median, standard deviation, minimum, and maximum.

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

The dose intensity (mg/kg/3 weeks), which is calculated as the cumulative actual dose (mg/kg) divided by expected duration of exposure in 3 weeks (last infusion date – first infusion date +21)/21), will also be summarized.

The dose intensity (mg/kg/6 weeks), which is calculated as the cumulative actual dose (mg/kg) divided by expected duration of exposure in 6 weeks (last infusion date – first infusion date +42)/42), will also be summarized.

Dose reductions will be summarized by number of reductions and reasons for reductions. Dose delays will be summarized by number of delays, reasons for the delays, and delay duration (days). For Q3W dosing, the number and percentage of the delays for intervals of 1-21, 22-42 and >42 days will be computed. For Q6W dosing, the number and percentage of the delays for intervals of 1-42, 43-84 and >84 days will be computed.

Dose modifications (reduction, interruption / delay) will be summarized by the categories of reasons that lead to the dose modification, including any AE, any AE or mKVA scale event, any non-ocular AE, any non-ocular AE or mKVA scale event and any ocular AE or mKVA scale event.

Duration of delays is defined as period from the expected start date of dose to actual start date of current dose. Calculation: (actual start date of current dose - expected start date of dose).

Expected start date of dose = actual start date of previous dose + 21; for Q3W dosing

Expected start date of dose = actual start date of previous dose + 42; for Q6W dosing

A summary of derived dose delay due to mKVA scale event will be provided in case multiple actions (dose interrupted/delayed and dose reduction) for the first occurrence of Grade3 corneal event(mKVA) can not be captured in the data. For a Q6W arm and a non-dosing visit with a Grade 3 corneal event(mKVA), the dose delay will be derived. The onset of dose delay is defined as previous dose date + 42 days (cycle length) + 3 days (visit window).

Primary reasons for dose reductions and dose delays will also be summarized by cycle. The duration of exposure to study treatment (from first day to last day of treatment) will be calculated and summarized using mean, median, standard deviation, minimum, and maximum.

A plot showing the number and percentage of subjects treated at different dose levels over time will be provided.

A by subject summary listing of data on exposure to all study treatments will be available through subject-level data via RAPIDO DV.

4.5.2. Adverse Events

Adverse events analyses including the analysis of adverse events (AEs), Serious AEs (SAEs) and other significant AEs will be based on GSK Core Data Standards.

An overview summary of AEs, including counts and percentages of participants with any AE, AEs related to study intervention, Grade 3 and 4 AEs, Grade 3 and 4 AEs related to study intervention, AEs leading to permanent discontinuation of study intervention, study intervention related AEs leading to permanent discontinuation of study intervention, AE leading to dose reductions, AEs leading to dose delays, SAEs, SAEs related to study intervention, fatal SAEs, non-fatal SAEs, and fatal SAEs related to study intervention will be produced. Unless otherwise specified, AEs will be summarized by treatment arms.

Events will be summarized by frequency and proportion of total participants, SOC, and preferred term (PT). 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.

The incidence of deaths and the primary cause of death will be summarized. Adverse events analyses including the analysis of AEs, SAEs and other significant AEs will be based on GSK Core Data Standards.

AEs will be coded using the standard Medical Dictionary for Regulatory Activates (MedDRA) and grouped by System Organ Class (SOC). Severity of corneal events will be graded using the KVA scale. Severity of all other AEs will be graded by the investigator according to the National Cancer Institute- Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

A summary of number and percentage of participants with any adverse events by maximum grade will be produced.

A separate summary will be provided for study intervention-related AEs. A study intervention-related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as “Yes”. A worst-case scenario approach will be taken to handle missing relatedness data, i.e., the summary table will include events with the relationship to study intervention as “Yes” or missing. The summary table will be displayed in descending order by SOC and PT.

A summary of cumulative incidence of AE by number of doses received at first occurrence will be provided.

In addition, Ocular AEs of Grade ≥2 will be summarized separately by PT.

All SAEs will be tabulated based on the number and percentage of participants who experienced the event. Separate summaries will also be provided for study intervention-related SAEs. The summary tables will be displayed by PT. The summary of all SAEs will also be created by SOC and PT. In addition, a summary of cumulative incidence of SAE by number of doses received at first occurrence will be provided.

A summary of non-serious AEs that occurred in 5% of the participants or above will be provided (no rounding for the percentage will be used in terms of 5% threshold, e.g., event with 4.9% incidence rate should not be included in this table). The summary will be displayed by SOC and PT.

4.5.2.1. Adverse Events of Special Interest (AESI)

AESIs for belantamab mafodotin are corneal events, thrombocytopenia, and IRRs. Severity of corneal events will be graded using the mKVA scale (provided in Table 8 of the CSP). Severity of thrombocytopenia and IRRs will be graded using NCI-CTCAE Version 5.0.

Summaries of the number and percentage of participants with these events will be provided for each type of events separately by PT and maximum CTCAE grade.

The time to onset and duration of first occurrence for each type of events will be summarized using summary statistics mean, SD, median, minimum, and maximum. The number and percentage of participants who have time to onset of first occurrence (1-21, 22-42, 43-63, >63) will be reported.

The number and percentage of participants who have duration of first occurrence (1-21, 22-42, 43-63, >63 days will be reported.

For IRRs, the number and percentage of participants who have time to onset of first occurrence (1-6, >6-12, >12-18, >18-24 hours) will be reported. The number and percentage of participant who have duration of first occurrence (0-12,>12-24, >24 hours) will be reported.

For an AESI which is based on a single AE term, the onset and duration will be calculated based on the start and end dates of the single term. For an AESI which is based on multiple AEs terms, the onset and duration will be calculated by looking across all terms for the AESIs. The derived start date is identified as the onset of any term defined as the AESI. The derived end date is identified as last end date for any terms once all concurrent terms for the AESI have resolved, i.e., the first time a participant is free of any AE term defined as the AESI.

The summary of event characteristics will be provided for each AESI respectively, including number of participants with any event, number of events, number of participants with any event that is serious, number of participants with any event that is related to study intervention, number of occurrences (One, Two, Three or more), maximum grade, maximum grade for events related to study intervention, outcomes and the action taken for the event. The percentage will be calculated in two ways, one with number of participants with event as the denominator and the other with total number of participants as the denominator. The worst-case approach will be applied at participant level for the maximum grade, i.e., a participant will only be counted once as the worst-case from all the events experienced by the participant. For action taken to an event, a participant will be counted once under each action, e.g., if a participant has an event leading to both study intervention discontinuation and dose reduction, the participants will be counted once under both actions.

For each of these events, a summary of cumulative incidence by number of doses received at first occurrence will be provided.

4.5.2.2. Adverse Events Leading to Discontinuation of Study Treatment and Other Significant Adverse Events

The following categories of AEs will be summarized separately in descending order of total incidence by PT only and separate supportive listings will be generated with participant level details for those participants:

- AEs leading to permanent discontinuation of study treatment.
- AEs leading to dose delays.
- AEs leading to dose reductions.

Only listings will be provided for the following:

- AEs leading to infusion stopped early and not completed.
- AEs leading to infusion interrupted but completed.

4.5.2.3. COVID-19 Assessment and COVID-19 AEs

A standardized MedDRA Query (SMQ) will be used to identify all COVID-19 AEs.

A display of summary will be produced for COVID-19 Assessments for subjects with Suspected, Probable or Confirmed COVID-19 case diagnosis.

4.5.3. Additional Safety Assessments

4.5.3.1. Laboratory Data

The evaluation of clinical laboratory tests will focus on selected laboratory analytes from the hematology and blood chemistry panel. Refer Section 10.13 Clinical Laboratory Tests of the CSP for protocol required laboratory test.

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.

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, as appropriate.

Summaries of worst-case grade increase from baseline grade will be provided for all the laboratory tests that are gradable by CTCAE v5.0. These summaries will display the number and percentage of participants with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum Grade 3 and any increase to a maximum Grade of 4. Missing baseline grade will be assumed as Grade 0. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia separately.

A supporting listing of laboratory data for participants with abnormalities of potential clinical concern will be provided. A separate listing of laboratory data with character values will also be available through subject-level data via RAPIDO DV.

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of participants with non-missing value at each particular visit.

Summaries of hepatobiliary laboratory events including possible Hy’s law cases will be provided in addition to what has been described above.

Possible Hy's law cases are defined as any elevated alanine aminotransferase (ALT) ≥3×upper limit of normal (ULN) **AND** total bilirubin ≥2×ULN (>35% direct bilirubin) **OR** international normalized ratio (INR) >1.5.

An e-DISH plot of maximum post baseline total bilirubin versus maximum post-baseline ALT will be created.

The following plots will also be provided:

Maximum post-baseline ALT vs baseline ALT

Maximum total bilirubin vs maximum post-baseline ALT.

A Summary of Liver Monitoring/Stopping Event Reporting will be provided. The medical conditions data for participants with liver stopping events will be listed. The substance use data for participants with liver stopping events will be listed.

4.5.3.2. Vital Signs

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

Listing of vital sign values of potential clinical importance will be available through subject-level data via RAPIDO DV.

4.5.3.3. Ocular Examinations

As outlined in study protocol Schedule of Activities (Table 1 of Section 1.3), ophthalmic exams are scheduled at screening, during the study, and follow-up period. The ocular findings from ophthalmic exams will be analyzed as described below-

Visual acuity

- The following categories of logMAR score changes from baseline are defined:

No change	change from baseline ≤ 0.1 logMAR
possible worsened vision	change from baseline > 0.1 to ≤ 0.3 logMAR
definite worsened vision	change from baseline >0.3 logMAR score

- A summary of characteristics of worsened vision (logMAR Score change from baseline >0.1) will be provided, including time to onset of first occurrence: summary statistics and frequency/percentage in categories (1-21, 22-42, 43-63, 64-105, >105 days); outcome of first occurrence, duration of first occurrence: summary statistics and frequency/percentage in categories (1-21, 22-42, 43-63, 64-105, >105 days); number of occurrences based on participants with worsened vision; outcome post treatment exposure; time to resolution post treatment exposure, outcome of last event. The duration is defined as time from onset of worsened vision to the first time the subject is free of

worsened vision (i.e. free of >0.1 logMAR Score change from baseline). It requires at least one day gap between the resolution of all worsened vision from first occurrence to the onset of second occurrence.

- A summary of characteristics of definite worsened vison (logMAR score change from baseline > 0.3) will be provided, including time to onset of first occurrence: summary statistics and frequency/percentage in categories (1-21, 22-42, 43-63, 64-105, >105 days); outcome of first occurrence, duration of first occurrence: summary statistics and frequency/percentage in categories (1-21, 22-42, 43-63, 64-105, >105 days); number of occurrences based on participants with worsened vision; outcome post treatment exposure; time to resolution post treatment exposure, outcome of last event. The duration is defined as time from onset of definite worsened vision to the first time the subject is free of worsened vision (i.e. free of > 0.3 logMAR Score change from baseline). It requires at least one day gap between the resolution of all worsened vision from first occurrence to the onset of second occurrence.

- In addition, a summary of worst change from baseline (based on the eye with worst change) in BCVA Score (logMAR Score) will be provided for categories “increase >0.1 to ≤0.3”, “increase >0.3 to ≤0.6”, “increase >0.6”.

- A summary of worst change from baseline (based on eye with worse eye and better eye) in BCVA score (logMAR score) will be provided for “>=3 line decrease”

“≥ 3 line decrease	logMAR change >= 0.3

- Shift table for visual acuity from baseline to worst case post-baseline by eye (R/L) will be provided

FUNDUS Photograph: Shift table from baseline to worst post-baseline by eye (R/L) and subject (worse eye) for Vitreous normal in appearance (Yes to No), PVD (No to Yes), Vitreous cell (No to Yes), Vitreous haze (No to Yes), Optic nerve normal in appearance (Yes to No), and Retina normal in appearance (Yes to No).

<u>Corneal Exam</u>

- Shift table from baseline to worst case post-baseline by eye (R/L) for corneal epithelium findings:
    - Corneal epithelium (Normal to Abnormal),
    - Microcyst-like deposits (No to Yes).
    - Subepithelial haze (No to Yes)
    - Stromal opacity (No to Yes)
    - Epithelial edema (No to Yes)
    - Corneal erosion (No to Yes)
    - Corneal ulcer (No to Yes)
    - Corneal neovascularization (No to Yes)
    - Superficial punctate keratopathy severity (No to yes)

- A summary of Microcyst-like deposits by grade will be provided for left, right and worse eye.

Lens

- Shift table from baseline to worst case post-baseline by eye (R/L) for lens findings:
  - Cataract (No to Yes)

4.5.3.4. Pregnancies

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 recorded as an AE or SAE as described in the protocol. If female study participant or female partner of male participant become pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

4.5.3.5. ECOG Performance Status

ECOG performance status will be summarized at baseline and each post-baseline scheduled visit. Summaries will use frequency and percentage of participants at each planned assessment time. A summary of change from baseline by scheduled visits will be performed, as well as the worst-case post-baseline and the best-case post-baseline changes during the study (improved, no change, deteriorated).

A supporting listing will also be available through subject-level data via RAPIDO DV.

4.6. Other Analyses

4.6.1. Subgroup analyses

Subgroup analyses of the primary endpoint and key secondary endpoints may be made to assess consistency of the intervention effect across the following subgroups

Subgroup	Categories
Age Group (at screening)	18 to <65, 65 to <75, ≥75 ; <65, ≥65
Sex	Male, Female
Ethnic Background	White, Black, Asian vs Other, Other
ISS Staging at Screening	I, II, III
Number of prior lines of therapy	3, ≥4

If the number of participants is too small (less than [10%]) within a subgroup, then the subgroup categories may be redefined prior to analysis.

4.6.2. 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" (Arm V) for the resulting dosing approach. Each virtual treatment arm can then be summarized for ocular toxicity and efficacy. Following virtual treatment arms will be created based on International Staging System (ISS) stage-based dosing -

Arm V1: 1.9 mg/kg Q3W for ISS I and II and 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 V2: 2.5 mg/kg Q6W for ISS I, 1.9 mg/kg Q3W for ISS II, and 2.5 mg/kg Q3W for ISS III.

Combine the ISS I participants at the 2.5 mg/kg Q6W dose from Arm C with ISS 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 2.5mg/kg Q6W in ISS I, 1.9 mg/kg Q3W in ISS II and 2.5 mg/kg Q3W in ISS III.

Arm V3: 1.9 mg/kg Q6W for ISS I, 1.9 mg/kg Q3Wfor ISS II, and 2.5 mg/kg Q3W for ISS III.

Combine the ISS I participants at the 1.9 mg/kg Q6W dose from Arm D with ISS 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 2.5mg/kg Q6W in ISS I, 1.9 mg/kg Q3W in ISS II and 2.5 mg/kg Q3W in ISS III.

Incidence rate of Grade ≥2 corneal events according to the KVA scale and ORR will be summarized for Virtual treatment arm.

Virtual treatment arms based on other baseline characteristics may be defined prior to analysis.

4.6.3. Arm E analyses

The endpoints specific to Arm E of this study are the incidence of keratopathy (all grades), visual acuity changes, ocular symptoms, related impacts based on OSDI, and corneal findings, changes from baseline in pre-specified symptomatic AEs and impacts measured by 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 and level of overall bother/tolerability as measured by the single item FACT-GP5.

All the analysis regarding to these endpoints will be performed on safety population who are assigned to arm E.

4.6.3.1. Endpoint definition and analyses

- **Changes from baseline in symptomatic AEs and impact measured by PRO-CTCAE**

  The Patient Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a patient reported outcome measure developed to evaluate symptomatic toxicity in patients on cancer clinical trials (Basch, 2014). In the present study, a subset of items selected from the PRO-CTCAE Version 1.0 item library will be administered to participants. These items include 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. More information can be found in section 4.4.
  For each selected item from the library: Maximum PRO-CTCAE score at post-baseline for each item attribute will be summarized by counts and proportions. Changes from baseline at each scheduled visit for each item will be provided.

- **Changes from baseline and proportion of participants with within-participant meaningful change in self-reported ocular symptoms and related impacts as measured by 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 includes a Total Score and 3 domain scores of Ocular Symptoms (sensitivity to light, gritty eyes, painful or sore eyes), Vision Related Functioning (blurred vision, poor vision, 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".

  $$Total\ OSDI\ Score = \frac{Sum\ of\ scores\ for\ all\ questions\ answered \times 100}{Total\ number\ of\ questions\ answered \times 4}.$$

  Subscale scores are computed similarly with only the questions from each subscale used to generate its own score.

  For each of the three sub-scales, the descriptive summary of the actual value and change from baseline at selected time points will be provided.

  Plots of mean change from baseline (including baseline) and 95% CI over time by visit, and at end of study treatment, last follow-up, and worst-case post-baseline for individual domains will also be provided.

- **Level of overall bother/tolerability as measured by the single item FACT-GP5**

  The FACT-GP5 item is a single item from the FACT-G [Cella, 1993], 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".

  The number and percentage will be reported for each category of FACT GP5 from 0 = Not at all, 1 = A little bit, 2 = Somewhat, 3 = Quite a bit, 4 = very much, 3+4, Any scale > 0, by visit.

- **Incidence of keratopathy (all grades), visual acuity changes, ocular symptoms, related impacts based on OSDI, and corneal findings**

  The number and corresponding percentage of participants with incidence of each of the events (keratopathy events (all grades and by number of doses), visual acuity based on KVA grades, ocular symptoms, and corneal findings) will be summarized for arm E along with the number and percentage of participants with the same event in control arm A.

  Also visual acuity score and Ocular dose modifications (dose reduction or dose delay) based on oncologist assessment will be summarized for arm E patients. For these two summaries.

  An additional sensitivity analysis may be performed excluding participants from Arm E sites with unresolvable data quality issues as determined and documented by sponsor review.

4.6.4. Pharmacokinetic Analyses

PK samples will be collected for belantamab mafodotin as indicated in the Schedule of activities tables of the protocol.

4.6.4.1. Derived Pharmacokinetic Parameters

PK parameters will be derived by non-compartmental and/or population pharmacokinetic analyses. If PK parameters will be derived by both approaches only one set of parameters may be summarized.

Standard non-compartmental analysis (NCA), if performed, will be conducted according to current working practices, using the currently supported version of Phoenix WinNonlin and will provide the parameters listed in the table below, as data permit. The pharmacokinetic parameters C-EOI and Ctrough will be determined directly from the concentration-time dataset, as data permit. For the dosing occasions with only pre-dose

and end of infusion samples Cmax and tmax will not be derived. Ctrough will not be reported for cys-mcMMAF.

Population pharmacokinetic analyses (popPK), if performed, are described in Section 4.6.5.

Belantamab Mafodotin and Cys-mcMMAF

For a NCA, if performed, the following pharmacokinetic parameters described below will be determined separately for each analyte, as data permit:

Belantamab mafodotin: Cmax, C-EOI, tmax, Ctrough, tlast, and AUC(0-τ). AUC(0-504h) may also be computed for the Q6W regimen

cys-mcMMAF: Cmax, C-EOI, tmax, tlast, and AUC(0-168h)

For a popPK analysis, if performed, the following pharmacokinetic parameters described below will be determined separately for each analyte, as data permit:

- Belantamab mafodotin: Cmax, Ctrough, Cavg, AUC(0-τ), t½, CL, Vss . AUC(0-504h) may also be computed for the Q6W regimen
- cys-mcMMAF: Cmax, Cavg, AUC(0-168h)

4.6.4.2. Summary Measures

Drug concentrations and NCA pharmacokinetic parameters will be listed, summarized descriptively (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV%, and 95% CI of log-transformed parameters) and graphically presented (where appropriate) by analyte, cycle or visit, and arm.

Details of the planned displays are provided in OPS document and will be based on GSK Data Standards and statistical principles.

4.6.4.3. Population of Interest

The pharmacokinetic analyses will be based on the Pharmacokinetic population, unless otherwise specified.

4.6.5. Population Pharmacokinetic (POPPK) Analysis

Belantamab mafodotin concentration-time data may be analysed using a population pharmacokinetic approach as data permit and may be combined with data from other studies. These analyses may use previously developed population pharmacokinetic model(s) to generate *post hoc* pharmacokinetic parameter estimates for the individual participants in this study. Based on the individual *post hoc* parameter values, dosing information, and sample collection times, drug 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. If performed, the analyses will be conducted by, or under the direct auspices of, Clinical Pharmacology Modelling and Simulation (CPMS),

GSK using the currently supported versions of all software packages. Results of these analyses may be provided in a separate report.

Further details are provided in Appendix 3 Population Pharmacokinetic (PopPK) Analyses.

4.6.6. Pharmacokinetic/Pharmacodynamic Analyses

4.6.6.1. Exposure-Response for Efficacy and Safety Endpoints

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 these analyses may be provided in a separate report. If performed, the analyses will be conducted by, or under the direct auspices of, Clinical Pharmacology Modelling and Simulation (CPMS), GSK using the currently supported versions of all software packages.

Further details are provided in Appendix 4: Pharmacokinetic/Pharmacodynamic Analyses.

4.6.7. Biomarker/Translational Research Analyses

If data permit, actual change and percent change of free BCMA expression level from baseline will be summarized using descriptive statistics (mean, SD, median, min, max) and displayed using boxplot by visit and time. If data permit, additional exploratory analyses may be performed exploring the relationship between clinical response and other biologic characteristics including BCMA expression on tumor cells, subsets of immune cell phenotypes, circulating free DNA, soluble BCMA concentrations and other novel biomarkers. Details of these analyses will be specified within a separate biomarker SAP and then if warranted, the results will be provided in a separate report.

4.6.8. Immunogenicity Analyses

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 at the same time as the pre-infusion belantamab mafodotin pharmacokinetic samples are taken). These samples will be tested by the sponsor or sponsor's designee.

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.

4.7. Interim Analyses

Once 15 participants each in Arms A to D have been enrolled and have received two doses of study treatment with one 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 out of 15 participants will be discontinued from further enrollment and arms with ≥3 responders will continue enrollment. Futility assessment will be based on Evaluable population defined under Table 2.

ORR will be based on investigator-assessed confirmed response as specified in

Table 3. Subjects with a confirmed PR or better (i.e., PR, VGPR, CR, and sCR) are called responders.

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) with dose modifications based on the mKVA scale, 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.

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

4.8. Independent Data Monitoring 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. 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 been enrolled and received two doses of study treatment with one disease assessment following 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.

4.9. Changes to Protocol Defined Analyses

There is no change to protocol defined analyses.

4.10. Post treatment switch analysis

If any of the Arms B, C, D, or E are stopped due to futility, participants in the stopped Arm 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.

The following analysis will be performed and included in the CSR for participants switched to Arm A and reported separately:

Adverse event overview, Adverse event by preferred term and maximum grade, Serious adverse event by preferred term and maximum grade, Ocular event overview (CTCAE) Corneal event overview (mKVA), Summary of overall response, summary/listing of PFS and listing of overall survival.

5. SAMPLE SIZE DETERMINATION

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

5.1. Sample Size Assumptions

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 operating characteristics in Table 8 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.

Table 8 Study Safety Operating Characteristics

Incidence rate of Grade ≥2 corneal event		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

Incidence rate of Grade ≥2 corneal event		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	
0.632	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
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

5.2. 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 9. 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.

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 the approved dose and schedule (2.5 mg/kg Q3W) with dose modification now based on the KVA scale instead of on ocular symptoms and visual acuity assessments.

Table 9 Safety Stopping Rule for Arm E

Number of Participants Dosed	Stop if Number of Participants with Grade4 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

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

A summary of the number of participants in each of the participant level analysis set will be provided. In this multi-center global study, enrolment will be presented by country and site.

6.1.1. Participant Disposition

A summary of the number of participants in each of the analysis populations described in Section 0 will be provided. In addition, the number of participants enrolled by center will be summarized by dose level using the ITT population. A separate summary for exclusions from each study population will be displayed. A listing of participants excluded from analysis populations will also be provided.

A summary of participant status and reason for study withdrawal will be provided. This display will show the number and percentage of participants who withdrew from the study, including primary reasons for study withdrawal. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF.

A summary of study treatment status will be provided. This display will show the number and percentage of participants who are ongoing or discontinued study treatment and a summary of the primary reasons for discontinuation of study treatment. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF. A listing of study treatment discontinuation will be generated. The listing will include last dose date, and reasons for study treatment discontinuation.

Summary of treatment discontinuation will be summarized by the categories of reasons that lead to the treatment discontinuation, including any AE, any AE or mKVA scale event, non-ocular AE, non-ocular AE or mKVA and any ocular AE or mKVA scale event.

6.1.1.1. 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.

6.1.1.2. Extended Loss to Follow-up or Extended Time without an Adequate Assessment

For participants, if two or more scheduled disease assessments are missed and are then followed by an assessment of PD or death, PFS will be censored at the last adequate assessment prior to PD or death. When the scheduled disease assessment is every 3 weeks, a window of 49 days (6 weeks +7 day window) will be used to determine whether there was an extended time without adequate assessment. That is, if the time

difference between PD/death and last adequate assessment is more than 49 days, then PFS will be censored at the last adequate assessment prior to PD/death.

6.1.1.3. 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., 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. After the primary analysis, the study will continue, and participants will remain on-treatment and continue to be followed-up. An updated analysis for OS will be performed at end of study.

The final analysis will occur 15 months from LSFD and the DREAMM-14 study will move into PACT. At that time 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 pre specified ocular data will be reported directly to the GSK. 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.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, baseline height, and baseline body weight and baseline BMI) will be summarized using mean, standard deviation, minimum, median, and maximum. The count and percentage will be computed for sex and ethnicity. A listing will be provided.

Disease history and characteristics (e.g., time since initial diagnosis in years, stage at initial diagnosis, date of initial diagnosis) at initial diagnosis and screening will be listed. Separate summaries of disease characteristics at initial diagnosis and screening will be provided. Disease characteristics at screening, including stage, type of multiple myeloma, number of prior lines, and types of therapy, myeloma light chain and myeloma immunoglobulin, extramedullary disease and lytic bone lesion will be summarized and listed.

Medical conditions collected at screening will be listed and will be summarized by past and current and by cancer-related and non-cancer related categories.

Substance use, including smoking history and alcohol use will be summarized.

Prior anti-cancer therapy will be coded using GSK Drug coding dictionary, then summarized by type of therapy and listed. A listing of prior anti-cancer therapy will show the relationship between ATC Level 1, Ingredient, and verbatim text. A summary of the best response to the most recent prior anti-cancer therapy will be provided. A summary of the number of prior anti-cancer therapy regimens will also be produced.

Prior anti-cancer therapy for multiple myeloma participants will also be summarized by type of therapy, and drug class. A summary of multiple myeloma participants' refractory to prior anti-cancer therapy by drug class will be provided.

Anti-cancer radiotherapy will be listed. Prior cancer and non-cancer related surgeries will be summarized. Prior and on-treatment cancer and non-cancer related surgeries will be listed.

6.1.3. Protocol Deviations

Important protocol deviations will be listed. No per protocol population was defined for the study, hence no exclusions from the analysis will be performed based on the population.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

6.1.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using GSK Drug coding dictionary, summarized, and listed. The summary of concomitant medications will show the number and percentage of participants taking concomitant medications by Ingredient. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients. Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information will be included in the dataset created but will not appear on the listing or summary.

Both prior medications and concomitant medications will be summarized by ATC classification drug class and GSK Drug coding dictionary name using the number and percentage of participants for each Arm. A participant reporting the same medication more than once will be counted only once when calculating the number and percentage of participants who received that medication in a given time category (prior or concomitant). The summary of concomitant medications will be ordered alphabetically by drug class and then by descending frequency of preferred name in total within the drug class. For drugs with the same frequency, sorting will be done alphabetically. Summaries will be based on the safety population.

Prophylactic medication for infusion -related reactions and prophylactic eye medications will be summarized by drug class and drug name and listed separately. In addition, the

percentage of duration of exposure that was on prophylactic steroid eye drop use will also be summarized.

Blood products or blood supportive care products with onset date within the on-treatment window will be included in the summary tables. The frequency and percentage of participants using blood products and blood supportive care products after the start of study medication will be provided. Supporting listings will also be provided.

6.1.5. Subsequent Anti-Cancer Therapies

The number and percentage of participants that received chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, small molecule targeted therapy, as subsequent anti-MM therapy will be summarized. Time from study treatment discontinuation to the first post-study treatment anti-MM therapy will also be included in this summary table, if available.

Follow-up anticancer therapy will be coded using GSK Drug coding dictionary, then summarized by Ingredient reporting first subsequent therapy and any subsequent therapy separately.

A by-participant listing of the type of follow-up anti-MM therapy received (chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, and small molecule targeted therapy) will be provided.

6.1.6. Additional Analyses Due to the COVID-19 Pandemic

A participant is defined as having a suspected, probable, or confirmed COVID-19 infection during the study if the answer is “Confirmed”, “Probable” or “Suspected” to the case diagnosis question from the COVID-19 coronavirus infection assessment eCRF. Numbers of participants with a suspected, probable, or confirmed COVID-19 infection, and of COVID-19 test results will be summarized.

6.2. Appendix 2 Electronic Clinical Outcome Assessment (eCOA) Compliance

6.2.1. Study Level compliance

Overall eCOA compliance (across all eCOAs and all participants) for the study is calculated as:

$$\frac{\text{Total number of complete eCOAs}}{\text{Expected number of complete eCOAs per participant} \times \text{Total number of participants}} \times 100$$

An eCOA is considered complete if there is no missing data within the assessment.

The target compliance for the study is 70%. The study eCOA compliance will be reported for each treatment group.

A participant is considered to be compliant with their eCOAs if at least 80% of their eCOAs are complete (have no missing data), i.e., a participant is eCOA compliant if they meet the following criteria:

$$\frac{\text{Total number of complete eCOAs}}{\text{Expected number of complete eCOAs}} \times 100 \geq 80\%$$

The number of participants who have 0-49%, 50-79% and 80%+ completed with eCOA assessments will be summarized.

6.2.2. Endpoint Level Compliance

Not applicable

6.3. Appendix 2 Data Derivations Rule

6.3.1. Criteria for Potential Clinical Importance

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern.

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0.3) will be used to assign grades to the relevant laboratory parameters, blood pressure and QTc.

In addition, the following criteria will be used to flag potential clinical importance:

Parameters	Unit	PCI Range
Heart rate	bpm	<60 (L); >100 (H)
QRS interval	Msec	<75 (L); >110 (H)

6.3.2. Study Period

Assessments and events will be classified according to the date/time of occurrence relative to date/time of first dose of study treatment.

Study Phase	**Definition**
Pre-Treatment	Date/time ≤ Study Treatment Start Date/time

On-Treatment	Study Treatment Start Date/time < Date/time ≤ Study Treatment Stop Date + 70 days
Post-treatment	Date/time > Study Treatment Stop Date + 70 days

6.3.3. Study Day and Reference Dates

Calculated as the number of days from First Dose Date:

- Ref Date = Missing → Study Day = Missing
- Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
- Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1.

6.3.4. Assessment Window

- 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.

6.3.5. Multiple measurements at One Analysis Time Point

Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented.

Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of “Any visit post-baseline” row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.

6.3.6. Handling of Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays. • However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for "slotting" data to study phases or for specific analysis purposes as outlined below. • Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. o Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as defined in Section 6.3.2. o Missing Stop Day: Last day of the month will be used. • Completely missing start dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • Completely or partially missing end dates will remain missing, with no imputation applied. Consequently, duration of such events will be missing.
Concomitant Medications/ Medical History	Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: o If the partial date is a start date, a "01" will be used for the day and "Jan" will be used for the month. o If the partial date is a stop date, a "28/29/30/31" will be used for the day (dependent on the month and year) and "Dec" will be used for the month. The recorded partial date will be displayed in listings.
New Anti-Cancer Therapy/ Radiotherapy/ Surgical Procedures for Efficacy Evaluation (e.g., response rate, time-to-event)	Start dates for follow up anticancer therapy, radiotherapy (where applicable), and surgical procedures (where applicable) will be temporarily imputed to define event and censoring rules for progression-free survival, response rate, time to progression, duration of response or time to response (i.e. start date for new anti-cancer therapy). The imputed dates will not be stored on the anticancer therapy, radio therapy, or surgical procedure datasets. If missing start day, month, and year, then no imputation for completely missing dates. If missing start day and month, then no imputation should be done. If missing start day, then do the following:

Element	Reporting Detail
	○ If partial date falls in the same month as the last dose of study treatment, then assign to earlier of (date of last dose of study treatment+1, last day of month). ○ If partial date falls in the same month as the participant's last assessment and the participant's last assessment is PD, then assign to earlier of (date of PD+1, last day of month). ○ If both rules above apply, then assign to latest of the 2 dates. Otherwise, impute missing day to the first of the month. If missing end date, then no imputation should be done.
Covariates for efficacy analysis (Date of initial diagnosis/Last recurrence/Last progression	If both month and day are missing, first of January will be used. If only day is missing, first of the month will be used.
Treatment end date	In general, completely missing end dates are not imputed, with the following exceptions for imputation of missing treatment end date at interim analyses. For imputation of missing exposure end date at an interim analysis when participants are still on treatment, the following conventions will be applied: ○ If the missing end date is in the last exposure record, the earliest of: ▪ the date of the data cut-off, ▪ the date of withdrawal from the study, or ▪ the death date will be used. ○ If the missing end date is not in the last exposure record, treatment start date for the record will be used. The imputed treatment end date will be used to calculate cumulative dose and duration of treatment as specified in Section 4.5.1. If treatment end date is missing for a cycle, treatment start date for the cycle will be used.

6.3.7. Treatment Emergent Adverse Events and On Treatment

Flag	Definition
Treatment Emergent	Study Treatment Start Date ≤ AE Start Date ≤ min (Study Treatment Stop Date + 70 day, Start of anti-cancer therapy) AE Start Date is missing.
On treatment	Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 70 day
NOTES: If the study treatment stop date is missing, then the AE will be considered to be On-treatment. Time of study treatment dosing and start/stop time of AEs should be considered, if collected.	

The “treatment emergent” definition of AEs will be used for all displays providing summaries by preferred term and maximum grade. All other AE displays will use the “on-treatment” definition.

6.3.8. Abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
AUC	area under the curve
BCVA	best corrected visual acuity
BCMA	B-cell maturation antigen
Cavg	average plasma concentration
Cmax	maximum plasma concentration
CI	Confidence interval
CSP	clinical study protocol
CTCAE	common terminology criteria for adverse events
CR	complete response
CSR	clinical study report
Ctau	trough plasma concentration
cys-mcMMAF	cysteine-maleimidocaproyl monomethyl auristatin F
ΔlogMAR	change in logarithm of the minimum angle of resolution
DNA	deoxyribonucleic acid
DoR	duration of response
ECG	electrocardiogram
eCRF	electronic Case Report Form
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
EOI	end of infusion
EOT	end of treatment
FACT-GP5	Functional Assessment of Cancer Therapy–General
GSK	GlaxoSmithKline
HRQoL	health-related quality of life
IMWG	International Myeloma Working Group
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
INR	international normalized ratio
ISS	International Staging System
ITT	Intent-to-Treat

IRR	infusion-related reaction
KVA	keratopathy visual acuity
mKVA	modified keratopathy visual acuity
LDH	lactate dehydrogenase
logMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activates
MRD	minimal residual disease
NE	not evaluable
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
OPS	Output and Programming Specification
ORR	overall response rate
OS	overall survival
OSDI	Ocular Surface Disease Index
PD	progressive disease
PACT	Post Analysis Continued Treatment
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic
PR	partial response
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PT	preferred term
RRMM	relapsed or refractory multiple myeloma
SAP	statistical analysis plan
SD	stable disease
sCR	stringent complete response
sBCMA	soluble B-cell maturation antigen
SOC	system organ class
TI	toxicity index
ToxT	toxicity over time
TTP	time to progression
TTR	time to response
VGPR	very good partial response
Q3W	every 3 weeks
Q6W	every 6 weeks

6.4. Appendix 3 Population Pharmacokinetic (PopPK) Analyses

If deemed appropriate and if data permit, belantamab mafodotin and/or cys-mcMMAF plasma concentration-time data may be analyzed by Pop PK methods using a non-linear mixed-effects modelling approach. The key objective of this analysis is to predict individual pharmacokinetic parameter values for belantamab mafodotin and/or cys-mcMMAF.

6.4.1. Systems

The population PK analysis will be performed using NONMEM (ICON Solutions) and PsN (Perl Speaks NONMEM) or another software platform deemed appropriate. Graphical displays and data summary will be produced using R (The R Foundation for Statistical Computing). The analysis will be performed by, or under the direct auspices of, Clinical Pharmacology Modelling and Simulation (CPMS), GSK using the currently supported versions of all software packages.

6.4.2. Data Assembly

Participant data will be collected in the electronic CRF and will be transmitted into a validated database by GSK data management. Derived/processed variables will be provided by or under the guidance of Clinical Programming. Plasma samples will be analyzed using approved analytical methodology. Data will be transferred electronically to data managers to be processed and stored in the GSK database. GSK or a designated third party will generate the analysis datasets.
Previously generated belantamab mafodotin and/or cys-mcMMAF PK data may be merged with the PK data in order to provide a pooled NONMEM data set.

6.4.3. Model Development

The initial analysis will use the population pharmacokinetic model developed for Study BMA117159 and Study 205678; a more current population PK model may be used, if available.
Initially, empirical Bayes estimates will be derived applying the current PopPK model to the Study 209628 dataset with the MAXEVAL=0 option. If the corresponding model diagnostics indicate that this PopPK model is appropriate to represent the belantamab mafodotin and/or cys-mcMMAF data from Study 209628 then individual PK parameter estimates will be based on the current PopPK parameters.

If the parameter set of the current PopPK model applied to the Study 209628 data set results in substantial bias or if a further exploration of the covariate effect in the Study 209628 population is deemed necessary, the parameters of the current PopPK model will be re-estimated for the Study 209628 PK data alone before generating the individual PK parameter estimates and/or for a pooled data set. Certain parameter values may be fixed to the value in the current PopPK model if they cannot be estimated with sufficient precision within the Study 209628 PK population. Covariates not available for the Study 209628 PK population but present in the current PopPK model may be removed from the

Study 209628 PopPK model. Lastly, a model refinement step, if needed, will include, but may not be limited to, a qualification and possible modification of the model's random effect structure.

6.4.4. Model Qualification

Any model development will be supported, and the final model will be qualified using the following criteria where appropriate:

- Scientific plausibility of parameter estimates
- Goodness of fit plots
- Relative standard errors (RSE) of the parameter estimates
- Objective function value
- Distribution and shrinkage of random effects.
- Successful minimization and execution of covariance step
- Condition number (ratio of the largest and smallest eigenvalue of the covariance matrix
- Visual predictive check
- Bootstrap (if deemed necessary/feasible)

6.5. Appendix 4: Pharmacokinetic/Pharmacodynamic Analyses

If deemed appropriate and if data permit, exposure-response analyses may be conducted using population methods to explore the relationship between exposure measures of belantamab mafodotin (ADC and/or cys-mcMMAF) and clinical activity and/or toxicity endpoints (e.g., response, AESIs). If data permit, the effects of covariates may be explored.

Exposure-response analyses will use the same systems and data assembly process as described in Appendix 3 Population Pharmacokinetic (PopPK) Analyses.

The final popPK models for ADC and/or cys-mcMMAF will be applied to generate the Following Dose 1 *post hoc* exposure measures to be used in efficacy and safety exposure response analyses: ADC maximum concentration (ADC Cmax), ADC trough concentration (ADC Ctau), ADC average concentration (ADC Cavg), and/or cys-mcMMAF Cmax, and cys-mcMMAF Cavg. Probability of occurrence of event of interest will be evaluated using logistics regression, while time to events endpoints may be analyzed using Kaplan-Meier plots or cox-proportional hazard models.

For each exposure-response analysis, univariate analysis will be performed first to identify the strongest individual associations of exposure and other relevant covariates to clinical endpoint using change in the objective function. Following the univariate analysis, covariate selection will be conducted using a stepwise forward inclusion and backward elimination method to determine the final multivariate model. Only covariates that meet the significance level of <0.01 in the univariate analysis will be included in the stepwise covariate search. Covariates will be retained in the model in a stepwise manner if their inclusion during forward addition decreased the objective function value (OFV) by =6.64 (P<0.01) over the previous model, with the most significant covariate being retained at each stage. This iterative process will continue until all significant covariates are included, thus defining the full model. Among all the exposure measures, only the most significant one (at the step where the covariate enters the model) will be selected. An exposure measure may be replaced by a more clinically relevant exposure measure, despite not meeting the criteria, in order to get alignment within similar endpoints. If none of the exposure measures are identified as statistically significant in the univariate analysis, further covariate exploration may be discontinued. From the full model, the significance of each covariate will be tested individually by removing one by one until all non-significant covariates have been excluded. A covariate will be retained if, upon removal, the OFV increased by more than 10.83 points (P< 0.001). The final model is defined as the model developed following the backward elimination step. A covariate may be retained in the final model, despite not meeting the criteria above, if there is a strong pharmacological or physiological rationale for its inclusion.

The results of these analyses may be provided in a separate report.

7. 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.

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.

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.

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.

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.

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.

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.

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.