Statistical Analysis Plan Amendment 1

Study ID: 209664

Official Title: A Phase 1, Randomized, Dose and Schedule Evaluation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of Belantamab Mafodotin Administered in Combination With Standard of Care in Participants With Newly Diagnosed Multiple Myeloma

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Abbreviated Title: DREAMM-9: Phase 1 Study of Belantamab Mafodotin Plus SoC in Newly Diagnosed Multiple Myeloma

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	28 Jun 2024	TMF-14223056 (12 Jan 2022)	Not Applicable	Original version
SAP Amendment 1	28-Jun-2024	Protocol Amendment 3 (11-Feb-2022)	Section 4.3.3.5: Added further detail about how compliance rates for patient-reported outcomes are derived, and added target compliance rate	Ensuring alignment with guidance provided by electronic Clinical Outcome Assessments (eCOA) Compliance Council

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report for study 209664 Details of the planned interim analyses, as well as the primary and 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 and Endpoints

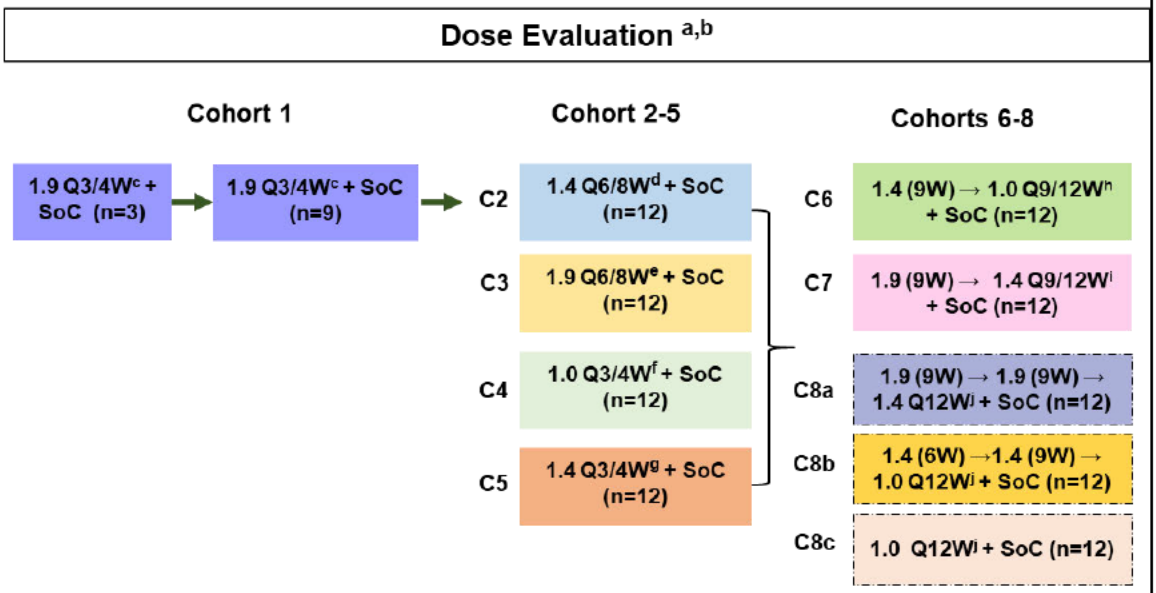
Objectives	Endpoints
Primary	
Determine safety and tolerability of belantamab mafodotin in combination with bortezomib (Velcade), Lenalidomide (Revlimid), and dexamethasone (VRd) to establish a recommended dose for participants with transplant ineligible (TI) newly diagnosed multiple myeloma (NDMM).	• Number (%) of participants with dose-limiting toxicities (DLTs). • Number (%) of participants with adverse events (AEs).
Secondary	
Effect of combining belantamab mafodotin with VRd in relation to lenalidomide & bortezomib relative dose intensity (RDI).	• Lenalidomide RDI after 4 cycles of treatment with belantamab mafodotin in combination with VRd. • Bortezomib RDI after 4 cycles of treatment with belantamab mafodotin in combination with VRd. • Cumulative administered dose of belantamab mafodotin after 4 cycles of treatment in combination with VRd.
To evaluate the pharmacokinetics (PK) profile of belantamab mafodotin, when administered in combination with VRd.	• Belantamab mafodotin, and Cysteine-maleimidocaproyl monomethyl auristatin F (cys-mcMMAF) PK parameters, as data permit.
To assess anti-drug antibodies (ADAs) against belantamab mafodotin.	• Incidence and titers of ADAs against belantamab mafodotin.
Assess the efficacy of belantamab mafodotin in combination with VRd in participants with NDMM.	• Overall Response Rate (ORR), defined as the percentage of participants with a confirmed Partial Response (PR) or better (i.e., PR, Very Good Partial Response [VGPR], Complete Response

Objectives	Endpoints
	[CR], stringent Complete Response [sCR]). • Complete Response Rate (CRR), defined as the percentage of participants with a confirmed CR or better (i.e., CR, sCR). • Rate of VGPR or better, defined as the percentage of participants with a confirmed VGPR or better (i.e., VGPR, CR, sCR).
Exploratory	
Assess minimal residual disease (MRD) in participants who achieve ≥VGPR or better.	• Number (%) of participants achieving MRD negativity.
Further assess the efficacy of belantamab mafodotin in combination with VRd in participants with TI NDMM.	• Duration of response (DoR), defined as the time from first documented evidence of PR or better until progressive disease (PD) or death due to PD among participants who achieve confirmed PR or better. • Time to Progression (TTP), defined as the time from the date of randomization until the earliest date of documented PD or death due to PD. • Time to Best Response (TTBR), defined as the interval of time between the date of randomization and the earliest date of achieving best response among participants with a confirmed PR or better. • Time to Response (TTR), defined as the time between the date of randomization and the first documented evidence of response (PR or better) among participants who achieve confirmed PR or better.
To evaluate the pharmacokinetics of total mAb when belantamab mafodotin is administered in combination with VRd.	• Total monoclonal antibody (mAb) PK parameters, as data permit.
To explore the exposure-response relationship between belantamab mafodotin exposure and clinical endpoints or combination drug(s) relative dose intensity in participants treated	• Belantamab mafodotin exposure (e.g., concentration, Cmax, or area under the concentration time curve [AUC]) vs. efficacy and/or safety endpoints (e.g.,

Objectives	Endpoints
with belantamab mafodotin in combination with VRd.	ORR, CRR, ocular events) and/or combination drug(s) RDI, as data permit.
To investigate the relationship between host genetic variation and the drugs under study.	• Effect of host genetic variation on response to drugs under study including but not limited to belantamab mafodotin.
To evaluate the safety and tolerability of Belantamab mafodotin based on self-reported symptomatic adverse effects when administered in combination with VRd.	• Changes from baseline in symptoms and related impacts as measured by patient-reported outcome Common Terminology Criteria for Adverse Events (PRO-CTCAE).
To evaluate self-reported ocular symptomatic adverse effects of belantamab mafodotin in combination with VRd.	• Changes from baseline in symptoms and related impacts as measured by Ocular Surface Disease Index (OSDI).
To further evaluate and compare changes in health-related quality of life (HRQoL).	• Change from baseline in HRQoL as measured by EORTC QLQ-C30, PGIS, PGIC.

1.2. Study Design

Overview of Study Design and Key Features



SoC = VRd = Velcade (bortezomib), Revlimid (lenalidomide), dexamethasone

a. *Based upon emerging data, not all dose cohorts may be explored*
b. *Cohort expansion (the enrollment of 8 additional participants) may be considered for a cohort(s) after the interim analysis*

Overview of Study Design and Key Features	
c. *Cohort 1: 1.9 Q3/4W = 1.9mg/kg on Day 1 of each cycle* d. *Cohort 2: 1.4 Q6/8W = 1.4mg/kg on Day 1 of every other cycle* e. *Cohort 3: 1.9 Q6/8W = 1.9mg/kg on Day 1 of every other cycle* f. *Cohort 4: 1.0 Q3/4W = 1.0mg/kg on Day 1 of each cycle* g. *Cohort 5: 1.4 Q3/4W = 1.4mg/kg on Day 1 of each cycle* h. *Cohort 6: 1.4 mg/kg on Day 1 of cycle 1, then 1.0 mg/kg on Day 1 of every third cycle from cycle 4* i. *Cohort 7: 1.9 mg/kg on Day 1 of cycle 1, then 1.4 mg/kg on Day 1 of every third cycle from cycle 4* j. *Cohort 8: Based on emerging data, either a) 1.9 mg/kg on Day 1 of cycle 1 and cycle 4, then 1.4 mg/kg on Day 1 of every third cycle from cycle 7; OR b) 1.4 mg/kg on Day 1 of cycle 1 and cycle 3, then 1.0 mg/kg on Day 1 of every third cycle from cycle 6; OR c) 1.0 mg/kg on Day 1 of cycle 1 and cycle 5, then 1.0 mg/kg on day 1 of every third cycle from cycle 9*	
Design Features	**Overall Design**: This is a randomized, open-label Phase 1, multicenter study evaluating the safety, pharmacokinetics, pharmacodynamics and clinical activity belantamab mafodotin in combination with standard of care in adult participants with NDMM. Currently, VRd is the standard of care backbone that will be evaluated in protocol 209664, and all participants must be transplant-ineligible. Other regimens and/or populations may be explored at a later date after regulatory approval of a substantial protocol amendment. The study will evaluate different doses/dose schedules of belantamab mafodotin in combination with VRd in up to 8 cohorts and will determine the Recommended Phase 3 dose (RP3D) for future studies in the newly diagnosed setting. **Number of Participants**: Up to 8 different dose cohorts may be evaluated, and up to 160 participants may be enrolled. **Intervention Groups and Duration**: • **Induction treatment**: Different doses/dose schedules of belantamab mafodotin plus VRd – 8 cycles (21-day cycles) • **Maintenance treatment**: Different doses/dose schedules of belantamab mafodotin plus Rd – Cycle 9 onwards (28-day cycles). Participants will receive study treatment until disease progression, unacceptable toxicity, death, withdrawal of consent from study, meeting the protocol defined safety stopping criteria, deviating from the protocol, investigator's discretion, LTFU or study is closed/terminated.
Study intervention	A total of 8 cycles of belantamab mafodotin + VRd induction treatment followed by belantamab mafodotin + doublet Rd maintenance treatment. o **Belantamab mafodotin** ▪ Induction: Belantamab mafodotin will be administered intravenously (IV) on Day 1, either every 21-day cycle, every other 21-day cycle, or every third 21-day cycle for the first 8 (induction) cycles in combination with VRd.

Overview of Study Design and Key Features	
	▪ Maintenance: Belantamab mafodotin will be administered intravenously (IV) on Day 1 either every 28-day cycle, every other 28-day cycle or every third 28-day cycle in combination with Rd. ○ **Bortezomib** ▪ Induction: Bortezomib will be administered at a dose of 1.3mg/m^2 subcutaneously (SC) on Days 1, 4, 8, and 11 of every 21-day cycle for the 8 induction cycles. ▪ Bortezomib will not be administered as part of maintenance treatment. ○ **Lenalidomide** ▪ Induction: Lenalidomide will be administered at a fixed dose of 25mg or 10mg, orally, on Days 1-14 of a 21-day cycle for the 8 induction cycles depending upon renal function*. ▪ Maintenance: Lenalidomide will be administered at a fixed dose of 25mg or 10mg orally on Days 1-21 of each 28-day cycle, depending upon renal function*, until PD or unacceptable toxicity. ▪ *In participants with estimated glomerular filtration rate (eGFR) 30-60mL/min/1.73 m^2 lenalidomide will be administered at 10 mg daily. Refer to Appendix 11 of the protocol amendment 02 for derivation of eGFR. ▪ In participants whose renal function improves during the study to eGFR >60mL/min/1.73 m^2 (confirmed over 2 measurements 2 weeks apart) the dose of lenalidomide can be increased accordingly, based on the Investigator judgement. ○ **Dexamethasone** ▪ Dexamethasone will be administered at 20mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day cycle for the 8 induction cycles. ▪ Dexamethasone will be administered at 40mg on Days 1, 8, 15, and 22 of a 28-day cycle from Cycle 9 onward, until PD or unacceptable toxicity. ▪ For participants who are older than 75 years, underweight (BMI<18.5), have poorly controlled diabetes mellitus, or prior intolerance/AE to steroid therapy, the dexamethasone dose may be administered at a dose of 10mg (Cycles 1-8) or 20mg (Cycles 9+) on the days indicated above.
Study intervention Assignment	Following screening, participants in cohort 1 will be enrolled until the cohort is full. Following screening, participants in cohorts 2-5 will be randomized in a 1:1:1:1 ratio to one of the four cohorts. Participants recruited in cohorts 6- 7 will be assigned in a 1:1 and cohort 8 will be enrolled into a dose cohort open at the time of recruitment.
Interim Analysis	• After the last participant from cohorts 2-5 complete 4 cycles of study treatment(s), an interim analysis will be performed for cohorts 2-5 to support the cohort expansion (an additional 6 participants) of the selected cohort(s). In addition, based on emerging data from other clinical studies in the belantamab mafodotin clinical development program, the decision on whether to evaluate cohort 6, 7, or 8 can take place. If cohorts 6-8 are open, after the last participant completes the end of Cycle 8 or if participants who experienced treatment cycle delays due to any reasons prior to the end of Cycle 8, they shall have completed at least 2 disease assessments and ocular exams after the last dose of belantamab mafodotin. If necessary, after at least 6 participants are completed the above-mentioned treatment in each dose cohort, additional interim analyses may also be conducted to aid in decision making regarding dose identification, cohort expansion or closure, and safety monitoring.

Overview of Study Design and Key Features	
	• An unplanned interim analysis has been approved to be performed based on 24 participants from Cohorts 2-5 (when the last participant reaches the end of Cycle 3 of their study treatment(s)) and 12 participants from Cohort 1, based on all data as of the data cut-off date. The unplanned interim analysis is intended only for internal strategic discussion in order to support the belantamab mafodotin clinical development plan. The dose decision will be made solely based on the protocol planned first interim analysis (see above), based on 60 participants from Cohorts 1-5 in order to maintain study and data integrity, hence the probability of meeting the success criteria to declare an optimal safe dose at the end of Cycle 4 for all dose cohorts will remain the unaltered. **NOTE**: The unplanned interim analysis is not referenced in the protocol but has been approved by senior management, with approval documented in Note to File document number TMF-14011347. • The primary analyses will take place when the last participant reaches the end of Cycle 8 in all dose cohorts after cohort expansion to determine the dose cohort (RP3D) that will be deemed safe for future studies in the newly diagnosed setting. • Further details are provided in Section 4.1 of SAP and Section 9.5 of the protocol (Version: Protocol Amendment 03, GSK Document Number TMF-14223056).

2. STATISTICAL HYPOTHESES

No formal statistical hypothesis is tested. Analysis of the data obtained will only utilize descriptive methods.

Safety data will be reviewed in an ongoing fashion. The number of participants in Cohorts 2-5 and, if applicable, Cohort 6, 7, and 8 who permanently discontinue study treatment due to AEs related to belantamab mafodotin within the first three (3), 21-day cycles of treatment will be continuously monitored. If the observed number of participants permanently discontinuing belantamab mafodotin in one of the cohorts is higher than 12% (at 1-sided alpha of 0.01), then the combination treatment at that dose level will be considered to have unacceptable toxicity and the dose cohort will be closed.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Study Population
Enrolled	• All participants who entered the study (who were randomized or received study intervention or underwent a post screening study procedure). • Participants included are: Randomized Participants (Cohorts 2-7), Non-randomized Participants (Cohort 1 and Cohort 8) and participants who were assigned a treatment. Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	• Study Population
DLT Evaluable Population	• The DLT Evaluable Population is defined as participants who have received treatment containing all agents (one full dose of belantamab mafodotin, dependent on the dose schedule, and ≥75% of planned administration of VRD in cycle 1) and followed up for the first three 21-day treatment cycles or withdrawn within first three 21-day cycles due to an AE meeting the definition of a DLT as defined in Section 4.1.1.1 of protocol.	• Summary of DLT at interim and primary analysis • Based on Cohort 2-8
Safety	• All randomized participants who received at least one (1) dose of study treatment(s). • This population will be based on the treatment the participant actually received.	• Safety based on actual treatment received

Analysis Set	Definition / Criteria	Analyses Evaluated
	Note: Participants who were not randomized but received at least one (1) dose of study treatment should be listed.	
COVID-19	• All participants in the Safety analysis set who had a confirmed, probable or suspected COVID-19 case diagnosis.	• Baseline Characteristics, Medical History, Laboratory Data, and Safety
ITT	• ITT Population will be the primary population for the analysis of efficacy data and defined in the following: • Cohort 1 and Cohort 8 will consist of non-randomized participants who take at least one (1) dose of any study treatment. Cohort 2-7 will consist of randomized participants whether or not randomized treatment was administered. This population will be based on the treatment to which the participant was randomized. Any participant who receives a treatment randomization number will be considered to have been randomized.	• ITT based on planned treatment received for study population and efficacy for randomized cohorts;
Efficacy	• All participants with documented MM and measurable disease[1] who have not received any prior therapies and are transplant ineligible; received at least one dose of study treatment(s) and will be used for efficacy data.	• Based on the planned treatment received for efficacy
Pharmacokinetic (PK)	• Participants in the Safety population from whom at least one PK sample was obtained, analyzed, and was measurable (belantamab mafodotin).	• PK

[1] Measurable disease at baseline is defined as, at baseline, a patient has been tested for Serum M-protein, Urine M protein and Serum FLC assay, and at least one of the following measurements: Serum M-protein ≥0.5 g/dL (≥5 g/L) or b. Urine M-protein ≥200 mg/24h or c. Serum FLC assay: Involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal

serum free light chain ratio (<0.26 or >1.65) were met.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Participants who are withdrawn or subsequently found to be ineligible from the study may be replaced with new participants if deemed non-evaluable.

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

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

It is anticipated that patient accrual will be spread thinly across centers and summaries of data by center would unlikely be informative and will not, therefore, be provided.

4.1.2. Baseline Definition

For all endpoints (except as noted in baseline definitions) 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 laboratory data, baseline will be the latest non-missing pre-dose value from local lab (or central lab where applicable). If no central lab value is available, the latest non-missing pre-dose value from local lab will be used.

For ECG analyses, if the latest, non-missing pre-dose values is from triplicate, the participant level baseline is defined as the mean of triplicate baseline assessments.

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

4.2. Secondary Endpoint(s) Analyses

4.2.1. Secondary efficacy endpoint(s)

The analyses will be based on the Intent-To-Treat and Efficacy Analysis Sets, unless otherwise specified.

4.2.1.1. Definition of endpoint(s)

Best Overall Response (BOR) is defined as the best confirmed response (stringent Complete Response [sCR] > Complete Response [CR] > Very Good Partial Response [VGPR] > Partial Response [PR] > Minimal Response [MR] > Stable Disease [SD] > Progressive Disease [PD] > Not Evaluable [NE]) from treatment start date until disease progression or initiation of new anti-cancer therapy, whichever is earlier, as derived per IMWG (2016). Details on derivation of confirmed response are provided in Table 1.

- **Overall Response Rate (ORR)** is defined as the percentage of participants with a confirmed PR or better as the BOR (i.e., PR, VGPR, CR, and sCR), per IMWG (2016). ORR at the end of 4th cycle will be analyzed based on confirmed responses, if available. However, in case a participant has achieved a response of PR or better at data cut, which was not confirmed due to the time constraints (too short timeframe for the next assessment), but with a potential to be confirmed through subsequent assessments after interim, the participant will also be considered as a responder; if the participant dies or discontinues study or starts other anti-cancer therapy prior to confirming the response, the participant will not be considered as a responder at the end of 4th cycle. Participants with only assessments of Not Evaluable (NE) or missing response will be treated as non-responders; i.e., they will be included in the denominator when calculating the percentage. Details on derivation of confirmed response are provided in Table 1.

- **Rate of VGPR or Better** is defined as the percentage of participants with a confirmed VGPR or better as the BOR (i.e., VGPR, CR and sCR), per IMWG (2016).

- **Complete Response Rate (CRR)** is defined as the percentage of participants with a confirmed CR or better as the BOR (i.e., CR and sCR), per IMWG (2016).

Table 1 Derivation of Confirmed Response for Multiple Myeloma Studies

	Response at the First Time Point	Response at Subsequent Time Point[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

	Response at the First Time Point	Response at Subsequent Time Point[1]	Confirmed Response at the First Time Point
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[4]	SD
12	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[4]	Unconfirmed sCR/CR/VGPR/PR/MR/PD Will be categorized as NE for ORR, Rate of VGPR or greater, and CRR analysis. For ORR, Rate of VGPR or greater, and CRR analysis at interim analysis, the UC response (PR or better) will be counted as responder.
13	PD (due to reasons other than imaging, i.e., plasmacytoma or bone lesion)	PD (any reason) OR No subsequent disease assessment: participant **died due to PD** before further adequate disease assessment[4]	PD
14	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[4] OR No subsequent disease assessment: participant **discontinued study** before	NE

	Response at the First Time Point	Response at Subsequent Time Point[1]	Confirmed Response at the First Time Point
		further adequate disease assessment[4]	
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 disease assessment following the first timepoint before starting other anti-cancer therapy which is not missing or NE before start of new anti-cancer therapy except for confirmation of PD, for which 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.
Where criteria are not mutually exclusive, take the first that applies.

4.2.1.2. Main analytical approach

- **ORR:** The number and percentage of participants with the BOR in the following response categories will be summarized: sCR, CR, VGPR, PR, overall response (sCR+CR+VGPR+PR), minimal response (MR), stable disease (SD), progressive disease (PD), and not evaluable (NE). CCI [redacted] A list of investigator-assessed response at each visit will be listed.

- **Rate of VGPR or Better:** The number and percentage of participants with the BOR in the following response categories will be summarized: sCR, CR, and VGPR. CCI [redacted]

- **CRR**: The number and percentage of participants with the BOR in the following response categories will be summarized: sCR and CR. CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]

4.2.2. Secondary pharmacokinetic analyses:

The analyses will be based on the PK Analysis Set, unless otherwise specified.

Concentration-time data collected after the first dose may be analyzed using standard non-compartmental methods, as data permit; some parameters will be determined for all participants and cycles. The concentration-time data may be combined with data from other studies and will be analyzed in a population approach using non-linear mixed effects modelling.

PK samples will be collected for belantamab mafodotin in Cycle 1 as well as later cycles as indicated in the SoA tables of protocol.

All PK, serum baseline B-cell maturation antigen (sBCMA), and anti-drug antibody (ADA) samples once collected (regardless of dosing) will be analyzed if the sample date and time have been recorded, refer to Table 18 of protocol for details (Version: Protocol Amendment 03, GSK Document Number TMF-14223056).

4.2.2.1. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters may be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin and/or using a population PK approach.

All calculations of PK parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the belantamab mafodotin and cys-mcMMAF concentration-time data, as data permits. The PK parameters Cmax, 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, the end of infusion sample will not be identified as Cmax. Ctrough will not be reported for cys-mcMMAF. The PK parameters provided in Table 2 will be summarized by cohort. Descriptive statistics will include mean, standard deviation, median, minimum, maximum, geometric mean, and standard deviation, Coefficient of Variation (Between) (CV_b%), and 95% CI of log-transformed parameters.

Table 2 Derived Belantamab Mafodotin Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-τ)	Area under the concentration-time curve from time zero to the end of the dosing interval will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-t')	Area under the concentration-time curve to a fixed time t'.

Parameter	Parameter Description
Cmax	Maximum observed concentration, determined directly from the concentration-time data for each cycle. Cmax will not be derived when only pre-dose and EOI samples were collected.
tmax	Time to reach Cmax, determined directly from the concentration-time data for each cycle.
Cτ , Ctrough	Trough concentration prior to the next dose for each cycle.
C-EOI	Observed plasma concentration at the end of infusion.
tlast	Time of last observed quantifiable concentration
CL	Clearance (only from population PK analysis for belantamab mafodotin)
Vss	Volume of distribution at steady state (only from population PK analysis for belantamab mafodotin)
t½	Apparent terminal half-life (only from population PK analysis for belantamab mafodotin)

NOTES:

- Additional parameters may be included as required.

Linear and semi-logarithmic individual concentration-time profiles and mean and median profiles (when appropriate) will be plotted for belantamab mafodotin, total mAb and cys-mcMMAF. Concentrations of belantamab mafodotin, total mAb and cys-mcMMAF will be listed for each participant and summarized (when appropriate) by planned time point and cohort. Parameters listed in Table 2 will also be summarized.

Population pharmacokinetic analyses (popPK), if performed, are described in Section 4.2.2.2.

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

4.2.2.2. 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 Section 6.3: Population Pharmacokinetic (PopPK) Analyses.

4.2.2.3. Pharmacokinetic/Pharmacodynamic Analyses

4.2.2.3.1. 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, CPMS, GSK using the currently supported versions of all software packages.

Further details are provided in Section 6.4: Pharmacokinetic/Pharmacodynamic Analyses.

4.2.3. Immunogenicity analyses

For each subject, the results and titers of anti-belantamab mafodotin binding antibodies and neutralizing antibody assay results will be listed for each assessment time point, along with ADC and total antibody concentration. The frequency and percentage of subjects with positive and negative anti-drug antibody and neutralizing antibody assay results will be summarized for each assessment time and overall for each subject by dose cohort. The categorization of results as conclusive will be based on the total antibody concentration.

The number and percentage of subjects with baseline anti-drug antibody results, overall and split by negative and positive samples in each treatment group will be provided. A further summary of subjects with post-baseline anti-drug antibody and neutralizing antibody results, anti-drug antibody negative (overall and for treatment-unaffected only), and treatment-emergent anti-drug antibody results (overall and split by treatment-induced and treatment-boosted) in each treatment group will be presented. Treatment-emergent anti-drug antibody is the sum of treatment-induced anti-drug antibody subjects and treatment-boosted anti-drug antibody positive subjects. Treatment unaffected anti-drug antibody is defined as a subject with an ADA-positive sample at baseline, in which postbaseline sample titer results are less than or equal to a four-fold increase in titer values relative to the baseline titer value (titer $\leq$ 4x baseline titer) or was ADA negative anytime post baseline.

For treatment-induced and treatment-boosted subjects, a summary of all their titer values will be presented. Treatment-induced anti-drug antibody is defined as a subject with at least one post-baseline anti-drug antibody positive sample and an anti-drug antibody negative or missing baseline sample. Treatment-boosted anti-drug antibody is defined as a subject with an anti-drug antibody positive baseline sample in which at least one postbaseline sample titer value is four-fold greater than the baseline titer value (titer > 4x baseline titer) or if titer result is missing at baseline or missing at all post-baseline assessments.

The immunogenicity analyses will be based on the Safety Analysis Set.

4.3. Exploratory Endpoint(s) Analyses

4.3.1. Exploratory Efficacy Analyses

The analyses will be based on the Intent-To-Treat and Efficacy Analysis Sets, unless otherwise specified.

- **Minimal Residual Disease (MRD) negativity rate** is defined as the percentage of participants who achieve MRD negative status (with thresholds 10^{-5} and 10^{-6}) at least once during the time of confirmed VGPR or CR, as assessed by next generation sequencing (NGS) per IMWG (2016). For analysis purposes, participants without MRD assessment will be considered as having non-negative MRD.

  MRD negativity rate at any timepoint will be summarized. the number and percentage of participants who have achieved MRD negativity will be summarized by dose level. The corresponding 95% exact CI will be provided. Information of MRD will be included in the listing of response.

- **Duration of response (DoR)** is defined as the interval of time (in months) from first documented evidence of confirmed PR or better to the time when disease progression is documented assessed by the investigator per IMWG (2016), or death due to PD among participants with a confirmed PR or better as the BOR. Responders without confirmed PD will be censored at the censoring time point for time to progression as specified in Table 3.

  If there are sufficient number of responders who subsequently progress or die due to PD, distribution of DOR will be summarized using the Kaplan-Meier method. The median, 25th and 75th percentiles of DOR will be estimated and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (1982). A figure and listing of DoR time will also be provided.

- **Time to disease progression (TTP)** is defined as the interval of time (in months) from date of randomization until the earlier date of PD per IMWG (2016), or the date of death due to PD. Determination of dates of TTP events and dates for censoring are described in Table 3.

The distribution of TTP will be estimated using the Kaplan-Meier method. The median, 25th and 75th percentiles of TTP will be estimated and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (1982). A figure and listing of TTP time will also be provided.

- **Time to response (TTR)** is defined as the interval of time (in months) between the date of randomization and the first documented evidence of response (PR or better) among participants with a confirmed PR or better as the BOR assessed by the investigator per IMWG (2016).

  If there are sufficient number of responses by dose level, time to response at will be summarized descriptively using median(s) and quartiles in the subset of subjects with a confirmed response of PR or better as the BOR and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (1982). A figure and listing of TTR time will also be provided.

- **Time to best response (TTBR)** is defined as the interval of time (in months) between the date of randomization and the earliest date of achieving BOR among participants with a confirmed PR or better as the BOR assessed by investigator per IMWG (2016).

  If there are sufficient number of responses by dose level, time to best response at will be summarized descriptively using median(s) and quartiles in the subset of subjects with a confirmed response of PR or better as the BOR and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (1982). A figure and listing of TTBR time will also be provided.

Table 3 Assignments for Progression and Censoring Dates for TTP Analysis

Situation	Date of Event (Progression/Death due to PD) or Censored[1]	Event (Progression/Death due to PD) Or Censored
No adequate baseline assessments[4] and the subject has not died (if the subject has died due to PD follow the rules for death indicted at the bottom of the table)	Randomization	Censored
No post-baseline assessments and the subject has not died (if the subject has died due to PD follow the rules for death due to PD indicted at the bottom of the table)	Randomization	Censored
Progression documented between scheduled visits	Date of assessment of progression	Event
With post-baseline assessment but no progression (or death due to PD)	Date of last ‘adequate’ assessment of response[2]	Censored

Situation	Date of Event (Progression/Death due to PD) or Censored[1]	Event (Progression/Death due to PD) Or Censored
No adequate post-baseline assessment before start of new anticancer therapy	Randomization	Censored
With adequate post-baseline assessment and new anticancer treatment started (prior to documented disease progression).[3]	Date of last 'adequate' assessment of response[2] (on or prior to starting anti-cancer therapy)	Censored
Death due to PD before first scheduled assessment (or Death at baseline or without any adequate assessments)	Date of death	Event
Death due to PD between adequate assessment visits	Date of death	Event
Death from causes other than PD before first scheduled assessment (or Death at baseline or without any adequate assessments)	Date of death	Censored
Death from causes other than PD between adequate assessment visits	Date of death	Censored
Death due to PD or progression after more than two missed scheduled assessment	Date of last 'adequate' assessment of response[2] (prior to missed assessments): If the disease assessment is • every 3 weeks for 6 months, a window of 45 days (6 weeks + 3 day window) will be used OR • every 4 weeks for further 18 months, a window of 59 days (8 weeks + 3 day window) will be used OR • every 8 weeks thereafter, a window of 119 days (16 weeks + 7 day window) will be used This is to determine whether there is extended time without adequate assessment. If the time difference between PD/death due to PD and last adequate disease assessment is more than 45, 59, or 119 days, depending on the disease assessment schedules, PFS will be censored at the last adequate disease	Censored

Situation	Date of Event (Progression/Death due to PD) or Censored[1]	Event (Progression/Death due to PD) Or Censored
	assessment prior to PD/death due to PD.	

[1] Event or censored are based on confirmed responses.
[2] An adequate assessment is defined as an assessment where the investigator assessed response is sCR, CR, PR, VGPR, MR, or SD .
[3] If PD and New anti-cancer therapy occur on the same day assume the progression was documented first e.g., outcome is progression and the date is the date of the assessment of progression).
[4] Adequate baseline assessment is defined as at baseline, a patient has at least one of the following measurements: a. Serum M-protein ≥0.5 g/dL (≥5 g/L) or b. Urine M-protein ≥200 mg/24h or c. Serum FLC assay: Involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum free light chain ratio (<0.26 or >1.65).

4.3.2. Pharmacodynamics and Biomarker Analyses

Pharmacodynamic and biomarker analyses may be specified within a separate biomarker SAP, which may explore actual change and percent change of free-BCMA expression level from baseline, circulating-free DNA assessments at baseline, during response, and at end of treatment; the relationship between clinical response and other biologic characteristics, including BCMA expression on tumour cells, and sBCMA concentrations. If warranted, the results of these additional analyses will be provided in a separate report.

4.3.3. Exploratory Patient Reported Outcome Analyses

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (Version 3.0) and the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) are the exploratory Health-Related Quality-of-Life (HRQoL) assessments that will be analyzed in this study.

In addition, the impact of potential corneal event on function and HRQoL will be assessed with the Ocular Surface Disease Index (OSDI) visual function questionnaire as an exploratory endpoint.

The analysis of EORTC QLQ-C30 will be based on the Efficacy and Intent-To-Treat Analysis Set; while the analysis of PRO-CTCAE and OSDI will be based on the Safety Analysis Set.

4.3.3.1. Patient-Reported Outcome Version of the Common Term Criteria for Adverse Events (PRO-CTCAE)

The PRO-CTCAE is a patient-reported outcome measure developed to evaluate symptomatic toxicity in participants on cancer clinical trials [Basch, 2014]. The PRO-CTCAE was designed to be used as a companion to the 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 [Kluetz, 2016]).

The levels and related code values for PRO-CTCAE are shown in Table 4.

CCI

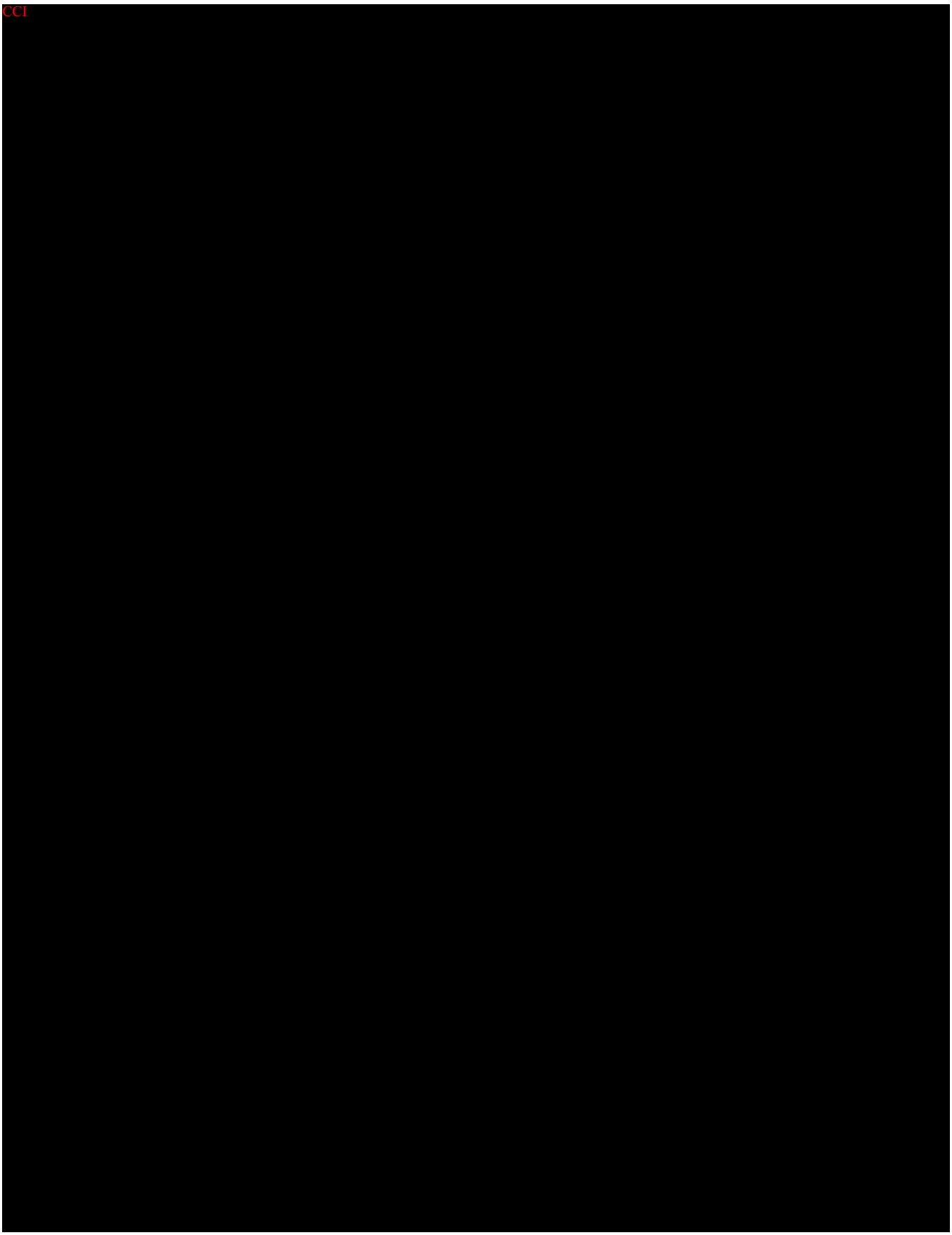


For each selected item from the library: proportion of PRO-CTCAE scores for attributes (frequency, severity and/or interference) will be presented with stacked bar charts by visit. Maximum PRO-CTCAE score at post-baseline for each item attribute will be summarized by counts and proportions. Proportion of participants with a maximum score of 3 or 4 for each item attribute ("Severe" or "Very severe", "Frequently" or "Almost constantly", "Quite a bit" or "Very much") will also be reported. Proportions will be based on the number of participants with available data and participants with missing response will be excluded from analysis.

CCI



CCI



4.3.3.4. Patient Global Impression Items

The Patient Global Impression of Severity (PGIS) assesses global impression of symptoms severity at baseline and subsequent timepoints. 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].

PGIS and PGIC data will be collected and the analysis will be described in a separate analysis plan.

4.3.3.5. Compliance of PRO-CTCAE, OSDI, and EORTC QLQ-C30

Summary measures of the overall participant compliance rate, and the participant compliance rate over time for each patient-reported outcome (PRO) instrument will be derived, respectively. These will be based upon the following definitions:

- Expected questionnaire: a questionnaire that is expected to be completed at a scheduled assessment time e.g. a questionnaire from a participant who is still under PRO follow-up at the specified assessment time.

- Evaluable questionnaire: a questionnaire with a completion date and at least one subscale that is non-missing

Overall participant compliance rate for each PRO instrument is defined for each treatment group as: Total number of participants with an evaluable baseline and at least one evaluable follow-up questionnaire, divided by the total number of participants expected to have completed at least a baseline questionnaire multiplied by 100. The target compliance for each instrument is 90%.

Participant compliance over time is calculated separately for each scheduled assessment (including baseline) as the number of participants providing an evaluable assessment at that assessment divided by the number of participants expected to have provided an assessment.

4.4. Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

4.4.1. Extent of Exposure

Extent of exposure to belantamab mafodotin, bortezomib, lenalidomide, and dexamethasone will be summarized separately for each component.

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

4.4.1.1. Induction Treatment

For the induction treatment (Cycles 1-8), the following will be summarized for dose intensity:

Belantamab mafodotin:

- Duration of exposure in days = end date of last cycle – first dose date + 1 day.
    - End date of last cycle will be calculated as the earliest of:
        - Last dose date + 20 days (Q3/4W) or 41 days (Q6/8W; 6W) or 62 days (Q9/12W; 9W) or 83 days (Q12W) or the death date if the participant discontinues study or dies before expected end of last cycle:
- The dose intensity (mg/kg/cycle) calculation for overall induction treatment are described below:
    - Dose intensity (mg/kg/cycle) = cumulative actual dose (mg/kg) / duration of exposure in a cycle (duration of exposure (days)/Y):
        - Y= 21 days (Q3/4W), 42 days (Q6/8W; 6W), 63 days (Q9/12W; 9W), 84 days (Q12W).
- The relative dose intensity (%) calculation for overall induction treatment are described below:
    - Relative dose intensity (%) = dose intensity / planned dose intensity
        - Planned dose intensity = (X mg/kg)/cycle (Y days):
            - X =
                - 1.9mg/kg GSK916 Q3/4W (cohort 1),
                - 1.4mg/kg GSK916 Q6/8W (cohort 2),
                - 1.9mg/kg GSK916 Q6/8W (cohort 3),
                - 1.0mg/kg GSK916 Q3/4W (cohort 4),
                - 1.4mg/kg GSK916 Q3/4W (cohort 5),
                - 1.4 (9W) to 1.0 mg/kg GSK916 Q9/12W (cohort 6),
                - 1.9 (9W) to 1.4 mg/kg GSK916 Q9/12W (cohort 7),
                - 1.9 (9W) to 1.4 mg/kg GSK916 Q12W OR 1.4 (6/9W) to 1.0 mg/kg GSK916 Q12W OR 1.0 mg/kg GSK916 Q12W (cohort 8A-8C)
            - Y= 21 days (Q3/4W), 42 days (Q6/8W; 9W), 63 days (Q9/12W; 9W), 84 days (Q12W).

Bortezomib:

- Duration of exposure in days = end date of last cycle – first dose date + 1.
    - End date of last cycle will be calculated as the earliest of: start date of the last treatment cycle + 20 days or the death date if the participant discontinues study or dies before expected end of last cycle (start date of last treatment cycle + 20 days).
- Dose intensity (mg/m^2/cycle) = cumulative actual dose (mg/m^2) / duration of exposure in a cycle (duration of exposure (days)/21).
- Relative dose intensity (%) = dose intensity / planned dose intensity
    - Planned dose intensity = (1.3 × 4 mg/m^2)/cycle (21 days).

Note: For the calculation of m^2, baseline body surface area (BSA) computation will be used (Haycock , 1978):

Baseline BSA (m^2) = 0.024265 × height(cm)$^{0.3964}$ × weight (kg)$^{0.5378}$.

Lenalidomide and dexamethasone (IV and PO):

- Duration of treatment will be calculated similarly as for bortezomib.
- Cumulative dose (mg) = sum of all actual doses taken across the treatment.
- Dose intensity (mg/day) = cumulative dose/duration of treatment.
- Dose exposure = total number of days on the study drug during the treatment phase, periods of dose break per protocol or missed doses will be excluded.
- Average daily dose = cumulative dose / dose exposure (mg/days).
- Relative dose intensity (**lenalidomide only**) = dose intensity / planned dose intensity:
    - Planned dose intensity (participants with eGFR 30-60 mL/min/1.73m^2) = 10mg ×14/21 days.
    - Planned dose intensity (participants with eGFR >60 mL/min/1.73m^2) = 25mg ×14/21 days.

4.4.1.2. Maintenance Treatment

For the maintenance treatment (Cycles 9+), the following will be summarized for dose intensity:

Belantamab mafodotin:

- Duration of exposure in days = end date of last cycle – first dose date + 1 day.
    - End date of last cycle will be calculated as the earliest of:
        - Last dose date + 27 days (Q3/4W) or 55 days (Q6/8W) or 83 days (Q9/12W; Q12W) or the death date if the participant discontinues study or dies before expected end of last cycle (last dose date + X days).
- Dose intensity (mg/kg/cycle) = cumulative actual dose (mg/kg) / duration of exposure in a cycle (duration of exposure (days)/Y):
    - Y= 28 (Q3/4W), 56 (Q6/8W), 84 (Q9/12W; Q12W).
- Relative dose intensity (%) = dose intensity / planned dose intensity
    - Planned dose intensity = X mg/kg / cycle (Y days):
        - X =
            - 1.9mg/kg GSK916 Q3/4W (cohort 1),
            - 1.4mg/kg GSK916 Q6/8W (cohort 2),
            - 1.9mg/kg GSK916 Q6/8W (cohort 3),
            - 1.0mg/kg GSK916 Q3/4W (cohort 4),
            - 1.4mg/kg GSK916 Q3/4W (cohort 5),
            - 1.4 (9W) to 1.0 mg/kg GSK916 Q9/12W (cohort 6),
            - 1.9 (9W) to 1.4 mg/kg GSK916 Q9/12W (cohort 7),
            - 1.9 (9W) to 1.4 mg/kg GSK916 Q12W OR 1.4 (6/9W) to 1.0 mg/kg GSK916 Q12W OR 1.0 mg/kg GSK916 Q12W (cohort 8A-8C)
            - Y= 28 days (Q3/4W), 56 days (Q6/8W), 84 days (Q9/12W; Q12W).

Lenalidomide and dexamethasone (IV and PO):

- Duration of treatment (cycles) = the end date of the last cycle of the study treatment – first date of study treatment + 1.
    - End date of last cycle will be calculated as the earliest of: start date of the last treatment cycle + 27 days or treatment discontinuation date or the death date if the participant discontinues study or dies before expected end of last cycle (start date of last treatment cycle + 27 days).

- Cumulative dose, dose intensity, dose exposure, average daily dose, will be calculated similarly as lenalidomide and dexamethasone for induction treatment.

- Relative dose intensity (**lenalidomide only**) = dose intensity / planned dose intensity:

    - Planned dose intensity (participants with eGFR 30-60 mL/min/1.73m^2) = 10mg ×21 / 28 days;

    - Planned dose intensity (participants with eGFR >60 mL/min/1.73m^2) = 25mg×21 / 28 days.

Missed doses will be summarized by number of missed doses. Dose reductions will be summarized by number of reductions and reasons for reductions. Dose delays will be summarized by number of delays and reasons for delays. Infusion interruptions will be summarized by number of interruptions and reasons for interruptions.

The number and percentage of the delays for the following intervals will be computed:

Belantamab mafodotin:

- Q3/4W: 1-21, 22-42, and 43-168, >168 days

- Q6/8W: 1-42, 43-84, and 85-336, >336 days

- Q9/12W: 1-63, 64-126, and 127-504, >504 days

- Q6/9W to Q12W: 1-42, 43-105, and 106-168, >168 days

- Q12W: 1-84, 85-168, and 169-252, >252 days.

Dexamethasone:

- 1-21, 22-42, and 43-168, >168 days.

Bortezomib:

- 1-21, 22-42 and >42 days.

Primary reasons for missed doses, dose reductions, dose delays, and infusion interruptions will also be summarized by cycle and by induction and maintenance therapies.

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).

Belantamab mafodotin:

The protocol allows a window of +/- 3 days for administration of belantamab mafodotin so a dose will only be considered delayed if it is 4 or more days after the scheduled dose date.

- Induction therapy: Expected start date of dose = actual start date of previous dose + 21 (Q3/4W), actual start date of previous dose + 42 (Q6/8W; 6W), actual start date of previous dose + 63 (Q9/12W; 9W), and actual start date of previous dose + 84 (Q12W)

- Maintenance therapy: Expected start date of dose = actual start date of previous dose + 28 (Q3/4W), actual start date of previous dose + 56 (Q6/8W), and actual start date of previous dose + 84 (Q9/12W; Q12W).

Bortezomib and dexamethasone:

- Induction therapy: Expected start date of dose = actual start date of previous dose + 21.

- Maintenance therapy: Expected start date of dose = actual start date of previous dose + 28.

The summaries of dose modifications will be provided. All the missed doses, dose reductions, dose interruptions, and dose delays will be listed separately.

A by-subject summary listing of data on exposure to all study treatments will be produced.

A by subject listing of drug accountability for lenalidomide and dexamethasone based on dispensed versus returned data will be produced.

A plot of the cumulative exposure to belantamab mafodotin will be produced that displays the number or percentage of participants exposed to the study treatment by time on study.

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 horizontal bar graph of duration of treatment will be produced that displays duration of treatment in months for each participant.

Duration of follow-up will be summarized and is defined as the interval of time (in months) from randomization to last contact or death.

4.4.2. Adverse Events

Adverse events analyses including the analysis of adverse events (AEs), Serious (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 interruptions/delays, SAEs, SAEs related to study intervention, fatal SAEs, and fatal SAEs related to study intervention will be produced.

A summary of non-serious adverse events that occurred in strictly 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 4.99% incidence rate should not be included in this table). The summary will be displayed by SOC and PT and induction and maintenance therapies.

Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary) and graded by the investigator according to the NCI-CTCAE, (version 5.0).

A summary of number and percentage of participants with any AEs by maximum grade will be produced. AEs will be sorted by Preferred term (PT) in descending order of total incidence and by overall, induction, and maintenance therapies. The summary will use the following algorithms for counting the participant:

- **Preferred term row**: Participants experiencing the same AE PT several times with different grades will only be counted once with the maximum grade.

- **Any event row**: Each participant with at least one AE will be counted only once at the maximum grade no matter how many events they have.

In addition, the frequency and percentage of AEs (all grades) will be summarized and displayed in two ways:

1.) In descending order of total incidence by PT only, and
2.) In descending order of total incidence by System Organ Classes (SOC) and PT and Maximum Grade.

In the SOC row, the number of participants with multiple events under the same system organ class will be counted once.

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 of total incidence by PT and Maximum Grade and by induction and maintenance therapies.

A listing of adverse events recorded as dose-limiting toxicities during the determinative period related to study treatments will be provided. The number of participants experiencing DLTs related to belantamab mafodotin and VRd will be summarized separately based on the DLT evaluable population.

All AEs will be listed which will include participant IDs for each individual AE.

Details of the planned displays are provided in the OPS.

4.4.2.1. Adverse Events of Special Interest

The following will be considered adverse events of special interest (AESI) for belantamab mafodotin for the purpose of analyses: eye disorders (any MedDRA PT in the Eye Disorder SOC (includes ocular AEs/symptoms as separate from ophthalmic exam findings)), corneal events per KVA scale, thrombocytopenia, and infusion-related reactions. A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. For infusion related reactions (IRR), events are only considered IRR if the event was reported on an infusion day after the start of infusion or within 24 hours following end of infusion and led to a temporary interruption or prolongation of infusion time or treatment withdrawal. For keratopathy events (CTCAE) under eye disorders, events are considered keratopathy events if the synonym = "keratopathy/keratitis".

For ocular exam visits based on the ocular worksheet under the original protocol, GSK scale was used in cohort 1 prior to cohort expansion. For ocular exam visits based on the ocular worksheet under the protocol amendment 1 onwards, Keratopathy Visual Acuity (KVA) scale was used in cohort 1 expansion and cohort 2-8. Section 6.2.8 includes details of the similarities and differences between the GSK and KVA corneal event scales. Corneal examination findings, visual acuity assessments, and corneal events (composite grade based on corneal examination findings and visual acuity assessments) associated with belantamab mafodotin will be graded according to GSK scale for cohort 1 and KVA scale for cohort 2-8. Other treatment-related ocular AEs/symptoms are to be reported based on NCI-CTCAE v5.0 criteria for eye disorders. The severity of all other AESIs will be graded utilizing the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) (v.5.0). Additional AEs of special interest may be identified during the study and will also be summarized separately. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in Section 6.6 of the protocol. Dose modifications for belantamab mafodotin corneal events will be based on grading of corneal events according to the guidelines of KVA Scale (Study Protocol Amendment 03: GSK Document Number TMF-14223056).

Summaries of the number and percentage of participants with these events will be provided for each type of events separately by preferred term and maximum grade and induction and maintenance therapies. The time of onset and duration of first occurrence of each type of events will be summarized using summary statistics mean, standard deviation, median, minimum value, and maximum. The number and percentage of participants who have time of onset of first occurrence and participants who have duration of first occurrence will be reported in the following:

Thrombocytopenia, Eye Disorders, and Grade 2+/Grade3+ Corneal Events (KVA scale):

- **Q3/4W Schedule:**

  - 1-21, 22-42, and 43-168, >168 days.
- **Q6/8W Schedule:**
  - 1-42, 43-84, and 85-336, >336 days.
- **Q9/12W Schedule:**
  - 1-63, 64-126, and 127-504, >504 days.
- **6/9W to Q12W Schedule:**
  - 1-42, 43-105, and 106-168, >168 days.
- **Q12W Schedule:**
  - 1-84, 85-168, and 169-252, >252 days.

Infusion-Related Reactions:

- **All schedules:**
  - Time of first occurrence: 0-6, >6-12, >12-18, >18-24 hours
  - Duration of first occurrence: 0-12, >12-24, >24 hours

For thrombocytopenia, infusion-related reactions, and eye disorders, the summary of event characteristics will also be provided by induction and maintenance therapies, 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 treatment, number of occurrences (One, Two, Three or more), maximum grade 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, participant will be counted once under each action, e.g., if a participant has an event leading to both study treatment discontinuation and dose reduction, the participant will be counted once under both actions. For grade 2 or above and grade 3 or above corneal events (KVA scale), the event characteristics will be summarized similarly as the AESIs.

For thrombocytopenia, number, and percentage of participants with grade 3 or 4 platelet count decreased (based on lab data) and concomitant grade 2 or above bleeding event will be summarized. A bleeding event will be considered as concomitant only if the start date is within ± 3 days of the lab event.

The following outputs will be provided for corneal events (KVA Scale):

- Summary of Corneal Events (KVA Scale) by Grade and Visit (interim analyses only)
- Summary of Worst Post-baseline Corneal Events (KVA Scale)
- Listing of Grade 3 or higher corneal event (KVA scale) during cycle 2-4

Details of the planned displays are provided in the OPS.

4.4.2.2. Death and Serious Adverse Events

All deaths will be summarised based on the number and percentage of participants. This summary will classify participants by time of death relative to the last dose of treatment (>30 days or ≤30 days) and primary cause of death (disease under study, SAE possibly related to study treatment, or other). A supportive listing will be generated to provide participant-specific details on participants who died.

A supportive listing will be generated to provide participant-specific details on participants who died and have fatal SAEs.

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 treatment-related SAEs. The summary tables will be displayed in descending order of total incidence by SOC and PT and induction and maintenance therapies.

A study treatment-related SAE is defined as an SAE for which the investigator classifies the relationship to study treatment as "Yes". A worst-case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing.

SAEs are included in the listing of all adverse events. Separate supportive listings with participant-level details will be generated for non-fatal SAEs.

4.4.2.3. Adverse Events Leading to Discontinuation and Dose Modifications

The following categories of AEs will be summarized for separately in descending order of total incidence by SOC and PT and induction and maintenance therapies 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 Interruptions/Delays
- AEs Leading to Dose Reductions

4.4.2.4. Ocular Findings from Ophthalmic Exam

As outlined in study protocol (GSK Document Number TMF-14223056), ophthalmic exams are scheduled at screening, during the study, end of treatment, and follow-up period. The ocular findings from ophthalmic exams will be summarized descriptively:

- From baseline to last follow-up, the following analysis will be performed:
  Visual Acuity:
    - The best corrected visual acuity (BCVA) summary will be based on the Logarithm of the Minimum Angle of Resolution (logMAR score), where:
      $\text{logMAR score} = -\log_{10}(\text{Snellen Acuity Score})$
    - In addition, change from baseline will be summarized by eye (R/L) and participant (worse eye and better eye). The following categories of logMAR score changes from baseline are defined: No change/improved vision is defined as a change from baseline <0.12; A possible worsened vision is defined as a change from baseline ≥0.12 to <0.3; A definite worsened vision is defined as a change from baseline ≥0.3 logMAR score.
    - Summary of Best Corrected Visual Acuity (BCVA) scores (logMAR score) due to corneal events (KVA Scale)
    - A summary of worst BCVA change from baseline (based on the eye with worst change and best change) in Snellen will be provided for categories: Improved BCVA is defined as a negative change in logMAR score from baseline BCVA; ≤2 lines decline in visual acuity is defined as change from baseline ≤0.37 logMAR score (or Grade 2 decline as defined Section 6.6.2.2 of the protocol); ≥3 lines decline in visual acuity is defined as change from baseline ≥0.38 logMAR score (or Grade 3 decline as defined Section 6.6.2.2 of the protocol).

Corneal Exam

- Shift table from baseline to worst post-baseline by eye (R/L) and subject (worse eye, defined as the eye with the maximum worsening change from baseline) for corneal epithelium findings and other exams:
    - Corneal exam (Normal to Abnormal)
    - Stripped peripheral corneal staining +/- vortex/whorl staining pattern (No to Yes)
    - Microcyst-like deposits (No to Yes)
    - Subepithelial haze (No to Yes)
    - Epithelial edema (No to Yes)
    - Corneal epithelial defect (Yes to No)
    - Corneal neovascularization (No to Yes)
    - Superficial epithelial microcyst-like changes (No to Yes)
    - Corneal ulcer (No to Yes)
- For superficial punctate keratopathy, summary table of worst grade post-baseline and most frequent grade post-baseline across ocular exams by eye (R/L) and subject (worse eye)
- Shift tables from baseline to worst post-baseline in response to ocular driving and reading
- Summary of findings for ocular driving and reading (interim analyses only)

4.4.3. Additional Safety Assessments

The analyses of non-laboratory safety test results including ECGs, LVEFs, and vital signs will be based on GSK Core Data Standards, unless otherwise specified. Details of the planned displays are provided in OPS.

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.

4.4.3.1. Laboratory Data

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Immunology laboratory tests, and liver function tests will be based on GSK Core Data Standards. Details of the planned displays are provided in the OPS. Summary of change from baseline by scheduled visits using mean, median, standard deviation, minimum and maximum will be provided.

Summaries of worst-case grade increase from baseline grade will be provided for all the lab tests that are gradable by CTCAE v5.0 and by induction and maintenance therapies. 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 of 3 and any increase to a maximum Grade of 4. The “Any Grade Increase” column will include all cases where the worst-case grade is 1 or higher and the baseline grade is missing. Likewise

the Increase to Grade X (where X=3 or 4) will include cases that are worst-case Grade X and the baseline grade is missing. 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.

For lab tests that are not gradable by CTCAE v5.0, summaries of worst-case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized for the worst-case post-baseline. If a participant has a decrease to low and an increase to high during the same time interval, then the participant is counted in both the "Decrease to Low" categories and the "Increase to High" categories.

Separate summary tables for hematology, chemistry, immunology, and hepatobiliary laboratory tests will be produced by induction and maintenance therapies. Liver function laboratory tests will be included with hepatobiliary laboratory tests.

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 provided. For lab test values that can be graded, values of Grade 1 or above are defined as values of potential clinical concern. For lab test values that cannot be graded, values out of the normal range are defined as values of potential clinical concern.

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.

4.4.3.2. Vital Signs

Values of vital signs (temperature, systolic and diastolic blood pressure, heart rate) as well as the change from baseline will be summarized by scheduled visit using mean, median, standard deviation, minimum and maximum.

A summary of changes in heart rate and temperature comparing the baseline value to the worst-case post baseline value will be provided. Heart rate will be categorized into 'Decrease to <60', 'Change to Normal or No Change' and 'Increase to >100'. Temperature (C) will be categorized into 'Low' (<35), 'Normal' (36-37), and 'High' (>=38) groups. The determination of the worst-case post baseline considers both scheduled and unscheduled assessments. If a participant has a decrease to low and an increase to high, then the participant is counted in both the "Decrease to <60" categories and the "Increase to >100" categories. Similarly, temperature will be categorized based on normal ranges.

In addition, summaries of grade increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) will be provided separately. These summaries will display the number and percentage of participants with any grade increase, increase to Grade 2 and increase to Grade 3 for worst-case post-baseline only. The grade definition for SBP (mmHg) is: Grade 0 (<120), Grade 1 (120-139), Grade 2 (140-159), Grade 3 (>=160).

The grade definition for DBP is: Grade 0 (<80), Grade 1 (80-89), Grade 2 (90-99), Grade 3 (>=100). The summaries will be produced for worst-case post baseline only.

4.4.3.3. ECG

A 12-lead electrocardiogram (ECG) is obtained at screening/baseline and then as clinically indicated as specified in the Schedule of Activities of protocol. The heart rate, PR, QRS, QT, and corrected QT (QTc) intervals according to Fridericia's formula (QTcF) will be obtained. No further ECGs are required but may be obtained as part of medical care.

A summary of the number and percentage of subjects who had normal and abnormal (clinically significant and not clinically significant) ECG findings will be displayed by scheduled visits as well as for the worst case post-baseline.

A listing of QTc values of potential clinical importance may be provided using the collected values based on Fridericia's formula.

4.4.3.4. LVEF

Absolute change from baseline in LVEF will be summarized in the worst case postbaseline only. Only the post-baseline assessments that used the same method (ECHO or MUGA) as the baseline assessments will be used to derive the change from baseline. The change from baseline will be categorized as follows:

- No change or any increase
- Any decrease
    - >0-<10 decrease
    - 10-19 decrease
    - o >=20 decrease
    - o >=10 decrease and >= LLN
    - o >=10 decrease and < LLN
    - o >=20 decrease and >= LLN
    - o >=20 decrease and < LLN

A listing of LVEF results may be provided.

4.4.3.5. Liver Function Tests

A summary of Liver Monitoring/Stopping Event Reporting will be provided. A Liver event profile which includes medical conditions data for subjects with liver stopping events, substance use data for subjects with liver stopping events, liver biopsy results for subjects and recorded outcomes of liver imaging assessments for subjects will be listed.

A summary of hepatobiliary laboratory abnormalities including possible Hy's law cases will be provided by induction and maintenance therapies.

Plots of maximum total bilirubin versus maximum ALT and maximum ALT versus baseline ALT will be generated.

4.4.3.6. Performance Status

ECOG performance status will be summarized at baseline and each post-baseline scheduled visit. Summaries will use frequency and percentage of subjects 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).

4.4.3.7. Profile Plot

A profile plot for subjects will be produced. This plot will display the duration of study treatment in days for each subject, along with an indication of each subject's actual dose over time, investigator assessed confirmed response, highlighting responders versus non-responders, and those ongoing on belantamab mafodotin study treatment.

4.4.3.8. Neutropenia

The summary of event characteristics and summary of events by preferred term and maximum grade and induction and maintenance therapies displays produced for AESIs will be repeated for neutropenia. Additionally, a summary of neutropenia and infection events will be provided, summarizing:

- number and percentage of participants with grade 3 or 4 neutrophil count decreased based on AE data
- number and percentage of participants with infection event based on AE data
- number and percentage of participants with concomitant grade 3 or 4 neutrophil count decrease and infection event. Infections will be considered concomitant only if started within +/-7 days of the neutrophil count decrease.

The severity of neutropenia will be graded utilizing NCI-CTCAE v5.0 criteria. A comprehensive list of MedDRA preferred terms for neutropenia based on clinical review will be used to identify each type of event. Neutropenia will be identified based on list of terms of interests which will be produced in Integrated Coding Dictionary System by

Clinical Dictionary Development & Management and provided to Statistics and Programming.

Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional risks; therefore, the list of terms to be used for each event and the specific events will be based on the safety review team (SRT) agreements in place at the time of reporting.

4.5. Other Analyses

4.5.1. Subgroup analyses

The list of subgroups (see Table 5) may be used in descriptive summaries and statistical analyses. Additional subgroups of clinical interest may also be considered.

- If the percentage of participants is small within a particular subgroup, then the subgroup categories may be redefined.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.

Table 5 Subgroup Analyses

Subgroup	Categories
Age	18 to <65, 65 to <75, ≥75
Sex	Male, Female
Ethnic Background	White, Other
ISS Staging at Screening & at Initial Diagnosis	I, II, III, Other (Unknown or Missing)
Type of myeloma	IgG, Non-IgG
Extramedullary disease	No, Yes, Missing
Cytogenetics Risk [1]	High, Other (non-high risk, not done, or missing)

NOTES:

- [1] A participant is considered as high risk if the participant has any of at least of the following cytogenetics: t(4;14), t(14;16), 17p13del, and del17p.

4.5.2. Other Efficacy Analyses

The analyses will be based on the Intent-To-Treat and Efficacy Analysis Sets, unless otherwise specified.

- **Time to VGPR or better** is defined as the interval of time (in months) between the date of first randomization and the first documented evidence of response (VGPR or better) among participants with a confirmed VGPR or better as the BOR assessed by the investigator per IMWG (2016).

If there are sufficient number of responses by dose level, time to response at will be summarized descriptively using median(s) and quartiles in the subset of subjects with a confirmed response of VGPR or better as the BOR and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (1982).

- **Time to CR or better** is defined as the interval of time (in months) between the date of first randomization and the first documented evidence of response (CR or better) among participants with a confirmed CR or better as the BOR assessed by the investigator per IMWG (2016).

If there are sufficient number of responses by dose level, time to response at will be summarized descriptively using median(s) and quartiles in the subset of subjects with a confirmed response of CR or better as the BOR and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (1982).

- **Maximum percent reduction from baseline in Serum M-protein or Urine M-protein or the difference between two types of serum FLC:**

Only the assessments from the start of treatment up to the start of new anti-cancer therapy will be considered and based on the Intent-To-Treat (ITT) and Efficacy analysis sets. Only new systemic anti-cancer drugs taken are considered as anti-cancer cancer therapy (radiotherapy and surgeries are not considered as systemic anti-cancer therapy for the purpose of this analysis).

The percent change from baseline for difference between two types of Serum FLC is defined as: (post-baseline difference-baseline difference) / baseline difference *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 = Kappa LC-Lambda 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 can not be determined (ratio is normal), and maximum percent reduction from baseline for difference between two types of Serum FLC won't be available.

  A waterfall plot showing the maximum percent reduction from baseline in Serum M protein, or Urine M-protein, or difference between two types Serum FLC [Kappa light chain (Kappa LC) and Lambda light chain (Lambda LC)] for each subject will be produced using by dose level. The plot will be color-coded for M-protein types and Serum FLC, etc. Indication of the best overall response will be provided below the plot. 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;

4.6. Interim Analyses

After the last participant from cohorts 2-5 complete 4 cycles of study treatment(s), an interim analysis will be performed for cohorts 2-5 to support the cohort expansion (an additional 6 participants) of the selected cohort(s). In addition, based on emerging data from other clinical studies in the belantamab mafodotin clinical development program, the decision on whether to evaluate cohort 6, 7, or 8 can take place. If cohorts 6-8 are open, after the last participant completes the end of Cycle 8 or if participants who experienced treatment cycle delays due to any reasons prior to the end of Cycle 8, they shall have completed at least 2 disease assessments and ocular exams after the last dose of belantamab mafodotin. If necessary, after at least 6 participants are completed the above-mentioned treatment in each dose cohort, additional interim analyses may also be conducted to aid in decision making regarding dose identification, cohort expansion or closure, and safety monitoring. Data considered to support dose decision will include but not limited to safety, available PK profile, and observed signs of clinical activity in addition to the DLT evaluation.

Further details of the dose evaluation review is provided in the dose evaluation plan. Details of the planned displays are provided in OPS.

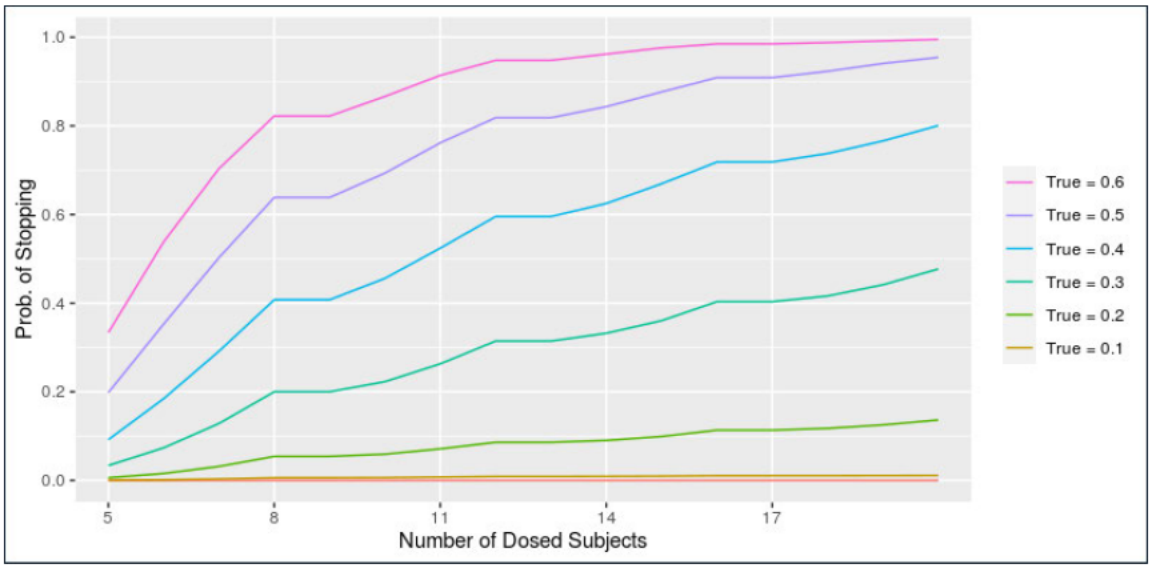
4.6.1. Safety Stopping Rules

Continuous monitoring will be conducted starting from when five (5) participants are dosed at each dose level. The observed number of participants who permanently discontinue study treatment due to AEs related to belantamab mafodotin within the first three (3) cycles will be compared against the safety stopping rule in Table 6. Enrollment may stop for the specific cohort if the safety stopping rule is met based on totality of safety data. For example, if out of five (5) participants, four (4) participants permanently discontinued study treatment within the first three (3) cycles due to AE related to belantamab mafodotin, enrollment for the specific cohort(s) may stop after review of all safety data; otherwise enrollment will continue.

Table 6 Safety Stopping Rules

Number of dosed participants	Stop if number of participants discontinuing study treatment within the first three (3) cycles due to AE related to belantamab mafodotin is larger or equal to this number	Observed rate
5-8	4	0.50-0.80
9-12	5	0.42-0.56
13-16	6	0.38-0.46
17-20	7	0.35-0.41

Figure 1 Operating Characteristics of Safety Stopping Rule



4.6.2. Unplanned Interim Analysis

An unplanned interim analysis has been approved as per Note to File document number TMF-14011347 to be performed when the last out of 24 participants randomized from Cohorts 2-5 reaches the end of Cycle 3 of their study treatment(s), and an additional

12 participants from Cohort 1, based on all observed data, as of the data cut-off date. This analysis deviated from the planned interim analysis as per Protocol Amendment 02 No.: TMF-13825366 [Dated: 28-JUL-2021].

The unplanned interim analysis is intended only for internal strategic discussion purposes in order to support the belantamab mafodotin clinical development plan. The dose decision will be made solely based on the protocol planned first interim analysis (see Section 4.6 for details), based on 60 participants from Cohorts 1-5 in order to maintain study and data integrity, thus the probability of meeting the success criteria to declare an optimal safe dose at the end of Cycle 4 for all dose cohorts will remain unaltered.

4.6.3. Primary Analysis

The primary analysis will be performed when the last participant reaching the end of Cycle 8 in all dose cohorts after cohort expansion to determine the safe dose for future studies.

4.6.4. Final Analysis

The final analysis will take place once all participants recruited have completed the study.

4.7. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol are detailed in Table 7.

Table 7 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
• Section 5.1. Statistical operating characteristics: To calculate the posterior probability of the DLT, a non-informative Beta prior (0.4, 0.2) from the available data of 1.9 mg/kg Q3/4W cohort (Cohort 1) will be used for each cohort. Under different assumptions of the true DLT rate, the operating characteristics are summarized based on 12 participants at the interim analysis, prior to cohort expansion, and up to 20 participants after cohort expansion	• To calculate the posterior probability, a non-informative Beta prior (0.25, 0.75) from the available data of 1.4 mg/kg Q6/8W cohort (Cohort 2) will be used for each cohort. Under different assumptions of the true DLT rate, the operating characteristics are summarized based on 11 participants at the interim analysis, prior to cohort expansion, and up to 19 participants after cohort expansion	• A patient from cohort 6, prior to cohort expansion, experienced a sub-dural haemorrhage (unrelated to study medication or study procedures) and passed away before completing their DLT observation period. The study team decided to not replace the patient. Therefore, an additional DLT operating characteristics were re-evaluated under different assumptions as detailed in Table 8.

Table 8 Operating characteristics of the study

True DLT rate	Probability of cohort expansion (≤3/11 with DLTs)	Probability of meeting success criteria to declare safe dose at end of Cycle 4 for all dose cohorts after cohort expansion
0.2	0.838	0.775
0.225	0.779	0.689
0.25	0.713	0.597
0.275	0.642	0.502
0.3	0.569	0.41
0.33	0.481	0.309
0.35	0.425	0.25
0.40	0.296	0.134
0.45	0.191	0.063
0.50	0.114	0.025
0.55	0.061	0.009

Note: The stopping boundary and success criteria are calculated using R program. Success criteria is the posterior probability of (DLT rate > 0.27)< 0.35.

5. SAMPLE SIZE DETERMINATION

The total number of participants to be enrolled will depend on the number of participants needed to characterize individual dose cohorts. The sample size is not driven by statistical considerations. However, based on assumptions that up to 8 different dose cohorts may be evaluated, it is anticipated that up to 160 participants will be enrolled. For dose evaluation, the total sample size will depend on the number needed to adequately characterize the DLT profile and determine the safe dose.

5.1. Statistical Operating Characteristics

Dose evaluation will be based on dose limiting toxicities (DLT) and a dose cohort will be deemed safe at the primary analysis if:

CCI

[redacted]

CCI



6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the Intent-to-Treat, Enrolled, Screened, and Safety Analysis Sets. Study population analyses including analyses of participant's disposition, demographic and baseline characteristics, protocol deviations, disease characteristics at initial diagnosis and at screening, prior and concomitant medications, follow-up anti-cancer therapy, surgical/medical procedures, substance use, duration of follow up, exposure, and treatment compliance will be based on GSK Core and Oncology Data Standards.

6.1.1. Participant Disposition

A summary of the number of participants in each of the analysis set described will be provided. In addition, the number of participants enrolled by country and site will be summarized using the Enrolled population. A listing of participants excluded from each study population will also be provided using the following rationales for exclusions in Table 10.

Table 10 Rationales for Participant Exclusions of Analysis Set

Analysis Set	Rationale for Exclusion
ITT	• Enrolled into study, but not randomized into cohorts 1-8
Efficacy	• All participants with or without documented MM and measurable disease who have received any prior therapies and are transplant ineligible
COVID-19	• Received study treatment(s), but are not suspected, probable, or suspected COVID-19 case diagnosis
DLT Evaluable	• Enrolled and received study treatment(s), but did not meet the DLT evaluable criteria
Safety	• Randomized or assigned into study, but did not receive study treatment(s)
Pharmacokinetic (PK)	• Received study treatment(s), but did not have at least one PK sample obtained

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.

A summary and listing of screening status and screen failures will be provided using the Screened population.

6.1.2. Demographics and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, baseline height, and baseline body weight and baseline body mass index [BMI]) will be summarized. Age, height, weight, and BMI will be summarized using the mean, standard deviation, minimum, median, and maximum. The count and percentage will be computed for sex and ethnicity.

Race and racial combinations will be summarized.

Disease history and characteristics (e.g., time since initial diagnosis in years, date of initial diagnosis) at initial diagnosis and screening will be listed. Separate summary table of disease characteristics at screening will be provided. Disease characteristics at screening, including stage, type of multiple myeloma, myeloma light chain and myeloma immunoglobulin, extramedullary disease, lytic bone lesion, and genetic characteristics (including high cytogenetic risk) will be summarized.

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

- Participants with most recent previous cancer with the date of initial diagnosis of more than 2 years before screening are considered as past medical conditions.
- Participants with most recent previous cancer with a date of initial diagnosis within 2 years of screening are considered as current medical conditions.
- For medical conditions relating to congestive heart failure:
    - Participants with past medical conditions relating to congestive heart failure and are ongoing during the screening visit and identified and collected in the "Other Medical Conditions" eCRF are considered as past medical conditions and current medical conditions.
    - Participants with medical conditions relating to congestive heart failure occurring during the treatment period, identified and collected in the "Congestive Heart Failure" eCRF, and the investigator classifies previous episode of heart failure as "Yes" are considered as past medical conditions and current medical conditions.
    - Participants with medical conditions relating to congestive heart failure occurring during the treatment period, identified and collected in the "Congestive Heart Failure" eCRF, and the investigator classifies previous episode of heart failure as "No" are considered as current medical conditions.

Medical conditions at onset of liver event will be summarized.

Substance use, including smoking history and alcohol use will be summarized. Smoking Pack Years which is calculated as (number of cigarettes smoked per day/20) × number of years smoked will be provided.

Anti-cancer radiotherapy will be listed. On treatment cancer and non-cancer related surgeries will be listed.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

In addition to the overall summary of important protocol deviations, separate summary will be produced for important protocol deviations related to COVID-19.

A separate summary 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 electronic Case Report Form (eCRF).

6.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using GSK Drug coding dictionary and summarized. 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 summary.

In the summary of concomitant medications, each participant is counted once within each unique ingredient. For example, if a participant takes Amoxycillin on two separate occasions, the participant is counted only once under the ingredient "Amoxycillin". In the summary of concomitant medications, the ingredients will be summarized by the base only, using CMBASECD and CMBASE. Note: In order to be considered a concomitant medication, the concomitant medication must have been taken at some point during the on-treatment window.

Blood products or blood supportive care products with onset date within the on-therapy 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-Myeloma Therapies

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

Follow-up anti-cancer therapy will be coded using GSK Drug coding dictionary, then summarized by ingredient. A listing of the type of follow-up anti-cancer therapy received (chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, and small molecule targeted therapy for each participant will be provided).

6.1.6. Study Intervention Compliance

Summaries of study treatment exposure and dose modifications (e.g., number of reductions, number for dose delays) will further characterize compliance. These analyses are described in Section 4.4.1.

6.1.7. 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.

A summary of the numbers of participants with a suspected, probable or confirmed COVID-19 infection, and of COVID-19 test results will be based on GSK Core Data Standards and will be summarized using the Safety Analysis Set. A Standardised MedDRA Query (SMQ) will be used to identify all COVID-19 AEs.

The incidence of AEs and SAEs (Fatal and Non-Fatal) of COVID-19, and COVID-19 AEs leading to study drug discontinuation will be obtained from standard AE and SAE summaries.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

See OPS.

6.2.2. Study Period

See OPS.

6.2.3. Study Day and Reference Dates

See OPS.

6.2.4. Assessment Window

For data summaries by visit, scheduled visits with nominal visit description as well as the worst-case post baseline will be displayed. Unscheduled visits will not be displayed or slotted into a visit window but will be included in the derivation of worst-case post baseline assessment. All un-scheduled visits will be displayed in the listing.

6.2.5. Multiple measurements at One Analysis Time Point

See OPS.

6.2.6. Handling of Partial Dates

See OPS.

6.2.7. Patient Reported Outcome

6.2.7.1. EORTC QLQ-C30

The EORTC QLQ-C30 is a 30-item questionnaire containing both single- and multi-item measures [Aaronson, 1993]. These include five functional scales (Physical, Role, Cognitive, Emotional, and Social Functioning), three symptom scales (Fatigue, Pain, and Nausea/Vomiting), a Global Health Status/QoL scale, and six single items (Constipation,

Diarrhea, Insomnia, Dyspnea, Appetite Loss, and Financial Difficulties). Table 11 shows the details.

CCI



Scores for each scale and single-item measure are averaged and transformed linearly to a score ranging from 0–100. (see below image for details). A high score for functional scales and for Global Health Status/QoL represent better functioning ability or HRQoL, whereas a high score for symptom scales and single items represents significant symptomatology [Proskorovsky, 2014].

Technical Summary

In practical terms, if items $I_1, I_2, \ldots I_n$ are included in a scale, the procedure is as follows:

Raw score
Calculate the raw score
$RawScore = RS = (I_1 + I_2 + \ldots + I_n)/n$

Linear transformation
Apply the linear transformation to 0-100 to obtain the score S,

Functional scales: $S = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$

Symptom scales / items: $S = \{(RS-1)/range\} \times 100$

Global health status / QoL: $S = \{(RS-1)/range\} \times 100$

Range is the difference between the maximum possible value of *RS* and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of *RS* equals the range of the item values. Most items are scored 1 to 4, giving *range* = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with *range* = 6, and the initial yes/no items on the earlier versions of the QLQ-C30 which have *range* = 1.

Handling of missing items

Single-item measures: if the item is missing, the score S will be set to missing.

Scales requiring multiple items: if at least half of the items from the scale are available, the score S will be calculated based on available items. If more than half of the items from the scale are missing, the score S will be set to missing (Fayers, 2001).

Minimal Important Difference (MID)

In a sample of patients who received chemotherapy for either breast cancer or small-cell lung cancer (n=246, n=80 respectively), the mean change in EORTC QLQ-C30 score between baseline and follow-up was about 5 to 10 points on a 0-100 scale for patients who indicated “A little” change on the Subjective Significance Questionnaire (SSQ), either for better or for worse (Osoba, 1998).

6.2.8. GSK and KVA Scales

The tables below show the similarities and differences in GSK and KVA scales used in DREAMM-9 study. Visual acuity (Table 12) is considered in all grading scales.

Table 12 Grading Scales: Visual acuity (BCVA)

	GSK scale	KVA scale
Grades	**1-4**	**1-4**
Unit of measure for BCVA	**Snellen**	**Snellen**
Grade 1	Decline of **1 line** from baseline	Decline of **1 line** from baseline
Grade 2	Decline of **2 or 3 lines** from baseline (BCVA not worse than 20/200)	Decline of **2 or 3 lines** from baseline (BCVA not worse than 20/200)
Grade 3	Decline of **>3 lines** from baseline (BCVA not worse than 20/200)	Decline of **>3 lines** from baseline (BCVA not worse than 20/200)
Grade 4	BCVA worse than 20/200	BCVA worse than 20/200

The 5 components of corneal examination findings (Table 13) considered for grading are:

- Superficial punctate keratopathy
- Microcyst-like deposits
- Subepithelial haze
- Active stromal opacity
- Corneal epithelial defect (includes corneal erosion and corneal ulcer)

Epithelial or stromal edema was not included in the KVA scale as one additional component in the GSK scale, as it was felt that it was variable and not necessarily a reflection of the severity of the corneal event.

Table 13 Grading Scales: Corneal Exam Findings

Corneal Exam:		GSK Scale	KVA Scale
Grades		1 to 4	1 to 4
Corneal exam components of relevance	Superficial Punctate Keratopathy (SPK)	Mild	Mild
		Moderate	Moderate
		Severe	Severe
	Microcysts	Mild/patchy	Patchy microcyst-like deposits
		Diffuse	Diffuse microcyst-like deposits involving central cornea
	Epithelial or Stromal Edema	Mild/patchy	N/A
		Diffuse	
	Subepithelial Haze	Peripheral	Peripheral
		Central	Central
	Active Stromal Opacity	Peripheral	Peripheral
		Central	Central
	Corneal Epithelial Defect	Present	Present

Key for grading:

Grade 1	Grade 2	Grade 3	Grade 4

6.3. 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.

6.3.1. 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, CPMS, GSK using the currently supported versions of all software packages.

6.3.2. 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.

6.3.3. 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 209664 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 209664 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 209664 data set results in substantial bias or if a further exploration of the covariate effect in the Study 209664 population is deemed necessary, the parameters of the current PopPK model will be re-estimated for the Study 209664 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 209664 PK population. Covariates not available for the Study 209664 PK population but present in the current PopPK model may be removed from the Study 209664 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.

6.3.4. 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)

6.4. 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 Section 6.3 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.

6.5. Abbreviations

Abbreviation	Description
ADA	Anti-Drug Antibodies
ADaM	Analysis Data Model
ADC	Anti-drug conjugate
AE	Adverse Event
Ae(0-t)	Amount of drug excreted in urine from dosing to time t
AESI	Adverse Event of Special Interest
AUC	Area under the concentration-time curve
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity
AUC(0-t)	Area under the concentration-time curve
AUC(0-τ)	Area under the concentration-time curve during the dosing interval
BCMA	B-cell maturation antigen
BCVA	Best Corrected Visual Acuity
BMI	Body mass index
BOR	Best Overall Response
CI	Confidence Interval
CL	Clearance
Cmax	Maximum observed plasma drug concentration
CPMS	Clinical Pharmacology Modelling & Simulation
CR	Complete Response
Ctrough	Concentration observed prior to the next dose
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
Cys-mcMMAF	microtubule inhibitor monomethyl auristatin-F with a cysteine linker
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Record Form
EOI	End of infusion
EORTC	European Organization for Research and Treatment of Cancer
FLC	Free light chain
GSK	GlaxoSmithKline
IgG	Immunoglobulin G
IMWG	International Myeloma Working Group
ISS	International Staging System
ITT	Intent-To-Treat
KVA	Keratopathy Visual Acuity
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Affairs
MM	Multiple Myeloma
MMAF	Monomethyl auristatin F
MR	Minimal response
MRD	Minimal residual disease
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NONMEM	Nonlinear mixed effects modelling
OPS	Output and Programming Specification
ORR	Overall response rate

Abbreviation	Description
PD	Pharmacodynamics
PD	Progressive disease
PK	Pharmacokinetics
PopPK	Population PK
PR	Partial response
PRO-CTCAE	Patient-Reported Outcome Version of the Common Term Criteria for Adverse Events
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire 30-item Core module
QoL	Quality of Life
RDI	Relative dose intensity
RP3D	Recommended Phase 3 Dose
SAP	Statistical Analysis Plan
SAE	Serious adverse event
sBCMA	Soluble B-cell maturation antigen
sCR	Stringent complete response
SD	Stable disease
SDTM	Study Data Tabulation Model
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SoC	Standard of Care
SOI	Start of infusion
SSQ	Subjective Significance Questionnaire
t½	Serum half-life
tlast	Time to last observed quantifiable concentration
tmax	Time to maximum drug concentration
TTBR	Time to best response
TTP	Time to progression
TTR	Time to response
VGPR	Very good partial response
VRd	Velcade (bortezomib), Revlimid (lenalidomide), dexamethasone
Vss	Terminal phase rate constant

6.6. Trademarks

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NONE	WinNonlin
NONE	SAS
NONE	NONMEM

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