Statistical Analysis Plan Amendment 4

Study ID: 208887

Official Title: A Phase I/II, Randomized, Open-label Platform Study Utilizing a Master Protocol to Study Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination With Anti-Cancer Treatments in Participants With Relapsed/Refractory Multiple Myeloma (RRMM) - DREAMM 5

NCT ID: NCT04126200

Date of Document: 13-Aug-2024

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title:	A Phase I/II, Randomised, Open-label Platform Study Utilizing a Master Protocol to Study Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination with Anti-Cancer Treatments in Participants with Relapsed/Refractory Multiple Myeloma (RRMM)
Study Number:	208887
Compound Number:	*GSK2857916; GSK3174998; GSK3359609; Nirogacestat, Dostarlimab (TSR-042); Isatuximab (SAR650984); Lenalidomide (Revlimid); Dexamethasone; Pomalidomide (Pomalyst)*
Abbreviated Title:	Platform Study of Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination with Anti-Cancer Treatments in Participants with RRMM
Acronym:	DREAMM-5

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
IND Number	*136133*
EudraCT Number	*2019-001138-32*

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	10 June 2021	Version 4 (14 December 2020)	Not Applicable	Original version
SAP amendment 1 (v10.0)	31 March 2022	Version 5 (21 January 2022)	Updated the Design Features table and Section 4.7 on interim analysis	Match the Interim Analysis specs in CE phase according to PA5
SAP amendment 2 (v11.0)	12 December 2022	Version 5 (21 January 2022)	Section 4.1.1: clarifying that DE and CE phase patients for a given treatment dose will be analysed separately at primary analysis. Section 4.2: clarifying that primary efficacy analysis will be performed on Safety population for DE phase and ITT population for CE phase. Section 4.3: clarifying that secondary efficacy analyses will be performed on Safety population for	Clarifying details of how analyses will be performed. Ensuring consistency between PFS and DOR outcomes.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			DE phase and ITT population for CE phase. Section 4.3.5.1: 1) Edits to ensure consistency between definition of adequate baseline disease assessment and that provided in Section 4.1.4. 2) Update to definition of Duration of Response outcome to include death from any cause as an event (previously only death due to PD included). Added definition of censoring. Section 4.4.1: clarifying that analyses of exploratory efficacy endpoints in the DE phase will be performed on the Safety population. Section 4.5.2 and 4.5.2.4:	

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			clarifying that analyses of treatment-related (S)AEs will only include events classified as 'treatment-emergent'. Across document: general updates to improve clarity and readability.	
SAP amendment 3 (v12.0)	29 February 2024	208887 Master Protocol Amendment 6 (11 July 2023)	Throughout: edits to language to improve readability and ensure greater alignment with terminology used in 208887 Master Protocol Amendment 6 Section 1.1: updates to wording in tables showing objectives and endpoints Section 1.2: general updates to description of study design Section 1.2: in 'design features' and 'interim	Alignment with Master Protocol Aligning with minor updates incorporated in Protocol Amendment 6 Greater alignment with

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			analysis' sections, updated description of planned interim analysis for DE phase participants in a sub-study Section 3: minor updates to wording of analysis sets Section 4.1.2: updates to definition of timing of final analysis for a sub-study Section 4.1.3: removed reference to Table 14 in 208887 Master Protocol Section 4.2: clarified that no 'formal' comparison of response rate across CE phase combination therapy cohorts is planned Section 4.2.2.1, Table 4: minor updates to language to	wording in Protocol Amendment 6 Better alignment with wording used in Protocol Amendment 6 Ensuring alignment with current terminology used across studies Alignment with updates in Protocol Amendment 6 Duplicate of table already included in SAP as Table 3

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			align with other DreaMM studies. As per other study SAPs, added additional row to clarify that an initial 'NE' assessment will result in a confirmed response of 'NE' regardless of response at subsequent time point Section 4.2.2.2: updates to description of analytical approach for CE phase primary endpoint Section 4.2.2.2: updated description of participant sample in Dreamm-2 used for informative prior for response rate with monotherapy in primary analysis Section 4.3.5.3: clarifying planned output from Kaplan-	Clarification Ensuring alignment with the same table in other DreaMM study analysis plans. No impact on analysis Clarifying language used to describe

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Meier estimation Section 4.5.1: clarifying definition of duration of exposure Section 4.5.2: removed unnecessary detail about evaluation of DLTs Section 4.5.2.1.1: removed reference to decision-making criteria for treatment changes in response to corneal events Section 4.5.3.4: removed table and instead added reference to where full details of grading of BCVA changes can be found Section 4.7.1: updated overview of planned interim analysis for DE phase cohorts to reflect increase	Bayesian inputs and outputs Correction Clarification Clarification, aligning with how dose intensity statistic is presented in output Update to improve readability

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			in maximum number of participants from 10 to 15. Added detail (already included in 208887 Master Protocol) that additional interim analyses may be performed for publication or decision-making purposes Section 4.7.2: updated Table 11 to reflect increase in maximum number of participants in the DE phase cohort for a dose level from 10 to 15. Added additional description of how results were derived, and the underlying assumptions Section 4.7.2.2: corrected number of combination arm events for some scenarios in Table 12;	Previous text was not relevant to analysis plan Full details of grading not required in analysis plan Alignment with update to max. number of patients in a DE phase dose level cohort made in 208887 Master Protocol Amendment 6. Greater alignment with

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			clarified the method used to determine these Section 5: update to reflect increase in maximum number of participants in the DE phase cohort for a dose level from 10 to 15 Section 5.1: added re-run of calculations of study operating characteristics (Table 21 in 208887 Master Protocol Amendment 6), reflecting increase in maximum number of participants in the DE phase cohort for a dose level from 10 to 15 Section 5.2: added re-run of forecasts illustrating the impact of the weighting given to the informative prior in the robust mixture	wording in Protocol about interim analyses Alignment with update to max. number of patients in a DE phase dose level cohort made in 208887 Master Protocol Amendment 6

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			prior for response rate with belantamab mafodotin monotherapy (Table 25 in 208887 Master Protocol Amendment 6), reflecting increase in maximum number of participants in the DE phase cohort for a dose level from 10 to 15 Section 6.2.8: updated definition of when a participant is considered to have completed the study to align with 208887 Master Protocol (Section 4.4 in Protocol Amendment 6) Section 6.3.1: reinstated broken reference	Reflecting update already made in 208887 Master Protocol Amendment 6 Alignment with update to max. number of patients in a DE phase dose level cohort made in 208887 Master Protocol Amendment 6 Alignment with update to max. number of patients in a DE phase dose level cohort made in 208887 Master Protocol Amendment

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
				Alignment with update to max. number of patients in a DE phase dose level cohort made in 208887 Master Protocol Amendment 6 Alignment with 208887 Master Protocol Amendment 6 Fix
SAP amendment 4 (v13.0)	13 Aug 2024	208887 Master Protocol Amendment 6 (11 July 2023)	Added electronic clinical outcome assessment (eCOA) compliance definition to Appendix 2	(eCOA) SAP update required across all GSK studies to ensure standardized definition and consistent monitoring of eCOA compliance

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Study 208887. Details of the planned interim analysis, as well as the final analyses, are provided.

1.1. Objectives and Endpoints

The primary, secondary and exploratory objectives, along with the corresponding endpoint for Dose Exploration (DE) are listed in Table 1; while the primary, secondary and exploratory objectives and endpoints for Cohort Expansion (CE) are listed in Table 2.

Table 1 Dose Exploration (DE)

Objectives	Endpoints
Primary	
To determine the safety and tolerability of belantamab mafodotin in combination with other anti-cancer treatments (in each sub-study), and to establish the recommended Phase 2 dose for each sub-study investigational combination treatment to explore in the CE Phase in participants with RRMM	• Percentage (number) of participants with dose limiting toxicities (DLTs) • Percent of subjects with AEs, changes in clinical signs and laboratory parameters
Key Secondary	
To evaluate the clinical measures of efficacy of belantamab mafodotin and combination treatments in each sub-study in participants with RRMM	• Clinical activity measured as Overall Response Rate (ORR) according to the International Myeloma Working Group (IMWG) Response Criteria [Kumar, 2016]
Secondary	
To further evaluate the clinical measures of efficacy of belantamab mafodotin and combination treatments in each sub-study in participants with RRMM	Rates of: • Partial Response (PR); • Very Good Partial Response (VGPR); • Complete Response (CR); • Stringent Complete Response (sCR)
To describe the exposure of belantamab mafodotin when administered in combination with each combination treatment within each sub-study in participants with RRMM	• Belantamab mafodotin observed concentrations
To describe the exposure of the partner anti-cancer treatment when administered in combination with belantamab mafodotin in each sub-study.	• Anti-cancer combination treatment's observed concentration
To assess anti-drug antibodies (ADAs) against belantamab mafodotin and against combination treatments (biologics) that are administered by IV infusion within each sub-study	• Incidence and titers of ADAs against belantamab mafodotin and combination treatments, when measured.

Objectives	Endpoints
To further determine the safety and tolerability of belantamab mafodotin in combination with other anti-cancer treatments (in each sub-study)	• Incidence of AEs of special interest (AESIs) for belantamab mafodotin • Incidence of AESIs for combination treatments • Incidence of ocular findings on ophthalmic exam
Exploratory	
To evaluate the pharmacokinetic (PK) profile of belantamab mafodotin when administered in combination with each combination treatment within each sub-study in participants with RRMM	• Belantamab mafodotin PK parameters, as data permit
To evaluate the PK profile of the partner anti-cancer treatment when administered in combination with belantamab mafodotin	• Anti-cancer combination treatment's PK parameters, as data permit
To further explore the anti-tumor activity of belantamab mafodotin in combination with treatments in participants with RRMM	• Clinical Benefit Rate (CBR) [Kumar, 2016] • Time to Response (TTR) • Overall Survival (OS) • Progression Free Survival (PFS) • Duration of Response (DoR)
To explore the relationship between clinical response and other biologic characteristics including, but not limited to, BCMA expression on tumor cells and serum sBCMA concentrations	• Assess various biomarkers at baseline and on treatment, by tumor and blood-based analysis of DNA, RNA and protein, including but not limited to evaluating baseline BCMA expression and/or immune status in tumor tissue and in the tumor microenvironment, and/or serum soluble BCMA levels, and their relationship to clinical response
To investigate pharmacogenomics in relation to belantamab mafodotin	• Evaluate the relationship between host genetic variation and response to belantamab mafodotin
To explore exposure-response relationships between belantamab mafodotin and/or combination treatment exposure and clinical endpoints	• Explore relationships between belantamab mafodotin and/or combination treatment exposure (e.g., dose, dose intensity, concentration, Cmax, or AUC) vs. clinical endpoints (e.g., response, corneal event), if data permit
To assess minimal residual disease (MRD) in participants who achieve VGPR or better	• MRD negativity rate, defined as: the percentage of participants who achieve MRD negative by Next Generation Sequencing.

Table 2 Cohort Expansion (CE)

Objectives	Endpoints
Primary	
To assess the clinical activity of belantamab mafodotin at each potential R2PD in combination with anti-cancer treatments compared to belantamab mafodotin monotherapy in participants with RRMM	• Overall Response Rate (ORR), according to the International Myeloma Working Group (IMWG) Response Criteria [Kumar, 2016]
Secondary	
To further assess clinical activity of combination treatments with belantamab mafodotin at each potential RP2D compared with monotherapy within each sub-study in participants with RRMM	• Clinical Benefit Rate (CBR) [Kumar, 2016] • Progression Free Survival (PFS) • Duration of Response (DoR) • Time to Response (TTR) • Rates of: Partial Response (PR); Very Good Partial Response (VGPR); Complete Response (CR); stringent Complete Response (sCR) • Overall Survival (OS)
To further characterize the safety of belantamab mafodotin and belantamab mafodotin in combination with anti-cancer treatments within each sub-study in participants with RRMM	• Incidence of adverse events (AEs), Serious Adverse Events (SAEs), AEs leading to discontinuation or dose reduction/delay, changes in clinical signs, and laboratory parameters • Incidence of AESIs for belantamab mafodotin • Incidence of AESIs for the individual partner for each sub-study • Incidence of ocular findings on ophthalmic exam for belantamab mafodotin
To evaluate plasma concentrations of belantamab mafodotin and combination treatments in participants within each sub-study with RRMM	• Belantamab mafodotin and combination treatment's plasma concentrations.
To assess anti-drug antibodies (ADAs) against belantamab mafodotin and against combination treatments (biologics) that are administered by IV infusion within each sub-study	• Incidence and titers of ADAs against belantamab mafodotin and combination treatments, when measured.
Exploratory	
To explore the relationship between clinical response and other biologic characteristics including, but not limited to, BCMA expression on tumor cells and sBCMA concentrations	• Assess various biomarkers, at baseline and on-treatment, by tumor and blood-based analysis of DNA, RNA and protein, including but not limited to evaluating baseline BCMA expression and/or immune status in tumor tissue

Objectives	Endpoints
	and in the tumor microenvironment, and/or serum soluble BCMA levels, and their relationship to clinical response
To investigate pharmacogenomics in relation to belantamab mafodotin	• Evaluate the relationship between host genetic variation and response to belantamab mafodotin
To evaluate disease and treatment-related symptoms and impact on function and health-related quality-of-life	• Qualitative telephone interview(s)
Evaluate tolerability of belantamab mafodotin in combination with anti-cancer treatments by assessing self-reported symptomatic AEs within each sub-study in participants with RRMM	• Changes from baseline in symptoms and related impacts as measured by ocular surface disease index (OSDI) and patient-reported outcomes version of the common terminology criteria for adverse events (PRO CTCAE)
To explore the effect of each potential RP2D of belantamab mafodotin with combination treatments on health-related quality of life in participants with RRMM	• Changes from baseline in health-related quality of life as measured by the EORTC QLQ-C30 and EORTC IL52 (disease symptoms domain of the EORTC QLQ-MY20)
To evaluate the pharmacokinetic (PK) profile of belantamab mafodotin and combination treatments in participants with RRMM	• Belantamab mafodotin and combination treatments' PK parameters, as data permit
To explore exposure-response relationships between belantamab mafodotin and/or combination treatment exposure and clinical endpoints	• Explore relationships between belantamab mafodotin and/or combination treatment exposure (e.g., dose, dose intensity, concentration, Cmax, or AUC) vs. clinical endpoints (e.g., response, corneal event), if data permit
To assess MRD in participants who achieve VGPR or better	• MRD negativity rate, defined as: the percentage of participants who achieve MRD negative by Next Generation Sequencing.

1.2. Study Design

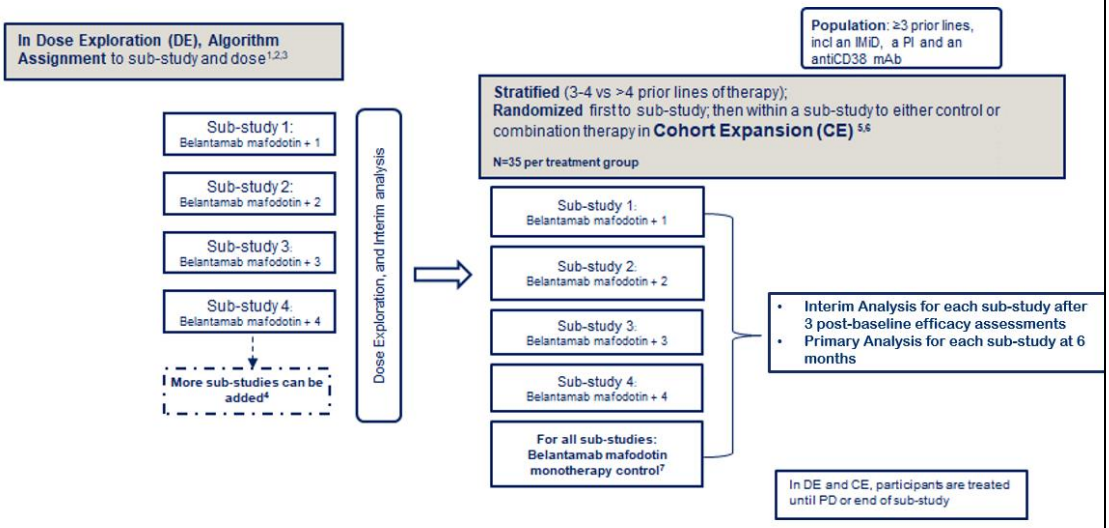
Overview of Study Design and Key Features

The Platform design is an efficient tool incorporating a single master protocol, wherein multiple treatment combinations will be evaluated in separate sub-studies. Each sub-study is defined as the data collected in DE and CE phases for each combination treatment arm and its associated shared control arm (in CE only) within Study 208887.

There is a dose exploration (DE) phase which will evaluate the safety and tolerability profile of Belantamab mafodotin when administered in combination with other anti-cancer treatments. The number of dose levels explored will vary per sub-study, and up to 15 participants per dose level will be evaluated for safety and preliminary efficacy. One or more potential recommended Phase 2 doses (RP2Ds) for each combination treatment could be identified based on the safety and preliminary efficacy in DE.

Where appropriate, these will be followed by a cohort expansion (CE) phase which will evaluate the clinical activity of the combination treatment in comparison to monotherapy belantamab mafodotin, the shared control arm, in additional participants at each potential RP2D for each sub-study. The decision whether to initiate CE for a given combination/dose level will be based on the totality of the data, at the sponsor's discretion, including safety, efficacy, tolerability, PK, and pharmacodynamics.

- At the start of the first CE phase participants will initially be randomized 1:1 within that sub-study CE to either the investigational combination treatment or a shared monotherapy belantamab mafodotin control arm, until 35 participants have been assigned to the combination treatment arm. As new sub-studies are added to the study or closed during the trial, the randomization ratio will be adjusted if >35 participants have been randomized to the shared belantamab mafodotin control arm (see Table 14 in the 208887 Master Protocol).
- Randomisation within the CE phase of a sub-study will be stratified by number of prior lines of therapy (3-4 vs >4 prior lines)



Overview of Study Design and Key Features	
1. Each sub-study will start with a DE Phase guided by mTPI principles. 2. N per dose level is up to 15. 3. Assignment to sub-study in DE will be according to treatment slot availability. When more than one sub-study or dose level is enrolling, allocation will be by pre-determined algorithm. 4. Additional sub-studies may be added later by protocol amendment. 5. The number of sub-studies to be investigated and the dose level of combination to be moved forward in CE will be determined from safety, tolerability and interim analyses in DE. Each sub-study in the DE Phase will be evaluated independently and the number of sub-studies moving to CE will not be limited. Please note: The decision to graduate each sub study from DE to CE will be based on the totality of the data in DE; therefore, some sub-studies may not go forward into CE 6. Randomisation to combination or monotherapy treatment within the CE phase of a sub-study will be stratified by prior lines of therapy (3-4 vs >4). 7. Control arm may be >35 participants in order to be contemporaneous with enrolling investigational arms.	
Design Features	• The platform design allows for the introduction of new sub-studies, with either the shared control or potentially different control arms, as treatment paradigms evolve. The combination agents for each sub-study of this platform design will be chosen based on scientific rationale and/or available pre-clinical data. This will lead to generation of robust statistical data in the CE phase to inform future studies. Detailed information for each sub-study is provided in the respective sub-study protocol modules. • For each sub-study, an interim analysis (IA) will be performed at the end of the DE phase after up to 15 participants treated at each potential RP2D of the combination therapy have undergone 3 efficacy assessments (1 baseline and 2 post-baseline assessments), have discontinued study therapy or have progressed or died. • Two interim analyses may be performed in the CE phase for futility assessment. The combination treatment may be discontinued if the posterior probability of the response rate in combination being greater than the response rate in monotherapy is less than 40%. The primary analysis will be performed on participants from the CE phase for a given dose level of a sub-study at 6 months after the last participant has been dosed in that participant cohort. The final analysis will be performed at the end of each sub-study. • Combination therapies will be considered for further development if the posterior probability that ORR with the combination treatment is greater than that with the control treatment is at least 90%.
Study Intervention	• Refer to the individual 208887 sub-study Protocols for details about the treatment combinations and dose levels to be tested.
Treatment Assignment	• In the DE phase, participants will be assigned using a predefined algorithm. • In the CE phase, participants will be randomized to a sub-study, and within that sub-study to either the investigational or control arm
Interim Analysis	• For each sub-study, an interim analysis will be performed at the end of the DE phase after up to 15 participants treated at each potential RP2D of the combination treatment have had three efficacy (disease) assessments (1

Overview of Study Design and Key Features	
	baseline and 2 post-baseline), have discontinued study therapy, or have progressed or died. • Two interim analyses may be performed for futility evaluation for a particular dose level of a combination treatment in the CE phase. The first interim analysis will be conducted when at least 10 CE combination treatment subjects are evaluable. The second interim analysis may be performed when approximately 18 combination treatment participants are evaluable. Participants are considered evaluable if they have progressed/died, discontinued study treatment, or have had 3 post-baseline efficacy (disease) assessments or at least two planned doses of treatment. The cohort may be discontinued if the posterior probability of the response rate with combination treatment being greater than the response rate with control treatment is less than 40%.
Blinding	• This is an open label study. When both DE and CE phases are open, participants will be prioritized to the DE phase or CE phase. In the DE phase, participants will be assigned to available treatment slots by a predetermined algorithmic approach. In the CE phase, participants will be randomized to one of the open sub-study CE phases for which they meet the eligibility criteria, and then randomized to either the combination treatment or the shared belantamab mafodotin monotherapy arm. • Randomisation to treatment in a sub-study CE phase will be stratified according to the number of prior lines of therapy received (3-4 vs >4).

2. STATISTICAL HYPOTHESES

In the DE Phase, the primary endpoint is safety. One or more potential Recommended Phase 2 Doses (RP2Ds) of the treatment combination will be determined. No formal statistical hypothesis will be tested.

In the CE Phase, the primary objective of the study is to determine whether a given dose level of the treatment combination improves the response rate compared to belantamab mafodotin alone. This combination will be considered superior to belantamab mafodotin alone if the Bayesian posterior probability that ORR in the combination is greater than ORR in monotherapy is at least 90%. See Section 9.4.2 of the 208887 Master Protocol for further details of the primary efficacy analysis.

2.1. Multiplicity Adjustment

Analyses of any efficacy endpoints will not be subject to any multiplicity adjustment since each sub-study is analysed separately.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	• Study Population
Enrolled	• All participants who passed screening and entered the study • Note: screen failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility criteria but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	• Study Population
Safety	• All participants who received at least one dose of any component of the combination therapy in a combination arm/cohort or at least one dose of belantamab mafodotin in the monotherapy arm • This analysis set will be based on the intervention the subject actually received	• Safety • Secondary efficacy analyses in DE phase
Intent-to-Treat (ITT)	• All participants who were enrolled and randomised to study intervention • This analysis set will be based on the treatment the subject was randomised to	• Efficacy in CE phase
Modified Intent-to-Treat (mITT)	• All randomised participants who received at least one study treatment • This analysis set will be based on the treatment the subject was randomised to	• Efficacy in CE phase
Pharmacokinetic (PK)	• All participants in the Safety analysis set who had at least 1 non-missing PK assessment (non-quantifiable [NQ] values will be considered as non-missing values) • This analysis set will be based on the intervention the subject actually received	• PK
Pharmacodynamic (PD)	• All participants in the Safety analysis set for whom a biomarker sample was obtained, was analysed and found measurable. Non-quantifiable [NQ] values will be considered as non-missing values • This analysis set will be based on the intervention the subject actually received	• Biomarker
DLT Evaluable	• A subset of participants in the DE phase who received at least 80% of all components of the intended dose of treatment in Cycle 1 and were followed up for a period of one cycle length or withdrawn within the first cycle due to an	• Safety in DE phase

Analysis Set	Definition / Criteria	Analyses Evaluated
	adverse event (AE) meeting the definition of a Dose-Limiting Toxicity (DLT). • Participants who receive less than 80% of the intended dose in Cycle 1 due to an AE meeting the definition of a DLT are considered to be DLT evaluable	

Refer to the List of Displays in the Output and Programming Specification (OPS) document which details the analysis set used for each display.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. Primary Analysis

The primary analysis for the participants in the CE phase for a given dose level of a sub-study will be performed at 6 months after the last participant has been dosed in that participant cohort. The primary analysis for a particular sub-study will include separate analyses of participants in the CE Phase and those who were treated with the corresponding RP2D in the DE phase for that sub-study.

4.1.2. Final Analysis

The final analysis will be performed at the end of each sub-study.

If the primary analysis of the CE phase for a dose level in a sub-study meets the efficacy criteria defined in Section 9.4 of the 208887 Master Protocol, participants may be followed for Progression-Free Survival (PFS) and Overall Survival (OS) for up to 36 months.

A sub-study may close after or during the DE phase for safety or tolerability reasons or at the discretion of the Sponsor.

4.1.3. General Methodology

At the start of the CE phase for a dose level in a sub-study, participants will be randomized equally within the open sub-study CE phases to the control arm or combination treatment. If >35 participants have been randomized to the shared belantamab mafodotin control arm, the randomization ratio will be amended to 2:1 (see Section 4.1.2 in the 208887 Master Protocol and Table 3 below). Additionally, when new sub-studies or CE phases within a sub-study are added to the trial or closed during the trial, the randomization ratio may be adjusted based on the number of open CE phases, the number of participants already randomized to existing CE phases, etc.

Table 3 Randomization Ratio and Proportion of Participants Randomized to the Monotherapy Arm When There Are Concurrent Arms (CE only)

Sub-study CE phases	***Randomization Ratio* between each combination and control (Proportion of participants randomized to belantamab mafodotin control arm)***	
	≤35th participants	***>35th participants***
1 CE and the monotherapy control	*1:1 (50%)*	*2:1 (33%)*
2 CEs and the monotherapy control	*1:1 (33%)*	*2:1 (20%)*
3 CEs and the monotherapy control	*1:1 (25%)*	*2:1 (14%)*
4 CEs and the monotherapy control	*1:1 (20%)*	*2:1 (11%)*
5 CEs and the monotherapy control	*1:1 (17%)*	*2:1 (9%)*
6 CEs and the monotherapy control	*1:1 (14%)*	*2:1 (8%)*
7 CEs and the monotherapy control	*1:1 (13%)*	*2:1 (7%)*
8 CEs and the monotherapy control	*1:1 (11%)*	*2:1 (6%)*

**Randomization ratio refers to the overall ratio of # of subjects in each combination arm relative to monotherapy (e.g. when 2 CE phases are open, then the ratio 1:1 means 1[CE1 combination]:1[CE2 combination]:1[monotherapy].*

In the case of a participant being randomised to a treatment arm within the CE phase of a sub-study on the basis of stratification information that is subsequently updated by the site, analyses will use the updated stratum information, as collected in the CRF.

Confidence intervals will use 95% confidence level 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 participant accrual will be spread thinly across centres and summaries of data by centre are unlikely be informative and will not, therefore, be provided.

Study treatment and sub-group / dose level descriptors for sub-studies can be found in the individual sub-study SAPs.

4.1.4. Baseline Definition

For all endpoints (except as noted in an endpoint-specific baseline definition) 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 central lab. If no central lab value is available, the latest non-missing pre-dose value from local lab will be used. If there are multiple assessments on the same day, the mean will be used as the baseline value.

If there are triplicate baseline assessments for ECG, then mean of the values will be used as the baseline value.

Unless otherwise stated if baseline data is missing no derivation will be performed.

4.1.5. Examination of Covariates, Other Strata and Subgroups

The covariates and subgroups defined in the sections below are applicable only to the CE phase.

4.1.5.1. Covariates and Other Strata

The following list of covariates and other strata may be used in descriptive summaries. Additional covariates and other strata of clinical interest may also be considered.

Category	Details
Strata	Prior line therapies (3-4 and >4)

4.1.5.2. Examination of Subgroups

The list of subgroups below may be used in descriptive summaries and statistical analyses. Additional subgroups of clinical interest may also be considered.

- If the number of participants within a subgroup is small, then the subgroup categories may be refined (e.g. by combining subgroups).
- If these categories cannot be refined further, then descriptive rather than statistical comparisons may be performed for particular subgroups.

Subgroup	Categories
Age	<65, >=65
Sex	Male, Female
Ethnic Background	Hispanic, non-Hispanic
Race	American Indian or Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Mixed Race
Refractory to prior anti-cancer therapy	Any Proteasome Inhibitor (PI) Bortezomib Carfilzomib Ixazomib Any Immunomodulator (ImiD) Thalidomide Lenalidomide Pomalidomide PI+ImiD Anti-CD38
Cytogenetics Risk	High, Other (non-high risk, not done, or missing)

4.2. Primary Endpoint(s) Analyses

The primary analysis will be performed on participants from the CE phase for a given dose level of a sub-study at 6 months after last participant first dose in that cohort. Analyses of the primary endpoints will be based on the Safety analysis set for the DE phase and the ITT analysis set for the CE phase, unless otherwise specified.

The primary analysis for Overall Response Rate (ORR) in the CE phase will be reported and will be used to compare the response rate in combination therapy with the monotherapy. There is no intent to formally compare the response rates between combination therapies.

4.2.1. DE Phase

Primary analysis of DE phase participants who received a potential RP2D in a sub-study will include summarising the number and percentage of participants with DLT and AEs reported. Both DLTs and AEs will be summarised and listed.

4.2.2. CE Phase

4.2.2.1. Definition of Endpoint

Overall Response Rate (ORR): Defined as the percentage of participants with a confirmed PR or better as the best overall response (BOR) (i.e., Partial Response [PR], Very Good Partial Response [VGPR], Complete Response [CR], and stringent Complete Response [sCR]), as assessed by the investigator per IMWG (2016). Details of derivation of confirmed response are provided in Table 4. The date of the first of the two consecutive assessments will be used as the date of the confirmed response. The primary efficacy analysis of ORR in the CE phase will be based on the ITT analysis set, unless otherwise specified. A sensitivity analysis based on the mITT analysis set may also be provided.

Table 4 Derivation of Confirmed Response

Response at the First Time Point	Response at Subsequent Time Point[1]	Confirmed Response at the First Time Point
sCR	sCR	sCR
sCR	CR	CR
CR	sCR/CR	
sCR/CR	VGPR	VGPR
VGPR	sCR/CR/VGPR	
sCR/CR/VGPR	PR	PR
PR	sCR/CR/VGPR/PR	
sCR/CR/VGPR/PR	MR	MR
MR	sCR/CR/VGPR/PR/MR	
sCR/CR/VGPR/PR/MR	SD	SD
sCR/CR/VGPR/PR/MR	PD (any reason) OR No subsequent disease assessment: **participant died or discontinued study or started new anti-cancer therapy** before further adequate disease assessment	SD
PD (due to reasons other than bone marrow (BM) or imaging, i.e., plasmacytoma or bone lesion)	PD (any reason) including PD after initiation of new anti-cancer therapy OR No subsequent disease assessment: participant died due to PD before further adequate disease assessment, including death due to PD after initiation of new anti-cancer therapy	PD
PD (due to reasons other than BM or imaging, i.e., plasmacytoma or bone lesion)	sCR/CR/VGPR/PR/MR/SD OR No subsequent disease assessment: participant died due to reason other than PD before further adequate disease assessment OR No subsequent disease assessment: participant discontinued study before further adequate disease assessment	NE
sCR/CR/VGPR/PR/MR/PD (due to reasons other than BM or imaging, i.e.,	No subsequent disease assessment: participant has not died, discontinued from study	Unconfirmed sCR/CR/VGPR/PR/MR/PD

Response at the First Time Point	Response at Subsequent Time Point[1]	Confirmed Response at the First Time Point
plasmacytoma or bone lesion)	or (except for PD) started new anti-cancer therapy; but as yet has no further adequate disease assessments	Will be categorised as NE for final ORR analysis
SD[2]	Any OR No subsequent disease assessment	SD
PD due to BM assessment/ imaging (plasmacytoma or bone lesion)[3]	Any OR No subsequent disease assessment	PD
NE or missing	Any OR No subsequent disease assessment	NE

1 Subsequent disease assessment is defined as the next adequate disease assessment (following the first timepoint, where this first assessment was performed before starting other anti-cancer therapy) which is not missing or NE and also made before start of new anti-cancer therapy, except for confirmation of PD, for which PD or death due to PD after the start of new anti-cancer therapy are considered valid for confirmation of PD. No minimum 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 bone marrow or imaging (i.e., plasmacytoma or bone lesion) does not need to be confirmed

4.2.2.2. Main analytical approach

We assume that the number of observed responses y_* from the current n_* participants in a treatment arm within the CE phase cohort for a sub-study follows a binomial distribution with parameter $\psi_*\psi_*$, i.e., $binomial(n_*, \psi_*)$. The likelihood function for the observed data y_* is $L_{y_*} \propto \psi_*^{y_*}(1-\psi_*)^{n-y_*}$ $L_{y_*} \propto \psi_*^{y_*}(1-\psi_*)^{n_*-y_*}$.

Because the study is intended to initiate new experimental combinations over time, the robust mixture prior approach will be used in case of prior data conflict, including non-concurrent control data conflict.

The robust version of the mixture prior for the response rate with a treatment is:

$$\hat{P}HR(\psi_*) = (1-\omega_R)Beta(\psi_*|a_1, b_1) + \omega_R Beta(\psi_*|a_0, b_0),$$

Where a_1 and b_1 b_1 are the parameters of the informative prior, $a_0 a_0$= 0.5 and b_0 b_0= 0.5 are the parameters of the non-informative prior.

In the primary analysis of the DREAMM2 (205678) study 30 responders were observed from 97 participants with RRMM who failed ≥1 proteasome inhibitor, ≥1 immunomodulatory drug and anti-CD38 monoclonal antibody who received 2.5mg/kg of belantamab mafodotin. So a_1= 30, b_1= 67 are used as the parameters for the informative prior for response rate with belantamab mafodotin monotherapy.

For the combination treatment, the data observed from the corresponding DE phase cohort will determine the parameters used for the informative prior, i.e., a_1 a_1 and b_1 b_1 are not fixed.

□R is the prior probability that the new trial differs systematically from the historical trial. The choice of initial value for □R is based on the degree of confidence of the similarity between the new trial and the historical trial. To incorporate the information from the participants from the DE phase, the initial value of 0.1 for □R is used for the mixture for the combination treatment, while 0.5 for □R is used for the mixture prior for monotherapy to partially incorporate the data from the DREAMM2 study.

The posterior for response rate with a treatment can be derived,

$$\hat{P}HR(\psi_*|y_*) = (1-\tilde{\omega}_R)Beta(\psi_*|a_1+y_*, b_1+n_*-y_*) + \tilde{\omega}_R\ Beta(\psi_*|a_0+y_*, b_0+n_*-y_*)$$

where

$$\tilde{\omega}_R \propto \frac{\omega_R f_0}{\omega_R f_0+(1-\omega_R)f_1}, f_0 = \frac{B(a_0+y_*, b_0+n_*-y_*)}{B(a_0,b_0)}, f_1 = \frac{B(a_1+y_*, b_1+n_*-y_*)}{B(a_1,b_1)}.$$

Each dose level of a combination therapy that is put forward to the CE phase will be compared to belantamab mafodotin monotherapy separately. A particular dose level for a combination therapy will be considered superior to belantamab mafodotin monotherapy in ORR if the posterior probability of the response rate with combination treatment being greater than the response rate with monotherapy is at least 90%.

For calculating this probability, we will draw two sets of random samples, one from the posterior probability of the response rate with belantamab mafodotin monotherapy and another from the posterior for the response rate with combination therapy. Let us say, $\{x_i\}_{\{i=1,2,\ldots n\}}$ are n random samples from the posterior distribution for belantamab mafodotin monotherapy and $\{y_i\}_{\{i=1,2,\ldots n\}}$ are n random samples from the posterior distribution for combination therapy. So, the probability of superior response rate with combination treatment over monotherapy will be given by $\frac{1}{n}\sum_{i=1}^{n} I(x_i < y_i)$, where I is an indicator function with value = 1 if the condition is met and 0 otherwise.

4.2.2.3. Summary Measure

The above-mentioned Bayesian analysis will be summarised.

The number and percentage of participants with best overall response (BOR) in the following response categories will be summarized by treatment arm: sCR, CR, VGPR, PR, overall response (sCR+CR+VGPR+PR), minimal response (MR), stable disease (SD), progressive disease (PD), and not evaluable (NE). The corresponding 2-sided 95% exact CI for ORR will also be provided. Participants with only unknown or missing responses will be treated as non-responders, i.e., these participants will be included in the denominator when calculating percentages of response. A listing of investigator assessed response at each visit will be provided. The number and percentage of participants with best overall response in the above categories may be summarised by various subgroups which can be found in Section 4.1.5.

In addition to confirmed best overall response, analyses of the biomarkers used for disease assessment may be presented where appropriate. A waterfall plot showing the maximum percent reduction from baseline in Serum M-protein, or Urine M-protein, or difference between two types of Serum FLC [Kappa light chain (Kappa LC) and Lambda light chain (Lambda LC)] for each subject will be produced by treatment arm. 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. Only assessments from the start of treatment up to the start of new anti-cancer therapy will be considered. Only new systemic anti-cancer drugs taken are considered as anti-cancer therapy (radiotherapy and surgeries are not considered as systemic anti-cancer therapy for the purpose of this analysis).

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

[1] Plot Serum M-protein maximum percent reduction from baseline if data is available;

[2] If [1] is not feasible, plot Urine M-protein maximum percent reduction from baseline if data is available;

[3] If both [1] and [2] are not feasible, plot maximum percent reduction from baseline for difference between two types of Serum FLC if data is available

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 cannot be determined (ratio is normal), and maximum percent reduction from baseline for difference between two types of Serum FLC won't be available.

4.3. Secondary Endpoints Analyses

Secondary efficacy analyses will be based on the Safety analysis set for the DE phase and the ITT analysis set for the CE phase, unless otherwise specified. Sensitivity analyses based on the mITT analysis set may be performed for the CE phase.

4.3.1. Key Secondary Endpoint

4.3.2. DE Phase

4.3.2.1. Definition of Endpoint

Overall Response Rate (ORR): See Section 4.2.2.1 for the definition of ORR along with the derivation of confirmed response table; Table 4.

4.3.2.2. Main analytical approach

Details of the planned displays are provided in the List of Data Displays in the Output and Programming Specification (OPS) document and will be based on GSK data standards and statistical principles.

4.3.2.3. Summary Measure

ORR will be presented as described in Section 4.2.2.3.

4.3.3. Secondary Endpoints

4.3.4. DE Phase

4.3.4.1. Endpoints

Rates of best overall response classified as Partial Response (PR), Very Good Partial Response (VGPR), Complete Response (CR) and Stringent Complete Response (sCR) will be reported.

Refer to Section 4.2.2.1, Table 4 for more details.

Other secondary endpoints for the DE phase are listed in Table 1 of Section 1.1. Details about how these secondary endpoints will be collected, reported and analysed can be found in the corresponding sections: PK (Section 4.6.1), AESIs (Section 4.5.2.1) and Ocular Findings (Section 4.5.3.4).

4.3.4.2. Main Analytical Approach

Details of the planned displays are provided in the Output and Programming Specification (OPS) document and will be based on GSK data standards and statistical principles.

4.3.4.3. Summary Measure

Best overall response and corresponding response rates will be summarized using descriptive statistics (number and percentage of participants) and listed. Participants with unknown or missing responses will be treated as non-responders, i.e., these participants will be included in the denominator when calculating percentages of response.

4.3.5. CE Phase

4.3.5.1. Endpoints

Clinical Benefit Rate (CBR): Clinical Benefit Rate, defined as the percentage of participants with confirmed MR or better (i.e., MR, PR, VGPR, CR and sCR) as the best overall response assessed by the investigator per IMWG (2016).

Rates of PR, VGPR, CR, sCR: Refer to Section 4.3.4.

Progression-free Survival (PFS): Progression-free survival is defined as the interval of time (in months) from randomization until the earlier date of disease progression per IMWG (2016) or death due to any cause. Determination of dates of PFS events and dates for censoring are described in Table 5. Participants censored at randomisation will have survival time = 1 day.

Table 5 Assignments of Progression and Censoring Dates for PFS Analysis

Situation	Main analysis for PFS
No adequate baseline assessments[1] and the participant has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	Censored at randomisation
No adequate[2] post-baseline assessments and the participant has not died (if the subject has died follow the rules for death at the bottom of the table)	Censored at randomisation
Progression documented between scheduled visits	Event on date of assessment of progression[3]
With adequate[2] post-baseline assessment but no progression (or death)	Censored on date of last adequate assessment of response[2]
No adequate post-baseline assessment before start of new anticancer therapy	Censored at randomisation
With adequate post-baseline assessment and new anticancer treatment started (prior to documented disease progression).[4]	Censored on date of last adequate[2] assessment of response (on or prior to starting anti-cancer therapy)
Death before first scheduled assessment (or Death at baseline or without any adequate assessments)	Event on date of death
Death between adequate assessment visits	Event on date of death
Death (regardless of having baseline assessment) or progression after missing two or more scheduled assessments	Censored at date of last adequate assessment of response[2] (prior to missed assessments): If the disease assessment is every 3 weeks, a window of 49 days (6 weeks + 7-day window) will be used to determine whether there is extended time without adequate assessment. If the time difference between PD/death and last adequate disease assessment is more than 49 days, PFS will be censored at the last adequate disease assessment prior to PD/death.

[1]Adequate baseline assessment is defined as at baseline (see Section 4.1.4), a participant 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 ≥5 mg/dL (≥50 mg/L) and an abnormal serum free light chain ratio (<0.26 or >1.65).

[2]An adequate assessment is defined as an unconfirmed assessment where the determined response is sCR, CR, PR, VGPR, MR or SD

[3]The earliest of (i) Date of serum/urine PEP test (if progression is based on increase in serum or urine M-protein); or (ii) Date of radiological assessment of extramedullary disease (if progression is based on increase in the size of existing plasmacytoma or appearance of new soft tissue plasmacytoma, or (iii) Date of last radiological assessment of bone lesions (if progression is based on increase in the size of existing bone lesions or appearance of new bone lesions), or (iv) Date of lab test for free light chain (if progression is based on increase of

difference between involved and uninvolved FLCs) or (v) Date of bone marrow assessment (if progression is based on the bone marrow plasma cell percentage)

[4] If PD or death and new anti-cancer therapy occur on the same day assume the progression or death was documented first (e.g., outcome is progression or death and the date is the date of the assessment of progression or death).

Duration of Response (DOR): Duration of response, 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 by the investigator per IMWG (2016), or death from any cause among participants with a confirmed PR or better as the best overall response. Details of censoring rules can be found from Table 5 (participants with no further adequate post-baseline assessments are censored at date of first confirmed PR or better (survival time = 1 day), rather than date of randomization as for PFS endpoint). Participants who have not progressed or died prior to the end of the relevant reporting effort will be censored at the end of the reporting period.

Time to response (TTR): Time to response, 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 confirmed PR or better as the best overall response assessed by the investigator per IMWG (2016).

Overall Survival (OS): Overall Survival, defined as the interval of time (in months) from randomization to the date of death due to any cause. Participants who are alive will be censored at the date of last contact.

4.3.5.2. Main Analytical Approach

Details of the planned displays are provided in the List of Data Displays in the Output and Programming Specification (OPS) document and will be based on GSK data standards and statistical principles.

4.3.5.3. Summary Measure

For the CE phase, all summaries will be presented by treatment arm.

Clinical Benefit Rate (CBR) & Rates of PR, VGPR, CR, sCR: The number and percentage of participants with BOR in the following response categories will be presented: sCR, CR, VGPR, PR, MR, clinical benefit response (sCR+CR+VGPR+PR+MR), SD, PD, and NE. The corresponding exact 95% CI for CBR will also be provided. Participants with unknown or missing responses will be treated as non-responders, i.e., these participants will be included in the denominator when calculating percentages of response.

Progression-free Survival (PFS): If data permit, the distribution of PFS will be estimated using the Kaplan-Meier method. Where possible, the median, 25th and 75th percentiles of PFS (i.e. the times corresponding to 50%, 75% and 25% survival) will be estimated and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982]. Where possible, PFS rate at 3 months, 6 months, 9 months and 12 months and corresponding 95% CI will also be

estimated from the Kaplan-Meier analysis. PFS will also be summarised by prior lines of therapy if there are sufficient data.

Duration of Response (DOR): If data permit, the distribution of DOR will be summarized using the Kaplan-Meier method. Where possible, the median, 25th and 75th percentiles of DOR (i.e. the times corresponding to 50%, 75% and 25% DoR) will be estimated and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982]. DOR will also be summarised by prior lines of therapy if there are sufficient data.

Time to Response (TTR): Time to response will be summarized descriptively using median(s) and quartiles in the subset of participants with a confirmed response of PR or better as the best overall response.

Overall Survival (OS): If data permit, the distribution of OS will be estimated using the Kaplan-Meier method. Where possible, the median, 25th and 75th percentiles of OS (i.e. the times corresponding to 50%, 75% and 25% survival) will be estimated and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982]. Where possible, OS at 12 months, 18 months, 24 months and 36 months and corresponding 95% CI will also be estimated from the Kaplan-Meier analysis. OS will also be summarised by prior lines of therapy if there are sufficient data.

4.4. Exploratory Endpoints Analyses

4.4.1. DE Phase

Analyses of the following exploratory efficacy endpoints will be based on the Safety Analysis set for the DE phase.

4.4.1.1. Endpoints

Clinical Benefit Rate (CBR): CBR will be analysed as per Section 4.3.5.1 and Section 4.3.5.3.

Time to Response (TTR): Time to response, defined as the interval of time (in months) between the date of first dose and the first documented evidence of response (PR or better) among participants with confirmed PR or better as the best overall response assessed by the investigator per IMWG (2016). TTR will be analysed as in Section 4.3.5.3.

Overall Survival (OS): Overall Survival, defined as the interval of time (in months) from first dose to the date of death due to any cause. Participants who are alive will be censored at the date of last contact. OS will be analysed as in Section 4.3.5.3.

Progression-free Survival (PFS): Progression-free survival, defined as the interval of time (in months) from first dose until the earlier date of disease progression per IMWG (2016), or the date of death due to any cause. Determination of dates of PFS events and dates for censoring are described in Table 5 in Section 4.3.5.1, with date of first dose

used for DE phase participants instead of date of randomization. PFS will be analysed as in Section 4.3.5.3.

Duration of Response (DoR): DoR, defined as per Section 4.3.5.1, will be analysed as in Section 4.3.5.3.

Minimal Residual Disease (MRD) Negativity Rate: Minimal Residual Disease negativity rate, defined as the percentage of participants who are reported as MRD negative (with threshold 10^{-5}) and achieve confirmed VGPR, CR or sCR from treatment start date until disease progression or initiation of new anti-cancer therapy, whichever is earlier, as assessed by next generation sequencing (NGS) per IMWG (2016). Participants without MRD assessment will be considered as having positive MRD. The corresponding 95% exact CI will be provided.

4.4.2. CE Phase

4.4.2.1. Endpoints

Minimal Residual Disease Negativity Rate: The MRD negative rate analysis will be based on the ITT analysis set. It will be analysed as in Section 4.4.1.1.

4.5. Safety Analyses

Safety analyses will be based on the Safety analysis set and will be undertaken separately for both the DE and CE phase for a dose level of a sub-study, unless otherwise specified. For the CE phase, analyses will be presented separately by treatment group. Unless otherwise specified, on-treatment AEs will be reported (see Section 6.2.2.4 for definition).

4.5.1. Extent of Exposure

Extent of exposure to belantamab mafodotin monotherapy and combination therapy will be summarized. For the combination therapy, extent of exposure will be summarized separately for each drug component. The number of cycles of study treatment administered will be summarised with mean, median, standard deviation, minimum and maximum.

For ITT analysis set analyses, if participants were randomized but did not receive any dose they will be counted as having zero duration of exposure.

Cycle lengths vary by sub-study. The cycle length in days can be found in the individual sub-study SAPs to be used in calculations for treatment exposure.

The cumulative dose is the sum of the actual dose administered during each infusion / dosing occasion for a participant.

Dose delivered per cycle (mg/kg/cycle) or (mg/cycle) will be summarized using mean, median, standard deviation, minimum, and maximum by cycle and overall.

Overall dose intensity (mg/kg/cycle, mg/kg/cycle length or mg/cycle length) is calculated as the cumulative actual dose received (mg/kg or mg) divided by (duration of exposure in days / cycle length in days).

Duration of exposure in days is defined as min(end date of last cycle, death date) – first dose date + 1. End date of cycle is calculated as the cycle start date + cycle length. For belantamab mafodotin if the actual dose is collected in "mg" for a given cycle, then it should be converted into mg/kg using the weight of the participant at that visit.

For example, if a participant with protocol-defined cycle length of Q3W received a cumulative actual dose of 10mg/kg with duration of exposure over a total of 84 days, their overall dose intensity value would be: 10mg/kg / (84 days /21 days) = 10mg/kg / 4 = 2.5mg/kg/cycle.

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

Dose reductions will be summarised by number of and reasons for reductions. Dose delays/interruptions will be summarised by number of delays, and delay duration (days). These dose modifications will be summarised and listed according to GSK Oncology Data Standards. The number and percentage of delays/interruptions for intervals of 1-12, 22-42 and >42 days will be computed. Primary reasons for dose reductions and dose delays/interruptions will also be summarised by cycle.

Duration of delays/interruptions is defined as period from the expected start date of dose to actual start date of current dose. Calculation: (actual start date of current dose – expected start date of dose). Expected start date of dose = actual start date of previous dose + cycle length.

All dose reductions and dose delays/interruptions will be listed.

4.5.2. Adverse Events

Adverse events analyses including the analysis of adverse events (AEs), Serious Adverse Events (SAEs), immune-related adverse events (irAEs), other significant AEs and serious and other significant irAEs will be based on GSK Core Data Standards. The definition of treatment-emergent AEs is provided in Section 6.2.2.4. The details of the planned displays are provided in the List of Data Displays in the Output and Programming Specification (OPS) document.

A summary of non-serious adverse events that occurred in strictly 10% of the participants or more will be provided (no rounding for the percentage will be used in terms of 10% threshold, e.g., an event with 9.99% incidence rate should not be included in this table). The summary will be displayed by system organ class (SOC) and preferred term (PT).

Adverse events (AEs) will be graded by the investigator according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5. Adverse events will be coded using the Medical Dictionary for Regulatory Affairs

(MedDRA dictionary) and grouped by SOC. In addition, corneal toxicities will be graded using the GSK or KVA scale; details are provided in Table 6 and Table 7.

A summary of the number and percentage of participants with any adverse events by maximum grade will be produced. AEs will be sorted by PT in descending order of total incidence. The summary will use the following algorithms for counting participants:

- **Preferred term row**: Participants experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- **Any event row**: Each participant with at least one adverse event 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) may 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 SOC and PT and Maximum Grade. In the SOC row, participants with multiple events under the same system organ class will be counted once. Otherwise, if AEs are not listed in the NCI-CTCAE (version 5) then they will be summarized by maximum intensity.

A separate summary will be provided for study treatment-related AEs by individual treatment component (by treatment / dose level). A study treatment-related AE is defined as an AE for which the investigator classifies the relationship to study treatment 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 treatment as 'Yes' or missing. The summary table will be displayed in descending order of total incidence by SOC and PT and Maximum Grade. Only AEs classified as 'treatment-emergent' will be included in this summary.

All AEs will be listed. A listing of participant IDs for each individual AE may be produced.

A listing of adverse events recorded as dose-limiting toxicities during the determinative DE phase will be provided. Additionally, a summary of the number of DE cohort participants experiencing DLTs will be provided.

4.5.2.1. Adverse Events of Special Interest

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Adverse Events of Special Interest (AESIs) will be identified based on lists of terms of interest 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 adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting. A reference list of AESIs for belantamab mafodotin and each combination treatment can be found in the 208887 Master Protocol and each of the individual sub-study protocols.

A summary of event characteristics will be provided for each type of AESI, 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. A 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 for an event, a subject 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.

Details of planned displays are provided in the List of Data Displays in the Output and Programming Specification (OPS) document.

4.5.2.1.1. GSK2857916 (belantamab mafodotin)

Characteristics (e.g. number of occurrences, action taken, grade, etc) of the following AESIs will be summarized separately:

- Corneal events
- Thrombocytopenia
- Infusion related reactions

The severity of all AESIs will be graded utilizing the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) v.5. Severity of belantamab mafodotin treatment-related corneal toxicity will also be graded using the GSK or KVA scale based on corneal and visual acuity exam findings and should be used for evaluation of DLT. Corneal events have been graded according to the 208887 Protocol Amendment in place at the time of reporting:

Protocol amendment 1: corneal events were collected based on the GSK scale (Table 6).

Protocol amendments 2 and 3: corneal events were collected based on CTCAE v.5. Grading for corneal events was provided from ocular symptoms and visual acuity changes.

Protocol amendment 4 and later: corneal events were collected based on KVA scale grade (Table 7).

For data collected per protocol amendments 2 and 3 before March 29th 2021, neither GSK nor KVA grades will be reported due to incomplete data available to derive the grade. From March 29th 2021, sites on protocol amendments 2 and 3 were able to fully complete the Ocular Corneal Exam form, making it possible for the clinical programming team to derive the KVA grade for all corneal exam findings collected after this period.

Additional guidance on grading of visual acuity changes is provided in Section 4.5.3.4. This also includes details of summary displays and listings for corneal events and exam findings that may not have been reported as AEs.

Table 6 Grading Scale for Corneal Events Associated with Protocol Amendment 1 (GSK Scale)

Measure	Grade 1[a]	Grade 2	Grade 3	Grade 4
Ophthalmic exam findings	Mild superficial keratopathy (change from baseline)	Moderate punctate keratopathy and/or Mild/patchy microcysts and/or Mild/patchy Epithelial or stromal edema and/or Sub-epithelial haze (peripheral) and/or Active stromal opacity (peripheral)	Severe keratopathy and/or Diffuse microcysts and/or Diffuse Epithelial or stromal edema and/or Sub-epithelial haze (central) and/or Active stromal opacity (central)	Corneal ulcer
Visual Acuity [b, c]	Change of 1 line from baseline	Change of 2-3 lines from baseline and not worse than 20/200[b]	Change of more than 3 lines from baseline and not worse than 20/200[b]	Worse than 20/200 [b]

Note: Standardized guidance for grading ophthalmic findings associated with GSK2857916 is provided to sites in the eCRF and ophthalmology SRM information. Ophthalmic exam findings as described must be present in a participant to utilize the GSK grading scale.

a. Grading is based on most severe finding. If eyes differ in severity, GSK grading scale should be based on the more severe eye.
b. Change in visual acuity should be due to corneal events associated with GSK2857916. If change in vision is for reason other than corneal events, ophthalmic exam findings will drive event grading.
c. If a subject has a baseline visual acuity of 20/200 or worse in an eye, ophthalmic exam findings will drive event grading

Table 7 Grading Scale for Corneal Events Associated with Protocol Amendment 4 (KVA Scale)

Grade per KVA scale		Grade 1	Grade 2	Grade 3	Grade 4
Corneal Toxicities	Corneal examination finding(s)	Mild superficial keratopathy[a]	Moderate superficial keratopathy[b]	Severe superficial keratopathy[c]	Corneal epithelial defect[d]
	Change in BCVA[e]	Decline from baseline of 1 line on Snellen Visual Acuity	Decline from baseline of 2 or 3 lines (and Snellen Visual Acuity not worse than 20/200)	Decline from baseline by more than 3 lines (and Snellen Visual Acuity not worse than 20/200)	Snellen Visual Acuity worse than 20/200

a. Mild superficial keratopathy = mild superficial punctate keratopathy (documented worsening from baseline), **with or without** symptoms.
b. Moderate superficial keratopathy = any/or a combination of: moderate superficial punctate keratopathy, patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity.
c. Severe superficial keratopathy = any/or a combination of: severe superficial punctate keratopathy, diffuse microcyst-like deposits, sub-epithelial haze (central), or a new central stromal opacity.
d. Corneal epithelial defect such as corneal ulcers (with underlying stromal infiltration).
e. Changes in visual acuity due to treatment-related corneal findings.

BCVA = best corrected visual acuity

For **thrombocytopenia and infusion related events** summaries of the number and percentage of participants with these events will be provided for each type of event. The time of onset and duration of first occurrence of each type of event 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 (1-21, 22-42, 43-63, >63 days) will be reported for **thrombocytopenia**. The number and percentage of participants who have time to onset of first occurrence in categories of (0-6, >6-12, >12-18, >18-24, >24 hours) will be reported for **infusion-related reactions**

The number and percentage of participants who have duration of first occurrence (1-21, 22-42, >42 days) will be reported for **thrombocytopenia**. The number and percentage of participants who have duration of first occurrence in categories of (0-12, >12-24, >24 hours) will be reported for **infusion-related** reactions.

For **corneal events**, the number and percentage of participants with different grades of events at each visit will be reported.

For details on AEs, SAEs and irAEs specific to combination therapies refer to the individual sub-study SAPs.

4.5.2.2. COVID-19 Assessment and COVID-19 AEs

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

The impact of COVID-19 on DLTs during the DE phase of any sub-study will be monitored during the study conduct through review of protocol deviations and by the summary tables and listings described in Section 6.1.1.1. DLTs will be reported according to the DLT evaluable analysis set defined in Section 3.

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

4.5.2.3. Impact of COVID-19 Pandemic on Safety Results

The phases ‘before’ and ‘after’ the start of the COVID-19 pandemic are used for COVID-19 displays, as defined in Section 6.2.2.3.

4.5.2.4. Deaths and Serious Adverse Events

The number and percentage of participants reported to have died will be summarised. This summary will classify participants by time of death relative to the last dose of study medication (>30 days or ≤30 days) and primary cause of death. A supportive listing will be generated to provide participant-specific details on participants who died.

All SAEs and serious immune-related adverse events associated with belantamab mafodotin monotherapy will be tabulated based on the number and percentage of participants who experienced the event. Separate summaries will also be provided for study combination treatment-related SAEs and serious irAEs. The summary tables will be displayed in descending order of total incidence by SOC and PT.

A study treatment-related SAE (or serious irAE) is defined as an SAE (or serious irAE) 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. Only AEs classified as 'treatment-emergent' will be included in this summary.

SAEs are included in the listing of all adverse events and immune-related adverse events (irAEs). irAEs related to each combination treatment can be found in the separate sub-study protocols. Separate supportive listings with participant-level details will be generated for

- Fatal SAEs
- Non-Fatal SAEs.
- Fatal serious irAEs
- Non-Fatal serious irAEs

4.5.2.5. Adverse Events Leading to Discontinuation of Study Treatments and Other Significant Adverse Events

The following categories of AEs will be summarized separately by individual treatment component and treatment arm / dose level in descending order of total incidence by SOC and PT. Separate supportive listings will be generated with participant level details:

- AEs Leading to Permanent Discontinuation of Study Treatment
- AEs Leading to Dose Interruptions or Delays
- AEs Leadings to Dose Reductions
- All Treatment-related Serious Adverse Events

Any immune-related adverse events that should result in discontinuation of study treatments can be found in the corresponding sub-study protocol where applicable.

4.5.2.6. Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If a participant or their partner becomes pregnant whilst on the study, the information will be included in the narratives and no separate table or listing will be produced.

4.5.2.7. Clinical Laboratory Analyses

Laboratory evaluations including analyses of chemistry laboratory tests, hematology laboratory tests, urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in the Outcome and Programming Specification (OPS) document.

Summaries of change from baseline by scheduled visit using mean, median, standard deviation, minimum and maximum will be provided for clinical laboratory tests and hematology laboratory tests.

Summaries of worst-case grade change from baseline grade will be provided for clinical laboratory tests and haematology laboratory tests that are gradable by CTCAE v5. These summaries will display the number and percentage of participants with a maximum post-baseline grade increase relative to baseline grade. Missing baseline grade will be assumed to be grade 0. For laboratory tests that are graded for both low and high values, separate summaries will be produced and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

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

Separate summary tables for haematology, chemistry, urinalysis, and hepatobiliary laboratory tests will be produced. 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 laboratory test values that can be graded, values of grade 1 or above are defined as values of potential clinical concern. For laboratory test values that cannot be graded, values out of the normal range are defined as values of potential clinical concern.

Detailed derivation of baseline assessment value is specified in Section 4.1.4.

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

4.5.2.7.1. Analysis of Liver Function Tests

A summary of Liver Monitoring/Stopping Event Reporting will be provided. Medical conditions and substance use data for participants with liver stopping events will be listed. Liver biopsy results and recorded outcomes of liver imaging assessments for participants will be listed.

Summaries of hepatobiliary laboratory abnormalities including possible Hy's law cases will be provided. A summary of liver restart/re-challenge timings will be provided.

Plots of maximum total bilirubin versus maximum ALT and maximum ALT versus baseline ALT will be generated. Plots of Liver Function Test (LFT) participant profiles for possible Hy's Law cases and LFT shift from baseline to maximum will be generated, where applicable.

4.5.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. LVEF and performance status will be summarized and listed based on GSK Oncology Data Standards. The details of the planned displays are presented in the Output and Programming Specification (OPS) document.

4.5.3.1. Performance Status

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

A supporting listing will also be provided.

4.5.3.2. ECG

A summary of the number and percentage of subjects who had normal or abnormal (clinically significant and not clinically significant) ECG findings at screening will be provided.

The QTc values based on Fridericia formula will be rounded to the integer and the values will be categorized into the following ranges: Grade 0 (<450), Grade 1 (450-480), Grade 2 (481-500), and Grade 3 (≥501).

A listing of QTc will use the collected values based on Fridericia formula.

4.5.3.3. LVEF

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

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

LVEF results will also be listed with participant level details including absolute change from baseline.

4.5.3.4. Ocular Exam

The number and percentage of participants experiencing corneal clinical signs will be summarized by corneal clinical sign. The number and percentage of participants experiencing corneal clinical signs with/without reporting corneal events will be summarized. Visual acuity and abnormal corneal exam results, regardless of whether the abnormal corneal exam result represents a corneal clinical sign, will be listed for each eye at each visit. Whether the participant experienced corneal clinical signs and reported corneal events will also be listed. Corneal events will be graded according to the information presented in Section 4.5.2.1.1.

The remainder of the ophthalmic exam results will be provided separately, including but not limited to listing of abnormal conjunctival exam results; listing of abnormal sclera results; listing of abnormal slit lamp lens, slit lamp iris, and slit lamp anterior chamber exam results; listing of pupillary exam results; and listing of dilated fundoscopic exam and intra-ocular pressure results.

Details of how changes in BCVA are graded using the KVA scale are included in the ocular study reference manual for study 208887.

4.6. Other Analyses

4.6.1. Pharmacokinetic Analysis

PK samples will be collected for belantamab mafodotin and/or combination treatments in Cycle 1 as well as later cycles as indicated in the SoA tables in the 208887 Master Protocol and sub-study protocols. PK analyses will be done for each analyte measured for both the DE and/or CE phase, as data permit.

4.6.1.1. Derived Pharmacokinetic Parameters

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

Standard non-compartmental analysis (NCA), if performed, will be conducted according to current working practices, using the currently supported version of Phoenix WinNonlin and will provide the parameters listed in the table below, as data permit. The pharmacokinetic parameters C-EOI and Ctrough will be determined directly from the concentration-time dataset, as data permit. For dosing occasions with only predose and end of infusion samples Cmax and tmax will not be derived. Ctrough will not be reported for cys-mcMMAF.

Population pharmacokinetic analyses (popPK), if performed, are described in Section 4.6.2.

Belantamab Mafodotin, Total mAb, and Cys-mcMMAF

For a NCA, if performed, the following pharmacokinetic parameters (described in Table 8 below) will be determined separately for each analyte, as data permit:

- Belantamab mafodotin and total mAb: Cmax, C-EOI, tmax, Ctrough, tlast, and AUC(0-τ).
- cys-mcMMAF: Cmax, C-EOI, tmax, tlast, and AUC(0-168h)

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

- Belantamab mafodotin and total mAb: Cmax, Ctrough, AUC(0-τ), Cavg(0-τ), t½, CL, Vss .
- cys-mcMMAF: Cmax, AUC(0-168h), Cavg(0-τ)

Combination Partners

Pharmacokinetics of combination treatment drugs in the presence of belantamab mafodotin may be analyzed using standard non-compartmental methods, data permitting, according to the same methodology as described above, or analyzed using a published population pharmacokinetic model. Results of the population PK analysis may be provided in a separate report.

Table 8 PK Parameters Derived from Non-Compartmental Analysis

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid
AUC(0-τ)	Area under the concentration-time curve during the dosing interval
AUC(0-168h)	Area under the concentration-time curve from time zero to 168 hours.
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity will be calculated as: **AUC = AUC(0-t) + C(t) / lambda_z** Where C(t) is the last observed quantifiable concentration and lambda z is the terminal phase rate constant.
Cmax	Maximum observed concentration determined directly from the concentration-time data for Cycle 1. Cmax will not be derived post Cycle 1 since only pre-dose and end of infusion (EOI) samples were collected.
Tmax	Time to reach Cmax, determined directly from the concentration-time data for Cycle 1
Ctrough	Trough concentration prior to the next dose for each cycle
t½	Apparent terminal half-life will be calculated as: t½ = ln(2) / lambda_z
tlast	Time of last observed quantifiable concentration
CL	Clearance for drug administered IV, only
Vss	Volume of distribution at steady state for drug administered IV, only
λz, lambda_z	Terminal phase rate constant

NOTES:

- Additional parameters may be included as required.

4.6.1.2. Summary Measure

Parameters listed in Section 4.6.1.1 will be summarized using descriptive statistics, graphically presented (where appropriate), and listed. Drug concentrations and PK parameters will be listed and summarized descriptively (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV%, and 95% CI of log-transformed parameters) by analyte, combination partner, cycle or visit, and dose group.

4.6.1.3. Population of Interest

The PK analyses will be based on the PK analysis set, unless otherwise specified.

4.6.2. Population Pharmacokinetic (POPPK) Analysis

The belantamab mafodotin and/or combination treatment(s) concentration-time data may be combined with data from other studies and may be analysed using a population pharmacokinetic approach, as data permit. The planned analysis may use previously developed population pharmacokinetic (popPK) model(s) to generate *post hoc* PK 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.

Details of the population PK analyses may be reported under a separate SAP, and the results of these analyses may be provided in a separate report.

4.6.3. Exploratory Biomarker Analysis

Analyses of exploratory biomarker data are intended for hypothesis generation in relation to the pharmacodynamics of belantamab mafodotin and/or combination treatment(s), and for evaluation of potential diagnostic, prognostic or predictive biomarkers. Exploratory biomarker analyses may include, but not be limited to, evaluating expression of BCMA and other plasma cell (PC) or immune cell markers and/or immune status in tumor tissue and in the tumor microenvironment, soluble BCMA, cytokines, and circulating free DNA (cfDNA). Both baseline and changes in biomarker levels will potentially be examined relative to response or other clinical parameters. If deemed appropriate and if data permit, relationships between biomarkers and/or pharmacodynamics (PD) and clinical activity and/or toxicity (e.g., response, AESIs) may be explored. If data permit, the effects of covariates may be explored.

Details of these analyses will be reported under a separate SAP, and the results of these analyses will be provided in a separate report. The biomarker analyses will be based on the pharmacodynamic analysis set, unless otherwise specified.

4.6.4. Pharmacokinetic / Pharmacodynamic Analysis

4.6.4.1. Exposure-Response for Efficacy and Toxicity

If deemed appropriate and if data permit, exposure-response relationships between belantamab mafodotin exposure (e.g., dose, dose intensity, concentration, Cmax, or AUC) and clinical activity and/or toxicity (e.g., response, corneal event, AESIs) may be explored using logistic regression and time-to-event analysis methods, as appropriate. If data permit, the effects of covariates may be explored. Details of these analyses may be reported under a separate SAP, and the results may be provided in a separate report.

4.6.5. Immunogenicity Analysis

For each participant, 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 number and percentage of participants with positive and negative anti-drug antibody and neutralizing antibody assay results will be summarized for each assessment time and overall, by dose cohort.

4.6.6. Health-Related Quality of Life Analysis

The EORTC QLQ-C30 (version 3.0), EORTC QLQ-MY20, and the PRO-CTCAE are three oncology-specific Health-Related Quality-of-Life (HRQoL) assessments that will be analysed for the CE phase in this study.

In addition, the impact of corneal events on function and health-related quality-of-life will be assessed with the use of the visual function questionnaire Ocular Surface Disease Index (OSDI).

Data collected from the EORTC QLQ-C30 and EORTC QLQ-MY20 will be analysed for the ITT analysis set, while the analysis set for the PRO-CTCAE and OSDI will be the Safety analysis set.

Note that eCOA compliance will be summarized for each of the patient-reported outcome (PRO) instruments mentioned above. Please see Section 6.2.10 for further detail.

4.6.6.1. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module (EORTC QLQ-C30)

The EORTC QLQ-C30 is a 30-item questionnaire containing both single- and multi-item measures (Aaronson, et al., 1993). Details of deriving domain scores (9 scales and 6 single items) and summary score can be found in Section 6.3.1.

For summary score and each domain score, the following outputs will be provided:

- A descriptive summary of the actual value and change from baseline by visit.
- The number (and %) of participants with improvement in score ≥ 10, and ≥ 5 points from baseline respectively by visit.

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

The EORTC QLQ-MY20 is a supplement to the QLQ-C30 instrument used in patients with multiple myeloma (Aaronson, et al., 1993) [Cocks, 2007]. The module comprises 20 questions that address four myeloma-specific HRQoL domains: Disease Symptoms, Side Effects of Treatment, Future Perspective, and Body Image. Only the Disease Symptoms scale will be administered, which includes bone aches or pain, back pain, hip pain, arm or shoulder pain, chest pain, and pain increasing with activity. Details of deriving domain score can be found in Section 6.3.2.

The following outputs will be provided:

- A descriptive summary of the actual value and change from baseline by visit
- Summary of the number (%) of participants with improvement in score ≥ 10, and ≥ 5 points from baseline respectively by visit.

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

The Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a patient-reported outcome measure developed to evaluate symptomatic toxicity in patients on cancer clinical trials [Basch, 2014]. The PRO-CTCAE was designed to be used as a companion to the Common Terminology Criteria for Adverse Events (CTCAE), the standard lexicon for adverse event 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. The levels and related code values for PRO-CTCAE are shown in Table 9 .

Table 9 PRO-CTCAE Levels and Associated Code Values

	Levels and related code values				
Response scale	0	1	2	3	4
Frequency	Never	Rarely	Occasionally	Frequently	Almost Constantly
Severity	None	Mild	Moderate	Severe	Very severe
Interference	Not at all	A little bit	Somewhat	Quite a bit	Very much
Present/Absence	No	Yes			

For each selected item from the library, the proportion of responses corresponding to each PRO-CTCAE score for each item attribute (frequency, severity and/or interference) will be presented with stacked bar charts. Maximum PRO-CTCAE score post-baseline for each item attribute will be summarized by counts and proportions. The 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.

4.6.6.4. Ocular Surface Disease Index

The Ocular Surface Disease Index (OSDI) is a 12-item questionnaire designed to assess both the frequency of dry eye symptoms and their impact on vision-related functioning [Schiffman, 2000].

For the OSDI, the total score will be calculated as well as scores for the three subscales (ocular symptom: item 1-3; visual related function: item 4-9; and environmental triggers: item 10-12).

The total OSDI score = ([sum of scores for all questions answered × 100]/[total number of questions answered ×4]). Subscale scores are computed similarly using only the questions from the subscale of interest. A score of 100 corresponds to complete disability (a response of "all of the time" to all questions answered), while a score of 0 corresponds to no disability (a response of "none of the time" to all questions answered). Therefore, decrease in score from baseline means improvement.

For total score and each of the three sub-scales, a descriptive summary of the actual value and change from baseline by time will be provided.

In addition, summary of worst change from baseline in total score by worst grade of corneal event per GSK scale (0 vs 1-2, vs 3-4) will also be provided.

4.7. Interim Analyses

4.7.1. Dose Exploration (DE) Phase

An interim analysis (IA) for ORR will be performed in the DE phase after up to 15 participants treated at each potential RP2D of the combination therapy have progressed/died, discontinued study treatment, or have had 3 efficacy assessments (1 baseline and 2 post-baseline assessments). Additional interim analyses may be performed in the DE phase for publication purposes or decision making for other sub-studies.

If the true response rate is 40%, the probability of observing less than 3 responders from 15 participants (equivalent to a 20% response rate) is ~2.7%. A minimum response rate of ≥20% and a minimum of 2 responders from up to 15 participants will be needed in order to move a particular dose level of the combination therapy to the CE Phase. However, the IA decision for transitioning each potential RP2D into the CE phase will be based on the totality of the clinical safety assessments, laboratory assessments, PK, biomarkers (as data permit), efficacy and any other relevant information.

Outputs that will be generated by biostatistics for the IA performed at the end of the DE phase for a sub-study can be found within the List of Displays located within the Output and Programming Specification (OPS) document.

4.7.2. Cohort Expansion (CE) Phase

4.7.2.1. Interim Analysis for Futility

Two interim analyses may be performed for futility evaluation for a particular dose level of a combination treatment in the CE phase. The first interim analysis will be conducted when at least 10 CE combination treatment participants are evaluable. The second interim analysis may be performed when approximately 18 combination treatment participants are evaluable. Participants are considered evaluable if they have progressed/died, discontinued study intervention, or have had 3 post-baseline efficacy assessments or at least two planned doses.

At each interim analysis, the observed ORR difference between the group allocated to combination treatment and the control participants allocated to monotherapy will be assessed. The cohort may be discontinued if the posterior probability of response rate with combination treatment being greater than the response rate with monotherapy is less than 40%. The posterior probability will be calculated using the method described in Section 4.2.2.2. The final decision to continue or not will be based on the totality of available data.

At the primary analysis, a particular dose level of combination treatment will be considered superior to monotherapy if the posterior probability of the response rate with combination therapy being greater than the response rate with monotherapy is at least 90%.

The operating characteristics of the futility decision criteria are presented in Table 10. This is based on the following assumptions:

- 15 participants analysed at the interim analysis for the DE phase (note that this differs from 10 participants assumed in the simulations used to generate Table 22 in Section 9.5.2 of 208887 Master Protocol Amendment 6)
- If ≥3 responders at DE phase interim analysis, sub-study continues to CE for the same dose level (i.e. underlying response rate for combination treatment is the same in the DE and CE phases)
- 35 participants randomised to combination treatment and 35 to monotherapy in the CE phase

For each scenario, 10,000 simulations of the number of responders at the DE phase interim analysis, in the combination treatment and monotherapy groups at the first and second interim analysis, and at the primary analysis were run. For each simulation, the posterior probability of greater response rate with combination treatment at each of the first and second interim analyses and the primary analysis at CE phase was determined using 10,000 draws from the posterior for response rate with combination treatment and the posterior for monotherapy.

Table 10 Operating Characteristics of the Futility Decision Criteria

True ORR	Probability of Meeting Futility Criterion at CE Phase IA1[a] N=10	Probability of Meeting Futility Criterion at CE Phase IA2[b] N=18	Probability of Meeting Success Criterion at CE Phase Primary Analysis[c]
p0= 0.3, p1=0.3	0.338	0.081	0.060
p0= 0.3, p1=0.4	0.134	0.032	0.394
p0= 0.3, p1=0.5	0.036	0.007	0.825
p0= 0.3, p1=0.55	0.017	0.003	0.926
p0= 0.3, p1=0.6	0.009	0.001	0.971
p0= 0.4, p1=0.4	0.227	0.067	0.184
p0= 0.4, p1=0.5	0.091	0.027	0.567
p0= 0.4, p1=0.6	0.035	0.012	0.835
p0= 0.4, p1=0.65	0.024	0.006	0.906
p0= 0.4, p1=0.70	0.013	0.003	0.956

p0=true ORR with monotherapy; p1=true ORR with combination therapy. IA=interim analysis.

Futility criterion at CE phase IA1 and IA2 is the posterior probability (p1- p0>0) <0.40. Success criterion at the primary analysis for the CE phase is the posterior probability (p1- p0>0) ≥0.9.

a. The probability of passing DE phase futility threshold (≥3 responders) and then stopping at CE phase IA1.

b. The probability of passing DE phase futility threshold (≥3 responders) and passing the first IA futility threshold, and then stopping at CE phase IA2.

c. The probability of passing DE phase futility threshold (≥3 responders) and passing the CE phase IA futility threshold at both IAs, and then meeting the success criterion at primary analysis for CE phase.

4.7.2.2. Rolling Safety Evaluation

In the CE phase for a given combination treatment dose level within a sub-study, rolling evaluation for Grade 4 or higher treatment-related toxicity events which would trigger study stopping criteria (see Table 11) will be performed on a per 10 participants basis for those participants treated with at least one cycle of belantamab mafodotin plus combination treatment(s).

The observed number of treatment-related Grade 4 or higher AEs will be compared against the safety stopping rule in the following Table 11 . The combination treatment arm will be considered to have unacceptable toxicity if the number of treatment-related Grade 4 or higher AEs is significantly higher than the number of treatment-related Grade 4 or higher AEs in the belantamab mafodotin monotherapy common control arm at one-sided alpha of 0.025 (determined using Normal approximation without continuity correction). Enrolment may stop if the safety stopping rule is met, considering the totality of safety data.

Table 11 Safety Stopping Rules for the Cohort Expansion Phase

GSK2857916 monotherapy (control) arm			Combination arm
Number of participants enrolled	Number of participants with treatment-related Grade 4 or higher AE	Incidence of participants with treatment-related Grade 4 or higher AE	Stop if treatment-related Grade 4 or higher AEs larger or equal to this number (one sided alpha<0.025)
10	1	0.1	6
10	2	0.2	7
10	3	0.3	8
20	1	0.05	6
20	2	0.1	8
20	3	0.15	9
20	4	0.2	10
20	5	0.25	12
20	6	0.3	13
30	3	0.1	10
30	6	0.2	14
30	9	0.3	17

4.8. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 6 (Dated: 11-Jul-2023)

5. SAMPLE SIZE DETERMINATION

In the DE phase, approximately up to 15 participants will be assigned to a combination dose level.

If a response rate of ≥20% and at least 2 responders in up to 15 participants are observed for a combination treatment dose level, an additional 35 participants may be randomised to each arm (combination treatment, control) in the CE phase per sub-study. However, the decision to move to the CE phase for a treatment combination is based on the totality of the data. In the CE phase, eligible participants will be randomly allocated to an open sub-study CE phase and then randomised between combination treatment and the control arm within that sub-study, with randomisation to treatment group stratified by prior lines of therapy (3-4 vs >4 prior lines). Once 35 participants have been randomised to the shared belantamab mafodotin monotherapy arm, the randomisation ratio for new sub-study CE phases will change depending on the number of new CE phase cohorts and the timing of their entry to the study (see Section 4.1.3 and Table 3).

5.1. Statistical Operating Characteristics

In the 208887 Master Protocol Amendment 6, Section 9.2.1, Table 21, statistical operating characteristics based on simulations are presented, based on the assumption that up to 10 participants will be recruited to the DE phase for a dose level of combination treatment in a sub-study. Table 12 below provides updated forecasts based on a total of 15 participants in the DE phase. In the scenarios below, the following assumptions are made:

- 15 participants analysed at the interim analysis for the DE phase
- If ≥3 responders at DE phase interim analysis, sub-study continues to CE phase for the same dose level (i.e. underlying response rate for combination treatment is the same in the DE and CE phases)
- 35 participants randomised to combination treatment and 35 to monotherapy in the CE phase
- Within the CE phase, the sub-study continues to primary analysis regardless of the (non-binding) results of the interim futility analyses

For each scenario, the number of responders in the DE phase cohort and CE phase combination treatment and monotherapy arms was simulated 10,000 times. For each of these iterations, the posterior probability of greater response rate with combination treatment was determined using 10,000 draws from the posterior for response rate with combination treatment and the posterior for monotherapy.

Table 12 Operating Characteristics of the Study

True Response Rate[1]	Probability of Futility at End of DE phase (<3 responders)	Probability of Meeting Success Criterion at Primary Analysis for CE phase[2]
p0=0.3, p1=0.3	0.128	0.062
p0=0.3, p1=0.4	0.027	0.416
p0=0.3, p1=0.5	0.004	0.838
p0=0.3, p1=0.55	0.001	0.940
p0=0.3, p1=0.6	0.0004	0.978
p0=0.4, p1=0.4	0.028	0.188
p0=0.4, p1=0.5	0.002	0.579
p0=0.4, p1=0.6	0.0002	0.850
p0=0.4, p1=0.65	0.0002	0.922
p0=0.4, p1=0.7	0.0000	0.962

True Response Rate[1]	Probability of Futility at End of DE phase (<3 responders)	Probability of Meeting Success Criterion at Primary Analysis for CE phase[2]
p0=0.5, p1=0.5	0.003	0.231
p0=0.5, p1=0.6	0.0002	0.514
p0=0.5, p1=0.7	0.0000	0.784
p0=0.5, p1=0.75	0.0000	0.887
p0=0.5, p1=0.8	0.0000	0.960

1: p0 = response rate with monotherapy, p1 = response rate with combination treatment

2: Joint probability of ≥3 responders at DE phase interim analysis and posterior probability that response rate with combination treatment is greater than response rate with monotherapy at least 90%, i.e. poster probability (p1-p0>0) ≥0.90.

5.2. Impact of Initial Weight Given to the Historical Data

In the 208887 Master Protocol Amendment 6, Section 9.6.2, Table 25, presents an evaluation of the impact of the weight given to the historical data from the Dreamm-2 primary analysis in the specification of the robust mixture prior for response rate with monotherapy. Updated forecasts are presented in Table 13 below, based on the updated assumption of a total of 15 participants allocated to the DE phase of a combination treatment dose level in a sub-study. The key assumptions made are:

- 15 participants analysed at the interim analysis for the DE phase
- If ≥3 responders at DE phase interim analysis, sub-study continues to CE phase for the same dose level (i.e. underlying response rate for combination treatment is the same in the DE and CE phases)
- The first interim analysis for the CE phase is performed when 10 participants have been allocated to combination treatment and 10 to monotherapy
- The second interim analysis for the CE phase occurs when an additional 8 participants have been randomised to each arm
- The primary analysis in the CE phase uses data from 35 participants randomised to combination treatment and 35 to monotherapy

For each scenario, the number of responders in the DE phase cohort, and for the combination treatment and monotherapy arms at the first and second CE phase interim analyses and the primary analysis was simulated 10,000 times. For each of these iterations, for each of the three CE phase analyses the posterior probability of greater response rate with combination treatment was determined using 10,000 draws from the posterior for response rate with combination treatment and the posterior for monotherapy.

The probabilities of success shown represent the joint probability of a dose level passing the interim analysis for the DE phase (i.e. ≥3 responders recorded), then continuing through the first and second interim analyses in the CE phase (i.e. posterior probability ≥40% that the response rate with combination treatment is higher than with monotherapy), then meeting the success criterion at the primary analysis (posterior probability ≥90% that the response rate with combination treatment is higher than with monotherapy).

Table 13 Impact of the Initial Weight Given to Historical Data on Probability of Meeting Success Criteria

True Response Rate	Probability of Achieving Success Criteria				
	w.e = 0.9, w.c = 0.9	w.e = 0.9, w.c = 0.7	w.e = 0.9, w.c = 0.5	w.e = 0.9, w.c = 0.3	w.e = 0.9, w.c = 0.1
p0=0.3, p1=0.3	0.059	0.053	0.061	0.059	0.077
p0=0.3, p1=0.4	0.422	0.414	0.403	0.370	0.360
p0=0.3, p1=0.5	0.864	0.850	0.820	0.789	0.739
p0=0.3, p1=0.55	0.955	0.948	0.930	0.899	0.858
p0=0.3, p1=0.6	0.987	0.979	0.973	0.959	0.934
p0=0.4, p1=0.4	0.262	0.227	0.189	0.151	0.117
p0=0.4, p1=0.5	0.710	0.634	0.547	0.482	0.391
p0=0.4, p1=0.6	0.931	0.877	0.832	0.791	0.716
p0=0.4, p1=0.65	0.965	0.935	0.910	0.886	0.837
p0=0.4, p1=0.7	0.983	0.969	0.951	0.941	0.928
p0=0.5, p1=0.5	0.417	0.306	0.233	0.172	0.117
p0=0.5, p1=0.6	0.690	0.565	0.496	0.431	0.364
p0=0.5, p1=0.7	0.858	0.792	0.764	0.729	0.708

True Response Rate	Probability of Achieving Success Criteria				
	w.e = 0.9, w.c = 0.9	w.e = 0.9, w.c = 0.7	w.e = 0.9, w.c = 0.5	w.e = 0.9, w.c = 0.3	w.e = 0.9, w.c = 0.1
p0=0.5, p1=0.75	0.919	0.885	0.871	0.858	0.851
p0=0.5, p1=0.8	0.962	0.948	0.943	0.937	0.938

Note: w.e = weight assigned to results from the corresponding DE phase combination treatment dose level in the mixture prior for response rate with combination treatment (this remains unchanged); w.c = weight assigned to results from the Dreamm-2 study in the mixture prior for response rate with monotherapy

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

The study population analyses will be based on the Safety analysis set in the DE phase and ITT analysis set in the CE phase, unless otherwise specified.

Study population analyses including analyses of participant disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, anti-cancer therapy and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in the Output and Programming Specification (OPS) document.

6.1.1. Participant Disposition

A summary of the number of participants in each of the analysis sets described in Section 3 will be provided. In addition, the number of participants enrolled by country and site will be summarized using the Enrolled analysis set.

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; the number and percentage of participants who died, completed the study, and are ongoing for study treatment or follow up will also be presented.

In addition, a summary table and listing identifying reasons for screening failures will be presented based on the Screened analysis set. Since screen failures cannot be attributed to any one sub-study or phase within a sub-study, repeat reporting may occur in different sub-studies.

A summary of study treatment status will be provided. The 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. A listing of study treatment discontinuation will be generated. The listing will include last dose date and reasons for study treatment discontinuation as well as relatedness to study treatment.

6.1.1.1. COVID-19

Where relevant, a summary of recruitment by country and site, relative to COVID-19 pandemic measures will be produced. For the definition of the phases of the COVID-19 pandemic measures see Section 6.2.2.3.

A country level listing of the dates of the COVID-19 Pandemic measures, and a figure showing enrolment over time by country, relative to the COVID-19 Pandemic measures will be produced. See Section 6.2.2.3 for details of the country level dataset.

"Summary of Subject Status and Subject Disposition for the Study Conclusion Record" and "Summary of Treatment Status and Reasons for Discontinuation of Study Treatment" displays will be repeated, with the reason for withdrawal/discontinuation categorised as due to the COVID-19 pandemic or not due to the pandemic, based on information collected on the COVID-19 Pandemic Study Impact form. These summaries will be based on GSK Core Data Standards, and details are provided in the Output and Programming Specification (OPS) document.

6.1.2. Demographic and Baseline Characteristics

Demographic characteristics e.g., age, race, ethnicity, sex, baseline height, and baseline body weight will be summarized and listed for the Safety analysis set in the DE phase and the ITT analysis set in the CE phase.

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

Medical conditions collected at screening will be listed and will be summarized by past and current.

Substance use, including smoking history, tobacco use, and alcohol and drug history will be summarized. Blood and blood supportive care will be summarised and listed by study treatment / dose level.

6.1.3. Protocol Deviations

Important protocol deviations will be listed and summarised. Important protocol deviations will be based on the Safety analysis set in the DE phase and the ITT analysis set in the CE phase and will include inclusion/exclusion deviations as well as other deviations.

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

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

6.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using GSK Drug coding dictionary version 1.4 or higher, summarized, and listed. The summary of concomitant medications will show the number and percentage of participants taking concomitant medications by ingredient. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients. Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information will be included in the dataset created but will not appear on the listing or summary.

In the summary of concomitant medications, each participant is counted once within each unique ingredient. For example, if a participant takes Amoxicillin on two separate occasions, the participant is counted only once under the ingredient “Amoxicillin”. In the summary of concomitant medications, the ingredients will be summarized by the base only, using CMBASECD and CMBASE. If medication end date is after the study treatment start date, then the medication will be considered as concomitant medication.

6.1.4.1. Anti-Cancer Therapies

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

The number and percentage of participants who received chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radiation therapy and cancer-specific surgery as post study treatment anti-cancer therapy on follow-up will be summarized.

Both prior and follow-up anti-cancer therapy will be coded using GSK drug coding dictionary version 1.4 or higher, then summarized by ingredient. A listing of the type of anti-cancer therapy received at ATC level/preferred term level/verbatim level for each participant will be provided.

6.1.5. Study Intervention Compliance

Summaries of study treatment exposure and dose modifications (e.g., number of dose reductions, number of dose delays/interruptions) will further characterize compliance. These analyses are described in Section 4.5.1 ('Extent of Exposure') and also in individual sub-study SAPs.

6.1.6. Additional Analyses Due to the COVID-19 Pandemic

A participant is defined as having a suspected, probable or confirmed COVID-19 infection during the study if the answer is "Confirmed", "Probable" or "Suspected" to the case diagnosis question from the COVID-19 coronavirus infection assessment eCRF.

Summaries and listings of the numbers of participants with suspected, probable or confirmed COVID-19 infection, and of COVID-19 test results will be based on GSK Core Data Standards. The details of planned displays are provided in the Output and Programming Specification (OPS) document.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

To identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5) will be used to assign grades for laboratory parameters including clinical chemistry, hematology, urinalysis, liver function tests, thyroid function tests, QTc (Fridericia's) values, vital signs (heart rate, blood pressure, temperature) and LVEF.

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

6.2.2. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study treatment period.

Study Phase	Definition
Pre-Treatment	Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Date ≤ Study Treatment Stop Date For interim analysis when participants are still on treatment, Study Treatment Stop Date will be imputed following rules specified in Section 6.2.7..
Post-Treatment	Date > Study Treatment Stop Date

For an assessment or event on the first dosing day, whether it is classified as Pre-Treatment or On-Treatment should be based on time if available. If time is not available, the first dosing day (Day 1) is considered Pre-Treatment for ECOG, ECG, vital signs, liver events, laboratory tests, cardiac scan, and other safety domains, and On-Treatment for adverse events and concomitant medications.

6.2.2.1. Study Phases for Concomitant Medication and Blood and Blood Supportive Care

Study Phase	Definition
Prior	End Date < Study Treatment Start Date
During/Ongoing	Any medication that is not prior (e.g. a medication which has stop date >= Study treatment start date and medication start date is <= on treatment period)

NOTES:

Please refer to Section 6.2.7, 6.2.8 and 6.2.9: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

6.2.2.2. Study Phases for Vital Signs, ECG and Laboratory Values

Study Phase	Definition
Pre-Treatment	Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Date ≤ Study Treatment Stop Date+70 days

6.2.2.3. Phases of COVID-19 Pandemic Measures

Pandemic measures began in different countries at different times. A dataset containing the date when pandemic measures began, as determined by the GSK country Issue Management Teams (IMT), will be used to determine the start date of pandemic measures within each country. A copy of this dataset will be taken at the time of database freeze (DBF).

Adverse events will be summarised according to whether the onset date was before or after the start of the COVID-19 pandemic measures.

Pandemic Measures Phase	Definition
Before	AE onset date < pandemic measures start date
After	Pandemic measures start date ≤ AE onset date

6.2.2.4. Treatment Emergent and On-Treatment Flag for Adverse Events

Flag	Definition
Treatment Emergent	Study Treatment Start Date ≤ AE Start Date ≤ min(Study Treatment Stop Date + 70 days, Date of Start of Anti-Cancer Therapy). AE Start Date is missing
On-treatment	Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 70 days

NOTES:

- Time of study treatment dosing and start time of AEs should be considered, if collected

6.2.3. Study Day and Reference Dates

The safety reference date is the study intervention start date and will be used to calculate study day for safety measures.

The efficacy reference date for the CE phase is the date of randomization and will be used to calculate study day for efficacy measures and baseline characteristics, as well as efficacy durations. For the DE phase, the efficacy reference date is study intervention start date.

The study day is calculated as the number of days from First Dose Date:

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

6.2.4. Derived and Transformed Data

6.2.4.1. General

Change from Baseline
• Change from Baseline = Post-Baseline Visit Value – Baseline • % Change from Baseline= 100 x (Post-Baseline Visit Value – Baseline) / Baseline • Maximum Increase/Decrease from Baseline = maximum (Increase/Decrease from Baseline) • If either the Baseline or Post-Baseline Visit Value is missing, Change from Baseline and % Change from Baseline is set to missing
Date of Response
• For post-baseline disease assessments, the date of response (PR or better) is assigned to the latest date of disease assessments; for other response categories (MR, SD, NE, PD), the date of response is assigned to the earliest date of disease assessments.
Date of New Anti-Cancer Therapy
• Derived as the earliest date of new anti-cancer therapy or cancer-related surgical procedure • Missing or partial dates will be imputed for derivation of new anti-cancer therapy following rules specified in Section 6.2.7.
Derivation of KVA grade

• Ocular Corneal Exam
  ○ Grade given using Table 6 or Table 7
• Visual Acuity Exam
  ○ Grade given using Table 8
 	
Overall KVA grade is the largest grade out of the Ocular Corneal Exam and the Visual Acuity Exam.

6.2.4.2. Study Population

Extent of Exposure

• Missing treatment stop date will be imputed following rules specified in Section 6.2.7.
• Combination Treatments
  ○ Extent of exposure will be calculated for each treatment component
  ○ Participants who were randomized but did not report a treatment start date will be categorized as having zero days of exposure

Time since Initial Diagnosis

To report in months, divide the number of days by 30.4375; to report in weeks divide the number of days by 7; to report in years divide the number of days by 365.25.
• Calculated as the number of Days from the Date of Initial Diagnosis:
  ○ First Dose Date = Missing → Elapsed Time = Missing
  ○ Date of Initial Diagnosis = Completely/partially Missing → Elapsed Time = Missing
  ○ Otherwise → Elapsed Time = First Dose Date – Date of Initial Diagnosis + 1

6.2.4.3. Safety

Duration of AE

To report in months, divide the number of days by 30.4375; to report in weeks divide the number of days by 7; to report in years divide the number of days by 365.25.
• Calculated as the number of days from AE Start Date to AE Stop Date:
  • AE Start Date = Missing → Elapsed Time = Missing
  • AE Stop Date = Missing → Elapsed Time = Missing
  • Otherwise → Elapsed Time = AE Stop Date – AE Start Date + 1

ECHO/MUGA
• Change from Baseline for cardiac data, e.g., Left Ventricular Ejection Fraction (LVEF), will be calculated based on the same modality (ECHO or MUGA) throughout the study for each participant. Post-baseline assessments with a different cardiac scan modality will not be used to calculate change from Baseline.

6.2.5. Assessment Window

Assessment windows have been defined in the analysis section for each endpoint. No additional windows will be applied.

6.2.6. Multiple measurements at One Analysis Time Point

- Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented.
- If there are two values within a time window (as per Section 6.2.5) the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken.
- Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.

6.2.7. Handling of Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays. However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases (see Section 6.2.2) or for specific analysis purposes as outlined below. • Imputed partial dates will not be used to derive study day, duration (e.g., duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in the overall survival analysis dataset. • With the exception of new anti-cancer therapy start date in the time to event analysis dataset and exposure end date in the exposure analysis dataset, imputed dates will not be stored in datasets.
Adverse Events	• Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings. • The eCRF allows for the possibility of partial dates (e.g., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used. ○ Missing Start Month and Day: First of January will be used unless AE stop date is after treatment start date, in this case treatment start date will be used • Completely missing start dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • Completely or partially missing end dates will remain missing, with no imputation applied. Consequently, the duration of such events will be missing.
Concomitant Medications/Medical History	• Completely missing start dates will not be imputed • Partial start dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If day and month are missing: – If treatment start date is missing (i.e., participant did not start study treatment), a '01' will be used for the day and 'Jan' will be used for the month; – If treatment start date is not missing ▪ If year of start date = year of study treatment start date

Element	Reporting Detail
	• If stop date contains a full date which is earlier than the treatment start date, a '01' will be used for the day and 'Jan' will be used for the month; • else study treatment start date will be used ▪ else a '01' will be used for the day and 'Jan' will be used for the month ○ If day is missing: – If treatment start date is missing (i.e., participant did not start study treatment), a '01' will be used for the day; – If treatment start date is not missing ▪ If year and month of start date = year and month of study treatment start date • If stop date contains a full date which is earlier than the treatment start date, a '01' will be used for the day; • else study treatment start date will be used ▪ else a '01' will be used for the day and 'Jan' will be used for the month • Completing missing end dates will not be imputed • Partial end dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If day and month are missing – Earliest of (Dec 31st, date of last contact) will be used ○ If day is missing – Earliest of (last day of the month, date of last contact) will be used
New Anti-Cancer Therapy/ Radiotherapy/ Surgical Procedures for Efficacy Evaluation (e.g., response rate, time to event)	• Completely missing start dates will remain missing, with no imputation applied. • Partial start dates will be imputed using the following convention: ○ If both month and day are missing, no imputation will be applied; ○ If only day is missing: ▪ If the month of partial date is the same as the month of last dosing date, minimum of (last dosing date + 1, last day of the month) will be used for the day; ▪ If the month of partial date is the same as the month of last disease assessment and the last disease assessment is PD, minimum of (last date of disease assessment + 1, last day of the month) will be used for the day; ▪ If both conditions above are met, the later date will be used for the day; ▪ Otherwise, a '01' will be used for the day; Completely or partial missing end dates will remain missing, with no imputation applied;

Element	Reporting Detail
Treatment end date	• If there is more than one study treatment, imputation of missing treatment end date will be applied to all applicable treatments following rules below and treatment end date is the latest treatment end date across all study treatments. For daily oral treatment: • In general, completely missing end dates are not imputed, with the following exceptions for imputation of missing treatment end date at interim analyses. ○ For imputation of missing exposure end date at an interim analysis when participants are still on treatment, the following conventions will be applied: If the missing end date is in the last exposure record, the earliest of: the date of the data cut-off, the date of withdrawal from the study, or the death date will be used ○ If the missing end date is not in the last exposure record, treatment start date for the record will be used • The imputed treatment end date will be used to calculate cumulative dose and duration of treatment as specified in Section 6.2.4.2 For non-continual treatment: • If treatment end date is missing for a cycle, treatment start date for the cycle will be used.

6.2.8. Handling of Premature Withdrawals

Element	Reporting Detail
General	• Participant study completion (i.e. as specified in the protocol) was defined as: ○ For dose escalation phase, a participant is considered to have completed the study if the participant is treated through the DLT determinative period or has a DLT during the DLT determinative period, i.e., a completed participant is one who is evaluable for the determination of DLT rate. ○ For cohort expansion, a participant is considered to have completed the study if they received at least 1 cycle of combination/control study treatment, and: ▪ The participant is followed until death (even after starting a new anti-cancer treatment), or ▪ Has withdrawn consent, or ▪ Is lost to follow-up, or ▪ The participant is followed until the end of the sub-study • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

6.2.9. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated by the use of a "blank" in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

6.2.10. Electronic Clinical Outcome Assessment (eCOA) Compliance

Summary measures of the overall participant compliance rate, and the participant compliance rate over time for each 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 endpoint is defined for each randomized treatment group (i.e., CE Cohort) 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%. Note that this target will simply serve as a reference measure given the overall nature and objective of this study.

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.

6.3. Appendix 3: Heath Outcome Analysis

6.3.1. 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). The below image shows the details.

Table 1: Scoring the QLQ-C30 version 3.0

	Scale	Number of items	Item range*	Version 3.0 Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

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.

Scoring of the QLQ-C30 Summary Score

The EORTC QLQ-C30 Summary Score is calculated from the mean of 13 of the 15 QLQ-C30 scales (the Global Quality of Life scale and the Financial Impact scale are not included). Prior to calculating the mean, the symptom scales need to be reversed to obtain a uniform direction of all scales. The summary score should only be calculated if all the required 13 scale scores are available.

QLQ-C30 Summary Score = [Physical Functioning+ Role Functioning+ Social Functioning+ Emotional Functioning+ Cognitive Functioning+ (100- Fatigue)+ (100-Pain)+ (100-Nausea_Vomiting)+ (100-Dyspnoea)+ (100-Insomnia)+ (100-Appetite Loss)+ (100-Constipation)+ (100-Diarrhoea)]/13.

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 [Fayes, 2001].

6.3.2. EORTC QLQ-MY20

The EORTC QLQ-MY20 is a supplement to the QLQ-C30 instrument used in patients with multiple myeloma [Aaronson, 1993] [Cocks, 2007]. The module comprises 20 questions that address four myeloma-specific HRQoL domains: Disease Symptoms, Side Effects of Treatment, Future Perspective, and Body Image. Only the Disease Symptoms domain will be administered, which includes bone aches or pain, back pain, hip pain, arm or shoulder pain, chest pain, and pain increasing with activity.

Scoring

	Scale name	Number of items	Item range	QLQ-MY20 item numbers
Functional scales / items				
Future perspective	MYFP	3	3	18 – 20
Body image	MYBI	1	3	17
Symptom scales				
Disease symptoms	MYDS	6	3	1 – 6
Side effects of treatment	MYSE	10	3	7 – 16

Remarks

- Question 12 is considered scored "not at all" if question 11 is scored "not al all".

As with the QLQ-C30, Disease symptoms domain score of QLQ-MY20 is also averaged and transformed linearly to a score ranging from 0–100 (see below for details).

1) Raw score

Calculate the average of the disease symptoms items.

$$Raw\ Score = RS = (I_1 + I_2 + \ldots + I_n)/n$$

2) Linear Transformation

To obtain the Score S, standardize the raw score to a 0 – 100 range following the appropriate transformation:

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

A high score for Disease Symptoms represents a high level of symptomatology or problems, [Proskorovsky, 2014].

Missing items can be handled similarly to EORTC QLQ-C30 as described in Section 6.3.1.

6.4. Trademarks

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7. REFERENCES

Aaronson, N. et al., 1993. The European Organisation for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Institute*, 85(5), pp. 365-76.

Basch, E. et al., 2014. Development of the National Cancer Institute patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *J Natl Cancer Inst.* , Volume 106, pp. 1-11.

Brookmeyer, R. & Crowley, J., 1982. A Confidence Interval for the Median Survival Time. *Biometrics*, 38(1), pp. 29-41.

Cocks, K. et al., 2007. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQMY20) in assessing the quality of life of patients with multiple myeloma. *European Journal of Cancer*, 43(11), pp. 1670-8.

Fayes, P. et al., 2001. *EORTC QLQ-C30 Scoring Manual*. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer.

Kumar, S. et al., 2016. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *The Lancet Oncology*, pp. 17: 328-46.

Proskorovsky, I. et al., 2014. Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. *Health Qual Life Outcomes*, Volume 12, p. 35.

Schiffman, R. et al., 2000. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophrhalmol*, 118(5), pp. 615-621.