Statistical Analysis Plan

Study ID: 208887 Sub Study 7

Official Title of Sub Study 7: 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)-DREAMM5 - Sub-study 7 - Belantamab Mafodotin, Nirogacestat, Pomalidomide, and Dexamethasone in Combination

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TITLE PAGE

Protocol Title:	A Phase I/II, Randomised, Open-label Platform Study Utilising 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). Sub-study 7 – Belantamab Mafodotin, Nirogacestat, Pomalidomide and Dexamethasone in Combination
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Compound Number:	Belantamab Mafodotin (GSK2857916), Nirogacestat, Pomalidomide, Dexamethasone
Abbreviated Title:	Sub-study of Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination with Nirogacestat, Pomalidomide and Dexamethasone in Participants with RRMM
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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP v1.0	15 Dec 2023	208887 Master Protocol Amendment 6 (11-Jul-2023) 208887 Sub-study 7 Protocol Amendment 01 (10-Jul-2023) 208887 Master SAP (09-Dec-2022)	Not Applicable	Original version

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses to be included in the Clinical Study Report (CSR) for sub-study 7 of DREAMM-5 (study 208887). For more details about the statistical analysis plan for the overall study refer to the 208887 Master SAP.

Details of the planned interim and primary analyses, as well as the final analysis, are provided.

1.1. Objectives, Estimands and Endpoints

The primary and secondary objectives, along with the corresponding endpoints for both the Dose Exploration (DE) phase and Cohort Expansion (CE) phase are summarised in Section 1.1 of the 208887 Master Protocol.

1.2. Study Design

Overview of Study Design and Key Features

Please refer to the 208887 Master Protocol for the overall design for the study.

The schema for the DE phase of sub-study 7 is:

Investigational Product	Cohort 1 (Starting dose)	Cohort 2		Cohort 3	
		Cohort 2A	Cohort 2B	Cohort 3A	Cohort 3B
Belantamab Mafodotin	0.5 mg/kg IV Q4W	1.0 mg/kg IV Q4W for first cycle then Q8W or Q12W	1.0 mg/kg IV Q4W	1.4 mg/kg IV Q4W for first cycle then Q8W or Q12W	1.4 mg/kg IV Q4W
Nirogacestat	100 mg PO BID Continuously dosed starting Day -2 Cycle 1	100 mg PO BID Cycle 1: Day -2 to D28 Subsequent cycles: D1 to D28 (regardless of whether Q8W or Q12W cycles)	100 mg PO BID Continuously dosed starting Day -2 Cycle 1	100 mg PO BID Cycle 1: Day -2 to D28 Subsequent cycles: D1 to D28 (regardless of whether Q8W or Q12W cycles)	100 mg PO BID Continuously dosed starting Day -2 Cycle 1
Pomalidomide	4 mg PO QD on D1 to D21	4 mg PO QD on D1 to D21 QD D29 to 49 for Q8W and Q12W and QD D57 to 77 for Q12W only	4 mg PO QD on D1 to D21	4 mg PO QD on D1 to D21, QD D29 to 49 for Q8W and Q12W and QD D57 to 77 for Q12W only	4 mg PO QD on D1 to D21
Dexamethasone	40 mg or 20 mg[1] weekly, PO or IV	40 mg or 20 mg[1] weekly, PO or IV	40 mg or 20 mg[1] weekly, PO or IV	40 mg or 20 mg[1] weekly, PO or IV	40 mg or 20 mg[1] weekly, PO or IV

a. 1. Participants >75 years old or BMI <18.5 kg/m^2.

Overview of Study Design and Key Features

This figure illustrates the dosing schedules:

Figure 1a Dosing schedule of investigational product in Cycle 1

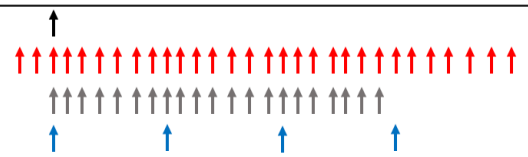
	Cycle 1: 28 days (Q4W or C1 Q4W from C2 Q8W) (Nirogacestat starts on Day -2, Belantamab mafodotin on D1)
28-Day Cycle	
Belantamab mafodotin Nirogacestat Pomalidomide Dexamethasone	

Figure 4b Dosing schedule of investigational product in Cycle 2 and beyond for Q8W dosing

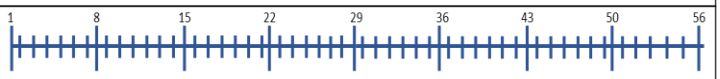
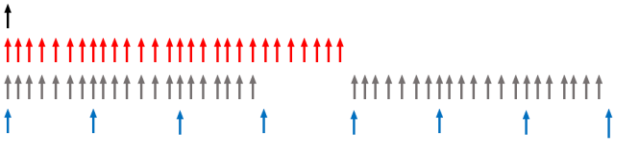
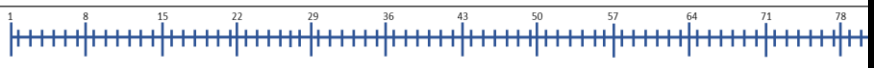
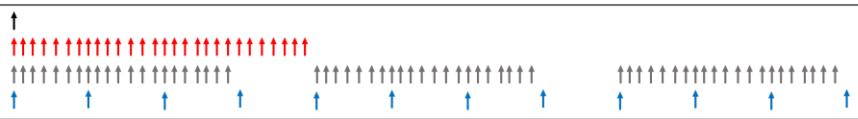
	Cycle 2 and beyond: 56 days (C1 Q4W from C2 Q8W only) (Nirogacestat for first 28 days only, Belantamab mafodotin on D1 of every 8-week cycle)
56-Day Cycle	
Belantamab mafodotin Nirogacestat Pomalidomide Dexamethasone	

Figure 4c Dosing schedule of investigational product in Cycle 2 and beyond for Q12W dosing

	Cycle 2 and beyond: 84 days (C1 Q4W from C2 Q12W only) (Nirogacestat for first 28 days only, Belantamab mafodotin on D1 of every 12-week cycle)
84-Day Cycle	
Belantamab mafodotin Nirogacestat Pomalidomide Dexamethasone	

Overview of Study Design and Key Features	
Design Features	• Refer to the 208887 Master SAP, 208887 Master Protocol and 208887 Sub-study 7 Protocol for the key design features of the study.
Study Intervention	• See Section 4.1.1 of 208887 Sub-study 7 Protocol for details of how the dose schedule for belantamab mafodotin from Cycle 2 onwards will be decided for Cohort 2A and Cohort 3A (Q8W or Q12W). This also provides detail on the order in which the cohorts will be opened. • For Cohort 1 (the starting dose level), belantamab mafodotin will be 0.5mg/kg every 4 weeks (Q4W). • For Cohort 2A, belantamab mafodotin will be 1.0 mg/kg Q4W for Cycle 1 then administered every 8 weeks (Q8W) or 12 weeks (Q12W) from Cycle 2 onwards. • For Cohort 2B, belantamab mafodotin will be 1.0mg/kg every 4 weeks (Q4W). • For Cohort 3A, belantamab mafodotin will be 1.4 mg/kg Q4W for Cycle 1 then administered every 8 weeks (Q8W) or 12 weeks (Q12W) from Cycle 2 onwards. • For Cohort 3B, belantamab mafodotin will be 1.4mg/kg every 4 weeks (Q4W). • For all cohorts, Cycle 1 will include a lead-in dose period for nirogacestat starting on Day -2. The DLT evaluation period starts from when all drugs of the combination treatment have been first administered (Day 1 to Day 28 inclusive). • For subsequent cycles, nirogacestat will be 100mg, taken twice a day from Day 1 to Day 28. For Cohort 2A and 3A, nirogacestat will then not be taken until Day 1 of the next cycle. • Pomalidomide will be 4mg daily from Day 1 to Day 21, inclusive, for Cycle 1 (all cohorts). For Cohort 1, 2B and 3B this will be repeated in subsequent cycles. • For subsequent cycles in Cohort 2A and 3A, pomalidomide will be taken daily from Day 1 to Day 21 inclusive, then from Day 29 to Day 49 inclusive. If belantamab mafodotin is Q12W, then pomalidomide will also be taken daily from Day 57 to Day 77 inclusive. • Dexamethasone will be 40mg (20mg for participants >75 years old or BMI <18.5 kg/m2) weekly, starting on Day 1 of Cycle 1. • Refer to the 208887 Sub-study 7 Protocol for further details of the study intervention.
Study Intervention Assignment	• In the DE phase, participants will be assigned to a dose level using a predefined algorithm. • In the CE phase, participants will be randomized to a sub-study, and within a sub-study to either the investigational or

Overview of Study Design and Key Features	
	belantamab mafodotin control arm. See Section 4.1.2 of the 208887 Master Protocol for further details.
Interim Analysis	• In the DE phase, an interim analysis of Overall Response Rate (ORR) will be performed after up to 15 participants treated at each potential Recommended Phase 2 Dose (RP2D) of the combination treatment have progressed/died, discontinued study treatment, or have had 3 efficacy assessments (1 baseline and 2 post-baseline assessments). • Two interim analyses focusing on ORR may be performed for futility evaluation for a particular dose level in the CE phase. The first interim analysis will be conducted when at least 10 CE phase 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 assessments or received at least two planned doses. • At each CE phase interim analysis, the observed ORR difference between the combination treatment and monotherapy groups will be assessed. The cohort may be discontinued if the posterior probability that ORR is greater with combination treatment than with monotherapy is <40%. See Section 9.4.2 of the 208887 Master Protocol for further details of the statistical methods to be used. • In addition to these interim futility analyses, for sub-study 7 a CE phase combination may be considered for termination for having convincing evidence of greater efficacy than monotherapy if the following conditions are met at the first interim analysis: o Observed ORR is ≥45% across all participants in the CE phase combination cohort and corresponding DE phase cohort who have at least 3 post-baseline efficacy assessments or have received at least 2 planned doses of belantamab mafodotin. o The posterior probability that the true rate of grade 3+ ocular toxicity events is lower with combination treatment than with monotherapy is >90%. This will be based on separate beta priors for the rate of grade 3+ events with combination therapy (using the rate observed in the corresponding DE phase cohort) and monotherapy (based on DREAMM-2; 42%, n = 97) and the rates observed in the CE phase combination cohort and all monotherapy CE phase participants.

Overview of Study Design and Key Features	
	• The definition of a qualifying grade 3+ ocular toxicity event will be finalised in an updated version of this SAP prior to initiation of the CE phase. • See Section 4.6 below for further details of the operating characteristics of these efficacy stopping criteria. • Additional interim analyses may also be conducted to aid decision making regarding dose identification, cohort expansion and safety monitoring; or for publication purposes.
Blinding	• This is an open label study. When both DE and CE phases are open, prospective participants will be prioritised to the DE phase or CE phase.

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 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

No multiplicity adjustment will be considered.

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/Exposed	• 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 participant actually received.	• Safety • Secondary efficacy analyses in DE phase
Intent-to-Treat	• All participants who were enrolled and randomised to study intervention. • This analysis set will be based on the treatment the participant was randomised to.	• Efficacy in CE phase
Modified Intent-to-Treatment (mITT)	• All randomised participants who received at least one dose of study intervention. • This analysis set will be based on the treatment participant 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 participant actually received.	• PK
Pharmacodynamic (PD)	• All participants in the Safety analysis set for whom a biomarker sample was obtained, was analysed and was found measurable. Non-quantifiable [NQ] values will be considered as non-missing values. • This analysis set will be based on the intervention the participant actually received.	• Biomarker

Analysis Set	Definition / Criteria	Analyses Evaluated
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 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.	• Safety in DE phase

4. STATISTICAL ANALYSES

4.1. General Considerations

Details about the primary and final analyses for this study, including the timing of these analyses, can be found in Section 4.1 in the 208887 Master SAP. This section in the Master SAP also describes the general methodology for this study.

4.1.1. Baseline Definition

Refer to the 208887 Master SAP, Sections 4.1.4 and Section 4.1.5, for details of baseline definitions, as well as details on the examination of covariates, other strata and subgroups.

The final list of subgroup-specific displays to be created for an analysis will be detailed in the associated Output and Programming Specification (OPS) document.

4.2. Primary Endpoint(s) Analyses

The primary analysis of a cohort will consist of a subset of the analyses outlined in the 208887 Master SAP. Refer to the List of Data Displays in the associated Output and Programming Specification (OPS) document for details.

See Section 4.2 of the 208887 Master SAP for details of the endpoints used for the primary analysis of DE phase and CE phase cohorts. 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.

4.2.1. Main analytical approach

Refer to Section 4.2.2.2 of the 208887 Master SAP and Section 9.4.2 of the 208887 Master Protocol for details of the main analytical approach to be used for the CE phase primary analysis.

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.

4.3.1. Key secondary endpoint

Refer to the 208887 Master SAP Section 4.3 for information on the analysis of the key secondary endpoint of Overall Response Rate (ORR) for the DE phase.

4.3.2. Supportive secondary endpoints

Section 4.3 in the 208887 Master SAP outlines the secondary efficacy endpoints for the DE and CE phases. This includes definitions of endpoints, the main analytical approaches, and summary measures being used. The secondary efficacy analyses will be based on the ITT analysis set for the CE phase and Safety analysis set for the DE phase, unless otherwise specified.

See Section 4.6 of the 208887 Master SAP for details of pharmacokinetic and pharmacodynamic analyses.

Refer to Section 4.4.2 below for information about analyses of adverse events (AEs), adverse events of special interest (AESIs) and findings from ophthalmic assessments in relation to belantamab mafodotin treatment.

4.4. Safety Analyses

Safety analyses will be based on the Safety analysis set, unless otherwise specified. Unless otherwise specified, ‘on-treatment’ adverse events will be reported. See Section 4.5 of the 208887 Master SAP for further details.

4.4.1. Extent of Exposure

Belantamab mafodotin

Refer to the 208887 Master SAP Section 4.5.1 for details on how extent of exposure is analysed for this study. The following table indicates the cycle length in days to be used in calculations for treatment exposure.

Cycle length term	Cycle length in days
Q4W	28 days
Q8W	56 days
Q12W	84 days

Dose intensity for belantamab mafodotin will be presented separately in units of mg/kg/4-weeks for Cycle 1 and in units of mg/kg/4-weeks, mg/kg/8-weeks or mg/kg/12-weeks for the period starting on day 29 (relative to date of first dose) as appropriate, depending on which cycle length is used for a cohort. Overall dose intensity for belantamab mafodotin will also be presented for the full duration a participant received treatment using units of mg/kg/cycle, i.e., an unweighted average of exposure per Q4W for Cycle 1 and exposure per Q4W/Q8W/Q12W for the subsequent dosing.

The number of separate doses of belantamab mafodotin received as a proportion of the total number of cycles expected will be derived for each participant and summarised (proportion of cycles received vs expected, %). The expected number of cycles will be calculated based on the duration between first dose and the latest of date of last dose administered / date of permanent discontinuation, assuming full adherence to the planned dose schedule.

An additional summary of dose modifications (dose interruptions/delays and dose reductions) for belantamab mafodotin will be produced by combining data from both Adverse Event and corneal event (KVA) CRF reports. This will present the number and percentage of participants with modifications due to an AE, due to a KVA-graded event and due to an AE or KVA-graded event.

Relative overall dose intensity (%) will be summarised for belantamab mafodotin. This will be calculated as the overall dose intensity for a participant as a proportion of the intended dose per cycle, as defined in the 208887 Sub-study 7 Protocol. For example, a participant in Cohort 3A with overall dose intensity of 1.1 mg/kg/cycle will have a relative dose intensity of 1.1/1.4 x 100 = 78.6%.

Nirogacestat

A summary of the number of cycles in which nirogacestat was administered (in any amount) will be presented. Duration of exposure to nirogacestat, calculated as the interval between first dose and date of last dose (if discontinued) / last reported dose received (if still on treatment), will be presented in days.

Overall dose intensity (mg/day) will be derived by first calculating overall dose received, based on the product of the reported dose and frequency of administration and the number of days of treatment reported for each cycle; the latter will be derived from the reported start and end date, assuming a constant daily dose without interruptions. This will then be divided by the total expected number of days of treatment based on the protocol-defined dosing schedule and the dates of first and most recent dose administered (date of stopping for participants who have permanently discontinued treatment). This will assume an incomplete last cycle if the date of last dose reported does not coincide with the planned last dosing date for nirogacestat in the last cycle.

Relative overall dose intensity (%) of nirogacestat will be calculated as the overall dose intensity for a participant as a proportion of the intended dose of 200mg/day.

A summary of dose modifications for nirogacestat (dose interruptions/delays and dose reductions) will present the number and percentage of participants with modification due to an AE, where nirogacestat was reported as a study treatment action was taken with.

Pomalidomide:

A summary of the number of cycles in which pomalidomide was administered (in any amount) will be presented. Duration of exposure to pomalidomide, calculated as the interval between first dose and date of last dose (if discontinued) / last reported dose received (if still on treatment), will be presented in days.

Overall dose intensity (mg/day) will be derived by first calculating overall dose received, based on reported daily dose received in mg per day, multiplied by the number of days treatment was taken; the latter will be derived from the reported start and end dates for each pomalidomide dosing period, assuming a constant daily dose without interruptions during each dosing period. This will then be divided by the total expected number of days of treatment based on the protocol-defined dosing schedule and the dates of first and last dose administered (date of stopping for participants who have permanently discontinued treatment). This will assume an incomplete last cycle if the date of last dose reported does not coincide with the planned last dosing date for pomalidomide in the last cycle.

Relative overall dose intensity (%) of pomalidomide will be calculated as the overall dose intensity for a participant as a proportion of the intended dose of 4mg/day.

A summary of dose modifications for pomalidomide (dose interruptions/delays and dose reductions) will present the number and percentage of participants with modification due to an AE, where pomalidomide was reported as a study treatment action was taken with.

Dexamethasone:

A summary of the number of cycles in which dexamethasone was administered (in any amount) will be presented. Duration of exposure to dexamethasone, calculated as the interval between first dose and date of last dose (if discontinued) / last reported dose received (if still on treatment), will be presented in days.

Overall dose intensity (mg/week) will be derived by dividing overall (cumulative) dose received in mg by the total expected duration of treatment in whole weeks: ceil[(date of last dose – date of first dose + 1) / 7].

Relative overall dose intensity (%) of dexamethasone will be calculated as the overall dose intensity for a participant as a proportion of the intended dose of 40mg/day (20mg/day for participants >75 years old or with BMI <18.5 kg/m^2 at baseline).

A summary of dose modifications for dexamethasone (dose interruptions/delays and dose reductions) will present the number and percentage of participants with modification due to an AE, where dexamethasone was reported as a study treatment action was taken with.

4.4.2. Adverse Events

Refer to the 208887 Master SAP Section 4.5.2 for details on analyses of AEs and adverse events of special interest (AESIs). Section 4.5.2.1.1 provides an overview of analyses of corneal events reported as AEs and graded using the KVA scale as part of ophthalmic assessments. Section 4.5.3.4 outlines analyses of data collected during ophthalmic assessments. AESIs for nirogacestat are no longer collected under 208887 Sub-study 7 Protocol Amendment 01 (10-Jul-2023).

Details of COVID-19 assessment and analysis of COVID-19 AEs are included in Sections 4.5.2.2 and 4.5.2.3 of the 208887 Master SAP.

Refer to the associated Output and Programming Specification (OPS) document for the full list of adverse event-related displays to be created for an analysis.

4.4.2.1. Laboratory Data

Refer to Section 4.5.2.7 of the 208887 Master SAP for more details of clinical laboratory analyses.

4.4.2.2. Vital Signs

Refer to Section 4.5.3 of the 208887 Master SAP for more details of analyses of vital signs data.

4.4.2.3. ECG

Refer to Section 4.5.3.2 of the 208887 Master SAP for more details of analyses of ECG results.

4.4.2.4. LVEF

Refer to Section 4.5.3.3 of the 208887 Master SAP for more details of analyses of LVEF assessments.

4.5. Other Analyses

Details of additional analyses that may be performed for sub-studies within 208887 are included in Section 4.6 of the 208887 Master SAP.

4.6. Interim Analyses

Refer to Section 4.7 of the 208887 Master SAP for details on interim analyses for both the DE and CE phase. Section 9.5 of the 208887 Sub-study 7 Protocol has further details of the CE phase interim analysis efficacy stopping criteria planned for this sub-study.

Table 20 and Table 21 of the 208887 Sub-study 7 Protocol (Amendment 01) show operating characteristics for the efficacy stopping criteria. These are based on calculations where the maximum number of participants in a DE phase cohort is 10. In 208887 Master Protocol Amendment 6 (11-Jul-2023) this was updated to a maximum of 15 participants. The tables below present updated calculations of the operating characteristics based on a total of 25 patients allocated to combination treatment from both the DE and CE phase at the efficacy stopping analysis. These calculations assume that all 25 patients have at least 3 post-baseline efficacy assessments or at least 2 planned doses, and that the proportion of participants with response recorded and the proportion with a grade 3+ ocular toxicity in the DE phase cohort for the combination treatment is the same as the proportion observed in the corresponding CE phase cohort. It is assumed that 10 patients are allocated to the monotherapy control arm in the CE phase. The probability of meeting the efficacy stopping criterion is calculated using the assumption that the dose level moves from the DE to CE phase regardless of the number of responders observed at the DE phase interim analysis. Results from additional simulations to estimate the joint probability of a dose level achieving ≥3 responders in the DE phase and then meeting the efficacy stopping criterion in the CE phase do not differ from those shown in Table 1.

Table 1 Operating Characteristics of Efficacy Stopping Criteria

True ORR	Probability of Meeting Efficacy Stopping Criterion
0.30	0.04
0.40	0.27
0.50	0.65
0.60	0.92
0.70	0.99
0.80	0.9999

Note: Results derived from binomial distribution where prob of event = true ORR and # trials = 25. Probability of meeting efficacy stopping criterion = Prob(≥12 events).

Table 2 Operating Characteristics of the Toxicity Criteria

Toxicity Rate		Probability of Meeting Stopping Criteria	
Monotherapy	**Combination Treatment**	**Probability of Meeting Toxicity Criterion**	**Probability of Meeting Both Toxicity and Efficacy Criteria***
0.42	0.42	0.09	0.09
0.42	0.30	0.46	0.46
0.42	0.20	0.86	0.85
0.42	0.15	0.96	0.95
0.42	0.10	0.995	0.99

* Assuming true ORR for combination in DE and CE phases = 0.70.

Note: Results based on 100,000 simulations of toxicity events for 15 participants in the DE phase and 10 participants in the CE phase for combination treatment and 10 participants in the CE phase for monotherapy. For each iteration, the DE phase event data was used to specify a beta prior for toxicity rate with combination treatment, which was combined with the CE phase event data to determine a beta posterior distribution. Similarly, the CE phase event data generated for the monotherapy group was combined with the pre-specified prior to determine a posterior distribution for the toxicity rate with monotherapy. For each simulation, the probability that the toxicity rate is lower with combination treatment was derived from the posterior distributions, and the proportion of

simulations where this was >0.90 used to identify the probability of meeting the ocular toxicity criterion. As there is no assumption of correlation between the response rate and the rate of toxicity events with combination treatment, the joint probability of meeting both the efficacy and toxicity criteria is Prob(meeting toxicity criterion) x Prob(meeting efficacy criterion). As an additional check, the results presented above were derived from simulations of the number of responders across the DE and CE phases in the combination treatment group. The probability of meeting both toxicity and efficacy criteria was determined using the proportion of simulations where the toxicity criterion was reached and there were ≥12 responders. Results from further simulations to estimate the joint probability of a dose level achieving ≥3 responders in the DE phase and then meeting a) the toxicity criterion and b) both the toxicity and efficacy stopping criteria in the CE phase do not differ from those shown in Table 2.

For additional insight into the probability of declaring success at the first interim analysis for the CE phase, the table below shows the results of simulations with different assumed true ORR with combination treatment.

Table 3 Operating Characteristics of Joint Toxicity Criteria and Efficacy Success Criteria at Interim Analysis

Toxicity Rate		Probability of Meeting Both Toxicity and Efficacy Criteria for Given ORR with Combination Treatment			
Monotherapy	**Combination Treatment**	**ORR = 0.30**	**ORR = 0.40**	**ORR = 0.50**	**ORR = 0.60**
0.42	0.42	0.004	0.02	0.06	0.08
0.42	0.3	0.02	0.12	0.30	0.42
0.42	0.2	0.04	0.23	0.56	0.79
0.42	0.15	0.04	0.26	0.63	0.89
0.42	0.1	0.04	0.26	0.65	0.92

4.7. Changes to Protocol Defined Analyses

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

5. SAMPLE SIZE DETERMINATION

In the DE Phase, 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 the combination therapy an additional 35 participants may be randomized to each arm 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. Eligible participants will be randomly allocated to an open sub-study CE Phase, and then randomized between combination treatment and monotherapy within that sub-study, with randomization to treatment group stratified by prior lines of therapy (3-4 vs >4). Unless a sub-study specific control group is used for the chosen CE cohort, patients randomized to monotherapy will enter the shared belantamab mafodotin monotherapy control arm, with data from this group used in CE analyses for all relevant sub-studies. Once 35 participants have been randomized to the shared belantamab mafodotin monotherapy arm, the randomization ratio for new sub-study CE Phases will change depending on the number of new CE cohorts and the timing of their entry to the study (refer to Table 14 in the 208887 Master Protocol).

6. SUPPORTING DOCUMENTATION

For supporting documentation for study 208887 please refer to Section 6 of the 208887 Master SAP.

For the DE phase of this sub-study, for calculations of study day first dose date will correspond to Cycle 1 Day 1, i.e., the date of first administration of belantamab mafodotin.

See Section 12.12 of the 208887 Sub-study 7 Protocol and Section 12.13 of the 208887 Master Protocol for information about trademarks.

7. REFERENCES

None.