Statistical Analysis Plan

Study ID: 208887 Sub Study 5

Official Title of Sub Study 5: 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 5 - Belantamab Mafodotin and Isatuximab 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 5 – Belantamab Mafodotin and Isatuximab in Combination
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Compound Number:	Belantamab Mafodotin (GSK2857916); Isatuximab (SAR650984)
Abbreviated Title:	Platform Study of Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination with Isatuximab 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 Jan 2024	208887 Master Protocol Amendment 6 (11-Jul-2023) 208887 Sub-study 5 Protocol Amendment 02 (10-Jul-2023) 208887 Master SAP v11 (09-Dec-2022)	Not Applicable	Original version

1. INTRODUCTION

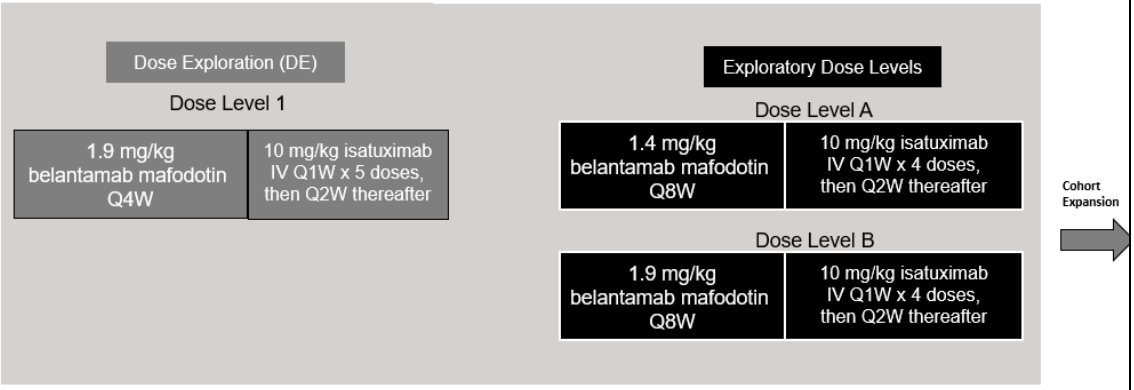
The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analyses to be included in the Clinical Study Report (CSR) for sub-study 5 of DREAMM-5 (study 208887). For more details about the statistical analysis plan for the overall study refer to the 208887 Master SAP.

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 5 is:  	
Design Features	• Refer to the 208887 Master SAP, 208887 Master Protocol and 208887 Sub-study 5 Protocol for the key design features of the study.
Study Intervention	• Dose Level 1 will be 1.9 mg/kg of belantamab mafodotin every 4 weeks (Q4W). Isatuximab will be 10 mg/kg weekly (Q1W) for the first 4 doses, followed by every 2 weeks (Q2W) thereafter, with the first dose in the Q2W schedule starting in week 5.

Overview of Study Design and Key Features	
	• A total of 2 additional dose levels may be evaluated: Dose Level A and Dose Level B. • Dose Level A will be 1.4mg/kg belantamab mafodotin every 8 weeks (Q8W). Isatuximab will be 10mg/kg Q1W for the first 4 doses, followed by Q2W thereafter, with the first dose in the Q2W schedule starting in week 5 as per Dose Level 1. • Dose Level B will be 1.9mg/kg belantamab mafodotin every 8 weeks (Q8W). Isatuximab will be 10mg/kg Q1W for the first 4 doses, followed by Q2W thereafter, with the first dose in the Q2W schedule starting in week 5 as per Dose Level 1. • The sponsor may decide not to evaluate all dose levels based on data external to this study. • For Dose Level 1 each cycle is Q4W. The DLT evaluation period for Cycle 1 will be 28 days. • For Dose Level A and Dose Level B each cycle is Q8W. If evaluated, the DLT evaluation period for Cycle 1 will be 56 days. • Refer to the 208887 Sub-study 5 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 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 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 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

Overview of Study Design and Key Features	
	the 208887 Master Protocol for further details of the statistical methods to be used. • 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 with 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	• Study Population

Analysis Set	Definition / Criteria	Analyses Evaluated
	Enrolled analysis set as they did not enter the study.	
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 the 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
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	• Safety in DE phase

Analysis Set	Definition / Criteria	Analyses Evaluated
	meeting the definition of a DLT are considered to be DLT evaluable.	

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, Section 4.1.4 and Section 4.1.5, for details of baseline definitions, as well as details on the examination of covariates and 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 4.4.2.2 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

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 for belantamab mafodotin (dose interruptions/delays and dose reductions) 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 5 Protocol. For example, a participant in Dose Level 1 with overall dose intensity of 1.5 mg/kg/cycle will have a relative dose intensity of 1.5/1.9 x 100 = 78.9%.

Isatuximab

A summary of the number of cycles in which Isatuximab was administered (in any amount) will be presented. Duration of exposure to Isatuximab, 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 weeks.

Summaries of dose reductions and dose delays/interruptions will be provided for Isatuximab, based on information provided in the Study Treatment form. These will show the number of participants affected, the number of separate treatment actions reported and the reason provided. For dose delays/interruptions, delay duration will be summarised, as outlined in the 208887 Master SAP; expected start date of dose will be determined from the actual start date of the previous dose + 7 days if the previous dose was ≤ 28 days from first dose date, and actual start date of previous dose + 14 days if the previous dose was ≥ 29 days from first dose date.

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

Dose intensity for Isatuximab will be presented in units of mg/kg/week for the 4-week period where participants are to be dosed Q1W. It will be calculated using overall (cumulative) dose received (in mg/kg) during the first 28 days from first dose, divided by the expected duration of treatment during this period: ceil[(min(date of last dose, day 28 date) – date of first dose + 1) / 7].

Dose intensity for Isatuximab during the subsequent period where doses are administered Q2W will be summarised separately, using units of mg/kg/2-weeks. This will be calculated using overall dose received from day 29 (relative to date of first dose), divided by the expected duration of treatment during this period: ceil[(date of last dose – day 29 date + 1) / 14]

Overall dose intensity for Isatuximab will also be presented for the full duration a participant received treatment using units of mg/kg/dose interval, i.e. an unweighted average of exposure per week during the Q4W period and exposure per 2-weeks during the Q2W period.

Relative overall dose intensity (%) of Isatuximab will be calculated as the overall dose intensity for a participant as a proportion of the intended dose of 10 mg/kg/dose interval.

An alternative measure of dose intensity for Isatuximab based on the specific cycle length for each dose level will also be presented (using units of mg/kg/cycle). This will be presented separately for the expected duration of Cycle 1 and for the expected duration of Cycle 2 onwards, depending on dose level. For Cycle 1, this will be calculated using overall dose received from day 1 to day 28 (for Dose Level 1) or day 56 (for Dose Level A and Dose Level B). For Cycle 2 onwards, this will be calculated as follows:

- Dose Level 1: overall dose received from day 29 (relative to date of first dose), divided by: ceil[(date of last dose – day 29 date + 1) / 28]
- Dose Level A and B: overall dose received from day 57 (relative to date of first dose), divided by ceil[(date of last dose – day 57 date + 1) / 56]

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 Isatuximab are presented in Section 8.3.10 of the 208887 Sub-study 5 Protocol.

Details of COVID-19 assessment and analysis of COVID-19 AEs are including 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 Master SAP for details on interim analyses for both the DE and CE phase.

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, participants 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.

See Section 12.12 of the 208887 Sub-study 5 Protocol and Section 12.13 of the 208887 Master Protocol for information about trademarks.

7. REFERENCES

None.