Statistical Analysis Plan

Study ID: 208887 Sub Study 4

Official Title of Sub Study 4: 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 4 - Belantamab Mafodotin and Dostarlimab (GSK4057190) in Combination

NCT ID of Sub Study 4: NCT06655818

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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 4 – Belantamab Mafodotin and Dostarlimab (GSK4057190) Combination

Study Number: *208887 Sub-study 4*

Compound Number: *GSK2857916; Dostarlimab* (GSK4057190)*;*

Abbreviated Title: Platform Sub-study of Belantamab Mafodotin (GSK2857916) in Combination with Dostarlimab (GSK4057190) in Participants with RRMM

Acronym: DREAMM-5 Sub-study 4

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	**21** Sep 2022	PA5 (21-JAN-2022)	Not Applicable	Original version

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 200887 sub-study 4. For more details about the statistical analysis and plan for the overall study refer to the Master SAP. This sub-study was terminated early during the Dose Escalation (DE) phase; therefore, this sub-study SAP will focus only on the DE phase.

1.1. Changes to Protocol Defined Analyses

Effective October 2021, following an internal prioritization discussion, GSK made the decision to close this sub-study during the DE phase. As a result, all analyses corresponding to the CE phase, as well as the analysis of exploratory endpoints will not be performed.

Changes from the originally planned statistical analysis specified in the protocol are detailed in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
• Exploratory analyses ○ Biomarker analysis • Interim analysis for DE phase • All analysis related to CE phase	The listed protocol defined analyses will not be included in this sub-study.	This sub-study was terminated during DE phase due to observed lack of efficacy.

1.2. Objectives, Estimands and Endpoints

The primary and secondary objectives, along with the corresponding endpoints for DE phase are listed in Table 2

Table 2 Dose Exploration (DE)

Objectives	Endpoints
Primary	
To determine the safety and tolerability of belantamab mafodotin in combination with Dostarlimab and to establish the recommended Phase 2 dose for the 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

Objectives	Endpoints
Key Secondary	
To evaluate the clinical measures of efficacy of belantamab mafodotin and Dostarlimab in participants with RRMM	• Clinical activity measured as Overall Response Rate (ORR) according to the International Myeloma Working Group (IMWG) Response Criteria (Kumar , et al., 2016)
Secondary	
To further evaluate the clinical measures of efficacy of belantamab mafodotin and Dostarlimab 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 Dostarlimab in participants with RRMM	• Belantamab mafodotin observed concentration
To describe the exposure of Dostarlimab when administered in combination with belantamab mafodotin.	• Combination of belantamab mafodotin with Dostarlimab treatment's observed concentration.
To assess anti-drug antibodies (ADAs) against belantamab mafodotin and against combination treatments (biologics) that are administered by IV infusion.	• Incidence and titers of ADAs against belantamab mafodotin and its combination with Dostarlimab, when measured.
To further determine the safety and tolerability of belantamab mafodotin in combination with Dostarlimab	• AEs of special interest for belantamab mafodotin • AEs of special interest for belantamab mafodotin in combination with Dostarlimab • Ocular findings on ophthalmic exam

1.3. Study Design

<table>
<tr><th colspan="2">Overview of Study Design and Key Features</th></tr>
<tr><td colspan="2">Please refer to the 208887 Master SAP for overall Study Design for the study.</td></tr>
<tr><td>Design Features</td><td>• Refer to the 208887 Master SAP for the key design features for the study</td></tr>
<tr><td>Study intervention</td><td>• The Starting Dose (SD) for belantamab mafodotin in study 208887 will be 1.9 mg/kg Q3W in combination with other anti-cancer treatments but may vary by sub-study.
• Dostarlimab is to be given at least one hour following completion of belantamab mafodotin infusion.

<table>
<tr><th>Dose Level</th><th>Belantamab Mafodotin mg/kg IV Q 3 weeks</th><th>Dostarlimab mg IV Q 3 weeks</th><th>Dostarlimab mg IV Q 6 weeks</th></tr>
<tr><td>1</td><td>1.9 mg/kg</td><td>500 mg, cycles 1 – 4</td><td>1000 mg, cycle 5 and every odd cycle thereafter</td></tr>
<tr><td>2</td><td>2.5 mg/kg</td><td>500 mg, cycles 1 – 4</td><td>1000 mg, cycle 5 and every odd cycle thereafter</td></tr>
</table>

• Dostarlimab will be administered as a 30-minute IV infusion at the prescribed flat dosing</td></tr>
<tr><td>Time & Events</td><td>• Refer to Section 1.3: Schedule of Activities (SoA) in Sub-study 4 modular protocol</td></tr>
<tr><td>Treatment Assignment</td><td>• In DE phase, treatments will be assigned to participants with predefined algorithm.</td></tr>
<tr><td>Interim Analysis</td><td>• The Interim Analysis (IA) planned in the DE will not be carried out.</td></tr>
<tr><td>Blinding</td><td>• This is an open label study.
• In DE phase, participants will be assigned to available treatment slots by a predetermined algorithmic approach.</td></tr>
</table>

2. STATISTICAL HYPOTHESES

In the DE Phase, the primary objective is to determine the safety and tolerability of belantamab mafodotin and dostarlimab. No formal statistical hypothesis will be tested.

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

Refer to the 208887 Master SAP Section 3 for the complete list of analysis sets for this study.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. Final Analysis

GSK decided that no further enrolment will take place on this sub-study. As a result, all analyses corresponding to the CE phase, as well as the exploratory endpoints for both the DE and CE phase will not be performed.

The final analyses will be performed after all required database cleaning activities have been completed on available DE data and final database release (DBR) and database freeze (DBF) has been declared by Data Management.

4.1.2. Study Treatment & Sub-group Display Descriptors

Phase	Description
DE	1.9mg/kg GSK916 + 500mg Q3W DOSTAR
	1.9mg/kg GSK916 + 1000mg Q6W DOSTAR[1]
	2.5mg/kg GSK916 + 500mg Q3W DOSTAR[1]
	2.5mg/kg GSK916 + 1000mg Q6W DOSTAR[1]

[1] Note that this dose level was not used due to early termination

4.1.3. Baseline Definition

Refer to the Master SAP Section 4.1.4 for details on baseline definitions.

4.2. Primary Endpoint(s) Analyses

Primary analysis for the DE phase involves summaries of the number and percentages of participants with DLTs and AEs. Both DLTs and AEs will be summarised and listed. All analyses for the DE phase will be based on the Safety population, unless otherwise specified.

4.3. Secondary Endpoint(s) Analyses

Due to this sub-study being terminated early during the DE phase, there will be no primary efficacy analysis for the CE phase as these data were not collected.

4.3.1. Key Secondary Endpoint

For the definition of the key secondary endpoint, ORR, along with the derivation of confirmed response table please refer to Section 4.2.2.1 of the MSAP.

A summary of investigator assessed best response with confirmation will be produced, using the Safety population.

4.3.2. Secondary Endpoints

Best Overall Response rates (i.e Partial Response (PR) rate, Very Good Partial Response (VGPR) rate, Complete Response (CR) rate and Stringent Complete Response (sCR) rate) will be reported within the summary table described in Section 4.3.1.

The derivation of confirmed response table in Section 4.2.2.1 of the MSAP, will be used confirm the secondary endpoints.

BOR and corresponding response rates will be summarized using descriptive statistics and listed. The corresponding 95% exact CI 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.

Other secondary endpoints, PK, ADAs, and AESIs can be found in the sections below.

4.4. Exploratory Endpoint Analyses

Analysis of exploratory endpoints will not be performed for neither the DE nor CE phase, due to the early termination of the sub-study.

4.5. Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified. Unless otherwise specified, on-treatment AE's will be reported.

4.5.1. Extent of Exposure

Refer to the Master SAP Section 4.5.1 for details on the extent of exposure for this study. The cycle length term Q3W is equivalent to a cycle length in days of 21 days, to be used in calculations for treatment exposure.

Extent of exposure to belantamab mafodotin monotherapy and combination therapy will be summarized.

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

Dose reductions will be summarised by number of reduction and reasons for reductions. Dose delays/interruptions will be summarised by number of delays, and delay duration (days). All the dose reductions and dose delays/interruptions will be listed.

4.5.2. Adverse Events

Summaries of all AEs, all drug-related AEs, common non-SAEs, SAEs, and AEs leading to permanent discontinuation of study treatment will be reported by system organ class, preferred term and maximum grade.

Listings of all AEs, fatal SAEs, non-fatal SAEs, reasons for considering as a SAE and AEs leading to permanent discontinuation will be reported.

Dose limiting toxicities (DLTs) will also be summarised and listed.

4.5.2.1. Adverse Events of Special Interest

Refer to the Master SAP Section 4.5.2.1 for details on AESI. The list of terms and reporting requirements for GSK AESI, and the known list of AESIs for GSK'916 can be found in Section 8.3.10 of the Sub-Study 4 protocol.

A summary of corneal events by grade will be provided using the GSK scale for all those participants who has an event under protocol amendment 1; using CTCAE scale for all those participants who had an event under protocol amendment 2 or 3, and using KVA scale for those patients who had an event under protocol amendment 4. Corresponding listings for ocular events will also be reported, along with a listing of visual acuity by grade.

The grading scales for the GSK and KVA scale for corneal events can be found in Table 6 and Table 7 in the MSAP respectively. For guidance of grading based on changes in visual acuity refer to Table 8 in the MSAP.

4.5.2.2. Inmune-related Adverse Events (irAEs)

irAEs will be graded by the investigator according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5. irAE will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary, version 25.0) and grouped by SOC.

A summary of all immune-related adverse events by system organ class, preferred term and maximum grade, and a listing containing all immune-related adverse events will be produced.

4.5.2.3. 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. DLTs will be reported according to the DLT evaluable population in Section 3of the MSAP.

The incidence 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,

and COVID-19 AEs by severity, will be obtained from standard AE and SAE summaries and listings.

4.5.2.4. Deaths and Serious Adverse Events

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

All SAEs 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. 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.

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 combination (belantamab mafodotin monotherapy and GSK'190 (dostarlimab) + belantamab mafodotin) as collected in descending order of total incidence by SOC and PT and separate supportive listings will be generated with participant level details for those participants:

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

4.5.2.6. Pregnancies

Please refer to Section 4.5.2.6 of the MSAP

4.5.2.7. Clinical Laboratory Analysis

Refer to Section 4.5.2.7 of the MSAP for more details on the clinical laboratory analysis including the analysis of liver function tests.

Summaries of chemistry changes from baseline, haematology changes from baseline, and haematology results by maximum grade increase post-baseline relative to baseline will be produced. Supporting listings of laboratory data and urinalysis data for participants with any value of potential clinical importance will be provided.

4.5.3. Other Safety Assessments

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 Standard. The details of the planned displays are presented in the OPS document. For more detail please refer to Section 4.5.3 of the Master SAP.

4.6. Other Analyses

Due to the early termination of this sub-study, no POPPK, exploratory biomarker, or PK/PD analyses will be conducted. For this sub-study there will also be no health-related quality of life analysis or immunogenicity analysis due to early termination.

4.6.1. Pharmacokinetic Analysis

PK samples will be collected for belantamab mafodotin and/or dostarlimab in Cycle 1 as well as later cycles as indicated in the SoA tables of protocol. PK analyses will be done for each analyte measured in the DE phase, as data permit. For more details on these analyses refer to the Master SAP Section 4.6.1.

4.6.2. Immunogenicity Analysis

Refer to Section 4.6.5 of the Master SAP for more details on the analysis of incidence and titers of ADAs against belantamab mafodotin and its combination with dostarlimab, when measured.

4.7. Interim Analyses

An interim analysis for ORR would have been performed at the end of the DE phase, after 10 participants had been treated. However, due to the early termination of this sub-study neither of the 2 dose levels explored in this sub-study reached the 10-participant goal. Hence, no interim analysis will be performed.

5. SAMPLE SIZE DETERMINATION

In the DE phase, approximately up to 10 participants were to be assigned to the combination dose level. However, the study was terminated early due to lack of efficacy; therefore only 4 participants were enrolled onto dose 1.

6. SUPPORTING DOCUMENTATION

For more supporting documentation for this overall study please refer to Section 6 of the Master SAP for more details.

6.1. Appendix 1 Study Population Analyses

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

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in the OPS document.

6.1.1. Participant Disposition

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

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. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF.

In addition, a summary table and listing identifying reasons for screening failures will be presented based on the Screened Population.

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. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF. A listing of study treatment discontinuation will be generated. The listing will include last dose date and reasons for study treatment discontinuation as well as relatedness to the study treatment.

Screen failures will be summarized and listed. 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.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics e.g., age, race, ethnicity, sex, baseline height, and baseline body weight will be summarized and listed for Safety population in DE.

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

6.1.3. Protocol Deviations

Important protocol deviations will be listed and summarised. Important protocol deviations will be based on Safety Population in DE 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 [8/23/2019., V1.0]. 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. 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’ of the MSAP.

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7. REFERENCES

Kumar S., Paiva, B., Anderson, K. C., Durie, B., Landgren, O., Moreau, P., ... & Avet-Loiseau, H. (2016). International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. The lancet oncology, 17(8), e328-e346.