Statistical Analysis Plan

Study ID: 208887 Sub-study 1

Official Title of Sub-Study: Platform Sub-study of Belantamab Mafodotin (GSK2857916) in Combination with aOX40 (GSK3174998) in Participants with RRMM

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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 1 – Belantamab Mafodotin and aOX40 (GSK3174998) in Combination

Study Number: *208887 Sub-study 1*

Compound Number: *GSK2857916; GSK3174998*

Abbreviated Title: Platform Sub-study of Belantamab Mafodotin (GSK2857916) in Combination with aOX40 (GSK3174998) in Participants with RRMM

Acronym: DREAMM-5 Sub-study 1

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

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TABLE OF CONTENTS

PAGE

Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP		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 208887 sub-study 1. For more details about the statistical analysis and plan for the overall study refer to the Master SAP. This sub-study was terminated early in the Dose Exploration (DE) phase; therefore, this sub-study SAP will focus only on this DE phase.

1.1. Changes to Protocol Defined Analyses

Effective October 2020, GSK made the decision to close this sub-study at the DE phase. The data demonstrate that the participants in the aOX40 sub-study had negligible benefit from the combination, which could not be explained by known factors. As a result, all analyses corresponding to the Cohort Expansion (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 Dose Exploration 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 aOX40 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
Key Secondary	

Objectives	Endpoints
To evaluate the clinical measures of efficacy of belantamab mafodotin and aOX40 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 aOX40 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 aOX40 in participants with RRMM	• Belantamab mafodotin observed concentration
To describe the exposure of aOX40 when administered in combination with belantamab mafodotin.	• Combination of belantamab mafodotin with aOX40 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 aOX40, when measured.
To further determine the safety and tolerability of belantamab mafodotin in combination with aOX40	• AEs of special interest for belantamab mafodotin • AEs of special interest for belantamab mafodotin in combination with aOX40 • 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 feature for the study</td></tr>
<tr><td>Dosing</td><td>• The Starting Dose (SD) for belantamab mafodotin in study 208887 will be 1.9 mg/kg Q3W in combination with aOX40
• GSK'998 (aOX40) will initially be administered at a flat dose of 8 mg IV Q3W on Day 1 of each 21-day cycle after the infusion with belantamab mafodotin.

<table><tr><th>Dose level</th><th>Belantamab mafodotin dose</th><th>GSK'998 (aOX40) dose</th></tr><tr><td>1 (starting dose level)</td><td>1.9 mg/kg</td><td>8 mg</td></tr><tr><td>2</td><td>2.5 mg/kg</td><td>8 mg</td></tr><tr><td>3</td><td>2.5 mg/kg</td><td>24 mg</td></tr></table>
Note: Dose level 3 was not initiated in this sub-study due to the study being terminated early in the DE phase.</td></tr>
<tr><td>Time & Events</td><td>• Refer to Section 1.3: Schedule of Activities (SoA) in Sub-study 1 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 aOX40. 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. General Methodology

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

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

4.1.2.1. Study Treatment & Sub-group Display Descriptors

Phase	Description
DE	1.9mg/kg GSK916+8mg aOX40
	2.5mg/kg GSK916+8mg aOX40
	2.5mg/kg GSK916+24mg aOX40[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.

4.1.4. Examination of Covariates, Other Strata and Subgroups

As this sub-study was terminated during the DE phase, covariates, other strata, and subgroups are not applicable as these would have been used in the CE phase only.

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 (BOR) 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 Endpoints Analyses

Analysis of exploratory endpoints will be performed for neither the DE nor the CE phase, due to the early termination of aOX40.

4.5. Safety Analyses

The safety analyses will be based on the Safety population, unless otherwise specified. Similarly, 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. For the combination therapy, extent of exposure will be summarized.

A 'by participant' summary 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

The list of terms and reporting requirements for GSK AESI, and the known list of AESIs for GSK'998 can be found in section 8.3.10 of the Sub-Study 1 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, 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.

4.5.2.1.1. 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.

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

4.5.2.3. Deaths and Serious Adverse Events

Refer to Section 4.5.2.4 of the MSAP.

4.5.2.4. 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'998 (aOX40) + 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

4.5.2.5. Pregnancies

Refer to Section 4.5.2.6 of the Master SAP.

4.5.2.6. 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, hematology changes from baseline, and hematology/chemistry 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

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

4.6.1. Pharmacokinetic Analysis

PK samples will be collected for belantamab mafodotin and/or aOX40 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 aOX40, when measured.

4.7. Interim Analyses

The planned interim analysis can be found in more detail in Section 4.7 of the Master SAP.

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 will be assigned to the combination dose level. However, the study was terminated early due to lack of efficacy; therefore only 6 participants were enrolled onto dose 1 and 3 participants were enrolled onto dose 2.

6. SUPPORTING DOCUMENTATION

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

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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.