Statistical Analysis Plan

Study ID: 208887 Sub Study 3

Official Title of Sub Study 3: 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 3 - Belantamab Mafodotin and Nirogacestat 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 3 – Belantamab Mafodotin and Nirogacestat in Combination

Study Number: *208887 Sub-study 3*

Compound Number: *GSK2857916; Nirogacestat*

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

Acronym: DREAMM-5 Sub-Study 3

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP		PA4 (14-Dec-2020)	Not Applicable	Original version
SAP 2		PA5 (21-Jan-2022)	Updated the Design Features table and Section 4.7 on interim analysis	Match the Interim Analysis specs in CE phase according to PA5
3.0		PA5 (21-Jan-2022)	Section 4.2: Added detail on analyses specified for primary analysis. Across document: updates to improve clarity and readability.	Clarifying which analyses are to be performed at primary analysis.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 208887 sub-study 3. For more details about the statistical analysis and plan for the overall study refer to the Master SAP.

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

1.1. Objectives, Estimands and Endpoints

The primary, secondary, and exploratory objectives, along with the corresponding endpoints for both Dose Exploration (DE) and for Cohort Expansion (CE) are identical to those listed in the 208887 Master SAP Section 1.1.

1.2. Study Design

Overview of Study Design and Key Features	
BID = twice daily; CE = Cohort Expansion; DE= Dose Escalation Decision; Q3W = every 3 weeks; Q6W = every 6 weeks; QD = once daily.	
Design Features	• Refer to the 208887 Master SAP for the key design features for the study
Dosing	• The Starting Dose (SD) for belantamab mafodotin in study 208887 will be 0.95 mg/kg Q3W in combination with nirogacestat. • Dose Exploration (DE) in Sub-study 3 will involve 4 potential dosing cohorts of belantamab mafodotin in combination with nirogacestat (Cohorts 1-4). • Dose escalation between Cohorts 1 to 4 will depend on data observed in the preceding cohort. • Cohort 1 will explore 0.95 mg/kg of belantamab mafodotin once every 3 weeks (Q3W) in combination with nirogacestat twice a day (BID) at 100 mg, once daily (QD) at 100 mg, or QD at 50 mg, where the starting dose combination will be 0.95 mg/kg belantamab mafodotin Q3W with 100 mg BID nirogacestat. • Cohort 2 is divided into 4 sub-cohorts with staggered initiation exploring 1.9 mg/kg belantamab mafodotin Q3W or once every 6 weeks (Q6W) in combination with nirogacestat 100 mg BID or QD dose selected from Cohort 1 (50 or 100 mg.). • Cohort 3 will test 1 mg/kg belantamab mafodotin (Cycle 1 Q4W then Q8W from Cycle 2 onwards)) in combination with the selected nirogacestat 100 mg (BID). • Cohort 4 will test 1.4 mg/kg belantamab mafodotin (Cycle 1 Q4W then Q8W from Cycle 2 onwards) in combination with nirogacestat 100 mg (BID) and/or 1.4 mg/kg belantamab mafodotin (Q4W every cycle) in combination with nirogacestat 100 mg (BID).

Dose Level	Belantamab mafodotin Dose and Schedule	Nirogacestat Dose and Schedule
-2	0.95 mg/kg Q3W	50 mg QD
-1	0.95 mg/kg Q3W	100 mg QD

Overview of Study Design and Key Features	
	<table><tr><td>1</td><td>0.95 mg/kg Q3W</td><td>100 mg BID</td></tr><tr><td>2A</td><td>1.9mg/kg Q3W</td><td>100mg BID</td></tr><tr><td>2B</td><td>1.9 mg/kg Q3W</td><td>50 or 100mg QD</td></tr><tr><td>2C</td><td>1.9 mg/kg Q6W</td><td>100mg BID</td></tr><tr><td>2D</td><td>1.9 mg/kg Q6W</td><td>50 or 100mg QD</td></tr><tr><td>3</td><td>1.0 mg/kg Q4W then Q8W from Cycle 2 onwards</td><td>Selected nirogacestat 100 mg (BID)</td></tr><tr><td>4</td><td>1.4 mg/kg (Cycle 1 Q4W then Q8W from Cycle 2 onwards **and/or** Q4W every cycle)</td><td>100 mg (BID) in both cases</td></tr></table> • Four CE arms will be opened, 3 contingent on DE findings. CE1, CE3 and CE4 will be selected from Cohort 1, Cohort 3 and Cohort 4, respectively.
Time & Events	• [Refer to Section 1.3: Schedule of Activities (SoA) in Sub-study 3 modular protocol]
Treatment Assignment	• In DE phase, treatments will be assigned to participants with predefined algorithm. • In CE phase, participants will be randomized to a sub-study, and within a sub-study to either the investigational or belantamab mafodotin control arm
Interim Analysis	• An interim analysis for ORR will be performed in the DE phase after up to 10 participants treated with the combination dose have either progressed/died, discontinued study intervention, or have had three efficacy assessments (1 baseline and 2 post-baseline assessments). • Two interim analyses may be performed for futility evaluation 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, have had 4 efficacy assessments (1 baseline and 3 post-baseline assessments), or at least two planned doses. Additional interim analysis 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 are open, participants will be prioritized to the DE phase or CE phase. In DE, participants will be assigned to available treatment slots by a predetermined algorithmic approach. In CE, participants will be randomized to the open sub-studies for which they meet the eligibility criteria. A shared belantamab mafodotin control arm is included in each sub-study in CE. • Stratification factors include the number of prior lines of therapy. Randomisation in CE is designed to account for any selection bias anticipated from treatment administration.

Overview of Study Design and Key Features	
	• Additionally, nirogacestat may have different administration method and day of administration.

2. STATISTICAL HYPOTHESES

Success Criteria for CE1 – This will be based on:

- The difference in ORR between the combination and monotherapy arms will be tested using the normal approximation of the binomial proportion. On the RP2D combination arm we would expect at least as good efficacy as the monotherapy arm. Therefore, the hypothesis to be tested is H0: $p1 - p0 \leq 0$ vs H1: $p1 - p0 > 0$, where p1 is the response rate in the combination arm and p0 is the response rate in the control monotherapy arm. Success would be achieved if the lower bound of the 97.5% confidence interval exceeds the null value of 0.

and

- The safety evaluation for the low dose combination treatment will be based on the totality of the data. A comparison of corneal toxicity AEs will be reported. The rate of belantamab mafodotin-related ≥ Grade 2 corneal toxicity on the combination arm will be compared to that observed for the belantamab mafodotin monotherapy dose in the common control arm using a two-sample proportion test. Data from DREAMM-2 showed 71% corneal events on 2.5 mg/kg of belantamab mafodotin monotherapy (n=97). Therefore, based on these data, on the combination arm we would expect at least a 10% reduction in corneal events compared with monotherapy alone. The hypothesis for testing two proportions using the Z-test with unpooled variance will be H0: $p1 - p0 \geq 0$ vs H1: $p1 - p0 < 0$, where p1 denotes the proportion of corneal events on the combination arm and p0 denotes the proportion of corneal events on the monotherapy control arm. The power to detect a reduction in events from 1% to 31% ranges from 12% up to 93% at a significance level of 0.10 (Section 9.1 in Sub-study 3 modular protocol). As part of a sensitivity analysis in CE1, the two-sample proportion test will also be performed using pooled data from DE cohort 1 and CE.

- **Success Criteria for CE2, CE3 and CE4:** As per the master protocol, this is statistically defined as the posterior probability of ORR in the experimental combination arm selected as the RP2D being higher than the ORR in the monotherapy common control arm being greater than 90%. The common control arm is defined in the 208887 MP. For CE2, the combination arm will be the dose combination with 1.9 mg/kg belantamab mafodotin from DE phase. For CE3, the combination arm will the dose combination with 1.0 mg/kg belantamab mafodotin. For CE4, the combination arm will be the dose combination with 1.4 mg/kg belantamab mafodotin.

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

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 Master SAP. This section in the Master SAP also features the general methodology for this study.

4.2. Primary Analysis

The primary analysis of a cohort (as defined in Section 1.2 of this sub-study SAP) will consist of a subset of the analyses outlined in the Master SAP. Refer to the List of Data Displays in the associated OPS document for details.

4.2.1. Study Treatment & Sub-group Display Descriptors

Phase	Description
DE	0.95mg/kg Q3W GSK916 + 50mg QD NIRO
	0.95mg/kg Q3W GSK916 + 100mg QD NIRO
	0.95mg/kg Q3W GSK916 + 100mg BID NIRO
	1.9mg/kg Q3W GSK916 + 100mg BID NIRO
	1.9mg/kg Q3W GSK916 + 50 or 100mg QD NIRO
	1.9mg/kg Q6W GSK916 + 100mg BID NIRO
	1.9mg/kg Q6W GSK916 +50 or 100mg QD NIRO
	1.0mg/kg C1 Q4W and Q8W from C2 onwards GSK916 + 100mg BID NIRO
	1.4mg/kg C1 Q4W and Q8W from C2 onwards GSK916 + 100mg BID NIRO
	1.4mg/kg Q4W GSK916 + 100mg BID NIRO
CE	0.95 mg/kg Q3W GSK916 + 100mg BID or 50mg QD or 100 mg QD NIRO
	1.9 mg/kg Q3W or Q6W GSK916 + 100mg BID or 50mg QD or 100mg QD NIRO

	1.0mg/kg Q4W in C1 and Q8W from C2 onwards GSK916 + 100mg BID NIRO
	1.4mg/kg Q4W in C1 and Q8W from C2 onwards GSK916 + 100mg BID NIRO and/or 1.4mg/kg Q4W GSK916 + 100mg BID NIRO

4.2.2. Baseline Definition

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

4.3. Primary Endpoint(s) Analyses

Refer to the Master SAP Section 4.2 for information on primary endpoint analysis for the CE phase including definition of endpoints, the main analytical approach, and the summary measures. The primary efficacy analyses will be based on the ITT population for the CE phase, unless otherwise specified.

4.4. Secondary Endpoint(s) Analyses

Refer to the Master SAP Section 4.3 for information for the key secondary endpoint analysis for the DE phase and 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 population for the CE phase and Safety population for the DE phase, unless otherwise specified.

4.5. Exploratory Endpoints Analyses

Refer to the Master SAP Section 4.4 for definitions of the exploratory efficacy endpoints for the DE phase and CE phase.

4.6. 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.

4.6.1. Extent of Exposure

Refer to the Master SAP Section 4.5.1 for details on the extent of exposure 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
Q3W	21 days

Q4W	28 days
Q6W	42 days
Q8W	56 days

4.6.2. Adverse Events

Refer to the Master SAP Section 4.5.2 for details on analysis of adverse events.

4.6.2.1. Adverse Events of Special Interest

Refer to Section 4.5.2.1 of the Master SAP for general details of the reporting of adverse events of special interest.

4.6.2.1.1. Nirogacestat

For Nirogacestat, AESIs defined in section 8.3.10 of the modular protocol for sub-study 3 will be reported. Data emerging from other ongoing studies may highlight additional AESIs and therefore a full list at the time of analysis will be included in the reference data files.

4.6.2.2. COVID-19 Assessment and COVID-19 AEs

Refer to Section 4.5.2.2 of the master SAP for information about COVID-19 Assessment and COVID-19 adverse events.

4.6.2.3. Impact of COVID-19 Pandemic on Safety Results

Tables, as detailed in the List of Data Displays in the OPS document, showing the incidence rates for events occurring before or after the start of the COVID-19 pandemic will be produced. The phases (before and after the start of the COVID-19 pandemic) are defined in Section 6.2.2.3 of the Master SAP.

4.6.2.4. Deaths and Serious Adverse Events

Refer to Section 4.5.2.4 of the Master SAP.

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

The following categories of AEs will be summarized separately by treatment arm (belantamab mafodotin monotherapy and Nirogacestat + belantamab Mafodotin). 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

4.6.2.6. Pregnancies

Refer to Section 4.5.2.6 in the Master SAP

4.6.2.7. Clinical Laboratory Analysis

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

4.6.3. 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.

4.7. Other Analyses

Refer to the Master SAP Section 4.6 for details on other analyses that will be done, including: pharmacokinetic analysis, population pharmacokinetic (POPPK) analysis, biomarker analysis, pharmacokinetic/pharmacodynamic analysis, immunogenicity analysis, and health-related quality of life analysis.

4.8. Interim Analyses

Refer to Section 4.7 of the Master SAP for details on interim analyses for both the DE and CE phase.

4.9. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 5 (Dated: 21-JAN-2022).

5. SAMPLE SIZE DETERMINATION

In the DE phase, approximately up to 10 participants will be assigned to the combination dose level.

If at least 2 responses in up to 10 participants are observed for the combination therapy an additional 35 participants will be randomised to each arm in the CE phase per sub-study. However, the decision to move to the CE phase is based on the totality of the data. In CE phase, participants will be stratified by prior lines of therapy (3-4 vs >4 prior lines) and randomised equally to the belantamab mafodotin monotherapy and the available sub-studies until 35

participants are randomised to the belantamab mafodotin monotherapy. Once 35 participants have been randomised to the belantamab mafodotin monotherapy arm, the randomisation ratio for new combinations will change depending on the number of new combination therapies and the timing of their entry to the study (Refer to Table 13 in Protocol).

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

None.