Statistical Analysis Plan- Part 1 & Part 2

Study ID: 207504

Official Title of Study: A Phase I Open-Label, Dose Escalation Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, Immunogenicity and Clinical Activity of the Antibody Drug Conjugate GSK2857916 in Japanese Participants With Relapsed/Refractory Multiple Myeloma

NCT ID : NCT03828292

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Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for A Phase I Open-Label, Dose Escalation Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, Immunogenicity and Clinical Activity of the Antibody Drug Conjugate GSK2857916 in Japanese Participants with Relapsed/Refractory Multiple Myeloma (Part 1)
Compound Number	:	GSK2857916
Effective Date	:	Refer to Document Date

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report (Part 1) for Protocol 207504.
- This RAP is intended to describe the safety, pharmacokinetic, and efficacy analyses required for the study (Part 1).
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol: 2018N369488_05 (Dated: 12-NOV-2021). This RAP focuses on the analysis plan for monotherapy (Part 1), and the RAP focused on the analysis plan for combination therapy (Part 2) will be prepared separately.

Revision Chronology:		
2018N369488_00	25-JUL-2018	Original
2018N369488_01	07-DEC-2018	Amendment No. 1. Action taken for the response to inquiries from Pharmaceuticals and Medical Devices Agency (PMDA) (dated 27 NOV 2018) to the initial clinical trial notification. Added chest X-ray imaging. Added the dosing interval between the first and subsequent participants in each dose cohort and information that the dose-escalation will be determined considering all available information on AEs occurring in the DLT observation period. Clarified inclusion and exclusion criteria. Clarified use of growth factors as prohibited medication. Added timing and volume of blood collection for pharmacodynamic and pharmacokinetic analyses.
2018N369488_02	05-APR-2019	Amendment No. 2. Amendment to address feedback from investigators, clarification of study assessments and procedures, and administrative changes. Revised Schedule of Activities. Revised inclusion and exclusion criteria. Incorporated GSK Scale for Corneal Events Associated with GSK2857916, instructions for grading, and dose modification guidelines. Added IMWG criteria.
2018N369488_03	01-JUL-2020	Amendment No. 3. Amendment to add combination therapy cohorts of GSK2857916 with bortezomib and dexamethasone (Part 2 Arm A) or with pomalidomide and dexamethasone (Part 2 Arm B). Additional changes were incorporated which align with program revisions and/or updates based on data from the primary analysis of the Phase II study 205678 (DREAMM-2). Revised Schedule of Activities. Updated PK and PD of GSK2857916. Modifications corresponding to adding the combination cohorts of Part 2. Added interim analysis for Part 1 and Part 2.
2018N369488_04	15-JAN-2021	Amendment No. 4. Amendment to address feedback from investigators, to clarify study assessments and procedures, and to reflect administrative changes. Revised Schedule of Activities and Inclusion/Exclusion criteria. Clarified dosing and dose modifications for Part 2 cohorts.
2018N369488_05	12-NOV-2021	Amendment No. 5. Amendment to clarify the timing and purpose of analyses.

1.1. RAP Amendments

Revision chronology:

RAP Section	Amendment Details
238106 RAP 20210318 Part 1 1.0	
238106 RAP 20211214 Part 1 1.0 Amendment	
RAP Authors	• To update the RAP Author
GSK Review Confirmations	• To update the department name
Section 1.	• To update Revision Chronology for Protocol
Section 1.1.	• To add Revision chronology for RAP Amendments
Section 2.2.	• To clarify interim analysis
Section 3.1.	• To clarify interim analysis
Section 3.2.	• To clarify primary analysis and final analysis
Section 6.2.	• To remove the completed study treatment from the summary of study treatment status
Section 6.5.	• To add the derivation for the duration of exposure that was on prophylactic steroid eye drop use
Section 7.2.2.	• To remove the summary of unconfirmed ORR and CBR
Section 8.2.	• To add the description of additional analysis for corneal event
Section 8.5.	• To remove the supporting listing with subject level details for urinalysis
Section 14.7.2.1.	• To change the name of the element (from Medical History to Disease Characteristics) appropriately
Section 14.9.1.	• To add one abbreviation
Section 14.10.	• To change the title description appropriately (e.g., the removal of “Intact” from “Intact ADC” in the displays titles, typo correction)
Section 14.10.1.	• To change the data display numbering
Section 14.10.7.	• To add tables for corneal events • To amend IDSL example numbers

2. SUMMARY OF KEY PROTOCOL INFORMATION

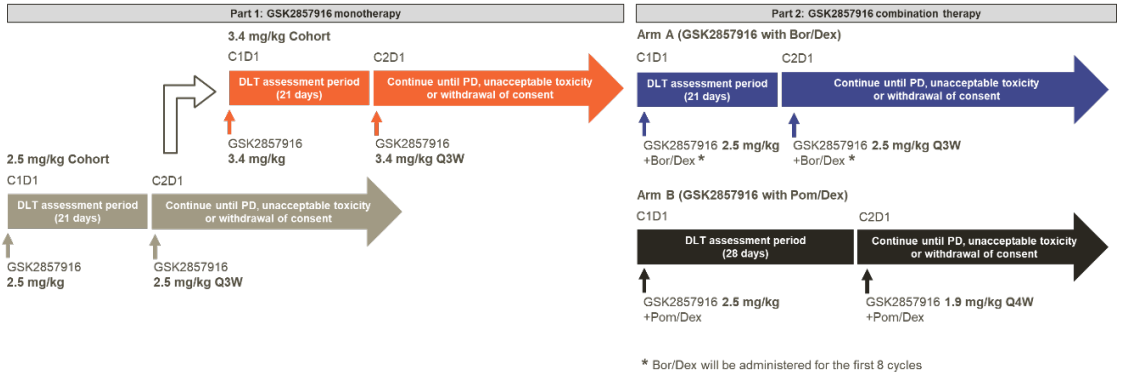
2.1. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate safety, tolerability of GSK2857916 in Japanese participants RRMM.	• Number of participants with DLTs • Adverse events (AEs) and changes in clinical signs and laboratory parameters.
Secondary Objectives	**Secondary Endpoints**
• To evaluate pharmacokinetic (PK) profile of GSK2857916 and cysteine maleimidocaproyl monomethyl auristatin F	• GSK2857916 and cys-mcMMAF PK parameters following IV single and repeat dose administration as data permit (e.g.,

Objectives	Endpoints
(cys-mcMMAF) after IV single and repeat dose administration in Japanese participants with RRMM.	AUCs, Cmax, tmax, CL, Vss, t½ [single dose], Ceoi, Ctrough, and Rac (Ceoi and Ctrough) [repeat dose]).
• To assess anti-drug antibody (ADA) formation after IV single and repeat dose administration of GSK2857916.	• ADA incidence and titers after IV single and repeat dosing of GSK2857916.
• To investigate the initial anti-tumor activity of GSK2857916 in Japanese participants with RRMM.	• Clinical activity measured as Overall Response Rate (ORR) and Clinical Benefit Rate (CBR) which are defined as follows: ○ ORR: the percentage of participants achieving confirmed partial response or better (≥PR) ○ CBR: the percentage of participants with minimal response (MR) or better

CCI [redacted]

2.2. Study Design

Overview of Study Design and Key Features	
	
Design Features	• This is a Phase 1, open label, dose escalation study to investigate safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and clinical activity of GSK2857916 when given as monotherapy on a once every 21 days schedule (Part 1), or given in combination with Bor/Dex on a once every 21 days schedule (Part 2 Arm A) or with Pom/Dex on a once every 28 days schedule (Part 2 Arm B). The study will consist of 2 parts. Part 1 is a dose escalation phase to evaluate the safety and tolerability of up to 2 dose levels of GSK2857916 monotherapy. Part 2 of the study will evaluate the safety and tolerability of 1 dose level of GSK2857916 in combination with 2 SoC regimens: Part 2 Arm A – GSK2857916 with Bor/Dex, and Part 2 Arm B – GSK2857916 with Pom/Dex. • The dose escalation model is based on 3 + 3 design. The maximum number of participants will be up to 12. The GSK2857916 will be IV administered over 30 min infusion once every 3 weeks (21 days = 1 cycle) or every 4 weeks (28 days = 1 cycle). The initial anti tumor activity of GSK2857916 based on response assessment criteria as defined by International Myeloma Working Group (IMWG) 2016 will also be assessed during the study [Kumar, 2016].
Dosing	• In Part 1, GSK2857916 is to be IV administered, via an infusion pump on Day 1 of each cycle over 30 minutes. Premedication is not required prior to infusion unless deemed medically necessary by the investigator, in which case it should be administered according to institutional recommendations. • In Part 2, GSK2857916 is to be IV administered via an infusion pump. Arm A will receive 2.5 mg/kg on Day 1 of each cycle, once every 3 weeks. In addition, Arm A will receive 1.3 mg/m^2 Bortezomib via subcutaneous injection on Day 1, Day 4, Day 8, Day 11 Q3W for 8 cycles and 20 mg Dexamethasone orally on Day 1, Day 2, Day 4, Day 5, Day 8, Day 9, Day 11, and Day 12, Q3W for 8 cycles. Arm B will receive 2.5 mg/kg on Day 1 of Cycle 1 and 1.9 mg/kg on Cycle 2 Day 1 and beyond, once every 4 weeks. In addition, Arm B will receive 4 mg orally daily on Days 1-21, Q4W and 40 mg Dexamethasone orally per day on Day 1, Day 8, Day 15, and Day 22 Q4W.
Time & Events	• Refer to Protocol Section 1.3, Tables 1-3 for the schedule of activities relating to Part 1 and Part 2.

Overview of Study Design and Key Features	
Treatment Assignment	• This is open-label study and consists of two parts (Part 1, Part 2). There are two cohorts (2.5 mg/kg and 3.4 mg/kg) in Part 1 and one cohort for each arm in Part 2 (2.5 mg/kg with Bor/Dex for Arm A, 2.5 mg/kg at C1D1 and 1.9 mg/kg at C2D1 with Pom/Dex for Arm B).
Interim Analysis	• In Part 1, available safety data will be reviewed after the completion of DLT evaluation period to determine if a dose-escalation is appropriate. Additionally, PK data will be reviewed after the completion of DLT evaluation period to assess PK similarity between Japanese and overseas populations. • In Part 2, available safety data will be reviewed after the completion of DLT evaluation period within each arm to determine if the combination dose regimen is tolerable. An interim analysis may be conducted when the last participant within any arm in Part 2 has completed at least one cycle of the combination treatment to evaluate safety, efficacy and PK profiles.

2.3. Statistical Hypotheses / Statistical Analyses

No specific statistical hypotheses are being tested in this study.

3. PLANNED ANALYSES

3.1. Interim Analyses

In Part 1, available safety data will be reviewed after the completion of the DLT evaluation period to determine if a dose-escalation is appropriate. Additionally, PK data will be reviewed after the completion of the DLT evaluation period to assess PK similarity between Japanese and overseas populations.

In Part 2, available safety data will be reviewed after the completion of DLT evaluation period per each arm to determine if the combination dose regimen is tolerable. An interim analysis may be conducted when the last participant within any arm in Part 2 has completed at least one cycle of the combination treatment to support a regulatory submission.

3.1.1. Dose Escalation Reviews

Dose escalation meetings will be held to discuss dose escalation decisions after all participants (3 or 6 participants following a 3+3 dose-escalation procedure) in the initial dosing cohort complete the DLT evaluation period of the first 21 days of intervention.

3 + 3 Dose Escalation: Dose-escalation will follow a 3 + 3 dose-escalation procedure as shown in Table 1. Evaluation of available safety data from at least 3 participants who have completed a minimum of 21 days (1 cycle: 21 days) is required to start the next dose cohort. Refer to Table 1 for more details. Dose levels to be tested in the study are provided in Table 2, Table 3, and Table 4.

GSK may consult with safety and efficacy evaluation committee as needed. Safety and efficacy evaluation committee will propose GSK necessity of additional participant.

Table 1 3 + 3 Dose-Escalation Guidelines

Number of Participants with DLT at a Given Dose Level	Action
0 out of 3 participants	Escalate to next dose level
1 out of 3 participants	Accrue 3 additional evaluable participants at current dose level for a total of 6 evaluable participants • If 0 of the additional 3 participants experience a dose-limiting toxicity (DLT), proceed to next dose level. • If 1 or more participants experience a DLT, the dose-escalation is stopped
1 out of 6 participants	Escalate to next dose level
2 or more participants in a dosing cohort (up to 6 participants)	Dose-escalation will be stopped.

Table 2 Dose Levels for Part 1

Dose Level	GSK2857916 (mg/kg)
0, starting dose	2.5
1	3.4

Table 3 Dose Levels for Part 2 Arm A

Dose Level	GSK2857916 (mg/kg)
0, starting dose	2.5

Table 4 Dose Levels for Part 2 Arm B

Dose Level	GSK2857916 (mg/kg)
0, starting dose	2.5 (C1) and 1.9 (C2+)

3.1.1.1. Displays to Be Created for Dose Escalation Review

For the dose escalation meeting, data listings will be provided by DML in Excel spreadsheets based on the enrolled population. Details of the planned displays are presented in Dose Escalation Plan.

3.2. Primary Analyses

A primary analysis will be conducted to evaluate safety, efficacy and PK profiles by the data cut-off performed after both EOT and the completion of AE and SAE collection (i.e., 70 days after the last dose of study treatment) for last participant in Part 1.

A primary analysis will be conducted per arm to evaluate safety, efficacy and PK profiles by the data cut-off performed after both EOT and the completion of AE and SAE collections (i.e., 70 days after the last dose of study treatment) for last participant in Part 2.

The later of the primary analyses for Arm A and Arm B in Part 2 will be the final analysis for the entire study.

4. ANALYSIS POPULATIONS

Population	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 screening failures (who never passed screening even if rescreened) and subjects screened but never enrolled into the study are excluded from the Enrolled population as they did not enter the study.	• Study Population
All Treated	• All eligible subjects who receive at least 1 dose of study treatment. An incorrect treatment schedule or drug administration or an early termination of treatment will not result in exclusion of subjects from this population.	• Study Population • Safety • Efficacy • Immunogenicity
DLT Evaluable	• All subjects fulfilling the 'All Treated' population criteria and having completed a minimum of 21 days or experienced a DLT before 21 days. Subjects who have been withdrawn from the study for reasons other than toxicity but prior to the 21-day DLT observation period are not included in this population	• Summary of DLT
Pharamacokinetic (PK)	• All subjects in the 'All Treated' population who had at least 1 non-missing PK assessment (Non-quantifiable ([NQ] values will be considered as non-missing values).	• PK
Pharmacodynamic (PD)	• All subjects in the 'All Treated' population from whom at least one PD sample was obtained, analysed, and was measurable.	• PD

4.1. Protocol Deviations

Important protocol deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management, or patient assessment will be summarised and all protocol deviations, including both major and minor, will be listed. The classification of important protocol deviations includes AE/SAE, disallowed devices, disallowed medications, inclusion/exclusion criteria, informed consent, IP administration/study treatment, procedures/tests, and withdrawal criteria. The protocol deviation terms are detailed in the Protocol Deviation Specification.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Specification.

- Data will be reviewed prior to database lock to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of 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.

There is no Per-Protocol Population for this study. Protocol deviations will not be used to determine membership in any particular study population for this study.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

This is a single-arm, dose escalation study of GSK2857916. In the data displays GSK2857916 will be abbreviated as GSK916. Data will be listed and summarised per the GSK reporting standards whenever applicable.

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment within 21 days prior to first dose with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. For laboratory data, baseline will be the latest non-missing pre-dose value. For PD assessments, only the Cycle 1 Day 1 pre-dose measurement will be used as baseline. If there are multiple assessments on the same day, the mean will be used as the baseline value.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Screening (within 21 days prior to first dose)	Day 1 (Pre-Dose)	
Efficacy			
Disease assessment	X		Screening visit
Safety			
Laboratory	X	X	Latest up to Day 1
Vital Signs	X	X	Latest up to Day 1
ECG	X	X	Latest up to Day 1

5.2.1. Change from baseline

Change from baseline is calculated as:

- For records occurring after baseline: (visit value) – baseline value.

Percent change from baseline is calculated as:

- For records occurring after baseline: ((change from baseline) / baseline value) * 100

If either the baseline or visit value is missing, the change from baseline and/or percent change from baseline is set to missing as well.

5.3. Multicenter Studies

Data from all participating centres will be pooled prior to analysis.

It is anticipated that subject accrual will be spread thinly across centres and summaries of data by centre would be unlikely to be informative and will not, therefore, be provided.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

All analyses are descriptive or unadjusted. No analyses are planned to adjust for any covariate and prognostic factor.

5.4.2. Examination of Subgroups

No subgroup analysis will be performed.

5.5. Multiple Comparisons and Multiplicity

No formal statistical comparison will be performed; therefore, no adjustments for multiple comparisons or multiplicity are planned.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
14.3	Appendix 3: Assessment Windows
14.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
14.5	Appendix 5: Data Display Standards & Handling Conventions
14.6	Appendix 6: Derived and Transformed Data
14.7	Appendix 7: Reporting Standards for Missing Data
14.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on All Treated population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, anti-cancer therapies, and exposure and treatment modification will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 10: List of Data Displays. The study population analyses will also be performed by dose (cohort) where necessary.

6.2. Disposition of Subjects

A summary of the number of subjects in each of the analysis populations described in Section 4 will be provided. In addition, a summary of screening status and reasons for screen failure will be provided using all screened population. A separate summary for exclusions from each study population will be displayed. A listing of subjects excluded from analysis populations will also be provided.

A summary of subject status and reasons for study withdrawal will be provided. This display will show the number and percentage of subjects who withdrew from the study, including primary reasons for study withdrawal. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF.

A summary of study treatment status will be provided. This display will show the number and percentage of subjects who 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.

6.3. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, baseline height, baseline body weight and baseline BMI calculated as body weight in kilograms divided by squared height in m^2) will be summarised and listed. Age, height, weight, and BMI will be summarised using the mean, standard deviation, minimum, median, and maximum. The count and percentage will be computed for sex and ethnicity.

Race and racial combinations as well as age ranges (Adult (18-64 years), >=65-84 years, >=85 years; <18 years, 18-<65 years, 65-<75 years, >=75 years) will also be summarised and listed.

Disease characteristics at initial diagnosis (e.g. time since initial diagnosis in years, stage at initial diagnosis, date of initial diagnosis) and screening will be listed.

Separate summaries of disease characteristics at initial diagnosis and screening will be provided. Disease characteristics for multiple myeloma subjects at screening, including stage, lines of prior therapy regimens, type of multiple myeloma, myeloma light chain and myeloma immunoglobulin will be summarised and listed.
Medical conditions present at screening will be listed and will be summarised by past and current.

Genetic characteristics for multiple myeloma subjects at screening will be summarised and listed. Cytogenetic risk for multiple myeloma subjects at screening will be summarised. A subject is considered as having high cytogenetic risk if the subject has any of the following cytogenetics: t(4;14), 17p13del, t(14;16).

Substance use, including smoking history and alcohol use, will be listed.

Prior and follow-up anti-cancer therapy will be coded using the GSK Drug code dictionary then summarised by type of therapy and listed. A listing of prior anti-cancer therapy will show the relationship between ATC Level 1 and verbatim text. A summary of the best response to the most recent prior anti-cancer therapy will be provided. A summary of the number of prior anti-cancer therapy regimens will also be produced.

Anti-cancer radiotherapy will be listed. Prior cancer and non-cancer related surgeries will be summarised. Prior, on treatment, and follow-up cancer and non-cancer related surgeries will be listed. A summary and listing of Stem Cell Transplant will be provided.

6.4. Extent of Exposure

Extent of exposure to GSK2857916 will be summarised.

The number of cycles administered to study treatment will be summarised with mean, median, standard deviation, minimum, and maximum. The number and percentages of subjects who received a given number of cycles (<=4, >4 cycles) will be reported. Note that the cycle will not be counted when the administration is interrupted/delayed.

Cumulative actual dose (sum of dose at each cycle) and dose intensity per cycle (mg/kg/cycle) will be summarised using mean, median, standard deviation, minimum, and maximum by overall, as well as dose delivered by cycle. The dose intensity (mg/kg/3 weeks), which is calculated as the cumulative actual dose (mg/kg) divided by expected duration of exposure in 3 weeks (Last Dose date – First Dose date + 21)/21), will also be summarised. A by-subject summary listing of data on exposure to all study treatments will be produced.

Dose reductions will be summarised by number of reductions and reasons for reductions. Dose delays will be summarised by number of delays, reasons for the delays, and delay duration (days). The number and percentage of the delays for duration intervals of 1-21, 22-42, and >42 days will be computed. Time to first delay will be summarised; first delay is defined as the first dose delay or first dose restarted after skipped dosing. Primary reasons for dose reductions and dose delays will also be summarised by overall.

Duration of delays is defined as period from the expected start date of dose to actual start date of current dose. Calculation: (actual start date of current dose - expected start date of dose). Expected start date of dose = actual start date of previous dose + 21.

Incomplete infusions and infusion interruptions will be summarised by number and reason for incomplete or interrupted infusion.

The summaries of dose modifications will be provided. All the dose reductions, infusion interruptions, incomplete infusions and dose delays will be listed.

The duration of exposure to study treatment (from first day to last day of treatment) will be calculated and summarised using mean, median, standard deviation, minimum, and maximum. A swimmer plot of duration of treatment including best response (PR, VGPR, CR, sCR, MR, SD, PD) and study status will be provided, where PR, VGPR, CR, sCR, MR, SD, and PD stand for partial response, very good partial response, complete response, stringent complete response, minimal response, stable disease, and progressive disease, respectively.

6.5. Concomitant Medications

Concomitant medications will be coded using GSK Drug coding dictionary, summarised, and listed. The summary of concomitant medications will show the number and percentage of subjects taking concomitant medications by Ingredient. Multi-ingredient products will be summarised by their separate ingredients rather than as a combination of ingredients. Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information will be included in the dataset created but will not appear on the listing or summary.

In the summary of concomitant medications, each subject is counted once within each unique ingredient. For example, if a subject takes Amoxycillin on two separate occasions, the subject is counted only once under the ingredient “Amoxycillin”. In the summary of concomitant medications, the ingredients will be summarised by the base only, using GSK Drug coding dictionary. Note: In order to be considered a concomitant medication, the concomitant medication must have been taken at some point during the on-treatment window.

Prophylactic medication for infusion-related reactions and prophylactic topical eye medications will be summarised by drug class and drug name and eye medications will be listed. In addition, the percentage of duration of exposure that was on prophylactic steroid eye drop use will also be summarised as below.

100*((Total number of days during treatment period on which subject exposed to concomitant medications identified as Steroid Eye Drops)/(Duration of treatment period))

Blood products or blood supportive care products with onset date within the on-treatment window will be included in the summary tables and listings. The frequency and percentage of subjects using these products after the start of study treatment will be

provided. Supporting listings will also be provided. Administration of on-treatment stem cell mobilization products will also be provided in a listing.

Prior medications will be listed.

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

No primary efficacy analysis is planned in the study.

7.2. Secondary Efficacy Analyses

The secondary efficacy analyses will be performed by dose (cohort).

7.2.1. Endpoint / Variables

7.2.1.1. Unconfirmed and Confirmed Responses

The hierarchy of response classifications from high to low is as follows: sCR, CR, VGPR, PR, MR, SD, PD, and NE. Response was assessed according to the IMWG Response Criteria [Kumar, 2016] (See Appendix 12: International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma).

The definitions and details to derive confirmed response are outlined below. For confirmed response derivations, only responses assessments from the start of treatment up to the start of new anti-cancer therapy will be considered.

Unconfirmed Response (Without confirmation)

Response assessments as provided by the investigator.

Confirmed Response (With confirmation)

The derivation of confirmed response shall be based on the algorithm specified in Table 5.

Table 5 Response confirmation algorithm

#	Response at the First Time Point	Response at Subsequent Disease Assessment[1]	Confirmed Response at the First Time Point	Date of Confirmed Response
1	sCR	sCR	sCR	First Time Point
2	sCR	CR	CR	First Time Point
3	CR	sCR/CR		
4	sCR/CR	VGPR	VGPR	First Time Point
5	VGPR	sCR/CR/VGPR		
6	sCR/CR/VGPR	PR	PR	First Time Point
7	PR	sCR/CR/VGPR/PR		
8	sCR/CR/VGPR/PR	MR	MR	First Time Point
9	MR	sCR/CR/VGPR/PR/MR		
10	sCR/CR/VGPR/PR/MR	SD	SD	First Time Point

11	sCR/CR/VGPR/PR/MR	PD (any reason) OR No subsequent disease assessment: **subject died or discontinued study or started new anti-cancer therapy** before further adequate disease assessment	NE	First Time Point
12	PD (due to reasons other than imaging, i.e., plasmacytoma or bone lesion)	PD (any reason) including PD after initiation of new anti-cancer therapy OR No subsequent disease assessment: subject **died due to PD** before further adequate disease assessment (including death due to PD after initiation of new anti-cancer therapy)	PD	First Time Point
13	PD (due to reasons other than imaging, i.e., plasmacytoma or bone lesion)	sCR/CR/VGPR/PR/MR/SD OR No subsequent disease assessment: subject died **due to reasons other than PD** before further adequate disease assessment OR No subsequent disease assessment: subject **discontinued study** before further adequate disease assessment[4]	NE	First Time Point
14	sCR/CR/VGPR/PR/MR/PD (due to reasons other than imaging, i.e., plasmacytoma or bone lesion)	No subsequent disease assessment: subject has not died, discontinued from study or (except for PD) started new anti-cancer therapy; but as yet has no further adequate disease assessments	Unconfirmed sCR/CR/VGPR/PR/MR/PD. Will be categorized as NE for final ORR analysis.	First Time Point
15	SD[2]	Any OR No subsequent disease assessment	SD	First Time Point
16	PD due to imaging (plasmacytoma or bone lesion)[3]	Any OR No subsequent disease assessment	PD	First Time Point
17	NE or missing	Any OR No subsequent disease assessment	NE	First Time Point

1. Subsequent disease assessment is defined as the next adequate (not missing or NE) disease assessment following the first timepoint before (or on the same date of) start of new anti-cancer

therapy except for confirmation of PD, for which PD or death due to PD after new anti-cancer therapy are considered for confirmation of PD. No minimal time interval is required for the subsequent disease assessment, but a different sample is required for confirmation.
2. SD does not need to be confirmed.
3. PD due to imaging (i.e., plasmacytoma or bone lesion) does not need to be confirmed.
4. Where criteria are not mutually exclusive, take the first that applies.

7.2.1.2. Best Overall Response (BOR)

Best Overall Response (Best response) will be derived from confirmed responses.

7.2.1.3. Overall Response Rate (ORR)

ORR is defined as the percentage of participants with a confirmed PR or better (i.e. PR, VGPR, CR and sCR) of best response, according to the IMWG Response Criteria [Kumar, 2016]. The number and percentage of participants with best overall response (BOR) in the following response categories will be summarised by dose level: sCR, CR, VGPR, PR, overall response (sCR+CR+VGPR+PR), minimal response (MR), stable disease (SD), progressive disease (PD), and not evaluable (NE).

7.2.1.4. Clinical Benefit Rate (CBR)

CBR is defined as the percentage of participants with a confirmed MR or better (i.e. MR, PR, VGPR, CR and sCR) of best response, according to the IMWG Response Criteria [Kumar, 2016].

7.2.2. Summary Measure for ORR and CBR

Summary of confirmed ORR and CBR will be provided. A two-sided exact 95% CI for ORR and CBR will also be provided. Participants with unknown or missing response will be treated as non-responders, i.e., these participants will be included in the denominator when calculating percentages of response.

7.2.3. Population of Interest

The analyses for ORR and CBR will be based on the All Treated population, unless otherwise specified.

7.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate), and listed. Listings of investigator assessed responses, extramedullary disease evaluation, disease assessment scan, and skeletal survey will be provided.

8. SAFETY ANALYSES

The safety analyses will be based on the All Treated population, unless otherwise specified. The safety analyses will also be performed by dose (cohort) where necessary. The safety analyses associated with Covid-19 will also be performed.

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs), treatment emergent AEs, and other significant AEs will be based on GSK Core Data Standards. Details of the planned analysis are provided in Appendix 10: List of Data Displays. Adverse events analyses will include On-treatment AEs unless otherwise specified. Dose limiting toxicity (DLT) will also be summarised and listed according to GSK Oncology Data Standards.

AEs aside from corneal events associated with GSK2857916 will be graded by the investigator according to the National Cancer Institute - Common Toxicity Criteria for Adverse Events (NCI-CTCAE) v4.03. AEs will be coded to the Preferred Term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA). Only AEs graded by NCI-CTCAE will be summarised unless otherwise specified.

An overview summary of AEs, including counts and percentages of subjects with any AE, AEs related to GSK2857916, Grade 3/4 AEs, Grade 3/4 AEs related to GSK2857916, AEs leading to dose reduction of GSK2857916, AEs leading to dose delay of GSK2857916, AEs leading to incomplete infusion, AEs leading to infusion interruption, AEs leading to permanent discontinuation of GSK2857916, any SAEs, SAEs related to GSK2857916, fatal SAEs, and fatal SAEs related to GSK2857916 will be produced.

A summary of non-serious AEs that occurred in greater than or equal to 2 subjects will be reported. This summary will contain the number and percentage of subjects with the event and the number of occurrences of the events. The summary table will be displayed by System Organ Class (SOC) and Preferred Term (PT).

The relationship between MedDRA SOC, PT, and Verbatim Text will be displayed.

A summary of number and percentage of subjects with any AEs by maximum grade will be produced separately by both SOC and PT and by PT only; however ocular related AEs (corneal, keratopathy, microcyst, haze, opacity) by maximum grade will be summarised separately because the GSK grading scale is used for ocular related AEs. AEs will be sorted by SOC (by PT) in descending order of total incidence. The summary will use the following algorithms for counting the subject:

- **Preferred term row:** Subjects experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- **Any event row**: Each subject with at least one AE will be counted only once at the maximum grade no matter how many events they have.

In addition, the frequency and percentage of AEs (all grades) will be summarised and displayed in descending order of total incidence by PT.

Summary of study treatment-related AEs will be provided. A study treatment-related AE is defined as an AE for which the investigator classifies the relationship to study treatment as "Yes". A worst case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing. The summary tables by maximum grade will be displayed in descending order of total incidence by PT.

All AEs and treatment emergent AEs will be listed. Additionally, a listing of subject IDs for each individual AE will be produced.

A summary of the number of subjects with suspected, probable, and confirmed COVID-19 infections will be provided. Additionally, the exposure adjusted incidence rate of all adverse events and adverse events occurring in >2 subjects pre, during, and post COVID-19 pandemic will be summarised. An adverse event will be defined as occurring during a time block if the start date is within the start and end date of the time block. The calculation for exposure adjusted incidence rate is the following:

Exposure adjusted incidence rate (rate/100 PY) = (number of subjects with the adverse event during the time block/total exposure duration across all subjects)*100

where exposure duration for each subject is calculated as:

- (treatment stop date[1] – treatment start date[2] + 1)/365.25 for subjects who do not experience the event
- (start date of AE – treatment start date[2] + 1)/365.25 for subjects that do experience the event

[1] minimum of 70 days after ending study therapy, last contact date, death, or end of time block.
[2] or start date of time block, whichever occurs later.

The details of the planned displays are provided in Appendix 10: List of Data Displays.

8.2. Adverse Events of Special Interest Analyses

Adverse events of special interest (AESI) for GSK2857916 are corneal events, thrombocytopenia, and infusion related reactions. Severity of corneal events associated with GSK2857916 and related ophthalmic exam findings or visual acuity will be graded using GSK scale. The severity of other AESI will be graded via CTCAE version 4.03. A comprehensive list of MedDRA terms based on the safety review team (SRT) will be used to identify each type of event.

Summaries of the number and percentage of subjects with these events will be provided for each type of event separately by preferred term and maximum grade. The time of onset and duration of first occurrence of each type of event will be summarised using the summary statistics mean, standard deviation, median, minimum value, and maximum.

The number and percentage of subjects who have time of onset of first occurrence (1-21, 22-42, 43-63, >63 days for CTCAE grading and 1-21, 22-42, 43-63, 64-105, and >105 for GSK scale grading) will be summarised. The number and percentage of subjects who have duration of first occurrence (1-21, 22-42, >42 days) will be summarised.

The summary of event characteristics will also be provided, including number of subjects with any event, number of events, number of subjects with any event that is serious, number of subjects with any event that is related to study treatment, number of occurrences (One, Two, Three or more), maximum grade, and the action taken for the event. The percentage will be calculated in two ways, one with number of subjects with event as the denominator and the other with total number of subjects as the denominator. The worst-case approach will be applied at subject level for the maximum grade, i.e. a subject will only be counted once as the worst case from all the events experienced by the subject. For action taken to an event, a subject will be counted once under each action, e.g. if a subject has an event leading to both study treatment discontinuation and dose reduction, the subject will be counted once under both actions.

Corneal events (GSK Scale) by grade and visit, corneal event (GSK Scale) overview and action taken with study treatment for corneal events (GSK Scale) by visit will be summarized. Also, corneal events (CTCAE Scale) overview will be summarized.

All AEs of special interest will be listed separately. The details of the planned displays are provided in Appendix 10: List of Data Displays.

8.3. Deaths and Serious Adverse Events

In the event that a subject has withdrawn consent, no data after the withdrawal of consent date from this subject including death is supposed to appear in the database, which should be part of the data cleaning process. All deaths will be summarised based on the number and percentage of subjects. This summary will classify subjects by primary cause of death. A supportive listing will be generated to provide subject-specific details on subjects who died.

All SAEs will be tabulated based on the number and percentage of subjects who experienced the event. The frequency and percentage of SAEs will be summarised in descending order of total incidence by SOC and PT. Separate summaries will also be provided for study treatment-related SAEs. A study treatment-related SAE is defined as an SAE 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.

SAEs are included in the listing of all adverse events. Separate supportive listings with subject-level details will be generated for

- Fatal SAEs
- Non-fatal SAEs

8.4. Adverse Events Leading to Discontinuation and Dose Modification of Study Treatment

The following categories of AEs and AESIs will be summarised separately in descending order of total incidence by PT only and separate supportive listings will be generated with subject level details for those subjects:

- AEs Leading to Permanent Discontinuation of GSK2857916
- AEs Leading to Dose Delays
- AEs Leading to Dose Reductions

Also, the following supportive listings will be generated with subject level details for those subjects:

- AEs Leading to Infusion interruptions
- AEs Leading to Incomplete infusions

8.5. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 10: List of Data Displays.

Clinical Laboratory Tests are listed in Table 6.

Table 6 List of Clinical Laboratory Tests

Hematology[1]			
Platelet Count	RBC Indices:		Automated WBC Differential:
Red blood cell (RBC) Count	Mean corpuscular volume (MCV)		Neutrophils
White blood cell (WBC) Count (absolute)	Mean corpuscular hemoglobin (MCH)		Lymphocytes
Reticulocyte Count	Mean corpuscular hemoglobin concentration (MCHC)		Monocytes
Hemoglobin			Eosinophils
Hematocrit			Basophils
Clinical Chemistry[1]			
Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin
Creatinine	Chloride	Alanine aminotransferase (ALT)	Uric Acid
Glucose	Spot urine (albumin / creatinine ratio)	Gamma glutamyl transferase (GGT)	Albumin
Sodium	Calcium	Alkaline phosphatase (ALP)	Total Protein
Magnesium	Phosphorous	Creatine kinase (CK)	Lactate dehydrogenase (LDH)
Estimated Glomerular filtration rate (eGFR)			
Urine[1]			
Routine Urine Dipstick (Urinalysis required if blood or protein is detected by dipstick)			
Specific gravity			
pH, glucose, protein, blood and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Other Safety			
C-reactive protein (CRP)[1]			
Troponin I or T[4]			
B-type natriuretic peptide (BNP)[4]			

Table 6 List of Clinical Laboratory Tests (cont.)

PK/ADA			
Pharmacokinetics (PK)[2]			
Anti-Drug Antibodies (ADA)[2, 3]			
Optional Testing			
Genetics[2]			
Disease Evaluation Laboratory Tests			
Urine Protein Electrophoresis (UPEP)[1]	urine Immunofixation[1]	24-hour urine collection for M-protein[1]	Calcium corrected for albumin (serum)[1]
Serum Protein Electrophoresis (SPEP)[1]	Serum M-protein calculation[1]	Serum Immunofixation[1]	Beta2 macroglobulin[1]
Serum Kappa, lambda free LC, FLC ratio[1]	IgG, IgA, IgM. IgD and IgE only in participants with IgD or IgE myeloma		
CCI [redacted]			
Soluble BCMA (sBCMA) (Serum)[2]			

1. To be performed at local laboratory.
CCI [redacted]
3. Not needed at screening
4. If not available from local laboratory, it can be performed at central laboratory.
5. FISH testing at least for: t(4;14), t(14;16), 17p13del. BM samples from within 60 days prior to first dose are acceptable for FISH analysis.

Laboratory grades will be reported using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.

Summary of change from baseline by scheduled visits using mean, median, standard deviation, minimum, and maximum will be provided. Count data will be used for automated WBC differential.

Summaries of worst-case grade increase from baseline grade will be provided for all the lab tests that are gradable by CTCAE v4.03. These summaries will display the number and percentage of subjects with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarised along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4.

Missing baseline grade will be assumed as grade 0. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g. sodium will be summarised as hyponatremia and hypernatremia.

For lab tests that are not gradable by CTCAE v4.03, summaries of worst case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarised for the worst case post-baseline. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the "Decrease to Low" categories and the "Increase to High" categories.

Separate summary tables for haematology, chemistry, and urinalysis laboratory tests will be produced.

A supporting listing of laboratory data for subjects with any value of potential clinical importance will be provided. A separate listing of laboratory data with character values will also be provided.

Detailed derivation of baseline assessment is specified in Section 5.2.

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

A summary of worst case urinalysis results post-baseline relative to baseline will be generated.

For lab tests that can be graded, values of grade 1 or above are defined as values of potential clinical concern. For lab test values that cannot be graded, values out of the normal range are defined as values of potential clinical concern.

8.5.1. Analyses of Liver Function Tests (LFT)

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided in addition to what has been described above.

Possible Hy's law cases are defined as any elevated ALT≥3×ULN, total bilirubin≥2×ULN and ALP<2×ULN/missing. Total bilirubin≥2×ULN can be within 28 days following the ALT elevation and if direct bilirubin is available on the same day, it must be ≥ 35% of total bilirubin. ALP<2xULN/missing means the criteria is satisfied unless the ALP is ≥2xULN at any time of bilirubin elevation within the 28 days window.

LFT patient profiles plots for subjects experiencing an ALT, AST, or total bilirubin of toxicity grade 2 or above will be produced.

A scatter plot of maximum total bilirubin versus maximum ALT will be generated. Also, a scatter plot of maximum vs baseline for ALT will be produced.

A Summary of Liver Monitoring/Stopping Event Reporting will be provided. The medical conditions data for subjects with liver stopping events will be listed. The substance use data for subjects with liver stopping events will be listed.

8.5.2. Analyses of Disease Evaluation

Summaries of disease evaluation changes from baseline as well as disease evaluation worst case change from baseline will be provided.

8.5.3. Analyses of eGFR

Summaries of eGFR, changes from baseline in eGFR, as well as eGFR worst case changes from baseline will be provided. A supporting listing of subjects with values outside of normal range will be provided.

8.6. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. Performance status (ECOG) will be summarised and listed and LVEF will be listed based on GSK Oncology Data Standard. The details of the planned displays are presented in Appendix 10: List of Data Displays.

8.6.1. Performance Status

ECOG performance status will be summarised at baseline and post-baseline scheduled visits. Summaries will use frequency and percentage of subjects at each planned assessment time. A summary of change from baseline by scheduled visits will be performed, as well as the worst-case post-baseline and the best case post-baseline changes during the study (improved, no change, deteriorated).

A supporting listing will also be provided.

8.6.2. ECG

12-lead ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, RR interval, QRS, QT and QTcF intervals. Baseline QTcF value is determined by Day 1 pre-dose QTcF result (either a single result or the mean of triplicate results). If these are not available, the screening ECG results should be used.

The QTc values based on Fridericia formula will be rounded to the integer and the values will be categorized into the following ranges: Grade 0 (<450), Grade 1 (450-480), Grade 2 (481-500), and Grade 3 (≥501).

The QTc will be based on the collected value using Fridericia formula. The ECG results, increase in QTcF, and amount of increase from baseline value will be summarised.

Listings of abnormal ECG findings and a listing of ECG values including Potential Clinical Importance will be provided. Potential clinical significance ranges are provided as follows:

	ECG Parameter	Units	Clinical Concern Range Low	Upper
Absolute	QTc Interval	msec		≥481
	PR Interval	msec	<110	>220
	RR Interval	msec	<60	>120
	QRS Interval	msec	<75	>110
Change from baseline	QTc Interval	msec		>30

8.6.3. LVEF

Absolute change from baseline in LVEF will be summarised by worst case post-baseline only. Only the post-baseline assessments that used the same method (ECHO) as the baseline assessments will be used to derive the change from baseline. The change from baseline will be categorized as follows:

- No change or any increase
- Any decrease
- >0-<10 decrease
- 10-19 decrease
- >=20 decrease
- >=10 decrease and >= LLN
- >=10 decrease and < LLN
- >=20 decrease and >= LLN
- >=20 decrease and < LLN

LVEF results will also be listed with subject level details including absolute change from baseline.

8.6.4. Ocular Exams

Ophthalmic exams are scheduled at screening, during the study, and follow-up period. The ocular findings from ophthalmic exams will be analysed as described below.

1. From baseline to EOT visit, the following analysis will be performed:

a. Best corrected visual acuity (BCVA): BCVA (logMAR score) at baseline, EOT visit, and last follow-up visit as well as worst and most frequent category (definite worsen, possible worsen, and no change/improved) of change from baseline will be summarised by eye (R/L) and subject (worse eye and better eye). BCVA for subjects with corneal finding will also be provided. The logMAR score is calculated as:

   logMAR score = $-1 * (\log_{10}(\text{Landolt ring value}))$

b. Intraocular Pressure (IOP): summary table of number (%) of subjects with IOP ≥ 22mm Hg anytime post-baseline.

c. Pupillary Exam: shift table (Normal to Abnormal) from baseline to worst post-baseline by subject (worse eye)
d. Extraocular Muscle Movement: shift table (Full Intact: Yes to No) from baseline to worst post-baseline by eye (R/L) and subject (worse eye)
e. External Exam: shift table (Ptosis: No to Yes) from baseline to worst post-baseline by eye (R/L) and subject (worse eye)
f. Lids/Lashes/Lacrimal System: shift table (Blepharitis/MGD: No to Yes) from baseline to worst post-baseline by eye (R/L) and subject (worse eye)
g. Conjunctival Exam:
    i. shift table and summary table (Chemosis: Absent to Present; Bulbar Conjunctiva White and Quiet: Yes to No; Palpebral Conjunctiva within normal limits: Yes to No) from baseline to worst post-baseline by eye (R/L) and subject (worse eye)
h. Sclera: shift table (Scleritis: No to Yes) from baseline to worst postbaseline by eye (R/L) and subject (worse eye)
i. Corneal Exam:
    i. Corneal epithelium findings:
        1. Shift table from baseline to worst post-baseline by eye (R/L) and subject (worse eye) for Corneal epithelium (Normal to Abnormal)
        2. Summary and shift tables for Microcystic edema (No to Yes), Microcystic without edema (Yes/No), Subepithelial haze (No to Yes), Corneal neovascularization (No to Yes), Stroma (Normal to Abnormal), Active opacity (No to Yes), and Active edema (No to Yes).
        3. For punctate keratopathy, summary table of worst grade and most frequent grade across ocular exams by eye (R/L) and subject (worse eye)
    ii. Corneal endothelium findings:
        1. Shift table from baseline to worst post-baseline by eye (R/L) and subject (worse eye) for Corneal endothelium (Normal to Abnormal)
        2. Summary table by eye (R/L) and subject (worse eye) for presence of Descemet's folds and Endothelial lesion at any post-baseline ocular exam.
j. Slit Lamp Exam:
    i. Shift table from baseline to worst post-baseline by eye (R/L) and subject (worse eye) for Anterior Chamber: Deep/Quiet (Yes to No); Iris: Flat, round and reactive (Yes to No); and Lens: Clear (Yes to No).
    ii. Summary tables of presence of iris findings ('Transillumination defect', 'Nodules', or 'Neovascularization') at any post-baseline ocular exam.
    iii. Shift table from baseline to worst post-baseline by eye (R/L) and subject (worse eye) for Nuclear sclerosis (No to Yes), Cortical cataract (No to Yes), and Posterior subcapsular cataract (No to Yes)
    iv. Summary tables of grade change in Cataract

k. FUNDUS Photograph: Shift table from baseline to worst post-baseline by eye (R/L) and subject (worse eye) for Vitreous normal in appearance (Yes to No), PVD (No to Yes), Vitreous cell (No to Yes), Vitreous haze (No to Yes), Optic nerve normal in appearance (Yes to No), and Retina normal in appearance (Yes to No).

2. From EOT visit to last follow-up visit: To assess the change in corneal findings after discontinuation of study treatment, among eyes and subjects (worse eye) with exam finding at EOT visit worse than baseline, the following analyses will be performed.

a. Summary of change (worsening, no change, improvement) from EOT to last follow-up visit based on categories defined below by eye (R/L) and subject (worse eye)
b. Summary of number (%) of eyes and subjects (worse eye) that resolve (improve to baseline level or better based on categories defined below), and descriptive summary of time from EOT visit to resolution among eyes and subjects (worse eye) that resolved

The parameters included in above analyses are:

1. BCVA change from baseline in log MAR scale (< 0.12, ≥ 0.12 to < 0.3, ≥ 0.3)
2. IOP (≥ 22mm Hg, <22mm Hg)
3. Corneal epithelium (Normal/Abnormal), Punctate Keratopathy (None/Mild /Moderate/Severe), Microcystic edema (No/Yes), Microcystic without edema (No/Yes), Subepithelial haze (No to Yes), Corneal neovascularization (No to Yes), Stroma (Normal/Abnormal); Active opacity (No/Yes); Active edema (No/Yes)
4. Corneal endothelium (Normal/Abnormal), Descemet's folds (No/Yes), Endothelial lesion (No/Yes)

All summary and shift tables will be provided by eye (R/L) and worse eye or better eye. If both eyes are diagnosed as abnormal, subject is counted as abnormal (yes, present, or others).

The ocular exam results are listed for the data related summary tables only. The details of the planned displays are provided in Appendix 10: List of Data Displays.

8.6.5. Vital Signs

Values of vital signs as well as the change from baseline will be summarised by scheduled visit using mean, median, standard deviation, minimum and maximum.

In addition, vital sign values will be categorized as follows:

- Systolic BP (mmHg):
  Grade 0 (<120), Grade 1 (120-139), Grade 2 (140-159) and Grade 3 (≥160)
- Diastolic BP (mmHg):
  Grade 0 (<80), Grade 1 (80-89), Grade 2 (90-99), and Grade 3 (≥100)

- Heart rate (beats/min):
  <60, 60-100, and >100
- Temperature (°C):
  ≤35, >35-<38, ≥38

Summaries of worst-case changes in vital signs from the baseline with respect to the categories defined above will be performed. The vital signs data will be listed.

8.6.6. Anti-Drug Antibody

For each subject, the anti-GSK2857916 (drug) binding antibody results and titers, and ADC and total antibody concentration will be listed for each assessment time point. The frequency and percentage of subjects with positive and negative anti-drug antibody will be summarised for each assessment and overall for each subject by dose cohort. The conclusive results will be based on the total antibody concentration.

8.6.7. Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If subjects become pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

9. PHARMACOKINETIC ANALYSES

9.1. Endpoint / Variables

9.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 14.5.3 Reporting Standards for Pharmacokinetic)

9.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. The parameters are listed in the following table:

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid
AUC(0-τ)	Area under the concentration-time curve during the dosing interval
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity will be calculated as: **AUC = AUC(0-t) + C(t) / lambda_z**
Cmax	Maximum observed concentration, determined directly from the concentration-time data for each cycle. For cys-mcMMAF, Cmax will not be derived when only predose and EOI samples were collected.
tmax	Time to reach Cmax, determined directly from the concentration-time data for each cycle
t½	Apparent terminal half-life will be calculated as: **t½ = ln(2) / lambda_z**
tlast	Time of last observed quantifiable concentration
CL	Clearance
Vss	Volume of distribution at steady state
λz, lambda_z	Terminal phase rate constant

All calculations of non-compartmental parameters will be based on actual sampling times. From the plasma concentration-time data, the following GSK2857916 (intact ADC, total antibody) and cys-mcMMAF PK parameters will be determined as data permit, for each dose of GSK2857916 and for each participant:

1) After single dose: area under the plasma concentration-time curve (AUC(0-t), AUC(0-tau) and/or AUC(0-∞)), maximum observed plasma concentration (Cmax), time to Cmax (tmax), last time point where the concentration is above the limit of quantification (tlast), systemic clearance (CL), volume of distribution

at steady state (Vss), terminal phase elimination rate constant (λz), terminal phase half-life (t½).

2) After repeat dose: concentration at end of infusion (Ceoi) after Cycles 3, 6, 9, and 12 and concentration pre-dose (Ctrough) prior to Cycles 3, 6, 9, and 12 for accumulation ratio analysis.

9.2. Population of Interest

The secondary pharmacokinetic analyses will be based on the Pharmacokinetic population, unless otherwise specified.

9.3. Statistical Analyses / Methods

GSK2857916 (intact ADC and total antibody) and cys-mcMMAF concentration-time data will be listed for each participant and summarised by descriptive statistics at each time point by dose (cohort). Linear and semi-logarithmic individual plasma concentration-time profiles and mean and median profiles (when applicable) by GSK2857916 dose will be plotted for GSK2857916 (intact ADC and total antibody) and cys-mcMMAF.

Pharmacokinetic parameters will be listed and summarised descriptively (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation of log-transformed parameters, CV% and 95% CI of log-transformed parameters) by dose cohort.

9.3.1. Assessment of Accumulation Ratio

To assess the extent of accumulation following GSK2857916 repeat dosing, the observed accumulation ratio (R_0) for GSK2857916 intact ADC, total antibody, and cys-mcMMAF will be determined as a ratio of Ceoi at cycles 3, 6, 9, and 12 to Ceoi at Cycle 1 and as a ratio of Ctrough at Cycles 2, 5, 8, and 11 to Ctrough at Cycle 1.

Subjects must receive the same dose as Cycle 1 without delay and receive the same dose for the previous 3 cycles relative to the cycle of interest to be included in this analysis (i.e. with dosing delays of ≤3 days).

R_0(Ceoi) = Ceoi(Cx) / Ceoi(C1); x=3, 6, 9, 12

R_0(Ctrough) = Ctrough(Cx) / Ctrough*(C1); x=2, 5, 8, 11
Ctrough(Cx)=Pre-dose at Cycle(x+1)
Ctrough*(C1)=Pre-dose at Cycle 2 Day 1 (trough of C1)

Accumulation ratio of Ceoi and Ctrough will be summarised using descriptive statistics by planned initial dose level, graphically presented (where appropriate), and listed. Additionally, geometric mean and 95% CI will be calculated by taking the exponential for the mean and 95% CI of the difference in log transformed concentration between the visit and Cycle 1 Day 1. These parameters will be summarized and plotted.

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

10. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

The primary goal of this analysis is to characterize the population pharmacokinetics of GSK2857916 and associated analytes after intravenous of GSK2857916 in participants with multiple myeloma, as data permit. The influence of subject demographics, baseline characteristics, including disease activity, and co-medication on the pharmacokinetics of GSK2857916 in this population may be investigated. The individual subject PK parameters may be estimated and documented for the purposes of any subsequent exposure-response (PK/PD) analyses. The analysis may be performed by CPMS and reported separately.

CCI

CCI

13. REFERENCES

Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. The Lancet Oncology. 2016;17: e328-e346.

14. APPENDICES

14.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

14.1.1. Exclusions from Per Protocol Population

This study does not have a per protocol population.

14.2. Appendix 2: Schedule of Activities

Refer to Protocol Section 1.3, Schedule of Activities (SoA).

14.3. Appendix 3: Assessment Windows

14.3.1. Definitions of Assessment Windows for Analyses

No assessment window will be applied.

14.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

14.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to date/time of first dose of study treatment.

Study Phase	Definition
Pre-Treatment	Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Date
On-Treatment AEs	Study Treatment Start Date < Date ≤ Study Treatment Stop Date + 70 days

For assessment or event on the first dosing day, whether it is Pre-Treatment or On-Treatment should be based on time if available. If time is not available, the first dosing day (Day 1) is considered Pre-Treatment for ECOG, ECG, vital signs, liver events, lab tests, cardiac scan, and other safety domains, and On-Treatment for adverse events and concomitant medications.

14.4.1.1. Study Phases for Concomitant Medication and Blood and Blood Supportive Care Product

Concomitant Medication and Blood and Blood Supportive Care and Stem Cell Mobilization Product start and end dates will be assigned to study time periods in relation to first dose of study treatment as defined below. The start date references time flag variables and end date reference time flag variables will be added to the concomitant medications and blood and blood supportive products datasets, respectively.

- **Start relative to treatment:** Assign to 'BEFORE' if start date is prior to study treatment start date or if subject has not taken any study treatment or (start date is missing and end date is before study treatment start date). Else assign to 'DURING' if the start date falls into the on-treatment period as defined above or if subject is ongoing (not all study treatment discontinuation records completed) or start date is missing. Else assign to 'AFTER' if start date is after the last study day.
- **End relative to treatment**: Assign to 'BEFORE' if end date is prior to study treatment start date or if subject has not taken any study treatment. Else assign to 'DURING' if start date falls into the on-treatment period or if subject is ongoing (not all study treatment discontinuation records completed) or (end date is missing and start relative to treatment not 'AFTER'). Else assign to 'AFTER' if start date is after the last study day or (end date is missing and start relative to treatment='AFTER').

Only on-treatment blood and blood supportive care and stem cell mobilization products that start after the start of study treatment are included in the Blood Products and Blood Supportive Care Product and Stem Cell Mobilization Products summaries. Therefore, for summary tables, include blood and blood supportive care product records where start relative to treatment in ('DURING') and end relative to treatment in ('DURING', 'AFTER'). All data will be reported in listings.

Concomitant medication starts relative to treatment and ends relative to treatment flags are used to select data to include in the Concomitant Medication summaries as follows:

- Summary of Concomitant Medications: This summary will contain medications including those with start date prior to study treatment start date and continue (missing end date or end date after study treatment start date) on therapy. Note that any medications with start date and end date prior to study treatment start date will be excluded. In addition, any medication that was started during post-therapy will be excluded. Include concomitant medication records where start relative to treatment in ('BEFORE', 'DURING') and end relative to treatment in ('DURING', 'AFTER').

14.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• Study Treatment Start Date <= AE Start Date <= Start of Anti-cancer Therapy • AE Start Date is missing.

NOTES:

- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

14.5. Appendix 5: Data Display Standards & Handling Conventions

14.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: US1SALX00259
HARP Compound	: arprod\gsk2857916\mid207504
Analysis Datasets	
• Analysis datasets are "analysis-ready" datasets, i.e., analysis datasets that have a structure and content that allows statistical analysis to be performed with minimal programming, as sorting of the observations or the selection of the appropriate records from the analysis dataset. No complex data manipulations such as transformations or transpositions are required to perform the supported analysis. Analysis datasets will be created according to CDISC standards using ADaM IG 1.1 specifications (where available) following PMDA-specific CDISC requirements wherever applicable, and data will be listed and summarised according to GSK Integrated Data Standards Library (IDSL) reporting standards. Formatting for dates, times, and decimal places will follow GSK standards except where specified.	
Generation of RTF Files	
• RTF files will be generated for all tables.	

14.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be located in the modular appendices as ICH or non-ICH listings

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures, and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.

• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits
• Unscheduled visits will not be included in summary tables and/or figures. For by planned time analysis, unscheduled visits will not be included. For worst-case analysis, unscheduled visits will be included • All unscheduled visits will be included in listings.
Descriptive Summary Statistics
Continuous Data: Refer to IDSL Statistical Principle 6.06.1
Categorical Data: N, n, frequency, %
Graphical Displays
• Refer to IDSL Statistical Principals 7.01 to 7.13.

14.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non-compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to SOP_00000314000: Non-Compartmental Analysis of Clinical Pharmacokinetic Data Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarised graphical displays only.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	The following PK parameters will be derived by the Programmer: • Ceoi and Ctrough • Accumulation ratios based on Cycles 1, 3, 6, 9 and 12 for Ceoi and Cycles 1, 2, 5, 8, and 11 for Ctrough
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to Standards for Handling NQ Impacted PK Parameters.
NR at pre-dose	NR (No Report) at pre-dose will be imputed as 0 for PK parameter derivation (GSK2857916 (ADC, Total Antibody)).
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards.

14.5.4. Reporting Standards for Pharmacodynamic

Pharmacodynamic Parameter Data	
NQ	NQ values for both CCI [redacted] and complexed CCI [redacted] will be imputed as each LLQ value.

14.6. Appendix 6: Derived and Transformed Data

14.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

14.6.2. Study Population

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = min(Last Dose Date+20, Death date) – First Dose Date + 1** • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose (mg/kg) = Sum of Dose at Each Cycle** • Dose intensity will be calculated based on the formula: Dose intensity (mg/kg/3 week) = Cumulative Dose/((Last Dose date – First Dose date +21)/21).

14.6.3. Safety

DLT
DLT
See Protocol Section 4.1.1.

Adverse Events
AE'S of Special Interest
• Thrombocytopenia • Infusion-Related Reactions • Corneal events

Ocular Exams
Most frequent
• The category that presents at the greatest number among all post-baseline visits will be designated as the most frequent. The worst category is chosen if more than one category is the mode.
Best corrected visual acuity (BCVA) score
• Partial BCVA score with trailing letter "p" is transformed to numeric value by removing the letter "p".

14.7. Appendix 7: Reporting Standards for Missing Data

14.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as ”A participant will be considered to have completed the study if he or she has received at least one dose of the study treatment and, has died or is still in follow-up when the study is closed, and has not withdrawn consent from study participation.”. • Participants who have been withdrawn from the study for reasons other than toxicity but prior to completion of DLT observation period will be replaced. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

14.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated using a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
Responder Analysis	• For endpoints which determine the percentage of responders, subjects with unknown/not evaluable or missing response will be assumed to be non-responders and will be included in the denominator when calculating the percentages.

14.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays. • Imputed partial dates will not be used to derive study day, duration (e.g. duration of adverse events), or elapsed time variables. In addition, imputed dates are not used for deriving the last contact date in the overall survival analysis dataset. • Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study time
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e. only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: o Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Study Phases and Treatment Emergent Adverse Events.

Element	Reporting Detail
	○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • Completely or partially missing end dates will remain missing, with no imputation applied. Consequently, duration of such events will be missing
Concomitant Medications/ Disease Characteristics	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

14.8. Appendix 8: Values of Potential Clinical Importance

14.8.1. Laboratory Values

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

To identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.03) will be used to assign grades to the relevant laboratory parameters. NCI-CTCAE v4.03 can be found at http://ctep.cancer.gov/reporting/ctc.html.

For laboratory data which are not listed in the NCI CTCAE v4.03, a summary of values outside the normal range will be provided.

14.8.2. ECG

For ECG, the most updated IDSL standard up to the RAP effective date will be followed.

14.8.3. Vital Signs

For vital signs, the most updated IDSL standard up to the RAP effective date will be followed.

14.9. Appendix 9: Abbreviations & Trademarks

14.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
BOR	Best Overall Response
CDISC	Clinical Data Interchange Standards Consortium
CPMS	Clinical Pharmacology Modelling & Simulation
CR	Complete Response
DBF	Database Freeze
DP	Decimal Places
eCRF	Electronic Case Record Form
EOT	End of Treatment
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
PD	Pharmacodynamic
PK	Pharmacokinetic
PopPK	Population PK
PR	Partial Response
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
SAC	Statistical Analysis Complete
sCR	Stringent Complete Response
SDSP	Study Data Standardization Plan
SOP	Standard Operation Procedure
vGPR	Very Good Partial Response

14.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
WinNonlin
SAS

14.10. Appendix 10: List of Data Displays

14.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.35	1.1 to 1.1
Efficacy	2.1 to 2.1	-
Safety	3.1 to 3.111	3.1 to 3.3
Pharmacokinetic	4.1 to 4.12	4.1 to 4.33
Population Pharmacokinetic (PopPK)	-	-
Pharmacodynamic and / or Biomarker	6.1 to 6.6	6.1 to 6.12
Pharmacokinetic / Pharmacodynamic	-	7.1 to 7.12
Section	**Listings**	
ICH Listings	1 to 54	
Other Listings	55 to 79	

14.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in a separate document detailing each mock shell for each display.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Population Pharmacokinetic (PopPK)	POPPK_Fn	POPPK_Tn	POPPK_Ln
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

14.10.3. Deliverables

Delivery	Description
SAC	Statistical Analysis Complete (Part 1)

14.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	All Treated	ES8	Summary of Subject Status and Reason for Study Withdrawal (Part 1)	Summarize: by ascending dose level, Total	SAC
1.2.	All Treated	SD4	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment (Part 1)	Summarize: by ascending dose level, Total	SAC
1.3.	All Screened	ES6	Summary of Screening Status and Reasons for Screen Failure (Part 1)		SAC
Protocol Deviation					
1.4.	All Treated	DV1	Summary of Important Protocol Deviations (Part 1)	Only include 'Any important protocol deviation' Summarize: by ascending dose level, Total	SAC
1.5.	All Treated	IE1	Summary of Inclusion/Exclusion Criteria Deviations (Part 1)	Summarize: by ascending dose level, Total	SAC
Population Analysed					
1.6.	All Screened	SP1	Summary of Study Populations (Part 1)	All screened, All treated, DLT evaluable population, PK population, PD population	SAC
1.7.	All Screened	SP2A	Summary of Exclusions from the Analysis Population (Part 1)	IDSL Summarize: by ascending dose level, Total	SAC
Demographic and Baseline Characteristics					

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.8.	All Treated	DM1	Summary of Demographic Characteristics (Part 1)	ICH E3, FDAAA, EudraCT Summarize age ranges as <18, 18 to <65, 65 to <75, >=75 Summarize: by ascending dose level, Total	SAC
1.9.	All Treated	DM5	Summary of Race and Racial Combinations (Part 1)	ICH E3, FDA, FDAAA, EudraCT Summarize: by ascending dose level, Total	SAC
1.10.	All Treated	DM11	Summary of Age Ranges (Part 1)	EudraCT Summarize: by ascending dose level, Total	SAC
1.11.	All Treated	DC1	Summary of Disease Characteristics at Initial Diagnosis (Part 1)	Summarize: by ascending dose level, Total Summarize time since initial diagnosis in years and stage at initial diagnosis	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.12.	All Treated	DC2	Summary of Disease Characteristics at Screening (Part 1)	Summarize: by ascending dose level, Total. Summarize stage, lines of therapy completed at screening (1-10 lines, More than 10 lines, Missing), Type of multiple myeloma (Nonsecretory, Secretory, Missing), Myeloma Light chain (Kappa Light Chain, Lambda Light Chain, Missing), Myeloma immunoglobulin (IgA, IgD, IgE, IgG, IgM Other, Missing), Extramedullary Disease, Lytic bone lesions	SAC
Prior and Concomitant Medications					
1.13.	All Treated	MH1	Summary of Past Medical Conditions (Part 1)	ICH E3 Summarize: by ascending dose level, Total	SAC
1.14.	All Treated	MH1	Summary of Current Medical Conditions (Part 1)	ICH E3 Summarize: by ascending dose level, Total	SAC
1.15.	All Treated	MH1	Summary of Genetic Characteristics and Cytogenetic Risk (Part 1)	ICH E3 Summarize: by ascending dose level, Total	SAC
1.16.	All Treated	CM8	Summary of Concomitant Medications (Part 1)	ICH E3 Summarize: by ascending dose level, Total	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.17.	All Treated	CM1	Summary of Prophylactic Medication for Infusion-Related Reactions by Drug Class and Drug Name (Part 1)	Medication will be identified based on verbatim term, and the drug class will be based on the medication group in the excel file provided by Clinical. Summarize: by ascending dose level, Total	SAC
1.18.	All Treated	CM1	Summary of Eye Medications by Drug Class and Drug Name (Part 1)	Medication will be identified based on verbatim term, and the drug class will be based on the medication group in the excel file provided by Clinical. Summarize: by ascending dose level, Total	SAC
1.19.	All Treated	[Non-Standard] POP_T1	Summary of Percentage of Duration of Exposure on Steroid Eye Drop Use (Part 1)	See 205678 RAP T1.0170 (Mock-up POP_T1) (“Prophylactic eye drops” will be ticked in the CM dataset and ATC4 will be identified as S01BA).	SAC
1.20.	All Treated	BP1A	Summary of Blood Products on Treatment (Part 1)	Summarize: by ascending dose level, Total	SAC
1.21.	All Treated	BP1C	Summary of Blood Supportive Care Products on Treatment (Part 1)	Summarize: by ascending dose level, Total	SAC
1.22.	All Treated	BP1A	Summary of Prior Stem Cell Transplant (Part 1)	Summarize: by ascending dose level, Total	SAC
Anti-Cancer Therapies					
1.23.	All Treated	[Non-Standard] POP_T2	Summary of Prior Anti-Cancer Therapy by Drug Class of Agents (Part 1)	Summarize: by ascending dose level, Total	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.24.	All Treated	CM8	Summary of Prior Dictionary Coded Anti-Cancer Therapy (Part 1)	Summarize: by ascending dose level, Total	SAC
1.25.	All Treated	AC3	Summary of Number of Prior Anti-Cancer Therapy Regimens (Part 1)	Summarize: by ascending dose level, Total	SAC
1.26.	All Treated	RE1A	Summary of Best Response to Most Recent Prior Anti-Cancer Therapy (Part 1)	Summarize: by ascending dose level, Total	SAC
1.27.	All Treated	[Non-Standard] POP_T2	Summary of Follow-up Anti-Cancer Therapy by Drug Class of Agents (Part 1)	Summarize: by ascending dose level, Total	SAC
1.28.	All Treated	CM8	Summary of Follow-up Dictionary Coded Anti-Cancer Therapy (Part 1)	Summarize: by ascending dose level, Total	SAC
1.29.	All Treated	OSP2	Summary of Prior Cancer and Non-Cancer Related Surgical Procedure (Part 1)	Summarize: by ascending dose level, Total	SAC
Exposure and Treatment Modification					
1.30.	All Treated	OEX5	Summary of Exposure (Part 1)	Summarize: by ascending dose level, Total # of cycles; Cumulative actual dose (mg/kg): sum of dose at each cycle; dose intensity per cycle (mg/kg/cycle);dose intensity (mg/kg/3 weeks) = cumulative actual dose / (Last Dose date – First Dose date + 21)/21)	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.31.	All Treated	OEX6	Summary of Actual Dose Delivered by Cycle (Part 1)	Actual dose delivered by cycle (mg/kg/cycle) summarised by ascending dose level, no Total needed, and by each cycle	SAC
1.32.	All Treated	ODMOD1	Summary of Dose Reductions (Part 1)	Summarize: by ascending dose level, Total	SAC
1.33.	All Treated	ODMOD3	Summary of Duration of Delay and Time to First Dose Delay (Part 1)	Summarize: by ascending dose level, Total Duration of delays = (actual start date of current dose - expected start date of dose). Expected start date of dose = actual start date of previous dose + 21 Duration of delays: 1-21 days, 22-42 days, >42 days First delay: first dose delay or first dose restarted after skipped dosing	SAC
1.34.	All Treated	ODMOD8	Summary of Incomplete Infusions (Part 1)	Summarize: by ascending dose level, Total	SAC
1.35.	All Treated	ODMOD9	Summary of Infusion Interruptions (Part 1)	Summarize: by ascending dose level, Total	SAC

14.10.5. Study Population Figures

Study Population: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exposure and Treatment Modification					
1.1	All Treated	OEX12	Swimmer Plot of Duration Treatment (Part 1)	Occurrences of onset PR, VGPR, CR, sCR, PD, and Study status	SAC

14.10.6. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Overall Response Rate (ORR) and Clinical Benefit Rate (CBR)					
2.1.	All Treated	RE1A	Summary of Overall Response and Clinical Benefit Rate (With Confirmation) per IMWG Response Criteria by Dose Level (Part 1)	Summarize: by ascending dose level, Total Unknown or missing response will be treated as no response, i.e. such subjects will be included in the denominator when calculating the rates Response confirmation algorithm is in Table 5 Best Response will be summarised. ORR and CBR will be summarised with 95% CI.	SAC

14.10.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Dose Limiting Toxicity (DLT)					
3.1.	All Treated	AE19	Summary of Dose-Limiting Toxicities during the Determinative Period (Part 1)	Summarize: by ascending dose level, Total Add a footnote “The determinative period is the first 21 days of intervention”	SAC
Adverse Events (AEs)					
3.2.	All Treated	AE13	Adverse Event Overview (Part 1)	Summarize: by ascending dose level, Total Include # and % of pts with any AE, related AE, Grade 3/4, Grade 3/4 related, dose reduction, dose delays, incomplete infusions, infusion interruptions, trt discon’t, SAE, related SAE, fatal, related fatal	SAC
3.3.	All Treated	AE15	Summary of Common (>=2 subjects) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences) (Part 1)	FDAAA, EudraCT	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.4.	All Treated	OAE07	Summary of All Adverse Events by Preferred Term and Maximum Grade (Part 1)	Summarize: by ascending dose level, Total Preferred term row: A subject with the same term multiple grades will be counted once with the maximum grade. Any event row: each subject with at least one AE will be counted only once at the maximum grade Similar to T3.0030 in BMA117159	SAC
3.5.	All Treated	OAE01	Summary of All Adverse Events by System Organ Class, Preferred Term, and Maximum Grade (Part 1)	Summarize: by ascending dose level, Total Preferred term row: A subject with the same term multiple grades will be counted once with the maximum grade. Any event row: each subject with at least one AE will be counted only once at the maximum grade See T3.0030 in BMA117159	SAC
3.6.	All Treated	OAE01	Summary of Study Treatment-related Adverse Events by System Organ Class, Preferred Term, and Maximum Grade (Part 1)	Summarize: by ascending dose level, Total	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.7.	All Treated	AE3	Summary of Non-Serious Study Treatment-Related Adverse Events by Overall Frequency (Part 1)	Summarize: by ascending dose level, Total	SAC
3.8.	All Treated	DTH1A	Summary of Deaths (Part 1)	Summarize: by ascending dose level, Total	SAC
3.9.	All Treated	AE3	Summary of Adverse Events by Preferred Term (Part 1)		SAC
3.10.	All Treated	AE3	Summary of Adverse Events Leading to Permanent Discontinuation of GSK2857916 by Preferred Term (Part 1)	Summarize: by ascending dose level, Total	SAC
3.11.	All Treated	AE3	Summary of Adverse Events Leading to Dose Reduction of GSK2857916 by Preferred Term (Part 1)		SAC
3.12.	All Treated	AE3	Summary of Adverse Events Leading to Dose Delay of GSK2857916 by Preferred Term (Part 1)		SAC
3.13.	All Treated	OAE07	Summary of Treatment Emergent Adverse Events by Preferred Term and Maximum Grade (Part 1)		SAC
Serious and Other Significant Adverse Events					
3.14.	All Treated	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) (Part 1)	Summarize: by ascending dose level, Total	SAC
3.15.	All Treated	AE3	Summary Study Treatment-related Serious Adverse Events in Descending Order of Total Incidence by Preferred Term (Part 1)		SAC
AEs of Special Interest					
3.16.	All Treated	OAE01	Summary of All Corneal Events (CTCAE) by Maximum Grade Events in Descending Order of Total Incidence by System Organ Class and Preferred Term (Part 1)	Summarize: by ascending dose level, Total	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.17.	All Treated	ESI1	Summary of Characteristics of Corneal Events (CTCAE) (Part 1)	Summarize: by ascending dose level, Total	SAC
3.18.	All Treated	ESI1	Summary of Characteristics of Corneal Events (GSK Scale) (Part 1)	Summarize: by ascending dose level, Total Use information in Ocular grading form	SAC
3.19.	All Treated	ESI2B	Summary of Onset and Duration of the First Occurrence of Corneal Events (CTCAE) (Part 1)	Summarize: by ascending dose level, Total	SAC
3.20.	All Treated	ESI2B	Summary of Onset and Duration of the First Occurrence of Corneal Events (GSK scale) of Grade 2 or Above (Part 1)	Summarize: by ascending dose level, Total Use information in Ocular grading form	SAC
3.21.	All Treated	AE3	Summary of Corneal Events Leading to Permanent Discontinuation of GSK2857916 (CTCAE) (Part 1)	Summarize: by ascending dose level, Total	SAC
3.22.	All Treated	AE3	Summary of Corneal Events Leading to Dose Reductions (CTCAE) (Part 1)	Summarize: by ascending dose level, Total	SAC
3.23.	All Treated	AE3	Summary of Corneal Events Leading to Dose Delays (CTCAE) (Part 1)	Summarize: by ascending dose level, Total	SAC
3.24.	All Treated	OAE07	Summary of Thrombocytopenia by Maximum Grade Events in Descending Order of Total Incidence by Preferred Term (Part 1)	Summarize: by ascending dose level, Total	SAC
3.25.	All Treated	ESI1	Summary of Characteristics of Thrombocytopenia (Part 1)	Summarize: by ascending dose level, Total	SAC
3.26.	All Treated	ESI2B	Summary of Onset and Duration of the First Occurrence of Thrombocytopenia (Part 1)	Summarize: by ascending dose level, Total	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.27.	All Treated	OAE07	Summary of Infusion-Related Reactions by Maximum Grade Events in Descending Order of Total Incidence by Preferred Term (Part 1)	Summarize: by ascending dose level, Total	SAC
3.28.	All Treated	ESI1	Summary of Characteristics of Infusion-Related Reactions (Part 1)	Summarize: by ascending dose level, Total	SAC
3.29.	All Treated	ESI2B	Summary of Onset and Duration of the First Occurrence of Infusion-Related Reactions (Part 1)	Summarize: by ascending dose level, Total	SAC
Laboratory: Chemistry					
3.30.	All Treated	LB1	Summary of Chemistry Changes from Baseline (Part 1)	ICH E3 Summarize: by ascending dose level, Total	SAC
3.31.	All Treated	LB1	Summary of Chemistry at Scheduled Visits (Part 1)	ICH E3 Summarize: by ascending dose level, Total	SAC
3.32.	All Treated	OLB9A	Summary of Chemistry Worst Case Grade Change from Baseline (Part 1)	Summarize: by ascending dose level, Total For lab tests that are graded by CTCAE v4.03;	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.33.	All Treated	OLB11A	Summary of Chemistry Worst Case Changes from Baseline with Respect to the Normal Range (Part 1)	Summarize: by ascending dose level, Total Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarised for the worst case post-baseline. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the "Decrease to Low" categories and the "Increase to High" categories.	SAC
Laboratory: Hematology					
3.34.	All Treated	LB1	Summary of Hematology Changes from Baseline (Part 1)	ICH E3 Summarize: by ascending dose level, Total	SAC
3.35.	All Treated	LB1	Summary of Hematology at Scheduled Visits (Part 1)	ICH E3 Summarize: by ascending dose level, Total	SAC
3.36.	All Treated	OLB9A	Summary of Hematology Worst Case Grade Change from Baseline (Part 1)	For lab tests that are graded by CTCAE v4.03;	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.37.	All Treated	OLB11A	Summary of Hematology Worst Case Changes from Baseline with Respect to the Normal Range (Part 1)	Summarize: by ascending dose level, Total For lab tests that are not gradable by CTCAE v4.03. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarised for the worst case post-baseline. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the "Decrease to Low" categories and the "Increase to High" categories.	SAC
Laboratory: Disease Evaluation					
3.38.	All Treated	LB1	Summary of Disease Evaluation Changes from Baseline (Part 1)	ICH E3 Summarize: by ascending dose level, Total Include: CACRALB, IGA, IGD, IGE, IGG, IGM, KLCLLC, KAPPALC, LMBDLC, MCPROT, MCPROTZ, MCPRT24Z (ELECTROPHORESIS), MCPRT24Z (IMMUNOFIXATI ON ELECTROPHORESIS)	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.39.	All Treated	OLB11A	Summary of Disease Evaluation Worst Case Changes from Baseline with Respect to the Normal Range (Part 1)	Summarize: by ascending dose level, Total Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarised for the worst case post-baseline. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the "Decrease to Low" categories and the "Increase to High" categories.	SAC
Laboratory: Urinalysis					
3.40.	All Treated	LB1	Summary of Urine Concentration Changes from Baseline (Part 1)	ICH E3 Summarize: by ascending dose level, Total	SAC
3.41.	All Treated	LB1	Summary of Urine Concentration at Scheduled Visits (Part 1)	ICH E3 Summarize: by ascending dose level, Total	SAC
3.42.	All Treated	UR1	Summary of the Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline (Part 1)	ICH E3 Summarize: by ascending dose level, Total	SAC
Laboratory: Hepatobiliary (Liver)					
3.43.	All Treated	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting (Part 1)	Summarize: by ascending dose level, Total	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.44.	All Treated	LIVER10	Summary Hepatobiliary Laboratory Abnormalities Including Possible Hy's Law Case (Part 1)	Summarize: by ascending dose level, Total Possible Hy's law cases are defined as any elevated ALT≥3×ULN, total bilirubin≥2×ULN and ALP<2×ULN/missing. Total bilirubin≥2×ULN can be within 28 days following the ALT elevation and if direct bilirubin is available on the same day, it must be ≥ 35% of total bilirubin. ALP<2xULN/missing means the criteria is satisfied unless the ALP is ≥2xULN at any time of bilirubin elevation within the 28 day window	SAC
Laboratory: Others					
3.45.	All Treated	LB1	Summary of eGFR Changes from Baseline (Part 1)	ICH E3 Summarize: by ascending dose level, Total	SAC
3.46.	All Treated	LB1	Summary of eGFR at Scheduled Visits (Part 1)	ICH E3 Summarize: by ascending dose level, Total	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.47.	All Treated	OLB11A	Summary of eGFR Worst Case Changes from Baseline with Respect to the Normal Range (Part 1)	Summarize: by ascending dose level, Total For lab tests that are not gradable by CTCAE v4.03. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarised for the worst case post-baseline. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the "Decrease to Low" categories and the "Increase to High" categories.	SAC
Performance Status					
3.48.	All Treated	PS1A	Summary of ECOG Performance Status at Baseline and Post-baseline Scheduled Visits (Part 1)	Summarize: by ascending dose level, Total	SAC
3.49.	All Treated	PS3A	Summary of Change in ECOG Performance Status from Baseline by Scheduled Visits and the Worst and Best Case Post-Baseline Changes During Study (Part 1)	Summarize: by ascending dose level, Total Categories are Improved, no change, deteriorated.	SAC
ECG					
3.50.	All Treated	EG1	Summary of ECG Findings (Part 1)	Summarize: by ascending dose level, Total	SAC
3.51.	All Treated	EG2	Summary of Change from Baseline in ECG Values (Part 1)	Summarize: by ascending dose level, Total	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.52.	All Treated	OECG1B	Summary of Increases in QTcF (Part 1)	Summarize: by ascending dose level, Total	SAC
3.53.	All Treated	OECG2B	Summary of Amount of Increase from Baseline Value in QTcF (Part 1)	Summarize: by ascending dose level, Total	SAC
3.54.	All Treated	OLVEF1A	Summary of Left Ventricular Ejection Fraction Change from Baseline (Part 1)	Summarize: by ascending dose level, Total	SAC
Vital Signs and Body Weight					
3.55.	All Treated	VS1	Summary of Vital Signs by Scheduled Visit (Part 1)	ICH E3 Includes Baseline values	SAC
3.56.	All Treated	VS1	Summary of Change from Baseline in Vital Signs by Scheduled Visit (Part 1)	ICH E3 Includes Baseline values	SAC
3.57.	All Treated	OVT1B	Summary of Worst Case Changes from Baseline in Heart Rate (Part 1)	ICH E3	SAC
3.58.	All Treated	OVT2B	Summary of Worst Case Increase from Baseline in Systolic Blood Pressure (Part 1)	ICH E3	SAC
3.59.	All Treated	OVT2B	Summary of Worst Case Increase from Baseline in Diastolic Blood Pressure (Part 1)	ICH E3	SAC
3.60.	All Treated	OVT1B	Summary of Worst Case Changes from Baseline in Temperature (Part 1)	ICH E3	SAC
Anti-Drug Antibody					
3.61.	All Treated	[Non-Standard] SAFE_T1	Summary of Human Anti-GSK2857916 Antibodies (ADA) Over Time (Part 1)		SAC
3.62.	All Treated	[Non-Standard] SAFE_T2	Summary of Human Anti-GSK2857916 Antibodies (ADA) (Part 1)	ICH E3 Summarize overall at post-baseline	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Ocular findings during on-treatment period (from Baseline to End of Treatment)					
3.63.	All Treated	[Non-Standard] SAFE_T3	Summary of Best Corrected Visual Acuity Test (BCVA) Scores (logMAR score) (Part 1)	Summarize: by ascending dose level, Total Use table 3.0501 from BMA117159 as template. Following "worst change from baseline'; add summary of change (category) for 'Most frequent change from baseline'.	SAC
3.64.	All Treated	[Non-Standard] SAFE_T3	Summary of Best Corrected Visual Acuity Test (BCVA) Scores (logMAR score) due to Corneal Finding (Part 1)	Summarize: by ascending dose level, Total Use table 3.0501 from BMA117159 study as template. Following "worst change from baseline'; add summary of change (category) for 'Most frequent change from baseline'.	SAC
3.65.	All Treated	[Non-Standard] SAFE_T4	Number (%) of Subjects with Intraocular Pressure (IOP) >= 22mm Hg Anytime Post-baseline (Part 1)	Summarize: by ascending dose level, Total	SAC
3.66.	All Treated	[Non-Standard] SAFE_T5	Shift in Pupillary Exam Findings from Baseline to Worst Post-Baseline (Part 1)	Summarize: by ascending dose level, Total, By eye (L/R) and subject (worse eye)	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.67.	All Treated	[Non-Standard] SAFE_T5	Shift in Extraocular Muscle Movement from Baseline to Worst Post-Baseline (Part 1)	Summarize: by ascending dose level, Total, By eye (L/R) and subject (worse eye)	SAC
3.68.	All Treated	[Non-Standard] SAFE_T5	Shift in Ptosis from Baseline to Worst Post-Baseline (Part 1)	Summarize: by ascending dose level, Total, By eye (L/R) and subject (worse eye)	SAC
3.69.	All Treated	[Non-Standard] SAFE_T5	Shift in Blepharitis/MGD from Baseline to Worst Post-Baseline (Part 1)	Summarize: by ascending dose level, Total, By eye (L/R) and subject (worse eye)	SAC
3.70.	All Treated	[Non-Standard] SAFE-T5	Shift in Conjunctival Exam Findings for Chemosis from Baseline to Worst Post-Baseline (Part 1)	Summarize: by ascending dose level, Total Create shift table for each of 3 findings: Chemosis (Absent/Present); By eye (L/R) and subject (worse eye)	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.71.	All Treated	[Non-Standard] SAFE_T5	Shift in Conjunctival Exam Findings for Bulbar and Palpebral Conjunctiva from Baseline to Worst Post-Baseline (Part 1)	Summarize: by ascending dose level, Total Create shift table for each of 3 findings: Bulbar Conjunctiva White and Quiet: (Yes/No); Palpebral Conjunctiva within normal limits (Yes/No); By eye (L/R) and subject (worse eye)	SAC
3.72.	All Treated	[Non-Standard] SAFE_T5	Shift in Scleritis from Baseline to Worst Post-Baseline (Part 1)	By eye (L/R) and subject (both eyes in same ocular exam)	SAC
3.73.	All Treated	[Non-Standard] SAFE_T5	Shift in Corneal Epithelium Findings from Baseline to Worst Post-Baseline (Part 1)	Summarize: by ascending dose level, Total, By eye (L/R	SAC
3.74.	All Treated	[Non-Standard] SAFE_T6	Summary of Findings for Punctate Keratopathy (Part 1)	Summarize: by ascending dose level, Total, across ocular exams, and by eye (L/R).	SAC
3.75.	All Treated	[Non-Standard] SAFE_T6	Summary for Findings Related to Microcystic Edema (Part 1)	Summarize: by ascending dose level, Total, across ocular exams, and by eye (L/R).	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.76.	All Treated	[Non-Standard] SAFE_T5	Shift in Findings Related to Microcystic Edema from Baseline to Worst Post-Baseline (Part 1)		SAC
3.77.	All Treated	[Non-Standard] SAFE_T6	Summary for Findings Related to Microcystic without Edema (Part 1)	Summarize: by ascending dose level, Total, across ocular exams, and by eye (L/R).	SAC
3.78.	All Treated	[Non-Standard] SAFE_T5	Shift in Findings Related to Microcystic without Edema from Baseline to Worst Post-Baseline (Part 1)		SAC
3.79.	All Treated	[Non-Standard] SAFE_T6	Summary for Findings Related to Subepithelial Haze (Part 1)	Summarize: by ascending dose level, Total, across ocular exams, and by eye (L/R).	SAC
3.80.	All Treated	[Non-Standard] SAFE_T5	Shift in Findings Related to Subepithelial Haze from Baseline to Worst Post-Baseline (Part 1)		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.81.	All Treated	[Non-Standard] SAFE_T6	Summary for Findings Related to Corneal Neovascularization (Part 1)	Summarize: by ascending dose level, Total, across ocular exams, and by eye (L/R).	SAC
3.82.	All Treated	[Non-Standard] SAFE_T5	Shift in Findings Related to Corneal Neovascularization from Baseline to Worst Post-Baseline (Part 1)		SAC
3.83.	All Treated	[Non-Standard] SAFE_T6	Summary for Findings Related to Stroma (Part 1)	Summarize: by ascending dose level, Total, across ocular exams, and by eye (L/R).	SAC
3.84.	All Treated	[Non-Standard] SAFE_T5	Shift in Findings Related to Stroma from Baseline to Worst Post-Baseline (Part 1)		SAC
3.85.	All Treated	[Non-Standard] SAFE_T6	Summary for Findings Related to Active Opacity (Part 1)	Summarize: by ascending dose level, Total, across ocular exams, and by eye (L/R). See section 8.6.4 and mock shell document for details.	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.86.	All Treated	[Non-Standard] SAFE_T5	Shift in Findings Related to Active Opacity from Baseline to Worst Post-Baseline (Part 1)		SAC
3.87.	All Treated	[Non-Standard] SAFE_T6	Summary for Findings Related to Active Edema (Part 1)	Summarize: by ascending dose level, Total, across ocular exams, and by eye (L/R). See section 8.6.4 and mock shell document for details.	SAC
3.88.	All Treated	[Non-Standard] SAFE_T5	Shift in Findings Related to Active Edema from Baseline to Worst Post-Baseline (Part 1)		SAC
3.89.	All Treated	[Non-Standard] SAFE_T5	Shift in Corneal Endothelium Findings from Baseline to Worst Post-Baseline (Part 1)	Summarize: by ascending dose level, Total, By eye (L/R).	SAC
3.90.	All Treated	[Non-Standard] SAFE_T4	Summary for Descemet's Folds Findings (Part 1)	Summarize: by ascending dose level, Total, Among eyes with Corneal endothelium = Abnormal in at least one post-baseline ocular exam. See section 8.6.4 and mock shell document for details.	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.91.	All Treated	[Non-Standard] SAFE_T6	Summary for Endothelial Lesion Findings (Part 1)	Summarize: by ascending dose level, Total, across ocular exams, and by eye (L/R). See section 8.6.4 and mock shell document for details.	SAC
3.92.	All Treated	[Non-Standard] SAFE_T5	Shift in Slit Lamp Exam Findings from Baseline to Worst Post-Baseline (Part 1)	Summarize: by ascending dose level, Total, By eye (L/R). See section 8.6.4 and mock shell document for details.	SAC
3.93.	All Treated	[Non-Standard] SAFE_T4	Number (%) of Eye with Iris Findings at Any Time Post-Baseline (Part 1)	Summarize: by ascending dose level, Total, By eye (L/R). Summary tables for number (%) of eyes with 'Transillumination defect', 'Nodules', or 'Neovascularization' at any post-baseline ocular exam	SAC
3.94.	All Treated	[Non-Standard] SAFE_T5	Shift in Cataracts from Baseline to Worst Post-Baseline (Part 1)	Summarize: by ascending dose level, Total, By eye (L/R). See section 8.6.4 and mock shell document for details.	SAC
3.95.	All Treated	[Non-Standard] SAFE_T5	Summary of Grade Change in Cataract from Baseline to Post-Baseline (Part 1)	Summarize: by ascending dose level, Total, By eye (L/R). See section 8.6.4 and mock shell document for details.	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.96.	All Treated	[Non-Standard] SAFE_T5	Shift in Findings from FUNDUS Photograph from Baseline to Worst Post-Baseline (Part 1)	Summarize: by ascending dose level, Total, By eye (L/R). See section 8.6.4 and mock shell document for details.	SAC
Ocular findings during Follow-up period (from EOT to Last Follow-up Visit)					
3.97.	All Treated	[Non-Standard] SAFE_T3	Summary of Change (Worsening, No Change, Improvement) in Best Corrected Visual Acuity (BCVA) from EOT Visit to Last Follow-Up Visit (Part 1)	Summarize: by ascending dose level, Total See section 8.6.4 Ocular Exams and mock shell for details	SAC
3.98.	All Treated	[Non-Standard] SAFE_T3	Summary of Change (Worsening, No Change, Improvement) in Intraocular Pressure (IOP) from EOT Visit to Last Follow-Up Visit (Part 1)	Summarize: by ascending dose level, Total See section 8.6.4 Ocular Exams and mock shell for details	SAC
3.99.	All Treated	[Non-Standard] SAFE_T6	Summary of Change (Worsening, No Change, Improvement) in Corneal Epithelium Findings from EOT Visit to Last Follow-Up Visit (Part 1)	Summarize: by ascending dose level, Total See section 8.6.4 Ocular Exams and mock shell for details	SAC
3.100.	All Treated	[Non-Standard] SAFE_T6	Summary of Change (Worsening, No Change, Improvement) in Corneal Endothelium Findings from EOT Visit to Last Follow-Up Visit (Part 1)	Summarize: by ascending dose level, Total See section 8.6.4 Ocular Exams and mock shell for details	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.101.	All Treated	[Non-Standard] SAFE_T7	Summary of Resolution Time from EOT in Best Corrected Visual Acuity (BCVA) (Part 1)	Summarize: by ascending dose level, Total, By eye (R/L). See section 8.6.4 Ocular Exams and mock shell for details	SAC
3.102.	All Treated	[Non-Standard] SAFE_T7	Summary of Resolution Time from EOT in Intraocular Pressure (IOP) (Part 1)	Summarize: by ascending dose level, Total, By eye (R/L). See section 8.6.4 Ocular Exams and mock shell for details	SAC
3.103.	All Treated	[Non-Standard] SAFE_T7	Summary of Resolution Time from EOT in Corneal Epithelium Findings (Part 1)	Summarize: by ascending dose level, Total, By eye (R/L). See section 8.6.4 and mock shell document for details	SAC
3.104.	All Treated	[Non-Standard] SAFE_T7	Summary of Resolution Time from EOT in Corneal Endothelium (Part 1)	Summarize: by ascending dose level, Total, By eye (R/L). See section 8.6.4 and mock shell document for details	SAC
COVID-19					
3.105.	Screened	PAN1	Summary of COVID-19 Assessment for Subjects with COVID-19 Adverse Events (Part 1)		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.106.	Screened	PAN10A	Summary of Exposure Adjusted Incidence Rates of Adverse Events Over Time (Part 1)		SAC
3.107.	Screened	PAN11	Summary of Exposure Adjusted Incidence Rates for Common Adverse Events (Part 1)	Include footnote: Note: Common adverse events include those occurring in >2 subjects.	SAC
Additional Tables for Corneal Events					
3.108.	All Treated	[Non-Standard] SAFE_T8	Summary of Corneal Events (GSK Scale) by Grade and Visit (Part 1)	See Section 8.6.4 and mock shell document for details	SAC
3.109.	All Treated	AE13	Corneal Event (GSK Scale) Overview (Part 1)	See Section 8.6.4 and mock shell document for details	SAC
3.110.	All Treated	[Non-Standard] SAFE_T9	Summary of Action Taken with Study Treatment for Corneal Events (GSK Scale) by Visit (Part 1)	Summarize: by ascending dose level, Total. See Section 8.6.4 and mock shell document for details	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.111.	All Treated	AE13	Corneal Event (CTCAE) Overview (Part 1)	See Section 8.6.4 and mock shell document for details	SAC

14.10.8. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Laboratory					
3.1.	All Treated	LB11	Liver Function Tests Patient Profiles Plot for Subjects with ALT/AST/Total Bilirubin of Toxicity Grade 2 or Above (Part 1)		SAC
3.2.	All Treated	LIVER14	Scatter Plot of Maximum vs. Baseline for ALT (Part 1)		SAC
3.3.	All Treated	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin (Part 1)		SAC

14.10.9. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Drug Concentration Measure					
4.1.	PK	PK01	Summary of Plasma GSK2857916 (ADC) PK Concentration-Time Data (Part 1)	By dose level	SAC
4.2.	PK	PK01	Summary of Plasma GSK2857916 (Total Antibody) PK Concentration-Time Data (Part 1)	By dose level	SAC
4.3.	PK	PK01	Summary of Plasma cys-mcMMAF PK Concentration-Time Data (Part 1)	By dose level	SAC
4.4.	PK	PK13	Listing of Derived GSK2857916 (ADC) PK Parameters (Untransformed) (Part 1)		SAC
4.5.	PK	PK13	Listing of Derived GSK2857916 (Total Antibody) PK Parameters (Untransformed) (Part 1)		SAC
4.6.	PK	PK13	Listing of Derived cys-mcMMAF PK Parameters (Untransformed) (Part 1)		SAC
Pharmacokinetic Parameters					
4.7.	PK	PK06	Summary of Derived GSK2857916 (ADC) PK Parameters (Part 1)	By dose level PK06 with both transformed and untransformed values.	SAC
4.8.	PK	PK06	Summary of Derived GSK2857916 (Total Antibody) PK Parameters (Part 1)	By dose level PK06 with both transformed and untransformed values.	SAC
4.9.	PK	PK06	Summary of Derived cys-mcMMAF PK Parameter (Part 1)	By dose level PK06 with both transformed and untransformed values.	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Accumulation Ratio					
4.10.	PK	PK05	Summary of Results of Accumulation Ratio Assessment for GSK2857916 (ADC) (Part 1)	By dose level Include R(Ctrough) and R(Ceoi) with 95%CI, SD log and %CVb in one table.	SAC
4.11.	PK	PK05	Summary of Results of Accumulation Ratio Assessment for GSK2857916 (Total Antibody) (Part 1)	By dose level Include R(Ctrough) and R(Ceoi) with 95%CI, SD log and %CVb in one table.	SAC
4.12.	PK	PK05	Summary of Results of Accumulation Ratio Assessment for cys-mcMMAF (Part 1)	By dose level Include R(Ctrough) and R(Ceoi) with 95%CI, SD log and %CVb in one table.	SAC

14.10.10. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Drug Concentration Measure					
4.1.	PK	PK17	Individual Plasma GSK2857916 (ADC) Concentration-Time Plots (Linear and Semi-Log) by Dose (Part 1)		SAC
4.2.	PK	PK17	Individual Plasma GSK2857916 (ADC) Concentration-Time Plots (Linear and Semi-Log) (Part 1)		SAC
4.3.	PK	PK17	Individual Plasma GSK2857916 (ADC) Concentration-Time Plots (Linear and Semi-Log) by Dose – Cycle 1 (Part 1)		SAC
4.4.	PK	PK17	Individual Plasma GSK2857916 (ADC) Concentration-Time Plots (Linear and Semi-Log)– Cycle 1 (Part 1)		SAC
4.5.	PK	PK17	Individual Plasma GSK2857916 (Total Antibody) Concentration-Time Plots (Linear and Semi-Log) by Dose (Part 1)		SAC
4.6.	PK	PK17	Individual Plasma GSK2857916 (Total Antibody) Concentration-Time Plots (Linear and Semi-Log) (Part 1)		SAC
4.7.	PK	PK17	Individual Plasma GSK2857916 (Total Antibody) Concentration-Time Plots (Linear and Semi-Log) by Dose – Cycle 1 (Part 1)		SAC
4.8.	PK	PK17	Individual Plasma GSK2857916 (Total Antibody) Concentration-Time Plots (Linear and Semi-Log) – Cycle 1 (Part 1)		SAC
4.9.	PK	PK17	Individual Plasma cys-mcMMAF Concentration-Time Plots (Linear and Semi-Log) by Dose (Part 1)		SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
4.10.	PK	PK17	Individual Plasma cys-mcMMAF Concentration-Time Plots (Linear and Semi-Log) by Dose - Limit the Maximum Concentration Value of 3000 (Part 1)	Maximum value of vertical axis is 3000.	SAC
4.11.	PK	PK17	Individual Plasma cys-mcMMAF Concentration-Time Plots (Linear and Semi-Log) (Part 1)		SAC
4.12.	PK	PK17	Individual Plasma cys-mcMMAF Concentration-Time Plots (Linear and Semi-Log) - Limit the Maximum Concentration Value of 3000 (Part 1)	Maximum value of vertical axis is 3000.	SAC
4.13.	PK	PK17	Individual Plasma cys-mcMMAF Concentration-Time Plots (Linear and Semi-Log) by Dose – Cycle 1 (Part 1)		SAC
4.14.	PK	PK17	Individual Plasma cys-mcMMAF Concentration-Time Plots (Linear and Semi-Log) by Dose – Cycle 1, Limit the Maximum Concentration Value of 3000 (Part 1)	Maximum value of vertical axis is 3000.	SAC
4.15.	PK	PK17	Individual Plasma cys-mcMMAF Concentration-Time Plots (Linear and Semi-Log) – Cycle 1 (Part 1)		SAC
4.16.	PK	PK17	Individual Plasma cys-mcMMAF Concentration-Time Plots (Linear and Semi-Log) – Cycle 1, Limit the Maximum Concentration Value of 3000 (Part 1)	Maximum value of vertical axis is 3000.	SAC
4.17.	PK	PK17	Mean (+SD) Plasma GSK2857916 (ADC) Concentration-Time Plots (Linear and Semi-Log) (Part 1)		SAC
4.18.	PK	PK17	Mean (+SD) Plasma GSK2857916 (ADC) Concentration-Time Plots (Linear and Semi-Log) – Cycle 1 (Part 1)		SAC
4.19.	PK	PK17	Mean (+SD) Plasma GSK2857916 (Total Antibody) Concentration-Time Plots (Linear and Semi-Log) (Part 1)		SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
4.20.	PK	PK17	Mean (+SD) Plasma GSK2857916 (Total Antibody) Concentration-Time Plots (Linear and Semi-Log) – Cycle 1 (Part 1)		SAC
4.21.	PK	PK17	Mean (+SD) Plasma GSK2857916 (ADC and Total Antibody) Concentration-Time Plots (Linear and Semi-Log) (Part 1)		SAC
4.22.	PK	PK17	Mean (+SD) Plasma GSK2857916 (ADC and Total Antibody) Concentration-Time Plots (Linear and Semi-Log) – Cycle 1 (Part 1)	See similar Fig14.0190 from BMA117159 (Primary_01)	SAC
4.23.	PK	PK17	Mean (+SD) Plasma cys-mcMMAF Concentration-Time Plots (Linear and Semi-Log) (Part 1)		SAC
4.24.	PK	PK17	Mean (+SD) Plasma cys-mcMMAF Concentration-Time Plots (Linear and Semi-Log) – Cycle 1 (Part 1)		SAC
4.25.	PK	PK18	Median Plasma GSK2857916 (ADC) Concentration-Time Plots (Linear and Semi-Log) (Part 1)		SAC
4.26.	PK	PK18	Median Plasma GSK2857916 (ADC) Concentration-Time Plots (Linear and Semi-Log) – Cycle 1 (Part 1)		SAC
4.27.	PK	PK18	Median Plasma GSK2857916 (Total Antibody) Concentration-Time Plots (Linear and Semi-Log) (Part 1)		SAC
4.28.	PK	PK18	Median Plasma GSK2857916 (Total Antibody) Concentration-Time Plots (Linear and Semi-Log) – Cycle 1 (Part 1)		SAC
4.29.	PK	PK18	Median Plasma GSK2857916 (ADC and Total Antibody) Concentration-Time Plots (Linear and Semi-Log) (Part 1)	See similar Fig14.0200 from BMA117159 (Primary_01)	SAC
4.30.	PK	PK18	Median Plasma GSK2857916 (ADC and Total Antibody) Concentration-Time Plots (Linear and Semi-Log) – Cycle 1 (Part 1)		SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
4.31.	PK	PK18	Median Plasma cys-mcMMAF Concentration-Time Plots (Linear and Semi-Log) (Part 1)		SAC
4.32.	PK	PK18	Median Plasma cys-mcMMAF Concentration-Time Plots (Linear and Semi-Log) – Cycle 1 (Part 1)		SAC
4.33.	PK	PK28	Plot of Individual (+Geometric Mean and 95%CI) of Accumulation Ratios for GSK2857916 Analytes (Linear and Semi-Log) (Part 1)	Plot accumulation ratios versus dose. Add a reference line at 1. Plot Ro(Ctrough) and Ro(Ceoi) on different plots. Only include geometric mean and 95%CI. Plot analytes: ADC, total antibody, and cys-mcMMAF on the same plot.	SAC

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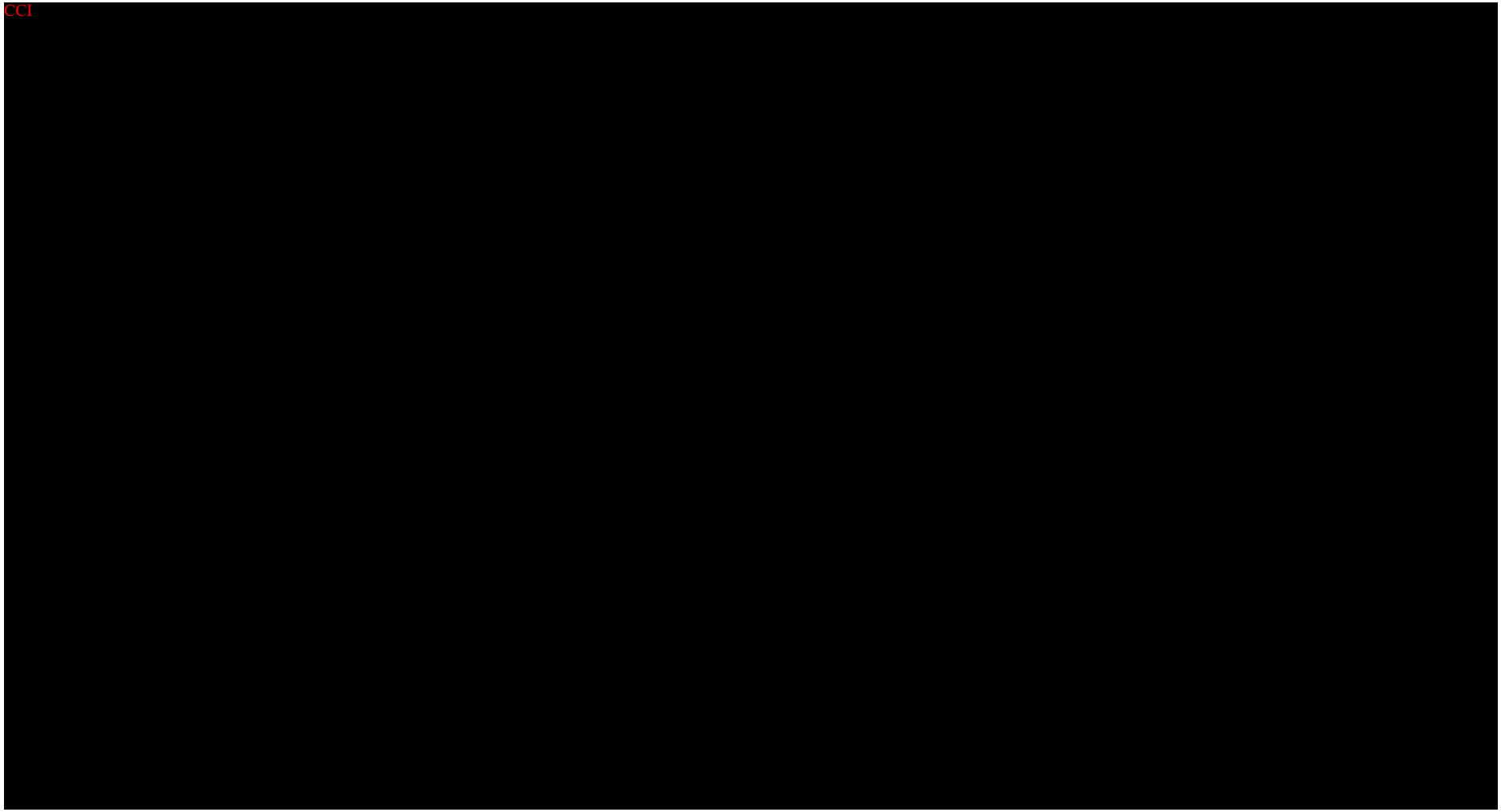

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14.10.14. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.	All Treated	ES2	Listing of Reasons for Study Withdrawal (Part 1)	ICH E3 Add column for Relatedness to COVID-19	SAC
2.	All Treated	SD2	Listing of Reasons for Study Treatment Discontinuation (Part 1)	ICH E3 The listing will include last dose date, and reasons for study treatment discontinuation. Add column for Relatedness to COVID-19	SAC
Protocol Deviations					
3.	All Treated	DV2	Listing of Protocol Deviations (Part 1)	Including a column “Important or not”	SAC
4.	All Treated	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations (Part 1)	ICH E3	SAC
Populations Analysed					
5.	All Treated	SP3	Listing of Participants Excluded from Any Population (Part 1)	ICH E3	SAC
Demographic and Baseline Characteristics					
6.	All Treated	DM2	Listing of Demographic Characteristics (Part 1)	ICH E3	SAC
7.	All Treated	DM9	Listing of Race (Part 1)	ICH E3	SAC
Exposure and Treatment Compliance					
8.	All Treated	TA1	Listing of Planned and Actual Treatments for Subjects with Actual Starting Dose Different from Assigned Dose (Part 1)	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
9.	All Treated	OEX8A	Listing of Exposure Data to GSK2857916 (Part 1)	Include start and stop dates, scheduled and actual dose, # of days on study treatment; sort by part, disease cohort, center, and subject id	SAC
10.	All Treated	ODMOD12A	Listing of Dose Delays (Part 1)	ICH E3	SAC
11.	All Treated	ODMOD10A	Listing of Dose Reductions (Part 1)	ICH E3	SAC
12.	All Treated	ODMOD17A	Listing of Infusion Interruptions (Part 1)	ICH E3	SAC
13.	All Treated	ODMOD14A	Listing of Incomplete Infusions (Part 1)	ICH E3	SAC
14.	All Treated	OEX9	Summary Listing of Overall Exposure and Dose Modifications (Part 1)		SAC
Dose-Limiting Toxicity					
15.	DLT Evaluable	DL3	Listing of Dose-Limiting Toxicities during the Determinative Period (Part 1)	ICH E3 Add footnote: “The determinative period is the first 21 days of intervention”	SAC
Adverse Events					
16.	All Treated	OAE04	Listing of Adverse Events (Part 1)	ICH E3	SAC
17.	All Treated	OAE03	Listing of Subject Numbers for Individual Adverse Events (Part 1)	ICH E3	SAC
18.	All Treated	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text (Part 1)	IDSL	SAC
19.	All Treated	OAE04	Listing of Treatment Emergent Adverse Events (Part 1)	ICH E3	SAC
Serious and Other Significant Adverse Events					

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
20.	All Treated	DTH3	Listing of Deaths (Part 1)		SAC
21.	All Treated	OAE04	Listing of Fatal Serious Adverse Events (Part 1)		SAC
22.	All Treated	OAE04	Listing of Non-Fatal Serious Adverse Events (Part 1)		SAC
23.	All Treated	OAE04	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment (Part 1)	Based on Action taken on AE	SAC
24.	All Treated	OAE04	Listing of Adverse Events Leading to Dose Reductions for GSK2857916 (Part 1)		SAC
25.	All Treated	OAE04	Listing of Adverse Events Leading to Dose Interruptions/Dose Delays for GSK2857916 (Part 1)		SAC
26.	All Treated	OAE04	Listing of Adverse Events Leading to Infusion Interruptions for GSK2857916 (Part 1)	ICH E3	SAC
27.	All Treated	OAE04	Listing of Adverse Events Leading to Incomplete Infusions for GSK2857916 (Part 1)	ICH E3	SAC
28.	All Treated	OAE04	Listing of Corneal Events (GSK Scale) (Part 1)		SAC
29.	All Treated	OAE04	Listing of Thrombocytopenia (Part 1)		SAC
30.	All Treated	OAE04	Listing of Infusion Related Reactions (Part 1)		SAC
Hepatobiliary (Liver)					
31.	All Treated	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events (Part 1)	IDSL	SAC
32.	All Treated	SU2	Listing of Substance Use for Participants with Liver Stopping Events (Part 1)	IDSL	SAC
All Laboratory					
33.	All Treated	OLB7	Listing of All Laboratory Data for Subjects with Lab Values of Potential Clinical Importance (Part 1)	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
34.	All Treated	UR2A	Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance (Part 1)		SAC
35.	All Treated	OLB7	Listing of eGFR for Subjects with Lab Values Outside of Normal Range (Part 1)		SAC
36.	All Treated	LB14	Listing of Laboratory Data with Character Results (Part 1)		SAC
Performance Status					
37.	All Treated	PS5A	Listing of ECOG Performance Status (Part 1)		SAC
ECG					
38.	All Treated	EG3	Listing of ECG Values of Potential Clinical Importance (Part 1)		SAC
39.	All Treated	EG5	Listing of Abnormal ECG Findings (Part 1)	IDSL	SAC
LVEF					
40.	All Treated	OLVEF2A	Listing of Left Ventricular Ejection Fraction Results (Part 1)		SAC
Vital Signs					
41.	All Treated	OVT7A	Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance (Part 1)	IDSL Display ALL Vital Signs for a subject who experienced a value of potential clinical importance.	SAC
42.	All Treated	OVT7A	Listing of All Vital Signs Data for Subjects (Part 1)	IDSL	SAC
Anti-Drug Antibody					
43.	All Treated	ADA01	Listing of Anti-GSK2857916 Antibody Results (Part 1)		SAC
Pharmacokinetic					
44.	PK	PK07	Listing of Plasma GSK2857916 (ADC) Pharmacokinetic Concentration-Time Data (Part 1)		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
45.	PK	PK07	Listing of Plasma GSK2857916 (Total Antibody) Pharmacokinetic Concentration-Time Data (Part 1)		SAC
46.	PK	PK07	Listing of Plasma cys-mcMMAF Pharmacokinetic Concentration-Time Data (Part 1)		SAC
47.	PK	PK15	Listing of GSK2857916 (ADC) Accumulation Ratio (Part 1)		SAC
48.	PK	PK15	Listing of GSK2857916 (Total Antibody) Accumulation Ratio (Part 1)		SAC
49.	PK	PK15	Listing of cys-mcMMAF Accumulation Ratio (Part 1)		SAC
CCI [redacted]					
Efficacy					
52.	All Treated	RE5	Listing of Investigator - Assessed Responses (with and without confirmation) per IMWG Response Criteria (Part 1)		SAC
53.	All Treated	RE5	Listing of Extramedullary Disease Evaluation (Part 1)		SAC
54.	All Treated	RE5	Listing of Skeletal Survey (Part 1)		SAC

14.10.15. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Demographic and Baseline Characteristics					
55.	All Treated	SU2	Listing of Substance Use (Part 1)		SAC
56.	All Treated	DC3	Listing of Disease Characteristics at Initial Diagnosis (Part 1)		SAC
57.	All Treated	DC4	Listing of Disease Characteristics at Screening (Part 1)		SAC
58.	All Treated	DC4	Listing of Genetic Characteristics and Cytogenetic Risk (Part 1)		SAC
Prior and Concomitant Medications					
59.	All Treated	CM2	Listing of Prior Medications (Part 1)		SAC
60.	All Treated	CM2	Listing of Concomitant Medications (Part 1)		SAC
61.	All Treated	CM2	Listing of Blood Products on Treatment (Part 1)		SAC
62.	All Treated	CM2	Listing of Blood Supportive Care Products on Treatment (Part 1)		SAC
63.	All Treated	CM2	Listing of Stem Cell Mobilization Products on Treatment (Part 1)		SAC
64.	All Treated	CM2	Listing of Eye Medications (Part 1)		SAC
Medical Conditions					
65.	All Treated	MH2	Listing of Prior Medical Conditions (Part 1)		SAC
66.	All Treated	CM2	Listing of Current Medical-Conditions (Part 1)		SAC
Anti-Cancer Therapy					
67.	All Treated	AC6	Listing of Prior Anti-Cancer Therapy (Part 1)		SAC
68.	All Treated	AC6	Listing of Follow-up Anti-Cancer Therapy (Part 1)		SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
69.	All Treated	AC7	Listing of Prior, On treatment, and Follow-up Anti-Cancer Radiotherapy (Part 1)		SAC
70.	All Treated	OSP3	Listing of Prior, On Treatment, and Follow-up Cancer and Non-Cancer Related Surgical Procedure (Part 1)		SAC
71.	All Treated	OSP3	Listing of Stem Cell Transplant (Part 1)		SAC
Ocular Exam					
72.	All Treated	[Non-Standard] SAFE_L1	Listing of Visual Acuity Results (Part 1)		SAC
73.	All Treated	[Non-Standard] SAFE_L1	Listing of Conjunctival Exam Results (Part 1)		SAC
74.	All Treated	[Non-Standard] SAFE_L1	Listing of Slit Lamp Anterior Chamber, Slit Lamp Iris and Slit Lamp Lens Exam Results (Part 1)		SAC
75.	All Treated	[Non-Standard] SAFE_L1	Listing of Indirect Fundoscopic Exam (Part 1)		SAC
76.	All Treated	[Non-Standard] SAFE_L1	Listing of Pupillary Exam Results (Part 1)		SAC
77.	All Treated	[Non-Standard] SAFE_L1	Listing of Extraocular Muscle Movement and External Exam Results (Part 1)		SAC
78.	All Treated	[Non-Standard] SAFE_L1	Listing of Lids, Lashes, Lacrimal System Exam and Scleritis Results (Part 1)		SAC
79.	All Treated	[Non-Standard] SAFE_L1	Listing of Corneal Results (Part 1)		SAC

14.11. Appendix 11: Example Mock Shells for Data Displays

Mock shells for data displays will be prepared separately from the RAP.

14.12. Appendix 12: International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma

Response	IMWG Criteria
Stringent complete response (sCR)	• Complete response as defined below plus normal FLC ratio[1] and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)[2]
Complete response (CR)	• Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow[3]
Very good partial response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response (PR)	• ≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; • If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; • If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)[4] of soft tissue plasmacytomas is also required
Minimal response (MR)	• ≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)[4] of soft tissue plasmacytomas is also required
Stable Disease (SD)	• Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease (PD)[5,6]	Any one or more of the following criteria: • Increase of 25% from lowest confirmed response value in one or more of the following criteria: - Serum M-protein (absolute increase must be ≥0·5 g/dL); - Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; - Urine M-protein (absolute increase must be ≥200 mg/24 h); • In participants without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); • In participants without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); • Appearance of a new lesion(s), ≥50% increase from nadir in SPD[4] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; • ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Relapse	Clinical relapse requires one or more of:

	• Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD§§ of the measurable lesion; • Hypercalcaemia (>11 mg/dL); • Decrease in haemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; • Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; • Hyperviscosity related to serum paraprotein

Overall Responders: PR, VGPR, CR, sCR
Clinical Benefit Rate: Overall responders + MR
Adapted from Kumar et.al. Lancet Oncol 2016; 17: e328–46
1 All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).
2 Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λL ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.
3 Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of participants having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in participants receiving monoclonal antibodies should be differentiated from the therapeutic antibody.
4 Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For participants with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumour size will be determined by the SPD.
5 Positive fixation alone in a participant previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, participants who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.
6 In the case where a value is felt to be a spurious result per physician discretion (e.g. a possible laboratory error), that value will not be considered when determining the lowest value.

Information Type:	Statistical Analysis Plan (SAP) Amendment for Part 2

TITLE PAGE

Protocol Title:	A Phase I Open-Label, Dose Escalation Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, Immunogenicity and Clinical Activity of the Antibody Drug Conjugate GSK2857916 in Japanese Participants with Relapsed/Refractory Multiple Myeloma
Study Number:	207504
Compound Number:	GSK2857916
Abbreviated Title:	A Phase I open label, dose escalation study in Japanese participants with relapsed/refractory multiple myeloma who have failed prior anti-myeloma treatments.
Acronym:	BCMA

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s): Not applicable

SAP Author(s):

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PPD Medical Writer, Medical Writing, Clinical Operations and Platforms, Japan Medical and Development, GlaxoSmithKline K.K.	27-APR-2023
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GSK Clinical Statistics & Clinical Programming Line Approvals (Method: E-mail)

Approver	Date
PPD Dev Biostats Stats Oncology, GlaxoSmithKline K.K.	28-APR-2023

TABLE OF CONTENTS

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1.0	27-APR-2022	Amendment 5 (12-NOV-2021)	Not Applicable	Original version
Amendment 1	X-APR-2023	Amendment 6 (10-Feb-2023)	1.Section 1.2 – To add the Post Analysis Continued Treatment (PACT) after final analysis data cut-off (DCO) 2.Section 3 & 4.2.2.1 – To clarify the definition for the ratio of the actual dose to the planned dose in terms of the DLT evaluable population 3.Section 4.3.3.2.2- To add the profile plot of GSK2857916 and response 4.Section 4.3.1.2.2 & 4.4.1.2 – To add how to address the calculation of SD when n is small 5.Section 4.3.3.2- To modify the confirmed response of #11 from NE to SD based on global project's policy change6. Section 6.1.1- To include "Participants who move to PACT" in the listing 7.Section 6.1.2-To remove the description of the "Race and Race combination will be summarised"	Changes followed the Protocol Amendment 3

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses to be included in the Clinical Study Report for Protocol: RPS-CLIN-050928 (Dated: 10-FEB-2023).

This SAP focuses on the analysis plan for combination therapy (Part 2). Reporting and analysis plan (RAP) focused on the analysis plan for monotherapy (Part 1) had been developed in a separate document and the analysis for Part 1 was completed on 28-JAN-2022.

Note that in line with the guidelines, this SAP will use the term "participant", while all data displays (Tables, Figures & Listings [TFL]) produced as part of the planned dry-run and Statistical Analysis Complete (SAC), will use the term "subject" which reflects GSK Data Display Standards terminology.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate safety, tolerability of GSK2857916 in Japanese participants RRMM.	• Number of participants with drug limiting toxicities (DLTs) • Adverse events (AEs) and changes in clinical signs and laboratory parameters.
Secondary	
• To evaluate pharmacokinetic (PK) profile of GSK2857916 and cysteine maleimidocaproyl monomethyl auristatin F (cys-mcMMAF) after IV single and repeat dose administration in Japanese participants with RRMM.	• GSK2857916 and cys-mcMMAF PK parameters following IV single and repeat dose administration as data permit (e.g., AUCs, Cmax, tmax, CL, Vss, t½ [single dose], Ceoi, Ctrough, and Rac (Ceoi and Ctrough) [repeat dose]).
• To assess anti-drug antibody (ADA) formation after IV single and repeat dose administration of GSK2857916.	• ADA incidence and titers after IV single and repeat dosing of GSK2857916.
• To investigate the initial anti-tumor activity of GSK2857916 in Japanese participants with RRMM.	• Clinical activity measured as Overall Response Rate (ORR) and Clinical Benefit Rate (CBR) which are defined as follows: o ORR: the percentage of participants achieving confirmed partial response or better (PR) o CBR: the percentage of participants with minimal response (MR) or better

Objectives	Endpoints
CCI	

1.2. Study Design

Overview of Study Design and Key Features	
Design Features	• This is a Phase 1, open label study of the antibody drug conjugate GSK2857916 in Japanese participants with relapsed/refractory multiple myeloma. • This study consists of 2 parts (Part 1 and Part 2). • Part 1 was dose escalation phase to evaluate the safety and tolerability of up to 2 dose levels of GSK2857916 monotherapy. • Part 2 will evaluate the safety of tolerability of 1 dose level of GSK2857916 in combination with 2 standard of care (SoC) regimens: Arm A – GSK2857916 with Bortezomib and Dexamethasone (Bor/Dex), and Arm B – GSK2857916 with Pomalidomide and Dexamethasone (Pom/Dex). • The dose escalation model in Part 1 was based on 3 + 3 design. The maximum number of participants was up to 12, up to 6 participants each for 2.5 mg/kg cohort and 3.4 mg/kg cohort. The maximum number of participants for Part 2 will be up to 12, up to 6 participants each for Arm A and Arm B based on 3 + 3 design. If participants prematurely discontinue during the DLT evaluation period for reasons other than toxicity, additional participants may be enrolled as replacement participants and assigned to the same dose level at the discretion of the Sponsor and in consultation with the investigator • In Part 1, GSK2857916 was given on a once every 21 days schedule. In Part 2, GSK 2857916 will be given in combination with Bor/Dex on a once every 21 days schedule (Arm A) or with Pom/Dex on a once every 28 days schedule (Arm B). • The initial anti-tumor activity of GSK2857916 based on response assessment criteria as defined by International Myeloma Working Group (IMWG) 2016 will also be assessed during the study [Kumar, 2016]. • A final DCO representing the end of data collection, prior to the End of Study (EOS), is defined as 21 months post last subject first dose. Following the final DCO date the study will move into the PACT phase and the clinical study database will be closed to new data. Participants who are receiving study treatment may continue to receive study treatment if they are gaining clinical benefit as assessed by the investigator until they meet any protocol-defined treatment discontinuation criteria. Although the clinical study database will be closed at the time of the final DCO date, the study remains open until all participants discontinue study treatment and complete the 70-day safety follow-up and the EOS definition is reached. • The EOS is defined as the date of the last visit of the last participant in the study (e.g. last dose plus 70 days AE reporting period) or last scheduled procedure

Overview of Study Design and Key Features	
	shown in the protocol Section 1.3 Schedule of Activities for the last participant in the study.
Treatment	• In Part 1, GSK2857916 was IV administered, via an infusion pump on Day 1 of each cycle over 30 minutes. Premedication was not required prior to infusion unless deemed medically necessary by the investigator, in which case it had been administered according to institutional recommendations. • In Part 2, GSK2857916 is IV administered via an infusion pump. Arm A receives 2.5 mg/kg on Day 1 of each cycle, once every 3 weeks. In addition, Arm A receives 1.3 mg/m^2 Bortezomib via subcutaneous injection on Day 1, Day 4, Day 8, Day 11 once every 3 weeks (Q3W) for 8 cycles and 20 mg Dexamethasone orally on Day 1, Day 2, Day 4, Day 5, Day 8, Day 9, Day 11, and Day 12, Q3W for 8 cycles. Arm B receives 2.5 mg/kg of GSK2857916 on Day 1 of Cycle 1 and 1.9 mg/kg on Cycle 2 Day 1 and beyond, once every 4 weeks. In addition, Arm B receives 4 mg Pomalidomide orally daily on Days 1-21, once every 4 weeks (Q4W) and 40 mg Dexamethasone orally per day on Day 1, Day 8, Day 15, and Day 22 Q4W.
Treatment Assignment	• This is an open-label study and consists of two parts (Part 1, Part 2). There are two cohorts (2.5 mg/kg and 3.4 mg/kg) in Part 1 and one cohort for each arm in Part 2 (2.5 mg/kg with Bor/Dex for Arm A, 2.5 mg/kg at C1D1 and 1.9 mg/kg at C2D1 with Pom/Dex for Arm B).
Time & Events	• Refer to protocol Section 1.3 Schedule of Activities
Interim Analysis	• In Part 1, available safety data was reviewed after the completion of DLT evaluation period to determine if a dose-escalation is appropriate. Additionally, PK data was reviewed after the completion of DLT evaluation period to assess PK similarity between Japanese and overseas populations. • For Part 2, available safety data will be reviewed after the completion of DLT evaluation period per each arm to determine if the combination dose regimen is tolerable. An interim analysis may be conducted when the last participant within each arm in Part 2 is followed for at least 1 cycle to evaluate safety, efficacy and PK profiles.

2. STATISTICAL HYPOTHESES

The primary objective is to evaluate safety, tolerability of GSK2857916 in Japanese participants RRMM. There are no formal statistical hypotheses planned.

2.1. Multiplicity Adjustment

No formal statistical comparison will be performed; therefore, no adjustments for multiple comparisons or multiplicity are planned.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	• Study Population
All Treated	• All participants who received at least 1 dose of study treatment. • An incorrect treatment schedule or study treatment administration or an early termination of treatment will not result in exclusion of participants from this population.	• Study Population • Safety • Efficacy • Immunogenicity
DLT Evaluable	• All participants fulfilling the 'All Treated' population criteria and having received a complete infusion of GSK2857916 and at least 75% of planned doses of bortezomib/dexamethasone (Arm A) or pomalidomide/dexamethasone (Arm B) in Cycle 1. • Participants who have been withdrawn from the study for reasons other than toxicity but prior to the 21-day DLT observation period (Arm A) and the 28-day DLT observation period (Arm B) are not included in this population. • The ratio of the actual dose to the planned dose of bortezomib/dexamethasone (Arm A) or pomalidomide/dexamethasone (Arm B) is to be calculated as the average of actual dose/planned dose for each drug (Bortezomib and dexamethasone, or Pomalidomide and dexamethasone) administered to Cycle 1.	• Summary of DLT
Pharmacokinetic (PK)	• All participants in the 'All Treated' population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).	• PK
Pharmacodynamic (PD)	• All participants in the 'All Treated' population from whom at least one PD sample is obtained, analyzed, and is measurable.	• PD

4. STATISTICAL ANALYSES

4.1. General Considerations

Given that no formal statistical hypotheses are being tested in this study, analysis of the data obtained from the study will only utilize descriptive methods.

4.1.1. General Methodology

Participants who prematurely withdrew from study will not be replaced. However, participants in Part 2 who have received less than 1 full dose of GSK2857916, or less than 75% of planned doses of Bor/Dex or Pom/Dex, or who have been withdrawn from the study for reasons other than toxicity but prior to completion of DLT observation period will be replaced.

Part 2 result will be reported with separate outputs unless otherwise stated. Results will be presented for Arm A and Arm B separately. The treatment display format is specified in Output and Programming Specification (OPS) Section 4.2 Appendix 2 Study Treatment Group and Descriptions.

Unless otherwise specified, endpoints defined in Section 1.1 will be summarized using descriptive statistics, listed, and graphically presented (where appropriate). Continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum, and maximum. The $\log_e$-transformed PK parameters based on the geometric mean will be summarized using geometric mean, 95% confidence interval (CI) and the between-participant coefficient of variance (CV), $\%CV_b$. Categorical data will be summarized as the number and percentage of participants in each category.

Confidence intervals will use 95% CIs unless otherwise specified.

It is anticipated that study participant accrual will be spread thinly across centers and summaries of data by center would unlikely be informative and will not, therefore, be provided.

4.1.2. Baseline Definition

For all endpoints, the baseline value will be the latest pre-dose assessment within 21 days prior to first dose with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessment are assumed to be taken prior to first dose and used as baseline. For laboratory data, baseline will be the latest non-missing pre-dose value. For PD assessment, only the Cycle 1 Day 1 pre-dose measurement will be used as baseline. For electrocardiogram, if triplicate 12-lead electrocardiograms (ECGs) are collected at the last pre-dose assessment, the average of the three measurements will be used as baseline record. If there are multiple assessments on the same day, the mean will be used as the baseline value.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Screening (within 21 days prior to first dose)	Day 1 (Pre-Dose)	
Efficacy			
Disease assessment	X		Screening visit
Safety			

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Screening (within 21 days prior to first dose)	Day 1 (Pre-Dose)	
Laboratory	X	X	Latest up to Day 1
Vital Signs	X	X	Latest up to Day 1
ECG	X	X	Latest up to Day 1

4.2. Primary Endpoints Analyses

The primary safety endpoints of this study are:

- Number of participants with DLTs
- AEs and changes in clinical signs and laboratory parameters.

4.2.1. Definition of Endpoints

DLT is defined as any observed toxicity in the first 21 days of treatment cycle in Part 2 Arm A and as any observed toxicity in the first 28 days of treatment cycle in Part 2 Arm B.

The following events occurring within the DLT reporting period (first 21 days cycle for Arm A or first 28 days cycle for Arm B) will be considered a DLT if its relationship to the investigational agent cannot be ruled out:

Hematologic:

- Grade 3 or greater febrile neutropenia lasting >48 hours despite adequate treatment
  - Grade 3 is defined as absolute neutrophil count (ANC) <1000/mm^3 with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour
  - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour, with life-threatening consequences and urgent intervention indicated
- Grade 4 thrombocytopenia <25,000/mm^3 accompanied by clinically significant bleeding.

Non-hematologic except corneal toxicity:

- Any Grade 3 or greater non-hematologic toxicity (other than corneal events) which does not resolved with appropriate supportive treatment within 48 hours
- Any Grade 3 or greater non-hematologic laboratory value if
  - The laboratory abnormality persists for >48 h despite supportive treatment
  - The abnormality leads to hospitalization

Corneal toxicity:

- Grade 4 per the modified corneal grading scale (See Protocol Appendix 7).

Other organ-specific toxicity:

- Liver toxicity meeting pre-specified GSK liver stopping criteria

4.2.2. Main Analytical Approach

The analyses described in the following sections will be performed using the All Treated analysis set, as defined in Section 3, unless otherwise specified. Missing data will not be imputed. Further analysis details are provided below.

4.2.2.1. Summary of DLT

Any participant who received a complete infusion of GSK2857916 and at least 75% of planned doses of Bor/Dex or Pom/Dex by the end of C1 is considered DLT-evaluable.

The ratio of the actual dose to the planned dose of Bor/Dex or Pom/Dex is to be calculated as the average of actual doseplanned dosefor each drug (Bortezomib and dexamethasone, or Pomalidomide and dexamethasone) administered to Cycle 1(C1). That means that subject will be considered as DLT-evaluable when the following formula is satisfied:

(dosing ratio (%) for Bor + dosing ratio (%) for Dex) /2 ≧ 75%

(dosing ratio (%) for Pom + dosing ratio (%) for Dex) /2 ≧ 75%

DLT will be listed according to GSK Oncology Data Standards.

4.2.2.2. Adverse Events

AEs analyses including the analysis of AEs, SAEs, treatment emergent AEs, and other significant AEs will be based on GSK Core Data Standards. Details of the planned analysis are provided in OPS Section 2.6. AEs analyses will include On-treatment AEs unless otherwise specified.

AEs will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA) central coding dictionary. AEs, aside from corneal events will be graded by the investigator according to the National Cancer Institute – Common Toxicity Criteria for Adverse Events (NCI-CTCAE) (Version 4.03). Only AEs graded by NCI-CTCAE will be summarized unless otherwise specified.

An overview summary of AEs, including counts and percentages of participants with any AE, AEs related to study intervention, Grade 3/4 AEs, Grade 3/4 AEs related to study intervention, AEs leading to dose reduction of study intervention, AEs leading to dose delay of study intervention, AEs leading to incomplete infusion, AEs leading to infusion interruption, AEs leading to permanent discontinuation of study intervention, any SAEs, SAE related to study intervention, fatal SAEs, and fatal SAEs related to study intervention will be produced. AEs leading to permanent discontinuation of study intervention will be summarized

The relationship between MedDRA SOC, PT, and Verbatim Text will be displayed.

A summary of number and percentage of participants with any AEs by maximum grade will be produced by PT; however ocular related AEs (corneal, keratopathy, microcyst, haze, opacity) by maximum grade will be summarised separately because the GSK grading scale is used for ocular

related AEs. AEs will be sorted by PT in descending order of the total incidence. The following algorithm for counting participants will be used in the summary:

- **Preferred term row:** Participants experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- **Any event row**: Each participant with at least one AE will be counted only once at the maximum grade no matter how many events they have.

Study treatment-related AEs, defined as an AE for which the investigator classified the relationship to study treatment as "Yes" will be summarised. A worst case scenario approach will be taken to handle data with missing relatedness. So the summary will include events with the relationship to study treatment as "Yes" or missing. The summary tables will be displayed by maximum grade in descending order of total incidence by PT.

All AEs and treatment emergent AEs will be listed. In addition, a listing of participant IDs for each individual AE will be produced.

4.2.2.2.1. Deaths and Serious Adverse Events

A listing of deaths will be generated to provide participant-specific details on participants who died.

All SAEs are included in the listing of all AEs. Separate supportive listings with participant-level details will be generated for

- Fatal SAEs
- Non-fatal SAEs

4.2.2.2.2. Adverse Events of Special Interest

The following will be considered adverse events of special interest (AESI) for the purpose of analyses:

- Corneal events
- Thrombocytopenia
- Infusion related reactions

The severity of AESIs other than corneal events will be graded using CTCAE version 4.03. A comprehensive list of MedDRA terms based on the safety review team (SRT) will be used to identify each type of event. Severity of corneal events associated with study intervention and related ophthalmic exam finding or visual acuity will be graded using GSK scale.

Summaries of the number and percentage of participants with AESIs by PT and maximum grade will be provided for each type of AESIs separately. The time of onset and duration of first occurrence of each type of AESIs will be summarised as a continuous variable. The number and percentage of participants who have time of onset of first occurrence (1-21, 22-42, 43-63, >63

days for CTCAE grading of Arm A and 1-21, 22-42, 43-63, 64-105 and >105 for GSK scale grading of Arm A; 1-28, 28-56, >56 days for CTCAE grading of Arm B and 1-28, 29-56, 57-84, 85-112 and >112 for GSK scale grading of Arm B) will be summarised. The number and percentage of participants who have duration of first occurrence (1-21, 22-42, >42 days for Arm A, 1-28, 29-56, >56 days for Arm B) will also be summarised.

A summary of event characteristics will be provided, including number of participants with any event, number of events, number of participants with any event that is serious, number of participants with any event that is related to study treatment, number of occurrence (One, Two, Three or more), maximum grade, and the action taken for the event. The percentage will be calculated in two ways, one with number of participants with events as the denominator and the other with total number of participants as the denominator. The worst-case approach will be applied at participant level for the maximum grade, i.e. a participant will only be counted once as the worst case from all the events experienced by the participant. For actions taken to an event, a participant will be counted once under each action, e.g. if a participant has an event leading to both study treatment discontinuation and dose reduction, the participant will be counted once under both actions.

Corneal events will be summarized with both CTCAE scale and GSK Scale. Corneal events with CTCAE scale overview will be summarized, including number of participants with events related to study treatment, with grade 3/4 events, with grade 3/4 events related to study treatment, with events leading to permanent discontinuation of study treatment, with events leading to dose reduction, and with events leading to dose interruption/delay. The summary for GSK scaled corneal events includes corneal events overview (same as CTCAE scaled summary), summary by grade and visit, and summary of action taken with GSK2857916.

All AESI will be listed separately. The details of the planned displays are provided in OPS Section 2.6, 2.12 & 2.13 (Safety Tables, ICH Listings, and Non-ICH Listings).

4.2.2.3. Clinical Laboratory Data

Clinical laboratory tests to be performed are listed in Appendix 3, including Chemistry laboratory test, Haematology laboratory tests, and Urinalysis. Laboratory evaluations will be based on GSK Core Data Standards. The details of the planned displays are provided in OPS Section 2.6.

Summary of change from baseline by scheduled visits using mean, median, standard deviation, minimum, and maximum will be provided. Count data will be used for automated white blood cell (WBC) differential. Detailed derivation of baseline assessment is specified in Section 4.1.2.

Laboratory grades will be reported using NCI-CTCAE Version 4.03. For these gradable laboratory tests, summaries of worst-case grade increase from baseline grade will be provided. These summaries will display the number and percentage of participants with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4.

Missing baseline grade will be assumed as grade 0. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g. sodium will be summarised as hyponatremia and hypernatremia.

For the laboratory tests that are not gradable by CTCAE v4.03, summaries of worst-case change from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarised for the worst-case post-baseline. If a participant has a decrease to low and an increase to high during the same time interval, the participant is counted in both the "Decrease to Low" categories and the "Increase to High" categories.

Separate summary tables for haematology, chemistry, and urinalysis laboratory tests will be produced. A separate listing of laboratory data with character values will also be provided.

A supporting listing of laboratory data for participants with any value of potential clinical importance will be provided. For lab tests that can be graded, values of grade 1 or above are defined as values of potential clinical concern. For lab test values that cannot be graded, values out of the normal range are defined as values of potential clinical concern. Please refer to Section 6.4.1 for the details of values of potential clinical importance defined in this study.

A summary of worst case urinalysis results post-baseline relative to baseline will be generated. Also, a supporting listing with participant level details will be provided.

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of participants with non-missing value at each individual visit.

4.3. Secondary Endpoints Analyses

Secondary endpoints include

- GSK2857916 and cys-mcMMAF PK parameters following IV single and repeat dose administration as data permit (e.g., AUCs, maximum observed plasma concentration [Cmax], time of maximum observed plasma concentration [tmax], CL, Vss, t1/2 [single dose], Ceoi, trough plasma concentration [Ctrough], and Rac (Ceoi and Ctrough) [repeat dose]).
- ADA incidence and titers after IV single and repeat dosing of GSK2857916.
- Clinical activity measured as ORR and CBR which are defined as follows:
  - ORR: the percentage of participants achieving confirmed partial response or better (≥PR)
  - CBR: the percentage of participants with MR or better

4.3.1. Pharmacokinetics

4.3.1.1. Definition of Endpoints

PK parameters will be calculated by standard non-compartmental analysis according to current GSK Clinical Pharmacology Modelling & Simulation (CPMS) working practices and using the currently supported version of WinNonLin (Currently version 8.0).

Calculation of non-compartmental parameters for the analysis will be based on actual sampling times. GSK2857916 (intact ADC, total antibody) and cys-mcMMAF PK parameters listed in Table 1 will be determined from the serum concentration-time data, as data permits, for each dose of GSK2857916 and for each participant:

1) After single dose: area under the plasma concentration-time curve (AUC(0-t), AUC(0-tau) and/or AUC(0-∞)), maximum observed plasma concentration (Cmax), time to Cmax (tmax), last time point where the concentration is above the limit of quantification (tlast), systemic clearance (CL), volume of distribution at steady state (Vss), terminal phase elimination rate constant (λz), terminal phase half-life (t½). Note that the pre-Cycle 2 Day 1 will be handled as the last of Cycle 1.
2) After repeat dose: concentration at end of infusion (Ceoi) after Cycles 4, 6, 9, and 12 and concentration pre-dose (Ctrough) prior to Cycles 4, 6, 9, and 12 for accumulation ratio analysis.

Table 1 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid
AUC(0-τ)	Area under the concentration-time curve during the dosing interval
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity will be calculated as: **AUC = AUC(0-t) + C(t) / lambda_z**
Cmax	Maximum observed concentration, determined directly from the concentration-time data for each cycle. For cys-mcMMAF, Cmax will not be derived when only predose and End of Infusion (EOI) samples were collected.
tmax	Time to reach Cmax, determined directly from the concentration-time data
t½	Apparent terminal half-life will be calculated as: **t½ = ln(2) / lambda_z**
tlast	Time of last observed quantifiable concentration
CL	Clearance
Vss	Volume of distribution at steady state
λz, lambda_z	Terminal phase rate constant

4.3.1.2. Main Analytical Approach

The secondary PK analyses will be based on the PK analysis set as defined in Section 3, unless otherwise specified. Missing data will not be imputed.

4.3.1.2.1. Drug concentration measures

GSK2857916 (intact ADC and total antibody) and cys-mcMMAF concentration-time data will be listed for each participant and summarized by descriptive statistics and each time point for Arm A and Arm B separately. If the difference between the number of participants with measurements and the number of imputations is 2 or less or if the number of participants with measurements is 1, SD will not be calculated. Linear and semi-logarithmic individual plasma

concentration-time profiles and mean and median profiles (when applicable) by GSK2857916 dose will be plotted for GSK2857916 (intact ADC and total antibody) and cys-mcMMAF.

4.3.1.2.2. Derived PK parameters

PK parameters defined in Section 4.3.1.1will be listed and summarized descriptively with mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation of log-transformed parameters, CV% and 95% CI of log-transformed parameters) for Arm A and Arm B separately. Data display specification for derived PK parameter summaries and listings are provided in OPS Section 2.7 & 2.8 (Pharmacokinetics Tables & Figures).

4.3.1.2.3. Assessment of Accumulation Ratio

To assess the extent of accumulation following GSK2857916 repeat dosing, the observed accumulation ratio (R_0) for GSK2857916 intact ADC, total antibody, and cys-mcMMAF will be determined as a ratio of Ceoi at Cycles 4, 6, 9, and 12 to Ceoi at Cycle 1 and as a ratio of Ctrough at Cycles 3, 5, 8, and 11 to Ctrough at Cycle 1.

Participants must receive the same dose as Cycle 1 without delay and receive the same dose for the previous 4 cycles relative to the cycle of interest to be included in this analysis (i.e. with dosing delays of ≤ 3 days). Note that receving1.9 mg/kg of GSK2857916 on Cycle 2 is not considered as the dose reduction from Cycle 1 for Arm B.

R_0(Ceoi) = Ceoi(Cx) / Ceoi(C1); x=4, 6, 9, 12

R_0(Ctrough) = Ctrough(Cx) / Ctrough*(C1); x=3, 5, 8, 11
Ctrough(Cx)=Pre-dose at Cycle(x+1)
Ctrough*(C1)=Pre-dose at Cycle 2 Day 1 (trough of C1)

Accumulation ratio of Ceoi and Ctrough will be summarised using descriptive statistics, graphically presented (where appropriate), and listed for Arm A and Arm B separately. Additionally, geometric mean and 95% CI will be calculated by taking the exponential for the mean and 95% CI of the difference in log-transformed concentration between the visit and Cycle 1 Day 1. These parameters will be summarized and plotted.

Details of the planned displays are provided in OPS Section 2.7 & 2.8 (Pharmacokinetics Tables & Figures) and will be based on GSK Data Standards and statistical principles.

4.3.2. Safety

4.3.2.1. Definition of Endpoints

The secondary safety endpoint is anti-GSK2857916 (drug) binding antibody.

4.3.2.2. Main Analytical Approach

For each participant, the anti-GSK2857916 (drug) binding antibody results and titers, ADC, and total antibody concentration will be listed for each assessment time point. The frequency and percentage of participants with positive and negative anti-drug antibody will be summarised for

each assessment and overall for each participant separately for Arm A and Arm B. The conclusive results will be based on the total antibody concentration.

4.3.3. Efficacy

4.3.3.1. Definition of Endpoints

The secondary efficacy endpoints are ORR and CBR. ORR is defined as the percentage of participants with a confirmed partial response (PR) or better (i.e. PR, very good partial response [VGPR], complete response [CR], and stringent complete response [sCR]) of best response, according to the IMWG Response Criteria [Kumar, 2016]. CBR is defined as the percentage of participants with a confirmed MR or better (i.e. MR, PR, VGPR, CR, and sCR) of best response, according to the IMWG Response Criteria [Kumar, 2016].

4.3.3.2. Main Analytical Approach

The hierarchy of response classifications from high to low is as follows: sCR, CR, VGPR, PR, MR, stable disease (SD), progressive disease (PD), and not evaluable (NE). Response was assessed according to the IMWG Response Criteria [Kumar, 2016] (See Section 6.5).

Unconfirmed response (without confirmation) are response assessments provided by the investigator. Confirmed response (with confirmation) is defined and the outline in derivation detailed in Table 2. For confirmed response derivations, only response assessments from the start of treatment up to the start of new anti-cancer therapy will be considered. Best Overall Response (BOR) will be derived from confirmed responses.

The analyses will be based on the All Treated analysis set as defined in Section 3, unless otherwise specified.

Table 2 Response confirmation algorithm

#	Response at the First Time Point	Response at Subsequent Disease Assessment[1]	Confirmed Response at the First Time Point	Date of Confirmed Response
1	sCR	sCR	sCR	First Time Point
2	sCR	CR	CR	First Time Point
3	CR	sCR/CR		
4	sCR/CR	VGPR	VGPR	First Time Point
5	VGPR	sCR/CR/VGPR		
6	sCR/CR/VGPR	PR	PR	First Time Point
7	PR	sCR/CR/VGPR/PR		
8	sCR/CR/VGPR/PR	MR	MR	First Time Point
9	MR	sCR/CR/VGPR/PR/MR		

10	sCR/CR/VGPR/PR/MR	SD	SD	First Time Point
11	sCR/CR/VGPR/PR/MR	PD (any reason) OR No subsequent disease assessment: **participant died or discontinued study or started new anti-cancer therapy** before further adequate disease assessment	SD	First Time Point
12	PD (due to reasons other than imaging, i.e., plasmacytoma or bone lesion)	PD (any reason) including PD after initiation of new anti-cancer therapy OR No subsequent disease assessment: participant **died due to PD** before further adequate disease assessment (including death due to PD after initiation of new anti-cancer therapy)	PD	First Time Point
13	PD (due to reasons other than imaging, i.e., plasmacytoma or bone lesion)	sCR/CR/VGPR/PR/MR/SD OR No subsequent disease assessment: participant died **due to reasons other than PD** before further adequate disease assessment OR No subsequent disease assessment: participant **discontinued study** before further adequate disease assessment	NE	First Time Point
14	sCR/CR/VGPR/PR/MR/PD (due to reasons other than imaging, i.e., plasmacytoma or bone lesion)	No subsequent disease assessment: participant has not died, discontinued from study or (except for PD) started new anti-cancer therapy; but as yet has no further adequate disease assessments	Unconfirmed sCR/CR/VGPR/PR/MR/PD. Will be categorized as NE for final ORR analysis.	First Time Point
15	SD	Any OR	SD	First Time Point

		No subsequent disease assessment		
16	PD due to imaging (plasmacytoma or bone lesion)	Any OR No subsequent disease assessment	PD	First Time Point
17	NE or missing	Any OR No subsequent disease assessment	NE	First Time Point

1. Subsequent disease assessment is defined as the next adequate (not missing or NE) disease assessment following the first timepoint before (or on the same date of) start of new anti-cancer therapy except for confirmation of PD, for which PD or death due to PD after new anti-cancer therapy are considered for confirmation of PD. No minimal time interval is required for the subsequent disease assessment, but a different sample is required for confirmation.

- SD does not need to be confirmed.
- PD due to imaging (i.e., plasmacytoma or bone lesion) does not need to be confirmed.
- Where criteria are not mutually exclusive, take the first that applies.

4.3.3.2.1. Summary Measure for BOR

Best Overall Response (BOR) will be derived from confirmed responses. The number and percentage of participants with BOR in the following response categories will be summarized for Arm A and Arm B separately: sCR, CR, VGPR, PR, overall response (sCR+CR+VGPR+PR), MR, SD, PD and NE.

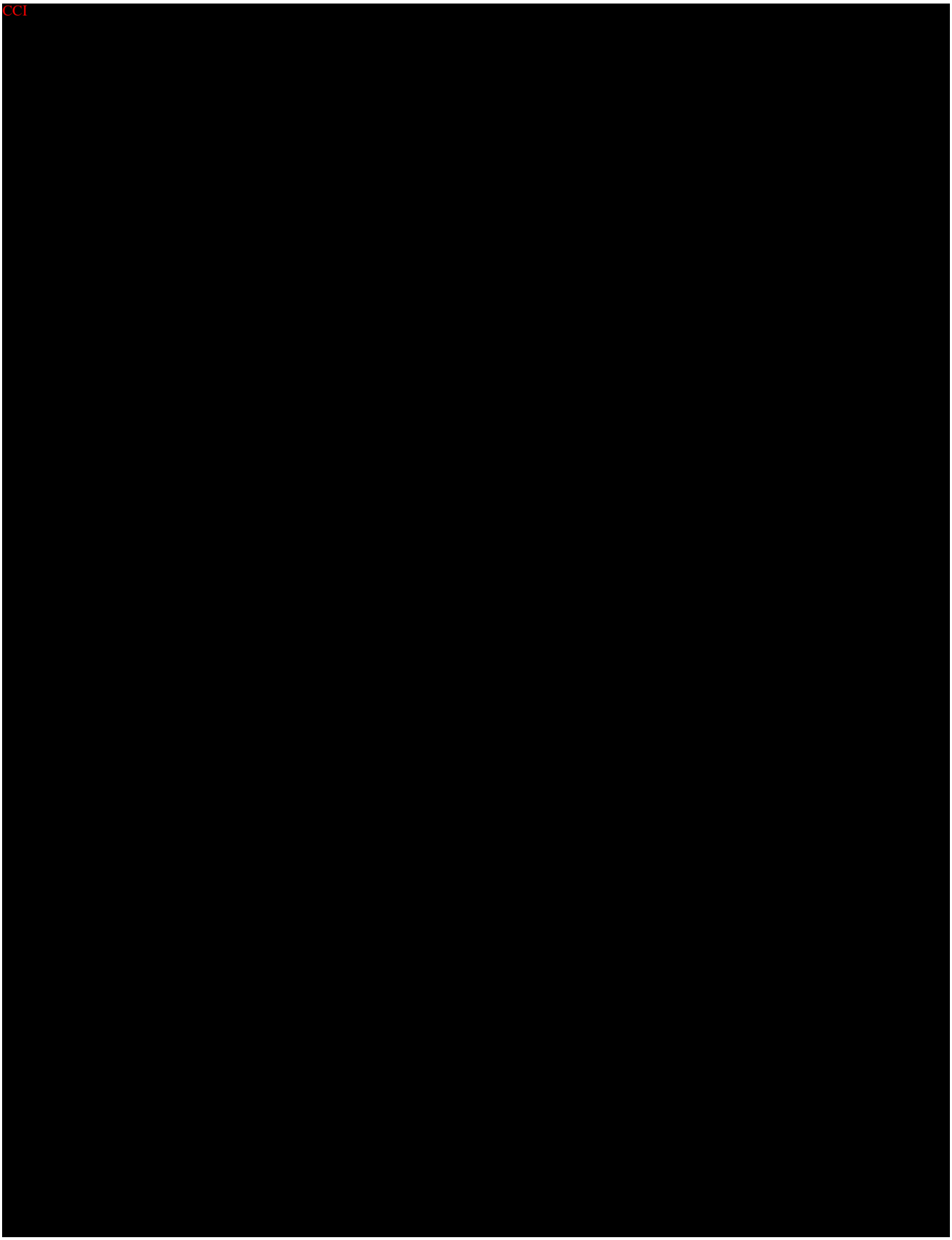
4.3.3.2.2. Summary Measure for ORR and CBR

Summary of ORR and CBR will be provided with the number and percentage of participants included. A two-sided exact 95% CI for ORR and CBR will also be provided. Participants with unknown or missing response will be treated as non-responders, i.e. these participants will be included in the denominator when calculating percentages of response.

In addition, A profile plot that displays the clinical response over time with the dose of GSK2857916 on each cycle will be produced. Listings of investigator assessed response, extramedullary disease evaluation, disease assessment scan, and skeletal survey will be provided. Details of the planned displays are provided in OPS Section 2.5, 2.6 &2.12 (Efficacy Tables, Efficacy Figure and ICH Listings).

CCI [redacted]

CCI



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4.5. Other Safety Analyses

4.5.1. Vital Signs

Vital signs analyses will be based on GSK Core Data Standard, unless otherwise specified. Vital sign data include blood pressure, heart rate, and temperature.

Vital signs data will be summarised with change from baseline (see Section 4.1.2) for detailed baseline derivation) as continuous variables.

In addition, vital sign values will be categorized as follows:

- Systolic blood pressure (mmHg):
  Grade 0 (<120), Grade 1 (120-139), Grade 2 (140-159) and Grade 3 (≥160)
- Diastolic blood pressure (mmHg):
  Grade 0 (<80), Grade 1 (80-89), Grade 2 (90-99), and Grade 3 (≥100)
- Heart rate (beats/min):
  <60, 60-100, and >100
- Temperature (°C):
  ≤35, >35-<38, ≥38

Summaries of worst-case changes in vital signs from baseline with respect to the categories defined above will be performed.

Listings with vital signs values as well as participants with abnormalities of potential clinical importance and grade will be provided.

4.5.2. Electrocardiograms

ECG data analyses will be based on GSK Core Data standards, unless otherwise specified. ECG data will include heart rate, PR, RR interval, QRS, QT and QTcF (QTc values based on Fridericia formula) intervals. Baseline QTcF value is determined by Day 1 pre-dose QTcF result (either a single result or the mean of triplicate resulted). If Day 1 pre-dose value is not available, the screening ECG results should be used. QTcF values will be rounded to the integer and categorized into the following ranges: Grade 0 (<450), Grade 1 (450-480), Grade 2 (481-500), and Grade 3 (≥501) and summarized.

The ECG results, increase in QTcF, and amount of increase from baseline value will be summarised.

Listings of abnormal ECG findings and a listing of ECG values including Potential Clinical Importance will be provided. Potential clinical significance ranges are provided in Section 6.4.1.

4.5.3. Ocular Exams

Ophthalmic exams are scheduled at screening, during the study, end of treatment (EOT) visit, and follow-up period. The ocular findings from ophthalmic exams will be analysed as described below.

1. From baseline to EOT visit, the following analysis will be performed:

> Best corrected visual acuity (BCVA): BCVA (logMAR score) at baseline, EOT visit, and last follow-up visit as well as worst and most frequent category (definite worsen, possible worsen, and no change/improved) of change from baseline will be summarised by eye (R/L) and participant (worse eye and better eye). BCVA for participants with corneal finding will also be provided. The logMAR score is calculated as:
>
> logMAR score = -1* (log10(Landolt ring value))

2. From EOT visit to last follow-up visit, the following analyses will be performed to assess the change in corneal findings after discontinuation of study treatment, for participants (worse eye) with exam finding at EOT visit worse than baseline.

a. Summary of change (worsening, no change, improvement) from EOT to last follow-up visit based on categories defined below by eye (R/L) and participant (worse eye).
b. Summary of number (%) of eyes and participants (worse eye) that resolve (improve to baseline level or better based on categories defined below), and descriptive summary of time from EOT visit to resolution among eyes and participants (worse eye) that resolved.

The parameters included in analyses are listed below:

1. BCVA change from baseline in log MAR scale (< 0.12, ≥ 0.12 to < 0.3, ≥ 0.3). This parameter is included in both analyses detailed above.
2. Corneal epithelium (Normal/Abnormal), Punctate Keratopathy (None/Mild/Moderate/Severe), Microcystic edema (No/Yes), Microcystic without edema (No/Yes), Subepithelial haze (No to Yes), Corneal neovascularization (No to Yes), Stroma (Normal/Abnormal), Active opacity (No/Yes), Active edema (No/Yes). These parameters are included only in analysis a) described above.

All summary and shift tables will be provided by eye (R/L) and worse eye or better eye. If both eyes are diagnosed as abnormal, participant is counted as abnormal (yes, present, or others).

The ocular exam results will be listed. The details of the planned displays are provided in OPS Section 2.6, 2.12, & 2.13 (Safety Tables, ICH Listings, and Non-ICH Listings).

4.5.4. Left Ventricular Ejection Fraction

Left ventricular ejection fraction (LVEF) data will be analysed based on GSK Oncology Data Standard. LVEF data are collected at screening and end of treatment visit. Post-baseline

assessments that used the same method of Echocardiogram (ECHO) as the baseline assessments will be used to derive the change from baseline. Absolute change from baseline in LVEF will be summarized by worst case post-baseline and by EOT. The change from baseline will also be categorized as follows:

- No change or any increase
- Any decrease
  - >0-<10 decrease
  - 10-19 decrease
  - ≥20 decrease
  - ≥10 decrease and ≥ lower limit of normal (LLN)
  - ≥10 decrease and < LLN
  - ≥20 decrease and ≥ LLN
  - ≥20 decrease and < LLN

LVEF results will be listed with participant level details, including absolute change from baseline.

4.5.5. Other Safety Measures

The medical conditions data for participants with liver stopping events will be listed. The substance use data for participants with liver stopping events will be listed.

Eastern Cooperative Oncology Group (ECOG) performance status is collected at baseline and post-baseline scheduled visits and all collected data will be listed based on GSK Oncology Data Standard.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If participants become pregnant while on the study, the information will be included in the narrative and no separate table or listing will be produced.

The safety analyses will be based on the All Treated Analysis Set as defined in Section 3, unless otherwise specified.

4.5.6. Extent of Exposure

Extent of exposure to GSK2857916, bortezomib, dexamethasone, and pomalidomide will be summarised.

The number of cycles administered to study treatment will be summarised with mean, median, standard deviation, minimum, and maximum. The number and percentages of participants who received a given number of cycles (<=4, >4 cycles) will be reported. Note that the cycle will not be counted when the administration is interrupted/delayed.

Cumulative actual dose (sum of dose at each cycle) and dose intensity per cycle (mg/kg/cycle) will be summarised using mean, median, standard deviation, minimum, and maximum by overall. The dose intensity (mg/kg/3 weeks) for Arm A, which is calculated as the cumulative

actual dose (mg/kg) divided by expected duration of exposure in 3 weeks (Last Dose date – First Dose date + 21)/21 and the dose intensity (mg/kg/4 weeks) for Arm B, which is calculated as the cumulative actual dose (mg/kg) divided by expected duration of exposure in 4 weeks (Last Dose date – First Dose date + 28)/28 will also be summarised. A by-participant summary listing of data on exposure to all study treatments will be produced.

Dose reductions will be summarised by number of reductions and reasons for reductions. Dose delays will be summarised by number of delays, reasons for the delays, and delay duration (days). The number and percentage of the delays for duration intervals of 1-21, 22-42, and >42 days for Arm A, of 1-28, 29-56, and >56 days for Arm B will be computed. Time to first delay will be summarised; first delay is defined as the first dose delay or first dose restarted after skipped dosing. Primary reasons for dose reductions and dose delays will also be summarised by overall.

Duration of delays for GSK2857916 is defined as period from the expected start date of dose to actual start date of current dose. Calculation: (actual start date of current dose - expected start date of dose). For Arm A, expected start date of dose = actual start date of previous dose + 21. For Arm B, expected start date of dose = actual start date of previous dose + 28.

The summaries of dose modifications will be provided. All the dose reductions, infusion interruptions, incomplete infusions and dose delays will be listed.

The duration of exposure to GSK2857916, bortezomib, dexamethasone, and pomalidomide(from first day to last day of treatment) will be calculated and summarised using mean, median, standard deviation, minimum, and maximum.

4.6. Other Analyses

4.6.1. Population Pharmacokinetic (POPPK) Analyses

The primary goal of this analysis is to characterize the population pharmacokinetics of GSK2857916 and associated analytes after intravenous of GSK2857916 in participants with multiple myeloma, as data permit. The influence of participant demographics, baseline characteristics, including disease activity, and co-medication on the pharmacokinetics of GSK2857916 in this population may be investigated. The individual participant PK parameters may be estimated and documented for the purposes of any subsequent exposure-response (PK/PD) analyses. The analysis may be performed by GSK CPMS and reported separately.

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4.7. Interim Analyses

An interim analysis may be conducted when the last participant within any arm in Part 2 has completed at least one cycle of the combination treatment.

4.8. Planned Analyses

A primary analysis will be conducted by the data cut-off performed after both EOT and the completion of AE and SAE collection (i.e., 70 days after the last dose of study treatment). The later of the primary analyses for Arm A (Bor/Dex) and Arm B (Pom/Dex) in Part 2 will be the final analysis for the study. See Section 4.2, Section 4.3, and Section 4.4 for all planned analysis for this study.

4.9. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 6 (Dated:10-Feb-2023).

5. SAMPLE SIZE DETERMINATION

The sample size planned for this study arises from the predefined criteria for dose escalation and is not driven by statistical considerations.

The maximum number of participants for Part 2 will be up to 12, up to 6 participants each for Arm A and Arm B based on the 3 + 3 designs.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

The study population analyses will be based on All Treated analysis set as defined in Section 3, unless otherwise specified. The analyses will also be performed for Arm A and Arm B separately.

Study population analyses including participant disposition, protocol deviations, participant demographic and baseline characteristic, prior and concomitant medications, anti-cancer therapies, and exposure and treatment modification will be based on GSK Core Data Standards. Details of the planned displays are presented in OPS section 2.4.

6.1.1. Participant Disposition

A summary of the number of participants in each of the analysis sets described in Section 3 will be provided. In addition, a listing of participants excluded from analysis populations will also be provided.

A summary of participant status and reasons 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. Reasons for study withdrawal will be presented in the order they are displayed in the electronic case report form (eCRF).

A summary of study treatment status will be provided. This display will show the number and percentage of participants who 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. Besides, the listing will also show participants who completed the study and move to PACT phase.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, baseline height, baseline body weight and baseline body mass index (BMI) calculated as body weight in kilograms divided by squared height in m^2) will be summarised and listed. Age, height, weight, and BMI will be summarised using the mean, standard deviation, minimum, median, and maximum. The count and percentage will be computed for sex and ethnicity.

Disease characteristics at initial diagnosis (e.g. time since initial diagnosis in years, stage at initial diagnosis, date of initial diagnosis) and screening will be listed.
Summary of disease characteristics at screening will be provided. Disease characteristics for multiple myeloma participants at screening, including stage, lines of prior therapy regimens, type of multiple myeloma, myeloma light chain and myeloma immunoglobulin will be summarised and listed.
Prior and current medical conditions will be listed and current medical conditions will be summarised.

Genetic characteristics for multiple myeloma participants at screening will be summarised and listed. Cytogenetic risk for multiple myeloma participants at screening will be summarised. A participant is considered as having high cytogenetic risk if the participant has any of the following cytogenetics: t(4;14), 17p13del, t(14;16).

Substance use, including smoking history and alcohol use, will be listed.

Prior and follow-up anti-cancer therapy will be coded using the GSK Drug code dictionary. A listing of prior anti-cancer therapy will show the relationship between Anatomical Therapeutic Chemical (ATC) Level 1 and verbatim text.
Anti-cancer radiotherapy will be listed. Prior, on treatment, and follow-up cancer and non-cancer related surgeries will also be listed. A listing of Stem Cell Transplant will be provided.

6.1.3. Protocol Deviations

Important protocol deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management, or patient assessment will be summarised and all protocol deviations, including both major and minor, will be listed. The classification of important protocol deviations includes AE/SAE, disallowed devices, disallowed medications, inclusion/exclusion criteria, informed consent, IP administration/study treatment, procedures/tests, and withdrawal criteria. The protocol deviation terms are detailed in the Protocol Deviation Specification.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Specification.

- Data will be reviewed prior to database lock to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of 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.

There is no Per-Protocol Population for this study. Protocol deviations will not be used to determine membership in any particular study population for this study.

6.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using GSK Drug coding dictionary and listed. ATC classification Level 1 (Body System) information will be included in the dataset created but will not appear on the listing.

Blood products or blood supportive care products with onset date within the on-treatment window will be included in the listings. Administration of on-treatment stem cell mobilization products will also be provided in a listing.

Prior medications will be listed.

6.1.5. Additional Analyses Due to the COVID-19 Pandemic

A standardized MedDRA Query (SMQ) will be used to identify all COVID-19 AEs.

The number of participants with suspected, probable, and confirmed COVID-19 infections will be summarised.

The details of the planned displays are provided in OPS Section 2.6 Safety Tables.

6.2. Appendix 2 Clinical Laboratory Tests

The tests detailed in Table 3 will be performed by the local laboratory.

Table 3 List of Clinical Laboratory Tests

Hematology[1]		
Platelet Count	RBC Indices:	Automated WBC Differential:
Red blood cell (RBC) Count	Mean corpuscular volume (MCV)	Neutrophils
White blood cell (WBC) Count (absolute)	Mean corpuscular hemoglobin (MCH)	Lymphocytes
Reticulocyte Count	Mean corpuscular hemoglobin concentration (MCHC)	Monocytes
Hemoglobin		Eosinophils
Hematocrit		Basophils

Table 3 List of Clinical Laboratory Tests (cont.)

Clinical Chemistry[1]			
Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin
Creatinine	Chloride	Alanine aminotransferase (ALT)	Uric Acid
Glucose	Spot urine (albumin / creatinine ratio)	Gamma glutamyl transferase (GGT)	Albumin
Sodium	Calcium	Alkaline phosphatase (ALP)	Total Protein
Magnesium	Phosphorous	Creatine kinase (CK)	Lactate dehydrogenase (LDH)
Estimated Glomerular filtration rate (eGFR)			
Urine[1]			
Routine Urine Dipstick (Urinalysis required if blood or protein is detected by dipstick)			
Specific gravity			
pH, glucose, protein, blood and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Other Safety			
C-reactive protein (CRP)[1]			
Troponin I or T[4]			
B-type natriuretic peptide (BNP)[4]			
PK/ADA			
Pharmacokinetics (PK)[2]			
Anti-Drug Antibodies (ADA)[2, 3]			
Optional Testing			
Genetics[2]			
Disease Evaluation Laboratory Tests			
Urine Protein Electrophoresis (UPEP)[1]	urine Immunofixation[1]	24-hour urine collection for M-protein[1]	Calcium corrected for albumin (serum)[1]
Serum Protein Electrophoresis (SPEP)[1]	Serum M-protein calculation[1]	Serum Immunofixation[1]	Beta2 macroglobulin[1]
Serum Kappa, lambda free light chain (LC), Free light chain (FLC) ratio[1]	IgG, IgA, IgM. IgD and IgE only in participants with IgD or IgE myeloma		
Bone Marrow Aspiration/Biopsy			
Bone marrow for disease assessment[1]			
Bone marrow biopsy to confirm sCR by IHC[1]			
Bone marrow for FISH testing[5]			

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1. To be performed at local laboratory.

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3. Not needed at screening
4. If not available from local laboratory, it can be performed at central laboratory.
5. FISH testing at least for: t(4;14), t(14;16), 17p13del. BM samples from within 60 days prior to first dose are acceptable for FISH analysis.

6.3. Appendix 3 Schedule of Activities (SoA)

Prefer to Protocol Section 1.3 Table 2 and Table 3 for Schedule of Activities for Part 2.

6.4. Appendix 4 Data Derivations Rule

6.4.1. Criteria for Potential Clinical Importance

6.4.1.1. Laboratory Values

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

To identify laboratory values of potential clinical importance, NCI-CTCAE Version 4.03 will be used to assign grades to the relevant laboratory parameters. NCI-CTCAE v4.03 can be found at http://ctep.cancer.gov/reporting/ctc.html.

For laboratory data which are not listed in the NCI-CTCAE v4.03, a summary of values outside the normal range will be provided.

6.4.1.2. ECG

Potential clinical importance ranges for ECG values are listed below.

	ECG Parameter	Units	Clinical Concern Range	
			Low	Upper
Absolute	QTc Interval	msec		>480
Change from baseline	QTc Interval	msec		>30

6.4.1.3. Vital Signs

For vital signs, the most updated IDSL standard up to the SAP effective date will be followed.

6.4.2. Study Phases

Assessments and events will be classified according to the time of occurrence relative to date/time of first dose of study treatment.

Study Phase	Definition
Pre-Treatment	Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Date
On-Treatment AEs	Study Treatment Start Date < Date ≤ Study Treatment Stop Date + 70 days

For assessment or event on the first dosing day, whether it is Pre-Treatment or On-Treatment should be based on time if available. If time is not available, the first dosing day (Day 1) is considered Pre-Treatment for ECOG, ECG, vital signs, liver events, lab tests, cardiac scan, and other safety domains, and On-Treatment for AEs and concomitant medications.

6.4.2.1. Study Phases for Concomitant Medication and Blood and Blood Supportive Care Product

Concomitant Medication and Blood and Blood Supportive Care and Stem Cell Mobilization Product start and end dates will be assigned to study time periods in relation to first dose of study treatment as defined below. The start date references time flag variables and end date reference time flag variables will be added to the concomitant medications and blood and blood supportive products datasets, respectively.

- **Start relative to treatment:** Assign to 'BEFORE' if start date is prior to study treatment start date or if participant has not taken any study treatment or (start date is missing and end date is before study treatment start date). Else assign to 'DURING' if the start date falls into the on-treatment period as defined above or if participant is ongoing (not all study treatment discontinuation records completed) or start date is missing. Else assign to 'AFTER' if start date is after the last study day.
- **End relative to treatment**: Assign to 'BEFORE' if end date is prior to study treatment start date or if participant has not taken any study treatment. Else assign to 'DURING' if start date falls into the on-treatment period or if participant is ongoing (not all study treatment discontinuation records completed) or (end date is missing and start relative to treatment not 'AFTER'). Else assign to 'AFTER' if start date is after the last study day or (end date is missing and start relative to treatment='AFTER').

Only on-treatment blood and blood supportive care and stem cell mobilization products that start after the start of study treatment are included in the Blood Products and Blood Supportive Care Product and Stem Cell Mobilization Products will be listed. Therefore, for listings include blood and blood supportive care product records where start relative to treatment in ('DURING') and end relative to treatment in ('DURING', 'AFTER').

Concomitant medication starts relative to treatment and ends relative to treatment flags are used to select data to include in the Concomitant Medication summaries as follows:

- Summary of Concomitant Medications: This summary will contain medications including those with start date prior to study treatment start date and continue (missing end date or end date after study treatment start date) on therapy. Note that any medications with start date and end date prior to study treatment start date will be excluded. In addition, any medication that was started during post-therapy will be excluded. Include concomitant medication records where start relative to treatment in ('BEFORE', 'DURING') and end relative to treatment in ('DURING', 'AFTER').

6.4.3. Study Day and Reference Dates

Study Day

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

6.4.4. Assessment Window

No assessment window will be applied in this study.

6.4.5. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• Study Treatment Start Date <= AE Start Date <= Start of Anti-cancer Therapy • AE Start Date is missing.

Notes: Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

6.4.6. Multiple measurements at One Analysis Time Point

In general, mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. For example, when triplicate ECG assessments are taken, mean of the measurement will be calculated first and summary statistics will be based on the calculated mean. This will apply to both baseline and post baseline assessment.

Participants having both high and low values for normal ranges an any post-baseline visit for safety parameters will be counted in both the high and low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant potential clinical importance summary tables.

6.4.7. Handling of Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>• Partial dates will be displayed as captured in participant listing displays.
• Imputed partial dates will not be used to derive study day, duration (e.g. duration of AEs), or elapsed time variables. In addition, imputed dates are not used for deriving the last contact date in the overall survival analysis dataset.
• Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study time.</td></tr>
<tr><td>Adverse Events</td><td>• The eCRF allows for the possibility of partial dates (i.e. only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. Partial dates for AE recorded in the CRF will be imputed using the following conventions:
<table>
<tr><td>Missing start day</td><td>First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Section 6.4.5 Treatment Emergent Flag for Adverse Events .</td></tr>
<tr><td>Missing start day and month</td><td>No Imputation</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td><table>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year), unless this is after the stop date of study treatment; in this case the study treatment stop date will be used.</td></tr>
<tr><td>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table></td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>
Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>Set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>A '01' will be used for the day and 'Jan' will be used for the month</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>A '31' will be used for the day and 'Dec' will be used for the month.</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
</table>

6.5. Appendix 5 International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma

Response	IMWG Criteria
Stringent complete response (sCR)	• Complete response as defined below plus normal FLC ratio[1] and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)[2]
Complete response (CR)	• Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow[3]
Very good partial response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response (PR)	• ≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; • If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; • If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)[4] of soft tissue plasmacytomas is also required
Minimal response (MR)	• ≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)[4] of soft tissue plasmacytomas is also required
Stable Disease (SD)	• Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease (PD)[5,6]	Any one or more of the following criteria: • Increase of 25% from lowest confirmed response value in one or more of the following criteria: - Serum M-protein (absolute increase must be ≥0·5 g/dL); - Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; - Urine M-protein (absolute increase must be ≥200 mg/24 h); • In participants without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); • In participants without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%);

	• Appearance of a new lesion(s), ≥50% increase from nadir in SPD[4] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; • ≥50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease
Relapse	Clinical relapse requires one or more of: • Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD§§ of the measurable lesion; • Hypercalcaemia (>11 mg/dL); • Decrease in haemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; • Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; • Hyperviscosity related to serum paraprotein

Overall Responders: PR, VGPR, CR, sCR

Clinical Benefit Rate: Overall responders + MR

Adapted from Kumar et.al. Lancet Oncol 2016; 17: e328–46

1 All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).

2 Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

3 Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of participants having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in participants receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

4 Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For participants with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumour size will be determined by the SPD.

5 Positive fixation alone in a participant previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, participants who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

6 In the case where a value is felt to be a spurious result per physician discretion (e.g. a possible laboratory error),

that value will not be considered when determining the lowest value.

6.6. Appendix 6 Abbreviations

Abbreviation	Description
ADA	Anti-drug antibody
ADaM	Analysis Data Model
ADC	Antibody Drug Conjugate
AE	Adverse Event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BCVA	Best corrected visual acuity
BMI	Body mass index
BNP	B-type natriuretic peptide
BOR	Best Overall Response
Bor/Dex	Bortezomib and Dexamethasone
BUN	Blood urea nitrogen
C1D1	Cycle 1 Day 1
C2D1	Cycle 2 Day 1
CBR	Clinical Benefit Rate
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CK	Creatine kinase
CL	Clearance
Cmax	Maximum observed plasma concentration
CPMS	Clinical Pharmacology Modelling & Simulation
CR	Complete Response
CRP	C-reactive protein
Ctrough	Trough plasma concentration
CV	Coefficient of Variation
Cys-mcMMAF	Cysteine maleimidocaproyl monomethyl auristatin F
DBF	Database Freeze
DCO	Data cut-off
DLT	Drug Limiting Toxicity
ECHO	Echocardiogram
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Record Form
eGFR	Estimated glomerular filtration rate
EOI	End of Infusion
EOT	End of Treatment
EOS	End of Study
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
FLC	Free light chain
GGT	Gamma glutamyl transferase
GSK	GlaxoSmithKline

Abbreviation	Description
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IHC	Immunohistochemistry
IMWG	International Myeloma Working Group
IV	Intravenous(ly)
LC	Light chain
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Affairs
MR	Minimal Response
NE	Not Evaluable
NCI-CTCAE	the National Cancer Institute – Common Toxicity Criteria for Adverse Events
NQ	Non-quantifiable
OPS	Output and Programming Specification
ORR	Overall Response Rate
PACT	Post analysis continued treatment
PD	Pharmacodynamic
PD	Progressive Disease
PK	Pharmacokinetic
Pom/Dex	Pomalidomide and Dexamethasone
PopPK	Population PK
PR	Partial Response
PY	Person Year
Q3W	Once every 3 weeks
Q4W	Once every 4 weeks
QTcF	Frederica's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RBC	Red blood cells
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
CCI [redacted]	[redacted]
sCR	Stringent Complete Response
SD	Stable Disease
SMQ	Standardized MedDRA Query
SoA	Schedule of activities
SoC	Standard of Care
SOC	System Organ Class
SPEP	Serum protein electrophoresis
SRT	Safety review team
T1/2	Terminal phase half-life
TFL	Tables, Figures & Listings
tlast	Time of last quantifiable concentration
Tmax	Time of maximum observed plasma concentration

Abbreviation	Description
UPEP	Urine protein electrophoresis
VGPR	Very Good Partial Response
vss	Volume of distribution at steady state
WBC	White blood cells
λz	Terminal phase elimination rate constant

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7. REFERENCES

GlaxoSmithKline Document Number RPS-CLIN-050928 Study ID 207504. A Phase I Open-Label, Dose Escalation Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, Immunogenicity and Clinical Activity of the Antibody Drug Conjugate GSK2857916 in Japanese Participants with Relapsed/Refractory Multiple Myeloma. Report Date 10-Feb-2023.

Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. The Lancet Oncology. 2016;17: e328-e346.