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.

Protocol Number: 207504

Compound Number:	GSK2857916

Study Phase: Phase I

Short Title: A Phase 1 open-label, dose escalation study in Japanese participants with relapsed/refractory multiple myeloma who have failed prior anti-myeloma treatments.

Sponsor Name and Legal Registered Address:

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Medical Monitor Name and Contact Information This information is included in Exhibit 1.

Regulatory Agency Identifying Number:

None

Approval Date: 10-Feb-2023

SPONSOR SIGNATORY:

Mari Matsubara	**Date**

Medical Affairs Lead (Hematology)
Oncology Medical and Development
Japan Medical and DevelopmentGlaxoSmithKline K. K

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 6	10-Feb-2023	RPS-CLIN-050928
Amendment 5	12-NOV-2021	TMF-14042588
Amendment 4	15-JAN-2021	2018N369488_04
Amendment 3	01-JUL-2020	2018N369488_03
Amendment 2	05-APR-2019	2018N369488_02
Amendment 1	07-DEC-2018	2018N369488_01
Original Protocol	25-JUL-2018	2018N369488_00

Amendment 6: 10-Feb-2023

Overall Rationale for the Amendment: This protocol has been amended to add Post Analysis Continued Treatment (PACT) to allow eligible participants to receive study treatment after final analysis data cut-off (DCO).

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.1 Synopsis Section 1.3 Schedule of Activities Section 4.1 Overall Design Section 4.4 EOS Definition Section 6.8 Continued Access to Study Intervention after the End of the Study Section 8.3.1 Time Period and Frequency for Collecting AE and SAE	Addition of an option for PACT to allow eligible participants to continue study treatment. Revised End of Study (EOS) definition. Addition subsection 6.8.1 Continued Access to Study Intervention After Final Analysis DCO prior to EOS. Added instructions of the scope and the time period of data collection and reporting during the PACT phase.	To allow continued access to study treatment in eligible participants and add guidance on data collection and reporting during the PACT phase
2.4.1. Risk Assessment	Updated based on the current version of the Investigator Brochure (v10.0).	To align with program language

Section # and Name	Description of Change	Brief Rationale
6.6.2. Prohibited Medications Other Sections	Updated the wording "anti-cancer therapy" into "anti-myeloma therapy" for clarification. Identified the anti-myeloma therapies that is prohibited.	To align with program level language.
8.6. Pharmacodynamics	Updated the requirement for sample collection after effective Amendment 6.	To update the data collection requirement with regards to over the program data availability and the completion of relevant data collected in this study.

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1. PROTOCOL SUMMARY

1.1. Synopsis

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.

Short Title: A Phase 1 open-label, dose escalation study in Japanese participants with relapsed/refractory multiple myeloma who have failed prior anti-myeloma treatments.

Rationale: Multiple myeloma (MM) is an incurable malignancy and accounts for 1.8% of all new cancers and for 13% of all hematologic malignancies. Worldwide, approximately 103,000 new cases are diagnosed annually and in the United States (US), 32,110 new cases and 12,960 deaths are estimated to occur in 2019. Incident cases from 1990 to 2016 increased by 126% globally. In Japan, the number of patients with MM was 8,200, and that of deaths was 4,200 in 2017. Due to aging of society, incidence of MM has increased recently. Despite the recent advances in therapy, MM remains an incurable disease, and novel approaches that induce deep and durable tumor regression with little cross-resistance with existing drugs are always needed to expand the therapeutic options against MM.

Over the past two decades, the median survival of patients with MM has significantly improved, from 3 to 4 years to approximately 7 to 8 years, mainly due to the application of high-dose conventional therapy with autologous stem-cell transplantation (HDT-ASCT) as a routine procedure for transplant-eligible MM patients; significant improvements in supportive care strategies; and the introduction and wide-spread use of the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide and the proteasome inhibitor, bortezomib. The survival outcome has significantly improved after the introduction of these novel agents. These novel agents nowadays represent the backbone of many current standard-of-care therapies for MM patients, both at diagnosis and in the relapse setting.

One such novel therapy, daratumumab is a human IgG1 kappa monoclonal antibody that was granted first approval in the US in November 2015, in Japan on 27 September 2017. While the data with daratumumab indicate that further prolongation of progression free survival (PFS) can be achieved, it is also increasingly recognized that patients continue to relapse after treatment with daratumumab, and will need additional treatment options to control the disease.

GSK2857916 is a first in class, antibody-dependent cell-mediated cytotoxicity (ADCC) enhanced, humanized IgG1 antibody-drug conjugate (ADC) that binds specifically to B-cell maturation antigen (BCMA), a target restricted to B cells at later stages of differentiation and expressed on tumor cells of all patients with MM. Upon binding to the cell surface, GSK2857916 is rapidly internalized and the active drug (cysteine maleimidocaproyl monomethyl auristatin F [cys-mcMMAF]) is released inside the cell. The cys-mcMMAF moiety disrupts microtubule networks, leading to cell cycle arrest and

apoptosis (ADC mechanism). This dual mechanism of action of GSK2857916 (ADCC and microtubule disruption) enables anti-tumor activity on both dividing and non-dividing cells. In addition, when MM cell lines expressing BCMA are exposed to GSK2857916, it may act as an inducer of immunogenic cell death (ICD), representing a potential third mechanism of action.

GSK2857916 has shown strong single-agent activity in the currently ongoing First Time in Human (FTIH) study (BMA117159).

Among the 35 participants in BMA117159 study, receiving GSK2857916 at the recommended Phase II dose (RP2D) of 3.4 mg/kg intravenous (IV), once every 3 weeks (Q3W), the following results were observed as of 31 August 2018:

- Overall response rate (ORR) of 60% [95% confidence interval (CI): 42.1, 76.1]
- Median PFS (mPFS) was 12.0 months [95% CI: 3.1, not estimable (NE)].
- The ORR in 32 participants refractory to both IMiDs and proteasome inhibitors was 56% (95% CI: 37.7, 73.6), and the mPFS in this subgroup was 7.9 months (95% CI: 2.3, NE).
- There were no dose limiting toxicities (DLTs) reported at doses up to 4.6 mg/kg; however the dose of 4.6 mg/kg was considered not tolerated. Most events were Grade 1/2. Overall, GSK2857916 was well tolerated and adverse events were manageable.

This data supports testing of GSK2857916 as a monotherapy in Japanese participants with relapsed/refractory multiple myeloma (RRMM).

In addition, given the strong single-agent activity of GSK2857916, the combination therapy of GSK2857916 with standard of care (SoC) agents is an attractive option to explore for patients with RRMM. Based on the mechanism of action of GSK2857916, the combination with SoC therapies (bortezomib and dexamethasone [Bor/Dex] or pomalidomide and dexamethasone [Pom/Dex]) is expected to result in additive, or potentially synergistic effects which could potentially translate into a deep and long-lasting response over what has been achieved with available agents.

The ongoing Phase I/II open-label, dose escalation and expansion study 207497 is evaluating the safety and clinical activity of GSK2857916 when given in combination with Bor/Dex in participants with RRMM who have received at least 1 prior line of therapy. Preliminary data from this study indicate that the combination of GSK2857916 at 2.5 mg/kg dose with Bor/Dex is safe and tolerable without DLTs and is showing early evidence of activity, given the prior and ongoing experience (from FTIH study BMA117159 and Phase II 205678 study) of single agent activity for this dose (2.5 mg/kg) of GSK2857916.

GSK2857916 at multiple dose levels in combination with Pom/Dex once every 4 weeks (Q4W) is being evaluated for safety and efficacy in patients with RRMM in an ongoing Phase I/II study conducted by the Myeloma Canada Research Network (MCRN 007 or study 209418). As of 01 February 2020, 11 participants have received GSK2857916 at

1.92 mg/kg dose, and 7 participants at 2.5 mg/kg dose in combination with Pom/Dex Q4W. Preliminary data showed that the GSK2857916/Pom/Dex combination at both dose levels has resulted in early signs of clinical activity, and an acceptable safety profile, consistent with the known safety profile of the individual components, GSK2857916 and Pom/Dex.

These data support testing GSK2857916 when administered in combination with approved regimens of either Bor/Dex (Arm A) or Pom/Dex (Arm B) in Japanese participants with RRMM in Part 2.

Objectives and Endpoints:

Objectives	Endpoints
Primary Objective	
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	
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: • 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]

Overall Design:

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 GSK2857916 will be administered IV 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].

Disclosure Statement: This is an open-label study; no masking.

Number of Participants:

The maximum number of participants for Part 1 will be up to 12, up to 6 participants each for 2.5 mg/kg cohort and 3.4 mg/kg cohort based on 3 + 3 design. 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.

Intervention Groups and Duration: Study treatment is defined as any investigational intervention intended to be administered to a study participant according to the study protocol. GSK2857916 will be administered IV over 30 minutes on Day 1 of each cycle.

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. Any participant experiencing an infusion-related reaction (IRR) must receive appropriate medical treatment. When the participant's condition is stable, the infusion may be restarted at a slower rate.

Participants will be treated until disease progression, withdrawal of consent or until unacceptable toxicity.

Inclusion Criteria: Participants are eligible to be included in the study only if all of the following criteria apply:

1. Provide signed written informed consent, which includes compliance with the requirements and restrictions listed in the consent form
2. Male or female, 20 years or older (at the time consent is obtained)
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2

4. Histologically or cytologically confirmed diagnosis of MM as defined according to IMWG 2014 [Rajkumar, 2014], criteria in a participant who fulfills **all** of the following:
   i. has undergone stem cell transplant, or is considered transplant ineligible,
   ii. **Part 1:** has received at least 2 prior lines of anti-myeloma drugs containing at least 1 proteasome inhibitor and at least 1 immunomodulator,
   Part 2: has received at least 1 prior line of anti-myeloma drugs,
   iii. **Part 1:** has demonstrated progression on, or within 60 days of completion of the last therapy.

   Part 2: has documented disease progression during or after their most recent therapy.
5. Has measurable disease with at least one of the following:
   a. Serum M-protein ≥0.5 g/dL (≥ 5 g/L)
   b. Urine M-protein ≥200 mg/24h
   c. Serum free light chain (FLC) assay: Involved FLC level ≥ 10 mg/dL (≥100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65).
6. Participants with a history of autologous stem cell transplant are eligible for study participation provided the following eligibility criteria are met:
   a. Transplant was > 100 days prior to study enrolment
   b. No active infection.
7. Female Participants: Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   A female participant is eligible to participate if she is not pregnant or breastfeeding and at least one of the following conditions applies:

   - Is not a woman of childbearing potential (WOCBP)

     OR

   - **For Part 1 and Part 2 Arm A:**

     Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, during the treatment period and for 4 months after the last dose of GSK2857916, and 7 months from the last dose of bortezomib (only Part 2 Arm A), and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.

     A WOCBP must have a negative highly sensitive serum pregnancy test (as required by local regulations) within 72 hours before the first dose of study treatment and agree to use effective contraception during the study and for 4 months after the last dose of GSK2857916, and 7 months from the last dose of bortezomib (only Part 2 Arm A).

For Part 2 Arm B:

Due to pomalidomide being a thalidomide analogue with risk for embryo-fetal toxicity and prescribed under a restricted distribution program, WOCBP participants will be eligible if they commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control, beginning 4 weeks prior to initiating treatment with pomalidomide, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of pomalidomide treatment. Thereafter, WOCBP participants must use a contraceptive method that is highly effective (with a failure rate of <1% per year) for a further 3 months, and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period.

Two negative pregnancy tests must be obtained prior to initiating pomalidomide therapy. The first test should be performed within 10 to 14 days and the second test within 24 hours prior to prescribing pomalidomide therapy.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

8. Male Participants: Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   Male participants are eligible to participate if they agree to the following from the time of first dose of study treatment until 6 months after the last dose of GSK2857916, 4 months after the last dose of bortezomib (only Part 2 Arm A), and 4 weeks after the last dose of pomalidomide (only Part 2 Arm B) to allow for clearance of any altered sperm:

   - Refrain from donating sperm

     PLUS either:

   - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

     OR

   - Must agree to use contraception/barrier as detailed below:

   Agree to use a male condom, even if they have undergone a successful vasectomy, and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as when having sexual intercourse with a woman of childbearing potential (including pregnant females)

9. All prior treatment-related toxicities (defined by National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.03, must be ≤Grade 1 at the time of enrolment except for alopecia. Participants with Grade 2 peripheral neuropathy can be enrolled into Part 1 and Part 2 Arm B but not into Part 2 Arm A.

10. Adequate organ system functions as defined in Table 10 or Table 11.

Exclusion Criteria: Participants are excluded from the study if any of the following criteria apply:

1. Systemic anti-tumor-therapy within 14 days, or plasmapheresis within 7 days prior to the first dose of study treatment.
2. Symptomatic amyloidosis, active 'polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes' (POEMS) syndrome, active plasma cell leukemia at the time of screening.
3. Use of an investigational drug within 14 days or 5 half-lives, whichever is shorter, preceding the first dose of study treatment. Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study treatment. Prior BCMA targeted therapy.
4. History of an allogeneic stem cell transplant.
5. Current use of prohibited medications/device or planned use of any of these during the study period.
6. Current corneal epithelial disease except mild punctate keratopathy.
7. Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect participant's safety). Participants with isolated proteinuria resulting from MM are eligible, provided they fulfil criteria given in Table 10 or Table 11.
8. Evidence of active mucosal or internal bleeding.
9. Any major surgery within the last 4 weeks.
10. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other conditions (including laboratory abnormalities) that could interfere with participant's safety, obtaining informed consent or compliance to the study procedures.
11. Active infection requiring treatment (antibiotic, antiviral, or antifungal treatment).
12. Evidence of severe or uncontrolled systemic diseases.
13. Malignancies other than disease under study are excluded, except for any other malignancy from which the participant has been disease-free for more than 2 years and, in the opinion of the investigators and Medical Monitor, will not affect the evaluation of the effects of this clinical study treatment on the currently targeted malignancy (MM).
14. Evidence of cardiovascular risk including any of the following:
    a. QTcF interval ≥470 msecs (the QT interval values must be corrected for heart rate by Fridericia's formula [QTcF]).
    b. Evidence of current clinically significant uncontrolled arrhythmias, including clinically significant ECG abnormalities such as 2nd degree (Type II) or 3rd degree atrioventricular (AV) block.
    c. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within 6 months of Screening.

d. Class III or IV heart failure as defined by the New York Heart Association functional classification system.

e. Uncontrolled hypertension.

15. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2857916 or any of the components of the study treatment.

16. Pregnant or lactating female or female who are interrupting lactation.

17. Known human immunodeficiency virus (HIV) infection.

18. Patients with Hepatitis B will be excluded unless the following criteria can be met.

Serology	Screening	During Study Treatment
• Hepatitis B surface antibody (HBsAb) + and/or Hepatitis B core antibody (HBcAb) + AND • Hepatitis B surface antigen (HBsAg) -	• HBV DNA undetectable	• Monitoring per protocol (Table 4) • Antiviral treatment instituted if HBV DNA becomes detectable

Note: Participants with positive HBsAb alone due to hepatitis B vaccination can be enrolled.

19. Positive hepatitis C antibody test result or positive hepatitis C ribonucleic acid (RNA) test result at screening or within 3 months prior to first dose of study treatment.

    Note: Participants with positive hepatitis C antibody due to prior resolved disease can only be enrolled, if a confirmatory negative hepatitis C RNA test is obtained.

    Note: Hepatitis RNA testing is optional and participants with negative Hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.

20. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis.

    Note: Stable chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) or hepatobiliary involvement of malignancy is acceptable if participant otherwise meets entry criteria.

21. Previously diagnosed with interstitial lung disease or current complication of interstitial lung disease.

Additional Exclusion Criteria for Part 2 Arm A

22. Intolerant to bortezomib or refractory to bortezomib.

23. Ongoing Grade 2 or higher peripheral neuropathy or neuropathic pain.

24. Intolerance or contraindications to herpes zoster prophylaxis.

Additional Exclusion Criteria for Part 2 Arm B

25. Prior pomalidomide use.
26. Intolerance or contraindications to antithrombotic prophylaxis.
27. Active or history of venous thromboembolism within 3 months prior to first dose of study treatment.

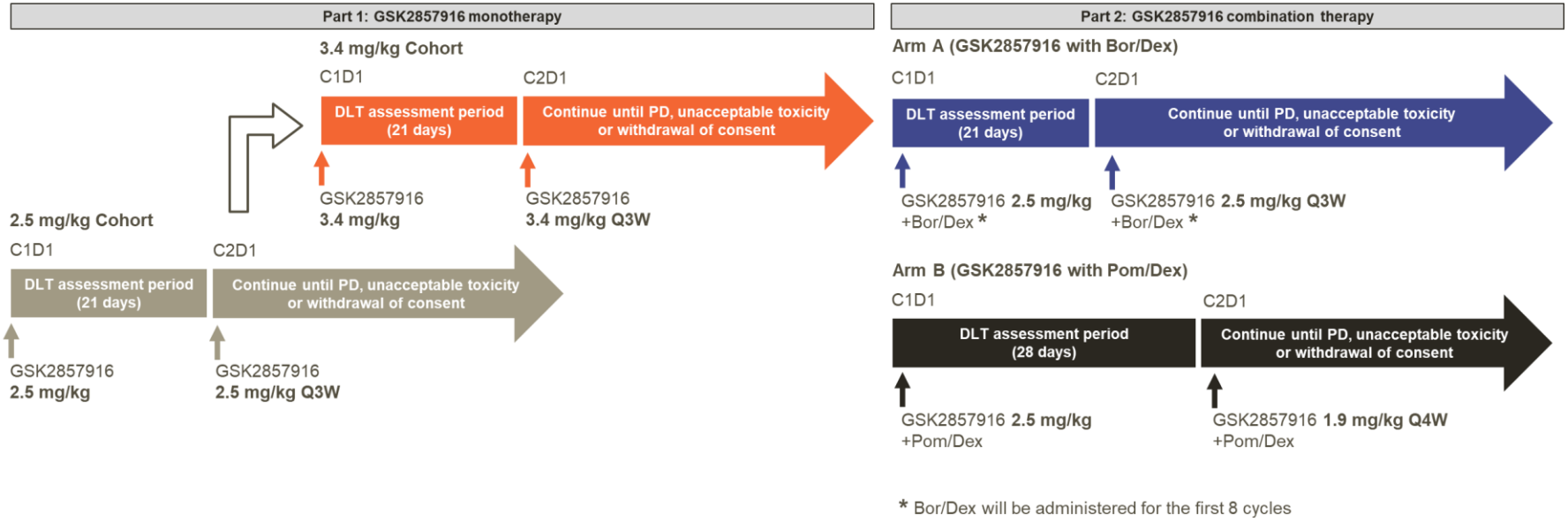
Data Monitoring Committee: No

End of Study Definition:

Following 21 months post last subject first dose, Study 207504 (DREAMM-11) will move into the PACT phase where the study remains open to provide continued access to study treatment for study participants who are continuing to derive clinical benefit. At that time, the collection of new data for participants who no longer receive study treatment will stop entirely and the clinical trial database will be closed. Those participants still benefiting from study drug in the opinion of their treating physician may continue to receive study drug and only SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases, and pre-specified ocular data will be reported directly to GSK. 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 shown in the Schedule of Activities for the last participant in the study.

1.2. Schema

Study Schematic



1.3. Schedule of Activities (SoA)

All assessments planned for participants in Part 1 of study 207504 are shown inTable 1. All assessments planned for participants in Part 2 Arm A and Arm B are shown in Table 2 and Table 3, respectively.

The details of these assessments are provided in footnotes to the table and Section 8.

PACT Phase: Participants who continue to receive study treatment during the PACT phase will be monitored and receive follow-up care in accordance with standard local clinical practice. Assessments will revert to the standard of care at a patient's particular study site and

only SAEs, AEs leading to discontinuation of study treatment, prespecified ocular data, overdoses and pregnancy cases will be reported directly to the Sponsor via paper forms (see Section 4.4 and Section 8.3.1).

Table 1 Schedule of Activities for Part 1 (GSK2857916 Monotherapy)

Time and Time Table (Cycle=21 days)								
Study Assessment[1]	**Screen[2]**	**D1 C1**	**D2 C1**	**D8 C1**	**D15 C1**	**D1 C2 to CX**	**End of Treatment Visit[3]**	**Follow-up Visit**
Informed Consent	X							
Baseline Demographics	X							
Medical History	X							
Physical Examination	X	X				X	X	
Ocular Examination	X[4]					X[5]	X[6]	X[6]
ECOG Performance Status	X	X				X	X	
Vital Signs (BP, HR, Body Temperature)	X	X[7]		X	X	X[7]	X	
Weight and Height	X	Weight Only				Weight Only	Weight Only	
Hematology	X	X[8]		X	X	X	X	
Clinical chemistry	X	X[8]	X	X	X	X	X	
Urine Dipstick	X	X[8]				X	X	
eGFR[9]	X	X				X	X	
Spot urine for Albumin /creatinine ratio[10]	X	X				X	X	
HBV/HCV tests	X							
Troponin[11], BNP[11]	X							
UPEP and urine Immunofixation	X					X	X	

Time and Time Table (Cycle=21 days)								
Study Assessment[1]	**Screen[2]**	**D1 C1**	**D2 C1**	**D8 C1**	**D15 C1**	**D1 C2 to CX**	**End of Treatment Visit[3]**	**Follow-up Visit**
SPEP and serum Immunofixation, Serum M-protein Calculation	X					X	X	
Kappa, lambda FLC, FLC Ratio	X					X	X	
24 hour urine protein	X					X	X	
Calcium corrected for albumin (serum)	X					X	X	
IgG, IgM, IgA	X					X	X	
IgD/E[12]	X					X	X	
CRP	X					X	X	
Beta2 microglobulin	X					X		
Pregnancy Test[13]	X	X				X	X	X
Skeletal survey[14]	X	As clinically indicated						
Chest X-ray imaging	X	As clinically indicated					X	
12-lead ECG[15]	X	X					X	
LVEF (ECHO)[16]	X						X	
Extramedullary plasmacytoma Imaging[17]	X					C5, C9, C13, And later only if clinically indicated	X[18]	
FISH testing[19]	X							

Time and Time Table (Cycle=21 days)								
Study Assessment[1]	**Screen[2]**	**D1 C1**	**D2 C1**	**D8 C1**	**D15 C1**	**D1 C2 to CX**	**End of Treatment Visit[3]**	**Follow-up Visit**
BM aspirate/biopsy for disease assessment	X[20]					At the time of CR or at time of suspected Progressive disease (only if not evident otherwise)	Only if CR has been achieved by this visit, or suspected Progressive disease not evident otherwise	
CCI								
Serum (anti-drug-antibodies)[22]		X				C2, C3, C6, C9, C12, C16	X	
Serial Pharmacokinetics (blood)		X[23]	X[23]	X[23]	X[23]	X[23]	X[24]	
Genetics Sample[25]	X							
Premedication if needed		X				X		
GSK2857916 administration[26]		X				X		
Preservative-free Artificial Tears		Administered in each eye at least 4-8 times daily beginning on C1D1 until EOT. In the event of ocular symptoms (i.e., dry eyes), the use of artificial tears may be increased up to every 2 hours, as needed.						
Cooling Eye Masks (optional)		On GSK2857916 dosing day, may apply cooling eye masks as long as tolerated from start of infusion and up to 4 hours						
Adverse Events[27]	X	Continuous						X
Concomitant Medications[27]	X							X
New anti-myeloma Therapy[28]								X

1. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. All other assessments can be performed within ±3 days of scheduled occurrence unless otherwise specified. For C1D2 assessments, no time window is permitted. C1D8 and C1D15 assessments can be performed within ±1 day of scheduled occurrence.
2. All Screening assessments must be performed within 21 days prior to first dose unless otherwise specified. Informed Consent must be signed before any study-specific assessments are performed.
3. The End of Treatment (EOT) will occur within 30 days (±3 days) after the last dose of any study medication or before the initiation of any other antimyeloma treatment. For participant discontinuing treatment in the PACT phase, no end of treatment visit is required.
4. Screening ocular examination will be performed by an ophthalmologist within 21 days prior to the first dosing (see Section 8.2.2 for the list of screening ophthalmic exam procedures).
5. On-study ophthalmic exams to be performed by an ophthalmologist every 3 weeks. See Section 8.2.2 for the list of ophthalmic exam procedures. If there are no corneal signs per the GSK scale at time of the C4 exam, participants may have their ophthalmologic exams decreased to once every 3 months. If a participant subsequently develops ocular symptoms, the participant should be evaluated by an ophthalmologist. Intraocular pressure must be monitored if steroid eye drops are used continuously more than 7 days. Additional exams may be performed by the ophthalmologist, as clinically indicated.
6. Ophthalmic exam at the EOT to be performed by an ophthalmologist. Participants with corneal signs per the GSK scale at the EOT Visit will continue to be followed at 3 weeks (±7 days) after the EOT visit and then every 6 weeks (±7 days) for up to 12 months, or until full resolution of findings defined as a return to participant's baseline or deemed clinically stable by an ophthalmologist, whichever comes first. See Section 8.2.2 for the list of ophthalmic exam procedures.
7. On initial (first infusion) dosing day, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +10 minutes (±5 minutes), EOI (±5 minutes), and 1 hour post EOI (±5 minutes). On subsequent dosing days, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI). The Sentinel Participant must be observed for at least 24 hours post EOI. On days where vital sign timepoints align with PK sampling timepoints, vital signs should be assessed prior to PK samples being drawn.
8. If completed within 72 hrs prior to the first dose, this assessment need not be repeated on C1D1. Refer to Table 32 for comprehensive list of laboratory tests.
9. eGFR is to be calculated via modified diet in renal disease (MDRD) calculation.
10. Albumin/creatinine ratios (spot urine from first void) at screening, C1, and every cycle thereafter.
11. Troponin I or T and B-type natriuretic peptide (BNP) will be measured at the local laboratory, or by central laboratory if not available locally. If cardiac workup is required due to safety concerns during the study, troponin I or T and BNP should be measured as clinically indicated.
12. Only in patients with IgD/IgE myeloma.
13. Perform only in women of child-bearing potential (WOCBP), see Appendix 3 for definition. A serum pregnancy test must be performed at screening; if the test is completed within 72 hours prior to the first dose of GSK2857916, this assessment does not have to be repeated on C1D1. For questionable cases, follicle-stimulating hormone (FSH) and estradiol (as needed in WOCBP) should be performed at local lab to determine childbearing potential. WOCBP must have a negative highly sensitive serum pregnancy test within 72 hours of dosing on C1D1. Subsequent pregnancy tests on dosing days may be either serum or

urine. Final pregnancy test (serum or urine) must be performed in WOCBP at the EOT Visit. Follow up pregnancy assessment by telephone (for WOCBP only) should be performed 4 months after the last dose of GSK2857916.

14. Skeletal Survey: Imaging of bones for lytic lesions by a method aligned with the institutional guidance (X-ray, CT, or MRI). Skeletal survey results within 30 days prior to C1D1 are acceptable.
15. On dosing days, ECG to be performed in singlet at predose (within 30 minutes prior to SOI).
16. Echocardiography for left ventricular ejection fraction (LVEF) performed within 35 days prior to first dose is acceptable as screening value.
17. Imaging is only required for participants with extramedullary disease (CT, MRI, or PET/CT can be applied per local guidance). Screening assessment may be performed up to 30 days prior to C1D1. The same modality should be used throughout the study (i.e., if CT scan was used as baseline, participant needs to be followed by CT scans). 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 skin only involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the Sum of the Products of the maximal perpendicular diameters of measured lesions (SPD).
18. In participants with extramedullary plasmacytoma, if the last radiographic assessment occurred ≥8 weeks prior to the participant's withdrawal from study treatment, and progressive disease has NOT been documented, –a new assessment for extramedullary disease should be obtained at the EOT.
19. FISH testing at least for: t(4;14), t(14;16), 17p13del. FISH results from samples taken within 60 days prior to first dose are acceptable.
20. Archival tissue from up to 60 days prior to study is acceptable.

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22. All ADA samples will be collected prior to each infusion. If a dose is delayed at C2, an ADA sample should be collected on a planned dosing day at C2 (21 [±3] days post dose on C1D1) (sample collection is not needed when a dose is delayed at or after C3).
23. PK samples to be taken (in all the study participants) for both GSK2857916 and cys-mcMMAF measurement: C1D1 at pre-dose (within 30 minutes prior to SOI), at EOI (just before EOI), 1 hour after EOI, 3 hours after EOI (±5 minutes), 8 hours after EOI (±15 minutes), 24 hours after EOI (±1hour) (D2); C1D8, 1 sample; C1D15, 1 sample; on C2D1, C3D1, C6D1, C9D1, and C12 D1, at pre-dose (within 30 minutes prior to SOI) and at the EOI (just before EOI); on C16D1 at pre-dose (within 30 minutes prior to SOI). If a dose is delayed at C2, a PK sample should be collected on a planned dosing day at C2 (21 [±3] days post dose on C1D1) (sample collection is not needed when a dose is delayed at or after C3).
24. Collect 1 PK sample at each participants' final visit.
25. Informed consent for optional genetics research should be obtained before collecting a sample. The sample will be collected between the first opportunity after a participant has met all eligibility requirements and the EOT Visit.
26. Study treatment administration ±3 day window only.

27. Any SAEs assessed as related to study participation or related to a GSK product will be recorded from the time a participant consent through any follow up. AEs and SAEs will be collected throughout the study until 70 days after the last dose of study treatment regardless of initiation of new anti-myeloma therapy. Concomitant medications administered after the EOT should only be recorded for SAEs/AESIs.
28. New anticancer therapy will be recorded through any follow up.

Table 2 Schedule of Activities for Part 2 Arm A (GSK2857916 in Combination with Bortezomib plus Dexamethasone)

Time and Time Table (Cycle=21 days)								
Study Assessment[1]	**Screen[2]**	**D1 C1 to C8**	**D4 C1 to C8**	**D8 C1 to C8**	**D11 C1 to C8**	**D1 C9 to CX**	**End of Treatment Visit[3]**	**Follow-up Visit**
Informed Consent	X							
Baseline Demographics	X							
Medical History	X							
Physical Examination	X	X				X	X	
Ocular Examination	X[4]	X[5]				X[5]	X[6]	X[6]
ECOG Performance Status	X	X				X	X	
Vital Signs (BP, HR, Body Temperature)[7]	X	X[8]	If clinically indicated			X[8]	X	
Weight and Height	X	Weight Only				Weight Only	Weight Only	
Hematology[7]	X	X[9]	X	X	X	X	X	
Clinical chemistry	X	X[9]	X	X	X	X	X	
Urine Dipstick	X	X[9]				X	X	
eGFR[10]	X	X				X	X	
Spot urine for Albumin /creatinine ratio[11]	X	X				X	X	
HBV/HCV tests	X							
Troponin[12], BNP[12]	X							
UPEP and urine Immunofixation[13]	X	X				X	X	

Time and Time Table (Cycle=21 days)								
Study Assessment[1]	**Screen[2]**	**D1 C1 to C8**	**D4 C1 to C8**	**D8 C1 to C8**	**D11 C1 to C8**	**D1 C9 to CX**	**End of Treatment Visit[3]**	**Follow-up Visit**
SPEP and serum Immunofixation, Serum M-protein Calculation[13]	X	X				X	X	
Kappa, lambda FLC, FLC Ratio[13]	X	X				X	X	
24 hour urine protein[13]	X	X				X	X	
Calcium corrected for albumin (serum)[13]	X	X				X	X	
IgG, IgM, IgA[13]	X	X				X	X	
IgD/E[13, 14]	X	X				X	X	
CRP[13]	X	X				X	X	
Beta2 microglobulin[13]	X	X				X		
Pregnancy Test[15]	X	X				X	X	X
Skeletal survey[16]	X	As clinically indicated						
Chest X-ray imaging	X	As clinically indicated					X	
12-lead ECG[17]	X	C1D1 only					X	
LVEF (ECHO)[18]	X						X	
Extramedullary plasmacytoma Imaging[19]	X	C5, C9, C13, And later only if clinically indicated				C5, C9, C13, And later only if clinically indicated	X[20]	
FISH testing[21]	X							

Time and Time Table (Cycle=21 days)								
Study Assessment[1]	**Screen[2]**	**D1 C1 to C8**	**D4 C1 to C8**	**D8 C1 to C8**	**D11 C1 to C8**	**D1 C9 to CX**	**End of Treatment Visit[3]**	**Follow-up Visit**
BM aspirate/biopsy for disease assessment	X[22]	At the time of CR or at time of suspected Progressive disease (only if not evident otherwise)				At the time of CR or at time of suspected Progressive disease (only if not evident otherwise)	Only if CR has been achieved by this visit, or suspected Progressive disease not evident otherwise	
CCI								
Serum (anti-drug-antibodies)[23]		X (See Section 8.9)				X (See Section 8.9)	X	
Pharmacokinetic blood sampling for GSK2857916[23]		X (See Table 34)						
Genetics Sample[24]	X							
Premedication if needed		X				X		
GSK2857916 administration[25]		X				X		
Bortezomib administration[26]		X	X	X	X			
Dexamethasone administration[27]		D1, D2, D4, D5, D8, D9, D11 and D12 of each 21-day cycle						
Preservative-free Artificial Tears		Administered in each eye at least 4-8 times daily beginning on C1D1 until EOT. In the event of ocular symptoms (i.e., dry eyes), the use of artificial tears may be increased up to every 2 hours, as needed.						
Cooling Eye Masks (optional)		On GSK2857916 dosing day, may apply cooling eye masks as long as tolerated from start of infusion and up to 4 hours						
Adverse Events[28]	X	Continuous						X

Time and Time Table (Cycle=21 days)								
Study Assessment[1]	**Screen[2]**	**D1 C1 to C8**	**D4 C1 to C8**	**D8 C1 to C8**	**D11 C1 to C8**	**D1 C9 to CX**	**End of Treatment Visit[3]**	**Follow-up Visit**
Concomitant Medications[28]	X							X
New anti-myeloma Therapy[29]								X

1. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. All other assessments can be performed within ±3 days of scheduled occurrence unless otherwise specified. D4, D8, and D11 assessments can be performed within ±1 day of scheduled occurrence.
2. All Screening assessments must be performed within 21 days prior to first dose unless otherwise specified. Informed Consent must be signed before any study-specific assessments are performed.
3. The End of Treatment (EOT) will occur within 30 days (±3 days) after the last dose of any study medication or before the initiation of any other antimyeloma treatment. For participant discontinuing treatment in the PACT phase, no end of treatment visit is required.
4. Screening ocular examination will be performed by an ophthalmologist within 21 days prior to the first dosing (see Section 8.2.2. for the list of screening ophthalmic exam procedures).
5. C1D1 ocular exam does not need to be repeated if within 21 days of screening exam. On-study ophthalmic exams will be performed by an ophthalmologist every 3 weeks prior to dosing, up to 6th dose of GSK2857916. At the time of the 6th dose of GSK2857916, if there are significant ophthalmic exam findings, participant's symptoms or vision changes, the frequency of ophthalmic exams may be decreased to every 3 months until EOT. If a participant subsequently develops vision changes or other ocular symptoms, the participant should be promptly evaluated by an ophthalmologist. In case of persistent ophthalmic exam findings, newly developed ocular symptoms or vision changes, the participants will have further ophthalmic exams, at least every cycle until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by an ophthalmologist. See Section 8.2.2. for the list of ophthalmic exam procedures. Intraocular pressure must be monitored if steroid eye drops are used continuously more than 7 days.
6. Ophthalmic exam at the EOT to be performed by an ophthalmologist. Participants with corneal signs per the GSK scale at the EOT Visit will continue to be followed at 3 weeks (±7 days) after the EOT visit and then every 6 weeks (±7 days) for up to 12 months, or until full resolution of findings defined as a return to participant's baseline or deemed clinically stable by an ophthalmologist, whichever comes first. See Section 8.2.2 for the list of ophthalmic exam procedures.
7. Hematology and vital signs (as clinically indicated) must be repeated prior to each dose of bortezomib.
8. On initial (first infusion) dosing day, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +10 minutes (±5 minutes), EOI (±5 minutes), and 1 hour post EOI (±5 minutes). On subsequent dosing days, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI). The Sentinel Participant must be observed for at least 24 hours post EOI. On days where vital sign timepoints align with PK sampling timepoints, vital signs should be assessed prior to PK samples being drawn.
9. If completed within 72 hrs prior to the first dose, this assessment need not be repeated on C1D1. Refer to Table 32 for comprehensive list of laboratory tests.

10. eGFR is to be calculated via modified diet in renal disease (MDRD) calculation.
11. Albumin/creatinine ratios (spot urine from first void) at screening, C1, and every cycle thereafter.
12. Troponin I or T and B-type natriuretic peptide (BNP) will be measured at the local laboratory, or by central laboratory if not available locally. If cardiac workup is required due to safety concerns during the study, troponin I or T and BNP should be measured as clinically indicated.
13. Baseline disease assessments completed within 21 days of C1D1 do not need to be repeated on C1D1.
14. Only in patients with IgD/IgE myeloma.
15. Perform only on women of childbearing potential (WOCBP), see Appendix 3 for definition. A serum pregnancy test must be performed at screening; if the test is completed within 72 hours prior to the first dose of GSK2857916, this assessment does not have to be repeated on C1D1. For questionable cases, follicle-stimulating hormone (FSH) and estradiol (as needed in WOCBP) should be performed at local lab to determine childbearing potential. WOCBP must have a negative highly sensitive serum pregnancy test within 72 hours of dosing on C1D1. Subsequent pregnancy tests on dosing days may be either serum or urine. Final pregnancy test (serum or urine) must be performed in WOCBP at the EOT Visit. Follow up pregnancy assessment by telephone (for WOCBP only) should be performed 4 months after the last dose of GSK2857916 or 7 months after the last dose of bortezomib, whichever is longest.
16. Skeletal Survey: Imaging of bones for lytic lesions by a method aligned with the institutional guidance (X-ray, CT, or MRI). Skeletal survey results within 30 days prior to C1D1 are acceptable.
17. On dosing days, ECG to be performed in singlet at predose (within 30 minutes prior to SOI).
18. Echocardiography for left ventricular ejection fraction (LVEF) performed within 35 days prior to first dose is acceptable as screening value.
19. Imaging is only required for participants with extramedullary disease (CT, MRI, or PET/CT can be applied per local guidance). Screening assessment may be performed up to 30 days prior to C1D1. The same modality should be used throughout the study (i.e., if CT scan was used as baseline, participant needs to be followed by CT scans). 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 skin only involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the sum of the products of the maximal perpendicular diameters of measured lesions (SPD).
20. In participants with extramedullary plasmacytoma, if the last radiographic assessment occurred ≥8 weeks prior to the participant's withdrawal from study treatment, and progressive disease has NOT been documented, –a new assessment for extramedullary disease should be obtained at the EOT.
21. FISH testing at least for: t(4;14), t(14;16), 17p13del. FISH results from samples taken within 60 days prior to first dose are acceptable.
22. Archival tissue from up to 60 days prior to study is acceptable.

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24. Informed consent for optional genetics research should be obtained before collecting a sample. The sample will be collected between the first opportunity after a participant has met all eligibility requirements and the EOT Visit.

25. Study treatment administration ±3 day window only.
26. If a bortezomib dose is delayed, subsequent doses should be adjusted to account for delay as all bortezomib doses must be at least 72 hours apart. Doses that need to be withheld are skipped and will not be made up later in the cycle. Individual doses within a cycle have a ±1-day window.
27. Dexamethasone 20 mg orally on Days 1, 2, 4, 5, 8, 9, 11, and 12 of every 21-day cycle. For participants with contraindications or intolerance to this dose, refer to Section 6.7 for instructions on dose modification guidelines. On days where bortezomib administration coincides with administration of GSK2857916, dexamethasone should be administered orally 1 to 3 hours prior to the infusion of GSK2857916. The starting dose of dexamethasone can be reduced to 10 mg in C1 to C8 for participants who are >75 years of age, for participants who have a body mass index (the weight in kilograms divided by the square of the height in meters) of less than 18.5, or for participants who had previous unacceptable side effects associated with glucocorticoid therapy. Participant diaries will be used to keep a record of self-administered oral study treatment(s) at home.
28. Any SAEs assessed as related to study participation or related to a GSK product will be recorded from the time a participant consent through any follow up. AEs and SAEs will be collected throughout the study until 70 days after the last dose of study treatment regardless of initiation of new anti-myeloma therapy. Concomitant medications administered after the EOT should only be recorded for SAEs/AESIs.
29. New anticancer therapy will be recorded through any follow up.

Table 3 Schedule of Activities for Part 2 Arm B (GSK2857916 in Combination with Pomalidomide plus Dexamethasone)

Time and Time Table (Cycle=28 days)									
Study Assessment[1]	**Screen[2]**	**C1**		**C2**		**C3 to CX**		**End of Treatment Visit[3]**	**Follow-up Visit**
		D1	**D8, D15, D22**	**D1**	**D8, D15, D22**	**D1**	**D15**		
Informed Consent	X								
Baseline Demographics	X								
Medical History	X								
Physical Examination	X	X		X		X		X	
Ocular Examination	X[4]			X[5]		X[5]		X[6]	X[6]
ECOG Performance Status	X	X		X		X		X	
Vital Signs (BP, HR, Body Temperature)	X	X[7]		X[7]		X[7]		X	
Weight and Height	X	Weight Only		Weight Only		Weight Only		Weight Only	
Hematology	X	X[8]	X	X	X	X	X	X	
Clinical chemistry	X	X[8]	X	X	X	X	X	X	
Urine Dipstick	X	X[8]		X		X		X	
eGFR[9]	X	X		X		X		X	
Spot urine for Albumin /creatinine ratio[10]	X	X		X		X		X	
HBV/HCV tests	X								
Troponin[11], BNP[11]	X								
UPEP and urine Immunofixation	X			X		X		X	

Time and Time Table (Cycle=28 days)									
Study Assessment[1]	**Screen[2]**	**C1**		**C2**		**C3 to CX**		**End of Treatment Visit[3]**	**Follow-up Visit**
		D1	**D8, D15, D22**	**D1**	**D8, D15, D22**	**D1**	**D15**		
SPEP and serum Immunofixation, Serum M-protein Calculation	X			X		X		X	
Kappa, lambda FLC, FLC Ratio	X			X		X		X	
24 hour urine protein	X			X		X		X	
Calcium corrected for albumin (serum)	X			X		X		X	
IgG, IgM, IgA	X			X		X		X	
IgD/E[12]	X			X		X		X	
CRP	X			X		X		X	
Beta2 microglobulin	X			X		X			
Pregnancy Test[13]	X	X	X	X		X		X	X
Skeletal survey[14]	X	As clinically indicated							
Chest X-ray imaging	X	As clinically indicated						X	
12-lead ECG[15]	X	X						X	
LVEF (ECHO)[16]	X							X	
Extramedullary plasmacytoma Imaging[17]	X					C5, C9, C13, And later only if clinically indicated		X[18]	

Time and Time Table (Cycle=28 days)									
Study Assessment[1]	**Screen[2]**	**C1**		**C2**		**C3 to CX**		**End of Treatment Visit[3]**	**Follow-up Visit**
		D1	**D8, D15, D22**	**D1**	**D8, D15, D22**	**D1**	**D15**		
FISH testing[19]	X								
BM aspirate/biopsy for disease assessment	X[20]					At the time of CR or at time of suspected Progressive disease (only if not evident otherwise)		Only if CR has been achieved by this visit, or suspected Progressive disease not evident otherwise	
CCI									
Serum (anti-drug-antibodies)[21]		X (See Section 8.9)		X (See Section 8.9)		X (See Section 8.9)		X	
Pharmacokinetic blood sampling for GSK2857916[21]		X (See Table 35)							
Genetics Sample[22]	X								
Premedication if needed		X		X		X			
GSK2857916 administration[23]		X		X		X			
Pomalidomide administration[24]		D1-D21 of each 28-day cycle							
Dexamethasone administration[25]		D1, D8, D15 and D22 of each 28-day cycle							
Preservative-free Artificial Tears		Administered in each eye at least 4-8 times daily beginning on C1D1 until EOT. In the event of ocular symptoms (i.e., dry eyes), the use of artificial tears may be increased up to every 2 hours, as needed.							

Time and Time Table (Cycle=28 days)									
Study Assessment[1]	**Screen[2]**	**C1**		**C2**		**C3 to CX**		**End of Treatment Visit[3]**	**Follow-up Visit**
		D1	**D8, D15, D22**	**D1**	**D8, D15, D22**	**D1**	**D15**		
Cooling Eye Masks (optional)		On GSK2857916 dosing day, may apply cooling eye masks as long as tolerated from start of infusion and up to 4 hours							
Adverse Events[26]	X	Continuous							X
Concomitant Medications[26]	X	Continuous							X
New anti-myeloma Therapy[27]									X

1. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. All other assessments can be performed within ±3 days of scheduled occurrence unless otherwise specified. D8, D15, and D22 assessments can be performed within ±1 day of scheduled occurrence.
2. All Screening assessments must be performed within 21 days prior to first dose unless otherwise specified. Informed Consent must be signed before any study-specific assessments are performed.
3. The End of Treatment (EOT) Visit will occur within 30 days (±3 days) after the last dose of any study medication or before the initiation of any other antimyeloma treatment. For participant discontinuing treatment in the PACT phase, no end of treatment visit is required.
4. Screening ocular examination will be performed by an ophthalmologist within 21 days prior to the first dosing (see Section 8.2.2. for the list of screening ophthalmic exam procedures).
5. On-study ophthalmic exams to be performed by an ophthalmologist every 4 weeks prior to dosing, up to the 6th dose of GSK2857916. At time of the 6th dose of GSK2857916, if there are no significant ophthalmic exam findings, participant's symptoms or vision changes, the frequency of ophthalmic exams may be decreased to every 3 months until EOT. If a participant subsequently develops vision changes or other ocular symptoms, the participant should be promptly evaluated by an ophthalmologist. In case of persistent ophthalmic exam findings, newly developed ocular symptoms or vision changes, the participants will have further ophthalmic exams, at least every cycle until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by an ophthalmologist. See Section 8.2.2. for the list of ophthalmic exam procedures. Intraocular pressure must be monitored if steroid eye drops are used continuously more than 7 days.
6. Ophthalmic exam at the EOT to be performed by an ophthalmologist. Participants with corneal signs per the GSK scale at the EOT Visit will continue to be followed at 3 weeks (±7 days) after the EOT visit and then every 6 weeks (±7 days) for up to 12 months, or until full resolution of findings defined as a return to participant's baseline or deemed clinically stable by an ophthalmologist, whichever comes first. See Section 8.2.2 for the list of ophthalmic exam procedures.

7. On initial (first infusion) dosing day, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), +10 minutes (±5 minutes), EOI (±5 minutes), and 1 hour post EOI (±5 minutes). On subsequent dosing days, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI). The Sentinel Participant must be observed for at least 24 hours post EOI. On days where vital sign timepoints align with PK sampling timepoints, vital signs should be assessed prior to PK samples being drawn.
8. If completed within 72 hrs prior to the first dose, this assessment need not be repeated on C1D1. Refer to Table 32 for comprehensive list of laboratory tests.
9. eGFR is to be calculated via modified diet in renal disease (MDRD) calculation.
10. Albumin/creatinine ratios (spot urine from first void) at screening, C1, and every cycle thereafter.
11. Troponin I or T and B-type natriuretic peptide (BNP) will be measured at the local laboratory, or by central laboratory if not available locally. If cardiac workup is required due to safety concerns during the study, troponin I or T and BNP should be measured as clinically indicated.
12. Only in patients with IgD/IgE myeloma.
13. Perform only in women of childbearing potential (WOCBP), see Appendix 3 for definition. A serum pregnancy test must be performed at screening. Two negative serum pregnancy tests must be obtained prior to initiating treatment; the first test should be performed within 10 to 14 days of C1D1, but the second must be performed within 24 hours of C1D1. After the first dose, pregnancy test will be done weekly during the first month, then every cycle thereafter (or every 2 weeks in females with irregular menstrual cycles). Subsequent pregnancy test on dosing days may be either serum or urine test. Each pregnancy test must be performed within 24 hours prior to dosing. Final pregnancy test (serum or urine) must be performed in WOCBP at the EOT visit and at 2 weeks (in case of irregular menses) and 4 weeks following treatment discontinuation. Follow up pregnancy assessment by telephone (for WOCBP only) should be performed 4 months after the last dose of GSK2857916 or 4 weeks after the last dose of pomalidomide, whichever is longest.
14. Skeletal Survey: Imaging of bones for lytic lesions by a method aligned with the institutional guidance (X-ray, CT, or MRI). Skeletal survey results within 30 days prior to C1D1 are acceptable.
15. On dosing days, ECG to be performed in singlet at predose (within 30 minutes prior to SOI).
16. Echocardiography for left ventricular ejection fraction (LVEF) performed within 35 days prior to first dose is acceptable as screening value.
17. Imaging is only required for participants with extramedullary disease (CT, MRI, or PET/CT can be applied per local guidance). Screening assessment may be performed up to 30 days prior to C1D1. The same modality should be used throughout the study (i.e., if CT scan was used as baseline, participant needs to be followed by CT scans). 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 skin only involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the Sum of the Products of the maximal perpendicular diameters of measured lesions (SPD).
18. In participants with extramedullary plasmacytoma, if the last radiographic assessment occurred ≥8 weeks prior to the participant's withdrawal from study treatment, and progressive disease has NOT been documented, –a new assessment for extramedullary disease should be obtained at the EOT.
19. FISH testing at least for: t(4;14), t(14;16), 17p13del. FISH results from samples taken within 60 days prior to first dose are acceptable.
20. Archival tissue from up to 60 days prior to study is acceptable.

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22. Informed consent for optional genetics research should be obtained before collecting a sample. The sample will be collected between the first opportunity after a participant has met all eligibility requirements and the EOT Visit.
23. Study treatment administration ±3 day window only.
24. On days where only pomalidomide and dexamethasone are taken at home, they should be taken in the morning approximately at the same time each day. Platelet count must be ≥50,000/mL to initiate new cycle. Refer to Section 6.7 for dose modification guidelines and instructions on dose delays. Participant diaries will be used to keep a record of self-administered oral study treatment(s) at home.
25. Dexamethasone 40 mg orally on D1, D8, D15, and D22 of every 28-day cycle. For participants who are >75 years or have comorbidities or are intolerant to 40 mg, the dose of dexamethasone can be reduced to 20 mg. Refer to Section 6.7 for dose modification guidelines and instructions on dose delays. On days where only pomalidomide and dexamethasone are taken at home, they should be taken in the morning approximately at the same time each day. On GSK2857916 dosing days, dexamethasone should be administered 1 to 3 hours prior to the first administration of GSK2857916. Participant diaries will be used to keep a record of self-administered oral study treatment(s) at home.
26. Any SAEs assessed as related to study participation or related to a GSK product will be recorded from the time a participant consent through any follow up. AEs and SAEs will be collected throughout the study until 70 days after the last dose of study treatment regardless of initiation of new anti-myeloma therapy. Concomitant medications administered after the EOT should only be recorded for SAEs/AESIs.
27. New anticancer therapy will be recorded through any follow up.

Table 4 Hepatitis B (HBV) SoA – additional procedures

Note: the procedures listed in this table apply ONLY to participants in screening and who have been enrolled and who have a history of Hepatitis B; all procedures must be done as needed **in addition** to the required procedures for all participants detailed in Table 2 and Table 3.

HBV Study Assessments	During Screening / Prior to starting treatment	During Treatment	EOT	Notes
HBV-DNA testing	X[1]	X[1]	X[1]	1. HBV-DNA testing prior to the start of GSK2857916 and subsequently every 3 months, or if LFT elevations requiring increased monitoring or stopping criteria occurs, or for any clinical suspicion of hepatitis reactivation.

2. INTRODUCTION

Multiple myeloma (MM) is a malignancy of the plasma cells that is characterized by monoclonal protein in blood and urine, and has multiple symptoms such as haematopoietic disorder, renal disorder, bone pains.

Multiple myeloma is an incurable malignancy and accounts for 1.8% of all new cancers and 13% of all hematologic malignancies [SEER CSR, 2018]. Worldwide, approximately 103,000 new cases are diagnosed annually [Cowan, 2018] and in the United States (US), 32,110 new cases and 12,960 deaths are estimated to occur in 2019 [Siegel, 2019]. Incident cases from 1990 to 2016 increased by 126% globally [Cowan, 2016]. In Japan, the number of patients with MM was 8,200, and that of deaths was 4,200 in 2017 [NCCN, 2017]. Due to aging of society, incidence of MM has increased recently [Ozaki, 2015].

There have been significant advances in treatment for MM, including novel therapies like second and third-generation proteasome inhibitors, immunomodulatory drugs (IMiDs), and recent addition of monoclonal antibodies (mAbs). Those advances have contributed to incremental gains in progression free survival (PFS) and overall survival (OS). Despite the recent advances in therapy, MM remains an incurable disease, and novel approaches that induce deep and durable tumor regression with little cross-resistance with existing drugs are always needed to expand the therapeutic options against MM.

2.1. Study Rationale

Over the past two decades, the median survival of patients with MM has significantly improved, from 3 to 4 years to approximately 7 to 8 years, mainly due to the application of high-dose conventional therapy with autologous stem-cell transplantation (HDT-ASCT) as a routine procedure for transplant-eligible MM patients; significant improvements in supportive care strategies; and the introduction and wide-spread use of the IMiDs thalidomide and lenalidomide and the proteasome inhibitor, bortezomib [Nijhof , 2018]. Similarly, IMiDs and proteasome inhibitors are the novel agents approved for treatment of relapsed/refractory multiple myeloma (RRMM) in Japan. The survival outcome has significantly improved after the introduction of these novel agents [Ozaki, 2015]. In Japan, the regiments with bortezomib, lenalidomide or thalidomide as salvage therapy, or ASCT are recommended for RRMM [Japanese Society of Hematology, 2013]. These novel agents nowadays represent the backbone of many current standard-of-care therapies for MM patients, both at diagnosis and in the relapse setting.

Daratumumab [DARZALEX, 2017], is a human immunoglobulin G (IgG) 1 kappa monoclonal antibody that targets CD38, a cell surface protein that is overexpressed on MM cells. The drug was granted accelerated approval as monotherapy for the treatment of RRMM in the US in November 2015 [Afifi, 2016] on the basis of the results from a Phase II monotherapy study (n=106) which reported 29.2% overall response rate (ORR) and median PFS (mPFS) 3.7 months in patients with RRMM. Daratumumab received approval in Japan on 27 September 2017.

While the data with daratumumab indicate that further prolongation of PFS can be achieved, it is also increasingly recognized that patients continue to relapse after treatment with daratumumab, and will need additional treatment options to control the disease.

GSK2857916 is a first in class, antibody-dependent cell-mediated cytotoxicity (ADCC) enhanced, humanized IgG1 antibody-drug conjugate (ADC) that binds specifically to B-cell maturation antigen (BCMA), a target restricted to B cells at later stages of differentiation and expressed on tumor cells of all patients with MM [Tai, 2015; Tai, 2006]. The normal function of BCMA is to promote cell survival by transduction of signals from two known ligands (BAFF[BlyS] and a proliferation-inducing ligand [APRIL]). The expression is restricted to B cells at later stages of differentiation, with expression on germinal center B cells in tonsil, blood plasma blasts and long lived plasma cells [Darce, 2007]. The expression levels in MM vary from patient to patient, but GlaxoSmithKline (GSK) studies demonstrate that all patients tested express detectable levels of BCMA protein on their tumor cells.

GSK2857916 has shown strong single-agent activity in 2 clinical studies conducted in heavily pre-treated participants with RRMM [Trudel, 2018; Trudel, 2019; Lonial, 2020].

Among the 35 participants in BMA117159 study, receiving GSK2857916 at the recommended phase II dose (RP2D) of 3.4 mg/kg intravenously (IV), once every 3 weeks (Q3W), the following results were observed as of 31 August 2018:

- ORR of 60% [95% confidence interval (CI): 42.1, 76.1]
- mPFS was 12.0 months [95% CI: 3.1, not estimable (NE)].
- The ORR in 32 participants to both IMiDs and proteasome inhibitors was 56% (95% CI: 37.7, 73.6), and the mPFS in this subgroup was 7.9 months (95% CI: 2.3, NE).
- Overall, GSK2857916 was well tolerated and adverse events (AEs) were manageable.

This data supports testing of GSK2857916 as a monotherapy in Japanese participants with RRMM.

In addition, given the strong single-agent activity of GSK2857916, the combination therapy of GSK2857916 with standard of care (SoC) agents is an attractive option to explore for patients with RRMM. Based on the mechanism of action of GSK2857916, the combination with SoC therapies (bortezomib and dexamethasone [Bor/Dex] or pomalidomide and dexamethasone [Pom/Dex]) is expected to result in additive, or potentially synergistic effects which could potentially translate into a deep and long-lasting response over what has been achieved with available agents.

The ongoing Phase I/II open-label, dose escalation and expansion study 207497 is evaluating the safety and clinical activity of GSK2857916 when given in combination with Bor/Dex in patients with RRMM who have received at least 1 prior line of therapy. Preliminary data from this study indicate that the combination of GSK2857916 at 2.5 mg/kg dose with Bor/Dex is safe and tolerable without dose limiting toxicities (DLT)

and is showing early evidence of activity, given the prior and ongoing experience (from first time in human [FTIH] study BMA117159 and Phase II 205678 study) of single agent activity for this dose (2.5 mg/kg) of GSK2857916.

GSK2857916 at multiple dose levels in combination with Pom/Dex once every 4 weeks (Q4W) is being evaluated for safety and efficacy in patients with RRMM in an ongoing Phase I/II study conducted by the MCRN (MCRN 007 or study 209418). As of 01 February 2020, 11 participants have received GSK2857916 at 1.92 mg/kg dose, and 7 participants at 2.5 mg/kg dose in combination with Pom/Dex Q4W. Preliminary data showed that the GSK2857916/Pom/Dex combination at both dose levels has resulted in early signs of clinical activity, and an acceptable safety profile, consistent with the known safety profile of the individual components, GSK2857916 and Pom/Dex.

These data support testing GSK2857916 when administered in combination with approved regimens of either Bor/Dex (Arm A) or Pom/Dex (Arm B) in Japanese participants with RRMM in Part 2.

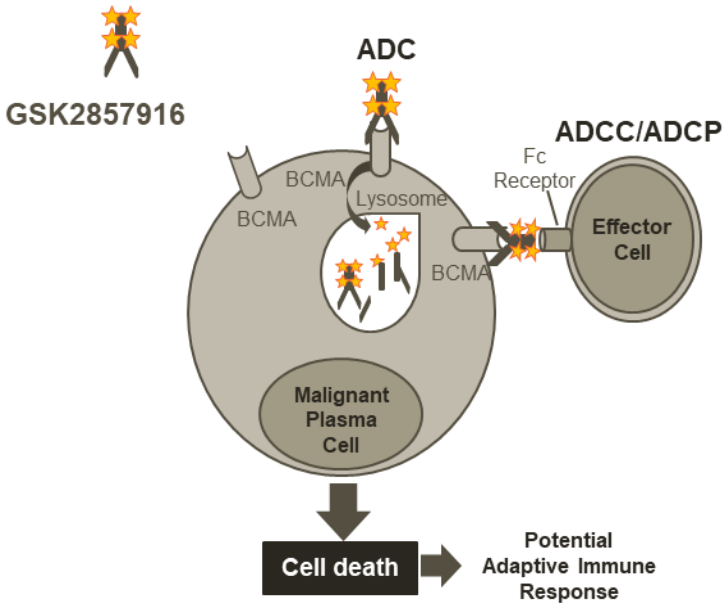
2.2. Background – BCMA and Multiple Myeloma

B-cell maturation antigen (BCMA also referred to as TNFRSF17 or CD269) is a member of the tumor necrosis factor (TNF) receptor superfamily and regulates a variety of cellular functions. BCMA is expressed in mature B lymphocytes and binds to two TNF family ligands BAFF (B-cell-activating factor belonging to the TNF family) and APRIL (a proliferation-inducing ligand) which promotes B-cell survival and proliferation. Mice deficient for BCMA are viable, have normal B-cell development, and exhibit normal humoral responses [Belnoue, 2008; Varfolomeev, 2004; Jiang, 2011]. BCMA is expressed on malignant plasma cells in all MM patients [Tai, 2015; Tai, 2006]. The restricted expression profile of BCMA in normal tissue, combined with its up-regulation and recognized survival function in MM [Tai, 2006; Sanchez, 2012; Novak, 2004] makes BCMA an attractive target for a therapeutic antibody with direct cell killing activity and with minimal off target effects [Tai, 2015]. BCMA has been validated as a therapeutic target in MM [Tai, 2015]. The BMA117159 study was the FTIH study demonstrating single-agent activity of GSK2857916 in heavily pre-treated MM participants.

2.3. Antibody-Drug Conjugate GSK2857916

GSK2857916 binds to BCMA and kills MM cells via a multi-modal mechanism including delivery of cytotoxic, monomethyl auristatin-F (MMAF) (cysteine maleimidocaproyl MMAF [cys-mcMMAF]) to BCMA-expressing MM cells, thereby inducing apoptosis, enhancing ADCC and antibody-dependent cellular phagocytosis (ADCP), and inducing immunogenic cell death (Figure 1) [Tai, 2014; Montes De Oca, 2019]. Exposure of dendritic cells to tumor cells undergoing immunogenic cell death is expected to result in an antigen-specific T-cell response, enhancing the immunogenic response against MM.

Figure 1 GSK2857916 Mechanism of Action



ADCC/ADCP=antibody-dependent cell-mediated cytotoxicity/antibody-dependent cellular phagocytosis

2.3.1. Human Experience with GSK2857916

2.3.1.1. Studies with GSK2857916 Monotherapy

Single-agent GSK2857916 has demonstrated to have a strong single-agent activity with a well-defined manageable safety profile in heavily pre-treated participants with RRMM (Q3W schedule vis IV administration). Safety data for single-agent GSK2857916 were pooled (data as of 20 September 2019) for study 205678 (DREAMM-2; NCT03525678) and supportive FTIH study BMA117159 (DREAMM-1; NCT02064387), by treatment cohorts of 2.5 mg/kg and 3.4 mg/kg.

FTIH study BMA117159/DREAMM-1

In the FTIH study BMA117159, which consisted of a dose escalation phase (Part 1, n=38) and a dose expansion phase (Part 2, n=35), as of the primary analysis cut-off date of 31 August 2018, a total of 73 participants with RRMM received at least 1 dose of GSK2857916 [GSK2857916 IB; Trudel, 2019].

As of the efficacy cut-off date of 31 August 2018, a total of 35 participants were treated at the 3.4 mg/kg dose in Part 2 of the DREAMM-1 study. Participants were heavily pre-treated: 57% of participants had 5 or more prior lines of therapy. The ORR was 60% (95% CI: 42.1, 76.1): comprised of partial response (PR), 6%; very good partial response (VGPR), 40%; complete response (CR), 9%; and stringent CR (sCR), 6%. The median duration of response (DoR) was 14.3 months (95% CI: 10.6, not reached [NR]). The mPFS in this population was 12.0 months (95% CI: 3.1, NE). For participants refractory to both IMiDs and proteasome inhibitors (n=32/35), the confirmed ORR was 56% (95% CI: 37.7, 73.6) and mPFS was 7.9 months (95% CI: 2.3, NE) [Trudel, 2019].

Phase II study 205678/DREAMM-2

The ongoing Phase II study 205678/DREAMM-2 is evaluating these two IV single agent doses (2.5 and 3.4 mg/kg) administered Q3W until disease progression in participants who have failed at least 3 prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and who are refractory to an IMiD and a proteasome inhibitor. A total of 194 participants received frozen drug product in the main cohort and 24 participants received 3.4 mg/kg lyophilized drug product. The study met its primary endpoint for ORR in both the 2.5 mg/kg and 3.4 mg/kg treatments, and the benefit of GSK2857916 was supported by the secondary endpoints. Primary analysis data from this study indicated no new safety signals, and the profile of AEs was similar to the experience in the DREAMM-1 study for both arms. Both dose levels, 2.5 and 3.4 mg/kg, were shown to have a positive benefit/risk profile [Lonial, 2020].

As of the cut-off date of 31 January 2020, the ORR in the 2.5 mg/kg treatment was 31% (97.5% CI: 21.7, 43.6) and in the 3.4 mg/kg treatment 35% (97.5% CI: 24.8, 47.0). The median DoR was 11.0 months (95% CI: 4.2, NR) at 2.5 mg/kg and 6.2 months (95% CI: 4.8, NR) at 3.4 mg/kg. The mPFS in this population was 2.8 months (95% CI: 1.6, 3.6) and 3.9 months (95% CI: 2.0, 5.8), respectively and the median OS was 13.7 months (95% CI: 9.9, NR) at 2.5 mg/kg and 13.8 months (95% CI: 10.0, NR) at 3.4 mg/kg. Positive clinical activity was also demonstrated at the 3.4 mg/kg lyophilised dose (ORR 52% [97.5% CI: 28.9, 74.5]).

2.3.1.1.1. Safety

Single-agent GSK2857916 was demonstrated to have a manageable safety profile in heavily pre-treated participants with RRMM. Safety data for single-agent GSK2857916 were pooled (data as of 20 September 2019) for DREAMM-2 study and supportive FTIH study DREAMM-1 by treatment cohorts of 2.5 mg/kg and 3.4 mg/kg.

The most common AEs in both treatment cohorts were keratopathy (corneal epithelium changes observed on ophthalmic examination), thrombocytopenia and anemia. The incidence of AEs, including Grade 3/4 AEs was comparable between GSK2857916 2.5 mg/kg and 3.4 mg/kg cohorts. AEs leading to dose delays, and reductions were less frequent in 2.5 mg/kg cohort, 51% and 32% compared with the 3.4 mg/kg cohort, 67% and 52%, respectively. AEs leading to permanent treatment discontinuation occurred in 10% and 11% of participants in the 2.5 and 3.4 mg/kg cohorts, respectively. More participants in the 3.4 mg/kg cohort experienced serious adverse events (SAEs) (50%) and fatal SAEs (6%) compared with the 2.5 mg/kg cohort (41% and 3%, respectively).

Single-agent GSK2857916 2.5 mg/kg was selected as the recommended dose based on comparable efficacy with a more favorable safety profile (i.e., lower incidence of thrombocytopenia and neutropenia and less frequent dose delays or reductions) compared with the 3.4 mg/kg dose.

Adverse Events of Special Interest

Adverse events of special interest (AESIs) for GSK2857916 are corneal events, thrombocytopenia and infusion-related reactions (IRRs), and are described below.

Corneal Events

Corneal events, reported in most cases as keratopathy, blurred vision and dry eye events are the most frequently reported AEs with GSK2857916.

In DREAMM-2 (data as of 31 January 2020), events in the Eye disorders system organ class occurred in 78% of participants treated with GSK2857916 2.5 mg/kg. The most common ocular AEs were keratopathy (71%, changes in corneal epithelium identified on eye exam, with or without symptoms), blurred vision (22%), and dry eye (13%). Decreased vision defined as Snellen score worse than 20/50 in the better seeing eye was reported in 18% of participants receiving GSK2857916 2.5 mg/kg. Severe vision loss defined as 20/200 or worse in the better seeing eye was reported in 1% of participants receiving GSK2857916 2.5 mg/kg.

The median time to onset of Grade 2 or above corneal findings (best corrected visual acuity or corneal examination) was 36 days (range: 19 to 143 days) in participants receiving GSK2857916 2.5 mg/kg. The median time to resolution of these corneal findings was 91 days (range: 21 to 201 days).

Participants with history of dry eye were more prone to develop corneal examination findings. Therefore, active management of dry eye symptoms prior to and during treatment is recommended (i.e., administration of preservative-free artificial tears).

The ocular sub-study of DREAMM-2 provided no evidence that corticosteroid eye drops are beneficial in preventing or mitigating corneal events.

Thrombocytopenia

In DREAMM-2 (data as of 31 January 2020), thrombocytopenic events (thrombocytopenia and platelet count decreased) occurred in 38% participants treated with GSK2857916 2.5 mg/kg; severity ranging between Grade 1 and 4. The incidence of Grade 3 bleeding events was low (2%), with no Grade 4 or 5 events reported in participants treated with GSK2857916 2.5 mg/kg.

Most participants had a decrease from baseline in their platelet counts during the study. In general, participants who initiated treatment with lower platelet numbers tended to continue to have thrombocytopenia while on treatment with GSK2857916.

Infusion-related reactions

IRRs are expected for biologic agents. In DREAMM-2 (data as of 31 January 2020), IRRs occurred in 21% of participants in the GSK2857916 2.5 mg/kg, which were Grade 1 - 3 in severity. Most IRRs occurred with the first infusion and few participants experienced IRRs with subsequent infusions.

Although not protocol-mandated, pre-medications for IRR prophylaxis (including paracetamol, antihistamines, and steroids) were administered to 26% - 27% of participants. One participant (2.5 mg/kg cohort) discontinued treatment due to IRRs (Grade 3 IRRs at first and second infusion).

2.3.1.2. Combination Studies of GSK2857916

GSK2857916 in Combination with Lenalidomide/Dexamethasone or in Combination with Bortezomib/Dexamethasone (Study 207497)

Study 207497 (NCT03544281, DREAMM 6) is an ongoing Phase I/II, open-label, dose escalation and expansion study of GSK2857916 in combination with 2 SoC regimens; lenalidomide/dexamethasone (Arm A) in a 28-day cycle, or with Bor/Dex (Arm B) in a 21-day cycle. Study 207497 will evaluate safety and clinical activity of the combination treatments in participants with RRMM after at least 1 prior line of therapy.

The study consists of 2 parts. Part 1 is a dose escalation phase to evaluate the safety and tolerability of various dose levels and up to 2 dosing schedules of GSK2857916 in combination with the above 2 SoC regimens. Part 2 of the study is intended to further evaluate the safety and clinical activity of up to 3 dose levels and up to 2 dosing schedules of GSK2857916 with lenamidomide and dexamethasone or Bor/Dex. In Part 1 (dose escalation), the starting dose for GSK2857916 in both arms was 2.5 mg/kg. Treatment arms are enrolled and analyzed independently. Based on data from 15 participants treated at the dose of 2.5 mg/kg Q3W, followed on study for 1 to 14 cycles (n= 6 participants with a range of 8 to 14 cycles, an average of 11 cycles and a median of 12 cycles as of 26 November 2019), this combination dose has been shown to have an acceptable safety profile.

During Part 1 (dose escalation) of the study, no DLTs were reported for the 3 evaluable participants at the 2.5 mg/kg Q3W dose of GSK2857916 in combination with Bor/Dex (Arm B) and GSK2857916 dose was escalated to 3.4 mg/kg Q3W. Part 2 (dose expansion) of the study is evaluating the safety and preliminary clinical activity of both the dose levels (GSK2857916 2.5 and 3.4 mg/kg) and 2 dosing schedules of GSK2857916 (administered as a single dose on Day (D) 1 of each cycle, and, administered as 2 equal divided dose a week apart on D1 and D8 of each cycle) in combination with Bor/Dex. Preliminary safety data from Study 207497 is broadly consistent with the clinical experience reported with GSK2857916 to date and standard combination treatments in the RRMM population. Based on benefit/risk assessment, a dose of GSK2857916 at 2.5 mg/kg Q3W has been selected in combination with Bor/Dex for patients with RRMM in at least 2-line settings.

GSK2857916 in Combination with Pomalidomide and Dexamethasone (Study 209418)

Study 209418 (or MCRN007) is an ongoing Phase I/II, dose-escalation study conducted by the Myeloma Canada Research Network (MCRN) to evaluate the safety and efficacy of GSK2857916 given IV Q4W in combination with Pom/Dex in patients with RRMM. The study consists of 2 parts: Part 1 is dose-finding and Part 2 is the expansion phase.

All participants receive multiple dose levels of GSK2857916 administered IV Q4W in combination with Pom/Dex in a 28-day treatment cycle. Pomalidomide is administered at 4 mg once daily (QD) on D1 to D21 of a 28-day cycle and dexamethasone at 40 mg QD (participants with 75 years of age or younger) or 20 mg QD (participants older than 75 years of age) on D1, D8, D15, and D22 of each 28-day cycle. Treatment will be

administered until disease progression or unacceptable toxicity. The Investigator Sponsor performed an analysis based on the instream live data for the purpose of an abstract submission (cut-off date of 01 February 2020). A total of 18 participants were included in this report, of which 11 participants GSK2857916 at 1.92 mg/kg dose level, and 7 participants at 2.5 mg/kg dose level.

The accumulative treatment cycles were ranged from 1 to 9 cycles in 1.92 mg/kg cohort and 3 to 9 cycles in at 2.5 mg/kg cohort. One participant was non-evaluable for DLT assessment in each dose cohort. Based on the dose escalation criteria, both 1.92 mg/kg and 2.5 mg/kg dose levels of GSK2857916 were considered to have cleared the DLT evaluation period. This combination regimen has an acceptable safety profile, consistent with the known safety profile of the individual components, GSK2857916 and Pom/Dex. The most frequently reported AEs were corneal and haematological toxicities and most events resolved (or were resolving) following protocol defined monitoring and dose modifications.

Responses obtained in the 2.5 mg/kg cohort were deep and rapid, with PR or VGPR responses achieved within first 2 cycles. However, in the 2.5 mg/kg dose cohort, all 7 participants treated at 2.5 mg/kg of GSK2857916 experienced Grade 2 or 3 ocular toxicities within 2 cycles of therapy requiring dose interruptions and dose reductions of GSK2857916 from 2.5 mg/kg to 1.92 mg/kg Q4W. Despite these dose modifications, all 7 participants achieved deep responses (best overall response 6 VGPR and 1 sCR) and 2 participants experienced disease progression.

The dose cohort of 1.92 mg/kg Q4W was better tolerated with less frequent dose interruptions of GSK2857916. However, the efficacy observed thus far (4 stable disease [SD], 2 PR and 4 VGPR, 2 participants had disease progression) appears inferior than the efficacy observed in the dose cohort of 2.5 mg/kg Q4W. One participant withdrew consent in the 1.92 mg/kg dose cohort.

2.3.1.3. Pharmacokinetics and Pharmacodynamics in Human

The pharmacokinetics (PK) and pharmacodynamics (PD) of GSK2857916 (antibody-drug conjugate, including complex with CCI [redacted] total mAb (including complex), and cys-mcMMAF were investigated in 291 participants with RRMM following IV administration at doses from 0.03 to 4.6 mg/kg Q3W in Study BMA117159 (n=73) and at doses of 2.5 or 3.4 mg/kg Q3W in Study 205678 (n=218).

Maximum observed concentrations (Cmax) of GSK2857916 and total mAb were observed at the end of infusion (EOI), while cys-mcMMAF Cmax values were generally observed on Day 2. On a molar basis, plasma concentrations of cys-mcMMAF were <1% of GSK2857916 concentrations. There was limited accumulation (less than 2-fold) of GSK2857916 or cys-mcMMAF during subsequent cycles.

GSK2857916 PK were described by a linear, two-compartment population model, with time-varying decrease in clearance in a population PK analysis. At Cycle 1 (C1), GSK2857916 had a systemic clearance of 0.92 L/day, steady-state volume of distribution of 10.8 L, and an elimination half-life of 12 days in participants with RRMM in Study

205678. Over time, clearance was reduced by 28%, resulting in an elimination half-life of 14 days. The time to 50% change in clearance was approximately 50 days.

No clinically significant differences in the PK of GSK2857916 or cys-mcMMAF were observed based on age (34 to 89 years), sex, race (African American/Black and White), body weight (42 to 130 kg), mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥ 30 mL/min/1.73m^2) or mild hepatic impairment (National Cancer Institute [NCI]-organ dysfunction working group classification). Higher serum levels of β_2-microglobulin, IgG, and CCI) and lower levels of albumin are associated with more advanced multiple myeloma or a higher multiple myeloma disease burden. Higher baseline IgG and CCI levels, and lower baseline albumin levels were associated with higher GSK2857916 clearance leading to lower average and trough concentrations of GSK2857916. Higher baseline IgG and CCI levels were associated with higher cys-mcMMAF central volume of distribution leading to lower cys-mcMMAF Cmax.

In nonclinical studies, cys-mcMMAF had limited metabolic clearance. *In vitro* data suggested that GSK2857916 and cys-mcMMAF are unlikely to perpetrate a drug-drug interaction or to be a victim of a drug-drug interaction with inhibitors or inducers of cytochromes P (CYP) 450. Cys-mcMMAF was an *in vitro* substrate of organic anion transporting polypeptides (OATP)1B1 and OATP1B3, multidrug resistance associated proteins (MRP)1, MRP2, and MRP3, a borderline substrate of bile salt export pump, and a possible substrate of P-glycoprotein (P-gp). Following the administration of GSK2857916 to participants with RRMM, only intact cys-mcMMAF was detected in pooled human urine, with no evidence of other MMAF-related urinary metabolites.

The PK of bortezomib and GSK2857916 were evaluated when administered in combination with dexamethasone in Study 207497. Based on preliminary PK data, as anticipated, GSK2857916 did not appear to impact the PK of bortezomib.

Free CCI levels were measured in Study BMA117159 and Study 205678. All participants exhibited reductions in free CCI concentration at EOI compared to baseline at C1, with a return to near-baseline level by seven days after dosing, reflecting binding of GSK2857916 to CCI. Maximum decreases ranged from 2% to 97%, which were qualitatively dose-dependent, with larger reductions in free CCI at higher doses.

Exposure-response analyses performed for Study 205678 and/or Study BMA117159 found that ocular safety endpoints were most strongly associated with GSK2857916 exposure, while efficacy endpoints had a weaker association with GSK2857916 exposure. Both safety and efficacy endpoints were associated with participant characteristics. GSK2857916 trough concentration was associated with probability of corneal events and keratopathy and cys-mcMMAF Cmax was associated with probability of thrombocytopenia. Probability of occurrence of dry eye, blurred vision, neutropenia and infusion related reaction were not associated with an exposure measure. In addition, the results of the analysis of concentration against corrected QT interval (QTc) demonstrated that GSK2857916 or cys-mcMMAF did not have a significant effect on cardiac repolarization.

Additional information related to GSK2857916 clinical PK, PD, and exposure-response relationships can be found in the Investigator's Brochure (IB) [GSK2857916 IB GSK Document Number 2013N175128_09, 2021].

2.4. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of GSK2857916 may be found in the GSK2857916 IB (GlaxoSmithKline Document Number 2013N175128); prescribing information for pomalidomide, bortezomib, and dexamethasone can be found in the Study Reference Manual (SRM).

2.4.1. Risk Assessment

Additional information about the known and expected benefits and risks, detailed information of nonclinical and clinical findings information regarding warnings, precautions, contraindications, AEs, and other pertinent information on GSK2857916 that may impact participant eligibility is provided in the IB [GSK2857916 IB].

Risk Assessment and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential Overlapping Toxicities for GSK2857916/Bortezomib/Dexamethasone (Part 2 Arm A) and GSK2857916/Pomalidomide/Dexamethasone (Part 2 Arm B)		
Thrombocytopenia	**GSK2857916:** GSK2857916 may cause transient thrombocytopenia in some participants, which for most cases recovered between doses. In the pooled safety population of study 205678 which included participants treated with GSK2857916 2.5 and 3.4 mg/kg, thrombocytopenia was noted in 46% of participants and ranged between Grade 1 to 4 in severity. **Part 2 Arm A** **Bortezomib:** Bortezomib is associated with thrombocytopenia that follow a cyclical pattern with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of subsequent cycle. **Part 2 Arm B** **Pomalidomide:** Pomalidomide is associated with thrombocytopenia.	Routine hematologic monitoring as outlined in the schedule of activities (SoA). Supportive therapy per local medical practice (e.g., platelet transfusion). Dose modification guidelines are detailed in Section 6.7.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Increased Infections due to Immunosuppression or neutropenia	**GSK2857916:** In nonclinical studies, GSK2857916 has been associated with decrease in immunoglobulins in monkeys, at all doses. An increase in immunoglobulins was seen in rats (rats are not an antigen-specific species for GSK2857916). Immunosuppression is frequently associated with an increased risk of infection. Serious and non-serious infections have been reported in GSK2857916 studies, including respiratory infections, pneumonia and sepsis. Neutropenic events, including febrile neutropenia have been observed with GSK2857916. **Dexamethasone:** Patients who are on corticosteroids are more susceptible to infections or exacerbation of latent infections than healthy individuals. Chickenpox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. **Part 2 Arm A** **Bortezomib:** Cases of herpes zoster reactivation and infection have been reported in patients receiving bortezomib. **Part 2 Arm B** **Pomalidomide:** Neutropenia was reported, rate of Grade 3-4 neutropenia was 46% and febrile neutropenia was 8%.	Patients with an active infection excluded. Monitoring for infections and immediate treatment of immunosuppression according to standard practice. Routine monitoring of hematologic panels as outlined in the SoA. Supportive therapy per local medical practice (*e.g.* growth factors). Prophylactic antibiotics, per local institutional guidance, in participants with Grade 3-4 neutropenia. Immediate hospitalization of participants with febrile neutropenia. Dose modification guidelines are outlined in Section 6.7. Participants on bortezomib will receive herpes zoster prophylaxis (e.g., acyclovir or other antiviral agent) according to institutional guidelines. If exposed to chickenpox, prophylaxis with Varicella-Zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immune globulin may be indicated.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other Hematological Effects	**GSK2857916:** Anemia is a common complication in the RRMM population and was frequently reported in GSK2857916 clinical program. **Part 2 Arm A** **Bortezomib:** Associated with thrombocytopenia and neutropenia that follow a cyclical pattern with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of subsequent cycle. **Part 2 Arm B** **Pomalidomide:** Associated with thrombocytopenia and anemia.	Routine hematologic monitoring as outlined in the SoA. Supportive therapy per local medical practice (e.g., growth factors). Recommendations for dose reduction and treatment discontinuation criteria are detailed in Section 6.7.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Pneumonitis	**GSK2857916:** Nonclinical safety experiments have demonstrated the presence of progressive microscopic changes in the lungs (prominent alveolar macrophages associated with eosinophilic material; mixed perivascular/neutrophilic inflammation) in rats at all doses tested. Cases of pneumonitis, including fatal events, have been observed with GSK2857916 although a causal association has not been established.. **Part 2 Arm A** **Bortezomib:** Acute respiratory distress syndrome and acute diffuse infiltrative pulmonary disease of unknown etiology, such as pneumonitis, interstitial pneumonia, and lung infiltration have been reported rarely in patients receiving bortezomib. Some of these events have been fatal. There have been reports of pulmonary hypertension associated with bortezomib administration in the absence of left heart failure or significant pulmonary disease. **Part 2 Arm B** **Pomalidomide:** Interstitial lung disease and related events, including cases of pneumonitis, have been observed with pomalidomide.	Monitoring for clinical signs and symptoms related to pulmonary toxicity. If a participant experiences new or worsening pulmonary symptoms, (e.g., cough, dyspnea) without obvious etiology, further diagnostic tests and management should be performed and further treatment with GSK2857916 delayed (refer to Section 6.7). An overall benefit/risk assessment should be considered for the participant prior to continuing GSK2857916 treatment. Further diagnostic tests and management will be implemented immediately as described in cases of suspected pneumonitis as described in Section 6.7. In the event of new or worsening cardiopulmonary symptoms, consider interrupting bortezomib until a prompt and comprehensive diagnostic evaluation is conducted.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Keratopathy (Changes to the Corneal Epithelium, Potentially Resulting in Vision Changes)	**GSK2857916:** Changes in corneal epithelium on ocular examination have been frequently observed with GSK2857916 and was most commonly associated with keratopathy (changes in the corneal epithelium upon examination), dry eyes, blurred vision, photophobia, and changes in visual acuity. Participants with a history of dry eye were more prone to develop changes in the corneal epithelium. Based on available follow-up data, vision returned to, or near baseline in most cases.. **Dexamethasone:** Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.	Active monitoring of the corneal epithelium and visual acuity as outlined in the SoA. Evaluation and management by an eye care professional. Dose modification guidelines are outlined in Section 6.7.
Embryo-Fetal Toxicity	**GSK2857916:** Nonclinical reproductive studies with GSK2857916 have not been conducted. Embryo-fetal toxicity is expected due to the cytotoxic component, cys-mcMMAF via nonspecific uptake and/or BCMA-mediated toxicity (due to reports of BCMA expression in human placental cells [Langat, 2008]). Use of GSK2857916 in pregnant women may cause fetal harm.	Pregnancy testing outlined in the SoA. Contraception requirements detailed in Section 11.3. Participants receiving pomalidomide must register with any pregnancy prevention/controlled distribution programme in place (see SRM for details).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Embryo-Fetal Toxicity	**Part 2 Arm A** **Bortezomib**: Bortezomib can cause fetal harm when administered to a pregnant woman. Bortezomib administered to rabbits during organogenesis at a dose approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area caused post-implantation loss and a decreased number of live fetuses. **Part 2 Arm B** **Pomalidomide**: Pomalidomide is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. Pomalidomide is available only through a pregnancy prevention/controlled distribution program	
Risks Related to GSK2857916 not Listed Under Potential Overlapping Toxicities		
Infusion-Related Reactions (IRR)	IRRs were reported in participants treated with GSK2857916. Most IRRs were Grade 1 to 2 and were manageable with treatment.	Close monitoring for signs of IRR. Consider premedication for IRR in participants at risk. If an IRR occurs, follow the guidance in Section 7.1.6.
Nephrotoxicity	Nonclinical safety experiments have demonstrated primary glomerular injury and tubular degeneration/regeneration (in rat and monkey). The morphologic changes were accompanied by large molecular weight proteinuria (albuminuria) and enzymuria. Single cell necrosis of the kidney and bladder urothelium was also noted in the chronic study. The renal changes were dose dependent and reversible. Severe tubular degeneration/regeneration and marked glomerulonephritis as a result of immune complex disease associated with anti-drug antibodies led to the early euthanasia of one monkey following 5 weekly doses of 10 mg/kg.	Kidney function monitoring including albumin/creatinine ratio. Education of participants on the need to maintain adequate urinary output. Dose reduction and treatment stopping criteria provided in Section 6.7.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Increase albumin/creatinine ratio (albuminuria) has been reported in participants receiving GSK2857916 not indicative of disease progression, and in such cases, appropriate monitoring and dose modification should be considered.	
Impaired Male and Female Fertility	In animal studies, GSK2857916 treatment has resulted in testicular toxicity and adverse effects on spermatogenesis. Reversibility of testicular and ovarian toxicity is unknown at this time. Ovarian toxicity (luteinized non-ovulatory follicles) was observed in a 3-week rat study (weekly dosing) and was not observed following 12 weeks off dose. In a 13-week rat study where drug was administered once every 3 weeks, these changes were not observed.	Men who may wish to father children in the future will be advised to have sperm samples frozen and stored prior to GSK2857916 treatment. Women of childbearing potential who may desire offspring in the future will be counselled about the option of having eggs frozen and stored before treatment. See contraception requirements in Section 11.3.
Potential for Other Laboratory Abnormalities	Increased magnitude of aspartate aminotransferase (AST) relative to alanine aminotransferase (ALT) consistent with increased skeletal troponin I was observed in the single dose monkey study. Increased skeletal troponin I and/or creatine kinase (CK) and aldolase was observed in the rat 3-week study. Cases of elevated AST, lactate dehydrogenase (LDH) and CK alone or concomitant with no clear clinical correlate have been observed in clinical studies.	Monitoring of laboratory parameters as outlined in the SoA. Participants with significant laboratory elevations (≥x3 ULN) should, where possible, have a sample sent for central testing of CK and LDH isoenzyme levels.
Risks Related to Bortezomib not Listed Under Potential Overlapping Toxicities (Part 2 Arm A)		
Allergic Reactions	Bortezomib is contraindicated for participants with hypersensitivity to bortezomib, boron, or mannitol, including anaphylactic reactions.	Participants with known hypersensitivity reactions to bortezomib, boron, or mannitol are not allowed on study. Bortezomib will be discontinued if such reactions are confirmed.
Peripheral Neuropathy	Bortezomib treatment causes a peripheral neuropathy that is predominantly sensory; however, cases of severe sensory and motor peripheral neuropathy have been reported.	Participants with ≥Grade 2 peripheral neuropathy at Screening excluded from study participation. Monitored for symptoms of neuropathy. Dose will be adjusted accordingly.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Bortezomib administered subcutaneously to reduce risk of peripheral neuropathy.
Hypotension	The incidence of hypotension (postural, orthostatic, and hypotension not otherwise specified) was 8%.	Participants with a history of syncope, or receiving medications associated with hypotension, or dehydrated will be closely monitored. Adjustment of antihypertensive medications, hydration and administration of mineralocorticoids and/or sympathomimetics will follow the institutional guidelines.
Posterior Reversible Encephalopathy Syndrome (PRES)	PRES; formerly termed reversible posterior leukoencephalopathy syndrome has been reported in patients receiving bortezomib.	Discontinue bortezomib if PRES occurs. The safety of reinitiating bortezomib therapy in patients previously experiencing PRES is not known.
Gastrointestinal Toxicity	Treatment with bortezomib can cause nausea, diarrhea, constipation and vomiting, sometimes requiring use of antiemetic and antidiarrheal medications; ileus can occur.	Maintain adequate hydration; fluid and electrolyte replacement should be administered to prevent dehydration. Interrupt bortezomib for severe symptoms.
Tumor Lysis Syndrome	Tumor lysis syndrome has been reported with bortezomib therapy.	Participants at risk for tumor lysis syndrome (i.e., high tumor burden) will be monitored and appropriate precautions instituted per local practice.
Thrombotic Microangiopathy	Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients receiving bortezomib.	Monitor for clinical signs and symptoms potentially related to thrombotic microangiopathy. If suspected, stop bortezomib and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting bortezomib.
Seizures	Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.	Participants with a history of seizures or epilepsy will be closely monitored. In the event of new onset or worsening seizures, consider interrupting bortezomib until a prompt and comprehensive diagnostic evaluation is conducted.
Progressive Multifocal Leukoencephalopathy (PML)	Very rare cases with unknown causality of John Cunningham virus infection, resulting in PML and death, have been reported in patients treated with bortezomib. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of	Participants should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of central nervous system problems. If a diagnosis of PML is suspected, participants should be referred to a specialist in PML and appropriate

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	PML were diagnosed within 12 months of their first dose of bortezomib.	diagnostic measures for PML should be initiated. Discontinue bortezomib if PML is diagnosed.
Hepatotoxicity	Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include hepatitis, increases in liver enzymes, and hyperbilirubinemia.	Only participants with well-preserved liver function per the inclusion/exclusion criteria will be allowed on study. Participants with Hepatitis B and C excluded. Liver function tests will be monitored per the SoA. In case of liver abnormalities, refer to Section 11.5 for further details. Liver stopping criteria outlined in Section 7.1.2.
Cardiotoxicity	Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction (LVEF) have occurred during bortezomib therapy, including reports in patients with no risk factors for decreased LVEF.	Participants with significant cardiac risk factors will be excluded from study participation. Electrocardiograms will be obtained at baseline and monitored as clinically indicated. Monitoring of other cardiac parameters as clinically indicated. Treatment as medically indicated.
Risks Related to Pomalidomide not Listed Under Potential Overlapping Toxicities (Part 2 Arm B)		
Venous and Arterial Thromboembolism	Venous thromboembolic events (deep venous thrombosis and pulmonary embolism) and arterial thromboembolic events (myocardial infarction and stroke) have been observed in patients treated with pomalidomide.	Thromboprophylaxis will be implemented as described in Section 6.6.1. Use of drugs that may increase thromboembolic risk (e.g., erythropoietic agents, estrogens, etc.) should be avoided, if possible.
Neuropathy	In studies combining pomalidomide with dexamethasone, neuropathy including peripheral neuropathy reported.	Monitor for symptoms of neuropathy.
Severe Cutaneous Reactions	Severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported.	Consider dose interruption or discontinuation for Grade 2-3 skin rash. Permanently discontinue lenalidomide for Grade 4 rash, exfoliative or bullous rash, or for other severe cutaneous reactions such as SJS, TEN or DRESS.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hypersensitivity	Hypersensitivity, including angioedema, anaphylaxis, and anaphylactic reactions have been reported.	Discontinue pomalidomide for angioedema or anaphylaxis.
Dizziness and Confusional State	In studies combining pomalidomide with dexamethasone, dizziness and confusional state have been reported.	Participants should avoid situations where dizziness or confusional state may be a problem and not to take other medications that may cause dizziness or confusional state without adequate medical advice.
Second Primary Malignancies	Cases of acute myelogenous leukemia have been reported in patients receiving pomalidomide as an investigational therapy outside of multiple myeloma (MM).	Participants will be monitored for the occurrence of new malignancies.
Tumor Lysis Syndrome	Tumor lysis syndrome may occur in patients treated with pomalidomide.	Participants at risk for tumor lysis syndrome (i.e., high tumor burden) will be monitored and appropriate precautions instituted per local practice.
Hepatotoxicity	Hepatic failure, including fatal cases and elevated levels of ALT and bilirubin reported.	Only participants with well-preserved liver function per the inclusion/exclusion criteria will be allowed on study. Participants with Hepatitis B and C excluded. Liver function tests will be monitored per the SoA. In case of liver abnormalities, refer to Section 11.5 for further details. Liver stopping criteria outlined in Section 7.1.2.
Risks Related to Dexamethasone not Listed Under Potential Overlapping Toxicities (Part 2 Arm A and Arm B)		
Vaccinations	Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.	Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted. Immunizations with live attenuated vaccines are not allowed in the study.
Viral infections	Chickenpox and measles can have a more serious or even fatal course in pediatric and adult participants on corticosteroids.	Participants who have not had these diseases, particular care should be taken to avoid exposure. If exposed to chickenpox, prophylaxis with VZIG may be indicated. If exposed to measles, prophylaxis with immune globulin may be indicated.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Allergic or Hypersensitivity Reactions	Contraindicated in patients who are hypersensitive to any components of this product. Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy.	Enrolment of participants with known hypersensitivity reactions to components of the formulation are prohibited.
Endocrine	Hypothalamic-pituitary adrenal axis suppression with the potential for corticosteroid insufficiency after withdrawal of treatment.	Avoid rapid withdrawal of corticosteroids if used at high doses for a prolonged period.
Gastrointestinal	Use with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation, or GI bleeding.	Hematologic parameters will be monitored as outlined in the SoA. New cases of anemia should be fully investigated, including the possibility of gastrointestinal bleeding.
Musculoskeletal	Decreased bone formation and increase bone resorption both through their effect on calcium regulation (i.e., decreasing absorption and increasing excretion) and inhibition of osteoblast function. Acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular disorders, or in patients receiving neuromuscular blocking drugs.	Ongoing monitoring of adverse events (AEs).
Neuropsychiatric	Psychic derangements may appear when corticosteroids, ranging from mild symptoms to severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.	Ongoing monitoring of AEs.
Cardiotoxicity	Average and large doses of corticosteroids can cause elevation of blood pressure, sodium and water retention, and increased excretion of potassium.	Participants with significant cardiovascular risk factors will be excluded from study participation.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risks from Study Procedures		
Bone Marrow Aspiration/biopsy	Pain, infection, bleeding may occur after the procedure.	Participants will be treated according to institutional practice.
Incidental Findings During Image Acquisition	During the acquisition of imaging data (e.g., magnetic resonance imaging, computed tomography, positron emission tomography), non-MM disease or clinically relevant abnormalities could be found by the radiographer performing the exams.	Copies of all medical images that include non-MM disease, clinically relevant abnormalities will be shared with the site for storage.

*Refer to GSK2857916 Investigator's Brochure and prescribing information for pomalidomide, bortezomib and dexamethasone for further information.

2.4.2. Benefit Assessment

GSK2857916 Monotherapy (Part 1)

The study population enrolled for Part 1 has a high unmet medical need. Participants failing multiple lines of prior treatments do not have many therapeutic options left, and even if response can be achieved with currently available drugs, it is usually of short duration.

Data from single-agent study BMA117159 support testing GSK2857916 in Japanese participants with RRMM failing currently available treatments.

The FTIH study BMA117159, as of 31 August 2018, indicated that GSK2857916 monotherapy administered at 3.4 mg/kg is active in participants with RRMM (n=35), with an ORR of 60% (95% CI: 42.1, 76.1) and a mPFS was 12.0 months (95% CI: 3.1, NE) [Trudel, 2019].

In the ongoing Phase II study 205678/DREAMM-2 (NCT03525678), the 2 single agent doses (2.5 mg/kg and 3.4 mg/kg) are being studied via a 2-arm, randomized design in participants who have failed at least 3 prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and who are refractory to an IMiD and a proteasome inhibitor. Both dose levels, 2.5 and 3.4 mg/kg, have a positive benefit/risk profile. As of the cut-off date of 31 January 2020, the ORR in the 2.5 mg/kg treatment was 31% (97.5% CI: 21.7, 43.6) and in the 3.4 mg/kg treatment 35% (97.5% CI: 24.8, 47.0). Overall, there were no new safety signals identified in the 205678 study, and the profile of AEs was similar to the experience in DREAMM-1 for both arms. Primary analysis show both dose levels of GSK2857916 (2.5 and 3.4 mg/kg) to have a positive benefit/risk profile.

Combination Therapy of GSK2857916 with Standard of Care (Part 2)

Increased anti-myeloma activity has been demonstrated when additional agents, with individual activity, are given in combination with Bor/Dex or Pom/Dex, including monoclonal antibodies. The combination treatment of a highly active drug, GSK2857916, with Bor/Dex or Pom/Dex is therefore expected to result in increased benefit to MM patients who have relapsed after at least 1 prior line of therapy. Preliminary data from Study 207497, which is an ongoing Phase I/II study evaluating the safety and clinical activity of GSK2857916 when given in combination with Bor/Dex in participants with RRMM, indicates that the combination of GSK2857916 at 2.5 mg/kg dose with Bor/Dex is safe and tolerable without DLTs and is showing early evidence of activity. The combination treatment of a highly active drug GSK2857916 with Pom/Dex is relatively safe with early signs of clinical activity as measured by objective response in an ongoing Phase I/II study conducted by the MCRN (Study 209418). It is reasonable to hypothesize that such combination will benefit MM patients, who are refractory to currently available treatments.

2.4.3. Overall Benefit: Risk Conclusion

GSK2857916 Monotherapy (Part 1)

Data from the FTIH study, BMA117159, demonstrate a manageable safety profile with thrombocytopenia and corneal events being the most frequently reported AEs. The corneal events most often manifested as blurry vision, photophobia, and dry eyes though a range of symptoms was possible, including increased lacrimation, pain and pruritus. Most events were Grade 1/2 and improved with dose interruptions and/or reduction.

GSK2857916 has shown strong single-agent activity. The confirmed ORR in Part 2 (MM) was 60% (95% CI, 42.1, 76.1) with 6% achieving sCR, 9% achieving CR, 40% achieving VGPR, and 6% achieving PR. The estimated mPFS of participants in Part 2 (MM) was 12.0 months (95% CI, 3.1%, NE). For participants refractory to both immunomodulators and proteasome inhibitors, the mPFS was 7.9 months (95% CI, 2.3, NE). Although maximum clinical benefit was observed at the 3.4 mg/kg dose level, frequent dose delays and dose reductions were required to manage AEs including thrombocytopenia/platelet count decreased and corneal events.

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with GSK2857916 are justified by the anticipated benefits that may be afforded to participants with RRMM.

Combination Therapy of GSK2857916 with Standard of Care (Part 2)

Considering the observed clinical activity of GSK2857916 as a single agent in participants with RRMM, and the observed safety profile in mono- and combination therapy, it is reasonable to assume that the combination of GSK2857916 with Bor/Dex or Pom/Dex may offer additional benefit to patients with RRMM.

Although there is the potential for overlapping toxicities, it is anticipated that combination therapy of GSK2857916 with Bor/Dex or Pom/Dex will have an acceptable risk/benefit profile, with manageable toxicities.

Considering the measures taken to minimize risk to participants, the potential risks associated with GSK2857916 when combined with Bor/Dex or Pom/Dex are justified by the anticipated benefits that may be afforded to participants with MM.

3. OBJECTIVES AND ENDPOINTS

The purpose of this study is to evaluate safety, PK, PD, immunogenicity and early efficacy of the GSK2857916 in Japanese participants with RRMM who have been pretreated with at least 2 regimens of anti-myeloma drugs. See Table 5 for the primary, secondary, and exploratory objectives, along with the corresponding endpoints.

Table 5 Objectives and Endpoints for Study 207504

Objectives	Endpoints
Primary Objective	
To evaluate safety, tolerability of GSK2857916 in Japanese participants with RRMM.	Number of participants with DLTs Adverse events (AEs) and changes in clinical signs and laboratory parameters.
Secondary Objectives	
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: • 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]	

4. STUDY DESIGN

4.1. Overall Design

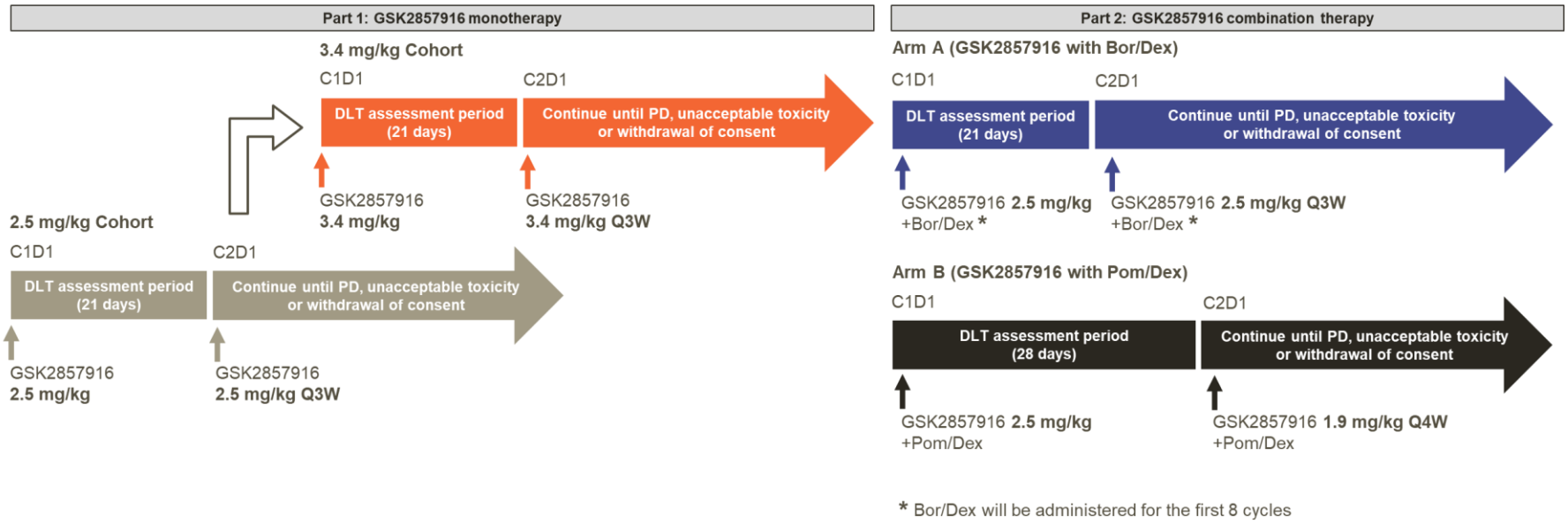
This is a Phase 1, open label, dose escalation study to investigate safety, tolerability, PK, PD, immunogenicity and clinical activity of GSK2857916 when given as monotherapy on a once every 21 days schedule (Part 1), or given in combination with Bor/Dex on a once every 21 days schedule (Part 2 Arm A) 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 maximum number of participants for Part 1 will be up to 12 participants, 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.

The dose escalation model is based on 3 + 3 design (Figure 2). The GSK2857916 will be administered (IV) via 30 min infusion Q3W (21 days = 1 cycle) or Q4W (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].

EOS Definition: Following 21 months post last subject first dose, Study 207504 (DREAMM-11) will move into the PACT phase where the study remains open only to provide continued access to study treatment for study participants who are continuing to derive clinical benefit. At that time, the collection of new data for participants who no longer receive study treatment will stop entirely and the clinical trial database will be closed. Those participants still benefiting from study drug in the opinion of their treating physician may continue to receive study drug and only SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases, and pre-specified ocular data will be reported directly to GSK. 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 shown in the Schedule of Activities for the last participant in the study.

Figure 2 Study Schematic



3 + 3 Dose Escalation: Dose-escalation will follow a 3 + 3 dose-escalation procedure as shown in Table 6. The first participant in each dose cohort should complete C1 to enrol subsequent participants. Evaluation of available safety data from at least 3 participants who have completed a minimum of 21 days (1 cycle: 21 days) or 28 days (1 cycle: 28 days) is required to start the next dose cohort. Dose-escalation will be determined considering all available information on AEs occurred in the DLT observation period. Refer to Table 6 for more details. Dose levels to be tested in the study are provided in Table 7, Table 8, and Table 9.

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

Table 6 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 7 Dose Levels for Part 1

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

Table 8 Dose Level for Part 2 Arm A

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

Table 9 Dose Levels for Part 2 Arm B

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

4.1.1. Dose-Limiting Toxicity

Any participant who received at least one dose of the study treatment will be evaluated for DLTs in Part 1. In Part 2, 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. Safety data together with DLTs will be reviewed prior to opening enrollment into subsequent cohorts.

In Part 1 and Part 2 Arm A, DLT is defined as any observed toxicity in the first 21 days of treatment cycle. In Part 2 Arm B, DLT is defined as any observed toxicity in the first 28 days of treatment cycle. If 1 of 3 participants experiences a DLT at a particular dose level, 3 additional participants will be enrolled at that dose level.

In Part 1, participants who have been withdrawn from the study for reasons other than toxicity but prior to completion of DLT observation period will be replaced. 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.

A following event occurring within the DLT reporting period (first 21 days cycle or first 28 days cycle) 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 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 resolve 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 Appendix 7).

Other organ-specific toxicity:

- Liver toxicity meeting pre-specified GSK liver stopping criteria.

A participant who develops a DLT will be allowed to stay on study if the toxicity did not meet stopping criteria and recovered to ≤ Grade 1 if the investigator and medical monitor agree that for a given participant the benefits may outweigh the risks.

4.2. Scientific Rationale for Study Design

GSK2857916 is the first-in-class ADC targeting BCMA. Clinical data for GSK2857916 monotherapy from 35 participants in the Study BMA117159 indicate an ORR of 60% [95% CI: 42.1, 76.1], with 54% of participants (n=19) having deep responses of VGPR or better. The median DoR was 14.3 months (95% CI: 10.6, NR); the mPFS in this population was 12.0 months [95% CI: 3.1, NE]. The majority of participants (57%) had 5 or more prior treatments. Of note, the ORR for participants refractory to both IMiDs and proteasome inhibitors (n=32) was 56% (95% CI: 37.7, 73.6).

The response rate observed in this population is higher than response rates observed in similarly defined patient populations treated with other recently approved drugs (ORR ranging from 23.7% to 33.1% for carfilzomib, pomalidomide and daratumumab) [Siegel, 2012; Usmani, 2016; Kumar, 2008]. The most frequent AEs were corneal events and thrombocytopenia/platelet count decrease, which were manageable following protocol-defined dose modification guidelines. Given the evidence of clinical activity and manageable safety/tolerability profile demonstrated to date, the current evidence supports further development for GSK2857916 monotherapy. Based on the results of BMA117159, the dosing regimen for GSK2857916 monotherapy is determined for further global development.

IMiD and proteasome inhibitors have been a cornerstone in the treatment of MM for many yearsKumar. Combining active agents with lenalidomide/dexamethasone or bortezomib/dexamethasone treatment may yield improved patient outcomes with acceptable toxicity profiles, establishing global SoC regimens.

Additional preclinical studies have been performed to evaluate the anti-tumor activity of GSK2857916 in combination with bortezomib, pomalidomide or dexamethasone in 2 established MM xenograft mouse models. GSK2857916 combinations with pomalidomide or bortezomib provided additional benefit compared to each single agent by significantly increasing survival in both mouse models.

Based on the nonclinical data available for the GSK2857916/pomalidomide combination and the clinical data for GSK2857916 monotherapy, it is therefore hypothesized that the combination of GSK2857916 with Bor/Dex or with Pom/Dex may result in significant additive or synergistic effect.

Preliminary data from the ongoing Phase I/II study (study 207497) evaluating the safety and clinical activity of GSK2857916 when given in combination with Bor/Dex indicates that the combination of GSK2857916 at 2.5 mg/kg dose with Bor/Dex is safe and tolerable without DLTs and is showing early evidence of activity. Initial safety and

efficacy data of GSK2857916 at multiple dose levels in combination with Pom/Dex Q4W has been evaluated in an ongoing Phase I/II study conducted by the MCRN (study 209418). Preliminary data showed that the GSK2857916 with Pom/Dex combination has resulted in early signal of clinical activity. The observed safety profile of GSK2857916 with Pom/Dex is consistent with the safety profile of GSK2857916 and pomalidomide.

Given the evidence of clinical activity and manageable safety/tolerability profile demonstrated to date, the current evidence supports further development for GSK2857916 combination therapy.

Based on the results of studies 207497 and 209418, the dosing regimens for GSK2857916 in combination with Bor/Dex or Pom/Dex are determined for further global development.

This is the first study targeting Japanese MM participants. Therefore, the primary objective of this study is to evaluate tolerability and safety of GSK2857916 monotherapy on a Q3W schedule in Part 1, and GSK2857916 in combination with Bor/Dex on a Q3W schedule and with Pom/Dex on a Q4W schedule in Part 2 in Japanese participants with RRMM. To evaluate tolerability and safety, the study uses a standard 3 + 3 dose-escalation design.

4.3. Justification for Dose

4.3.1. Justification for Dose for Part 1

In the ongoing BMA117159 study at the tested dose range of 0.03 to 4.6 mg/kg, GSK2857916 has demonstrated a manageable safety profile with thrombocytopenia and/or platelet count decreased and corneal events as the most commonly reported events. 3.4 mg/kg was selected as the RP2D after careful analysis of data from dose escalation across 10 dose levels and was based on the following:

- At 3.4 mg/kg, the ORR was 100% in Part 1 which was substantially higher than the ORR observed at all other dose levels.
- There were no DLTs across all tested dose levels, but the next higher dose of 4.6 mg/kg resulted in decreased tolerability.
- The overall safety profile was manageable at the 3.4 mg/kg dose.
- Estimated receptor binding saturation is achieved at doses ≥ 1.92 mg/kg.

Based on these results from the FTIH study (BMA117159), this study is designed to evaluate safety and tolerability of 3.4 mg/kg, which is determined as RP2D in Japanese patients. Also, GSK2857916 is administered to Japanese patients for the first time in this study. Therefore, 2.5 mg/kg, which is one level below the RP2D, is set as starting dose in order to conduct the study safely when administered on a Q3W schedule. 1.92 mg/kg may be explored if 2.5 mg/kg is not tolerated.

4.3.2. Justification for Dose for Part 2

4.3.2.1. GSK2857916

Arm A

GSK2857916 dose of 2.5 mg/kg Q3W is currently being evaluated in combination with bortezomib and dexamethasone in study 207497 in RRMM participants who have failed at least 1 prior line of therapy. Based on data from 15 participants treated at the GSK2857916 dose of 2.5 mg/kg Q3W, followed on study for 1 to 14 cycles (6 participants with a range of 8 to 14 cycles, an average of 11 cycles and a median of 12 cycles as of 26 November 2019), this combination dose has been shown to have an acceptable safety profile, with an AE profile consistent with each of the AE profiles for bortezomib, dexamethasone, and GSK2857916 monotherapy.

The PK of GSK2857916 were evaluated in combination with bortezomib and dexamethasone. Based on interim PK data, as anticipated, GSK2857916 did not appear to impact the PK of bortezomib, while Bor/Dex did not appear to alter the PK of GSK2857916.

Based on this information, a dose of 2.5 mg/kg of GSK2857916 was selected as recommended phase III dose (RP3D) when combined with bortezomib and dexamethasone.

In Study 207504, as of the data cut-off date of 09 July 2019, 2.5 mg/kg cohort has enrolled 4 participants. There were no DLTs and AEs leading to treatment discontinuation and study withdrawal in 2.5 mg/kg cohort. AE profile of 2.5 mg/kg in Japanese participants was generally consistent with known safety profile of GSK2857916. Therefore, 2.5 mg/kg was considered tolerable in Japanese participants. In addition, preliminary PK data showed that the ADC GSK2857916 and total mAb plasma concentrations in Japanese participants are similar to concentrations observed in participants in Study 205678. Consequently, notable inter-ethnic differences in ADC and total mAb exposures are not observed. Furthermore, same dose of Bor/Dex has been approved and used in both Japan and overseas.

Therefore, Part 2 Arm A is designed to evaluate safety and tolerability of 2.5 mg/kg, which is determined as RP3D when combined with bortezomib and dexamethasone, in Japanese patients.

Arm B

GSK2857916 at multiple dose levels Q4W is currently being evaluated in combination with Pom/Dex in the Phase I/II study 209418 conducted by the MCRN in RRMM participants who have failed at least 1 prior line of therapy. As of 08 January 2020, 11 participants have received GSK2857916 at 1.92 mg/kg dose, and 7 participants at 2.5 mg/kg dose Q4W in combination with Pom/Dex Q4W.

Based on the dose escalation criteria, both 1.92 mg/kg and 2.5 mg/kg doses of GSK2857916 have been considered to be safe with early signs of clinical activity when

administered in combination with Pom/Dex, Q4W. The observed safety profile of GSK2857916 with Pom/Dex is consistent with the safety profile of GSK2857916 and pomalidomide. All 7 participants in the 2.5 mg/kg dose level experienced ocular toxicity by C3 of therapy requiring dose interruptions and dose reductions to 1.92 mg/kg Q4W. Despite these dose modifications, all participants achieved deep responses (VGPR or CR).

GSK2857916 initial dose of 1.92 mg/kg was better tolerated without need for dose reduction of GSK2857916 when administered in combination with Pom/Dex Q4W. Preliminary early data showed a trend for early signs of clinical activity.

Based on the totality of the data from study 209418, the dosing regimen for Phase III study of GSK2857916 plus pomalidomide and dexamethasone will be 2.5 mg/kg in C1 followed by 1.9 mg/kg in Cycle 2 and beyond (C2+) when combined with Pom/Dex Q4W for maximizing the potential efficacy while limiting the dose delay/interruption; the dose of GSK2857916 in C2+ was changed from 1.92 mg/kg to 1.9 mg/kg to be consistent across the GSK2857916 studies.

In Study 207504, as of the data cut-off date of 09 July 2019, 2.5 mg/kg cohort has enrolled 4 participants. There were no DLTs and AEs leading to treatment discontinuation and study withdrawal in 2.5 mg/kg cohort. AE profile of 2.5 mg/kg in Japanese participants was generally consistent with known safety profile of GSK2857916. Therefore, 2.5 mg/kg was considered tolerable in Japanese participants. In addition, preliminary PK data showed that the ADC GSK2857916 and total mAb plasma concentrations in Japanese participants are similar to concentrations observed in participants in Study 205678. Consequently, notable inter-ethnic differences in ADC and total mAb exposures are not observed. Furthermore, same dose of Pom/Dex has been approved and used in both Japan and overseas.

Therefore, Part 2 Arm B is designed to evaluate safety and tolerability of the dosing regimen, which will be used for Phase III study when combined pomalidomide and dexamethasone, in Japanese patients.

4.3.2.2. Bortezomib/Dexamethasone Dose

Bor/Dex will be administered at the approved and clinically used dose. Details on Bor/Dex administration are provided in Section 6.2.1.

4.3.2.3. Pomalidomide/Dexamethasone Dose

Pom/Dex will be administered at the approved and clinically used dose. Details on Pom/Dex administration are provided in Section 6.2.2.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA).

A participant will be also considered to have completed the study if the participant has received at least 1 dose of the study treatment and has died.

A participant will be considered to have withdrawn from the study if any of the following apply:

- The participant has not died and is lost to follow-up.
- The participant has withdrawn consent.
- The participant is no longer being followed at the investigator's discretion.
- The study is terminated prematurely.

A final DCO representing the end of data collection, prior to the 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 shown in the Schedule of Activities for the last participant in the study. A participant is considered to have completed the study if he/she has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK study treatment that may impact participant eligibility is provided in the IB. Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

28. Provide signed written informed consent, which includes compliance with the requirements and restrictions listed in the consent form
29. Male or female, 20 years or older (at the time consent is obtained)

30. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (Appendix 6)
31. Histologically or cytologically confirmed diagnosis of MM as defined according to IMWG 2014 [Rajkumar, 2014], criteria in a participant who fulfills **all** of the following:
    i. has undergone stem cell transplant, or is considered transplant ineligible,
    ii. **Part 1:** has received at least 2 prior lines of anti-myeloma drugs containing at least 1 proteasome inhibitor and at least 1 immunomodulator,
    Part 2: has received at least 1 prior line of anti-myeloma drugs,
    iii. **Part 1:** has demonstrated progression on, or within 60 days of completion of the last therapy.
    Part 2: has documented disease progression during or after their most recent therapy.
32. Has measurable disease with at least one of the following:
    a. Serum M-protein ≥ 0.5 g/dL (≥ 5 g/L)
    b. Urine M-protein ≥200 mg/24h
    c. Serum free light chain (FLC) assay: Involved FLC level ≥ 10 mg/dL (≥ 100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65).
33. Participants with a history of autologous stem cell transplant are eligible for study participation provided the following eligibility criteria are met:
    a. Transplant was > 100 days prior to study enrolment
    b. No active infection.
34. Female Participants: Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    A female participant is eligible to participate if she is not pregnant or breast feeding, and at least one of the following conditions applies:

    - Is not a woman of childbearing potential (WOCBP)

      OR

    - **For Part 1 and Part 2 Arm A:**

      Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, during the treatment period and for 4 months after the last dose of GSK2857916, and 7 months from the last dose of bortezomib (only Part 2 Arm A), and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.

      A WOCBP must have a negative highly sensitive serum pregnancy test (as required by local regulations) within 72 hours before the first dose of study treatment and agree to use effective contraception during the study and for

4 months after the last dose of GSK2857916, and 7 months from the last dose of bortezomib (only Part 2 Arm A).

For Part 2 Arm B:

Due to pomalidomide being a thalidomide analogue with risk for embryo-fetal toxicity and prescribed under a restricted distribution program, WOCBP participants will be eligible if they commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control, beginning 4 weeks prior to initiating treatment with pomalidomide, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of pomalidomide treatment. Thereafter, WOCBP participants must use a contraceptive method that is highly effective (with a failure rate of <1% per year) for a further 3 months, and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period.

Two negative pregnancy tests must be obtained prior to initiating pomalidomide therapy. The first test should be performed within 10 to 14 days and the second test within 24 hours prior to prescribing pomalidomide therapy.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

35. Male Participants: Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    Male participants are eligible to participate if they agree to the following from the time of first dose of study treatment until 6 months after the last dose of GSK2857916, 4 months after the last dose of bortezomib (only Part 2 Arm A), and 4 weeks after the last dose of pomalidomide (only Part 2 Arm B) to allow for clearance of any altered sperm:

    - Refrain from donating sperm

      PLUS either:

    - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

      OR

    - Must agree to use contraception/barrier as detailed below:

    Agree to use a male condom, even if they have undergone a successful vasectomy, and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as when having sexual intercourse with a woman of childbearing potential (including pregnant females).

36. All prior treatment-related toxicities (defined by National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.03, must be ≤Grade 1 at the time of enrolment except for alopecia. Participants with Grade 2 peripheral neuropathy can be enrolled into Part 1 and Part 2 Arm B but not into Part 2 Arm A.

37. Adequate organ system functions as defined in Table 10 or Table 11.

Table 10 Criteria for Determining Adequate Organ System Function for Part 1

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.0 X 10^9/L
Hemoglobin	≥8.0 g/dL
Platelets	≥50 X 10^9/L
Hepatic	
Total bilirubin	≤1.5X ULN (Isolated bilirubin ≥1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
ALT	≤2.5 X ULN
Renal	
eGFR[1] Spot urine (albumin/creatinine ratios via spot urine)	≥30 mL/min/ 1.73 m^2 <500 mg/g (56 mg/mmol)
Cardiac	
LVEF (ECHO)	≥45%

1. eGRF via Modified Diet in Renal Disease

Table 11 Criteria for Determining Adequate Organ System Function for Part 2

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.5 X 10^9/L
Hemoglobin	≥8.0 g/dL
Platelets	≥75 X 10^9/L
Hepatic	
Total bilirubin	≤1.5X ULN (Isolated bilirubin ≥1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
ALT	≤2.5 X ULN
Renal	
eGFR[1] Spot urine (albumin/creatinine ratios via spot urine)	≥40 mL/min/1.73 m^2 <500 mg/g (56 mg/mmol)
Cardiac	
LVEF (ECHO)	≥45%

1. eGFR via Modified Diet in Renal Disease

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

38. Systemic anti-tumor-therapy within 14 days, or plasmapheresis within 7 days prior to the first dose of study treatment.
39. Symptomatic amyloidosis, active ‘polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes’ (POEMS) syndrome, active plasma cell leukemia at the time of screening.

40. Use of an investigational drug within 14 days or 5 half-lives, whichever is shorter, preceding the first dose of study treatment. Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study treatment. Prior BCMA targeted therapy.
41. History of an allogeneic stem cell transplant.
42. Current use of prohibited medications/device or planned use of any of these during the study period.
43. Current corneal epithelial disease except mild punctate keratopathy
44. Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect participant's safety). Participants with isolated proteinuria resulting from MM are eligible, provided they fulfil criteria given in Table 10 or Table 11.
45. Evidence of active mucosal or internal bleeding.
46. Any major surgery within the last 4 weeks.
47. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other conditions (including laboratory abnormalities) that could interfere with participant's safety, obtaining informed consent or compliance to the study procedures.
48. Active infection requiring treatment (antibiotic, antiviral, or antifungal treatment).
49. Evidence of severe or uncontrolled systemic diseases.
50. Malignancies other than disease under study are excluded, except for any other malignancy from which the participant has been disease-free for more than 2 years and, in the opinion of the investigators and Medical Monitor, will not affect the evaluation of the effects of this clinical study treatment on the currently targeted malignancy (MM).
51. Evidence of cardiovascular risk including any of the following:
    a. QTcF interval ≥470 msecs (the QT interval values must be corrected for heart rate by Fridericia's formula [QTcF])
    b. Evidence of current clinically significant uncontrolled arrhythmias, including clinically significant ECG abnormalities such as 2nd degree (Type II) or 3rd degree atrioventricular (AV) block.
    c. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within 6 months of Screening.
    d. Class III or IV heart failure as defined by the New York Heart Association functional classification system
    e. Uncontrolled hypertension
52. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK2857916 or any of the components of the study treatment.
53. Pregnant or lactating female or female who are interrupting lactation.
54. Known human Immunodeficiency virus (HIV) infection.

55. Patients with Hepatitis B will be excluded unless the following criteria can be met.

Serology	Screening	During Study Treatment
• HBsAb+ and/or HBcAb+ AND • HBsAg-	• HBV DNA undetectable	• Monitoring per protocol (Table 4) • Antiviral treatment instituted if HBV DNA becomes detectable

Note: Participants with positive HBsAb alone due to hepatitis B vaccination can be enrolled.

56. Positive hepatitis C antibody test result or positive hepatitis C ribonucleic acid (RNA) test result at screening or within 3 months prior to first dose of study treatment.

    Note: Participants with positive hepatitis C antibody due to prior resolved disease can only be enrolled, if a confirmatory negative hepatitis C RNA test is obtained.

    Note: Hepatitis RNA testing is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.

57. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis.

    Note: Stable chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) or hepatobiliary involvement of malignancy is acceptable if participant otherwise meets entry criteria.

58. Previously diagnosed with interstitial lung disease or current complication of interstitial lung disease.

Additional Exclusion Criteria for Part 2 Arm A

59. Intolerant to bortezomib or refractory to bortezomib.
60. Ongoing Grade 2 or higher peripheral neuropathy or neuropathic pain.
61. Intolerance or contraindications to herpes zoster prophylaxis.

Additional Exclusion Criteria for Part 2 Arm B

62. Prior pomalidomide use.
63. Intolerance or contraindications to antithrombotic prophylaxis.
64. Active or history of venous thromboembolism within 3 months prior to first dose of study treatment.

5.3. Lifestyle Considerations

Following lifestyle restrictions applies while the participants are in the study:

- Part 1 and Part 2:

  - Contact lenses are prohibited while the participant is receiving GSK2857916. Contact lens use may be restarted after an ophthalmologist confirms there are no other contraindications. Use of bandage contact lenses is permitted during study treatment as directed by the treating eye care specialist.

- Part 2 Arm B:
  - Participants must not donate blood when receiving pomalidomide, during dose interruptions, and for 28 days following discontinuation of pomalidomide, as transfused blood might be given to a pregnant female whose fetus must not be exposed to the drugs.

No other lifestyle restrictions are required for participants in this study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants must be assigned a new unique participant number that is different from the initial number.

6. STUDY TREATMENT

Study treatment is defined as any investigational intervention intended to be administered to a study participant according to the study protocol.

Refer to Table 12, Table 13, and the SRM for further details.

Table 12 Study Treatment Administered for Part 1

Product name:	**GSK2857916**
Dosage form:	Lyophilized powder, 100 mg/vial in single-use vial for reconstitution
Unit dose strength(s)/Dose Level(s):	100 mg/vial / 2.5 or 3.4 mg/kg
Route/ Administration/ Duration:	Delivered as IV solution over 30 min
Dosing instructions:	Reconstitute GSK2857916 lyophilized powder 100 mg/vial with water for injection before use.
Manufacturer/ Source of Procurement:	GSK

Table 13 Study Treatments Administered for Part 2

Study Treatment Name	GSK2857916 Arm A and Arm B	Arm A Standard of Care (21-Day Cycle)		Arm B Standard of Care (28-Day Cycle)	
		Bortezomib	Dexamethasone	Pomalidomide	Dexamethasone
Dosage Formulation	Lyophilized powder	Solution for injection for subcutaneous (SC)	Tablet for oral administration	Capsule for oral administration	Tablet for oral administration
Unit Dose Strength(s)	100 mg/vial in single-use vial for reconstitution	2.5 mg/mL solution	4 mg	1 mg, 4 mg	4 mg
Dosage Level(s)	**Arm A** 2.5 mg/kg on Day (D) 1 of each cycle, once every 3 weeks (Q3W) **Arm B** 2.5 mg/kg on D1 of Cycle (C) 1 and 1.9 mg/kg on C2D1 and beyond, once every 4 weeks (Q4W)	1.3 mg/m^2 (SC) on D1, D4, D8, and D11, Q3W for C1-C8	20 mg orally on D1, D2, D4, D5, D8, D9, D11, and D12, Q3W for C1-C8	4 mg orally daily on D1-D21, Q4W	40 mg orally per day on D1, D8, D15, and D22 Q4W
Route of Administration	Intravenous	SC	Oral	Oral	Oral
Dosing Instructions	Reconstitute GSK2857916 lyophilized powder 100 mg/vial with water for injection before use	Refer to labels for dosing	Refer to labels for dosing	Refer to labels for dosing	Refer to labels for dosing
Manufacturer/ Source of Procurement	GSK	Refer to Site Reference Manual (SRM)	Refer to SRM	Refer to SRM	Refer to SRM

6.1. GSK2857916 Treatments Administered for Part 1

GSK2857916 is to be administered at a calculated dose of 2.5 mg/kg or 3.4 mg/kg as an IV infusion, via an infusion pump on D1 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. The dose to be administered is based on actual body weight calculated at baseline (assessed on C1D1 prior to dosing). However, if the change of body weight is greater than 10%, the dose must be recalculated based on the actual body weight at the time of dosing. Refer to the SRM for more details on preparation and handling, and administration instructions for GSK2857916.

Administration of GSK2857916 will be documented in the clinic source documents and reported in the electronic case report form (eCRF). The time of start and end of infusion will be documented in eCRF.

Any participant experiencing an IRR must receive appropriate medical treatment. When the participant's condition is stable, the infusion may be restarted at a slower rate. For details on restarting the GSK2857916 infusion after interruption for IRR, please see Section 6.7.

In general, upon restarting, the infusion rate must be decreased by half at the time the infusion was interrupted.

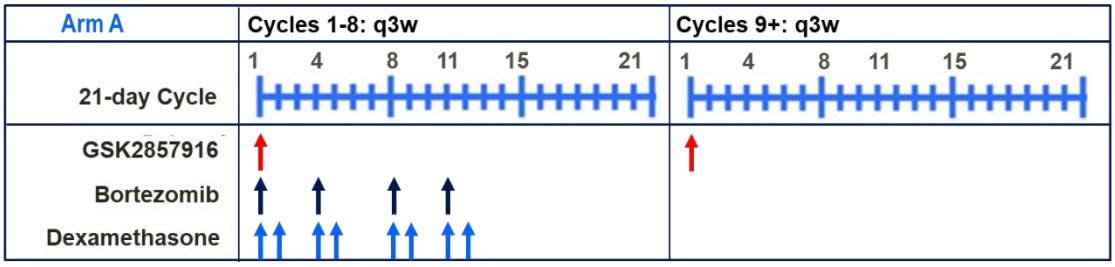
Participants will be treated until disease progression, until unacceptable toxicity (Section 7.1 and Section 7.1.1).

6.2. Treatments Administered for Combination Therapy for Part 2)

6.2.1. GSK2857916 with Bortezomib/Dexamethasone (Arm A) 21-day Cycle

The dosing schedule for Arm A is depicted in Figure 3.

Figure 3 Summary of Dosing Schedule for Arm A



GSK2857916

GSK2857916 will be administered IV at the dose of 2.5 mg/kg on D1 of every 21-day cycle until disease progression, unacceptable toxicity, or withdrawal of consent. The

dose to be administered is based on actual body weight calculated at baseline (assessed on C1D1 prior to dosing). However, if the change of body weight is greater than 10%, the dose should be recalculated based on the actual body weight at the time of dosing. A window of ±3 days is acceptable for administration GSK2857916 after C1D1, but at least 21 days should elapse between consecutive planned doses of GSK2857916.

Bortezomib

Bortezomib 1.3 mg/m^2 will be administered subcutaneously (SC) on D1, D4, D8, and D11 of every 21-day cycle for a total of 8 cycles. Bortezomib should be administered approximately 1 hour after the GSK2857916 infusion is complete, assuming the participant is clinically stable. In participants who experience an IRR during or after GSK2857916 administration, the administration of bortezomib will be delayed until the IRR has resolved and the participant is considered clinically stable. At least 72 hours should elapse between consecutive doses of bortezomib.

Dexamethasone

Dexamethasone 20 mg (orally) should be administered on D1, D2, D4, D5, D8, D9, D11, and D12 (the day of and the day after bortezomib treatment) of every 21-day cycle for a total of 8 cycles.

Dexamethasone should be taken approximately at the same time of each day and may be taken at home. On days where bortezomib administration coincides with administration of GSK2857916, dexamethasone should be administered orally 1 to 3 hours prior to the infusion of GSK2857916.

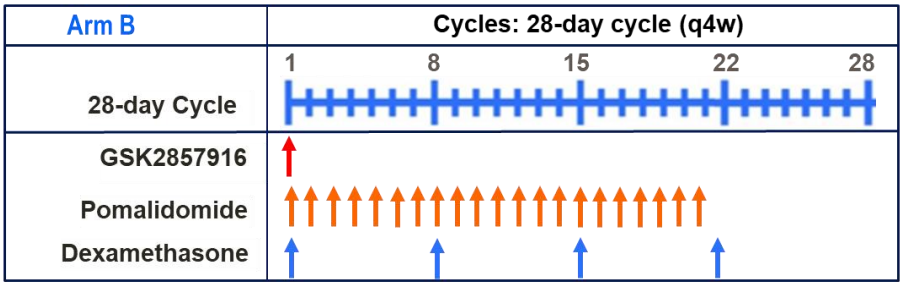
For participants who are unable to retain oral medications due to toxicity, dexamethasone can be administered IV.

Refer to the SRM for further details on preparation, handling, and administration contained in package inserts.

6.2.2. GSK2857916 with Pomalidomide/Dexamethasone (Arm B) 28-day Cycle

The dosing schedule for Arm B is depicted in Figure 4.

Figure 4 Summary of Dosing Schedule for Arm B



GSK2857916

GSK2857916 will be administered IV at the dose of 2.5 mg/kg dose on C1D1 and 1.9 mg/kg on D1 of C2+ Q4W until disease progression, unacceptable toxicity, or withdrawal of consent. The dose to be administered is based on actual body weight calculated at baseline (assessed on C1D1 prior to dosing). However, if the change of body weight is greater than 10%, the dose should be recalculated based on the actual body weight at the time of dosing. A window of ±3 days is acceptable for administration of GSK2857916 after C1D1, but at least 28 days should elapse between consecutive planned doses of GSK2857916.

Pomalidomide

Pomalidomide will be taken orally 4 mg per day on D1 to D21 of 28-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent. On days where only pomalidomide and dexamethasone are taken at home, they should be taken in the morning approximately at the same time each day.

Pomalidomide is an analogue of thalidomide, which is known to cause severe life-threatening human birth defects. Because of this potential toxicity and to avoid fatal exposure, pomalidomide is only available under a restricted distribution program called RevMate®. Site staff including investigators and participants must comply with the requirements of the RevMate® program.

Dexamethasone

Dexamethasone will be administered orally at a dose of 40 mg per day on D1, D8, D15, and D22 of each 28-day cycle. For participants who are older than 75 years of age or have comorbidities or are intolerant to 40 mg, dexamethasone may be administered at the lower dose of 20 mg at the discretion of the investigator. On days of administration of GSK2857916, dexamethasone should be administered orally 1 to 3 hours prior to the infusion of GSK2857916. On days where only pomalidomide and dexamethasone are taken at home, they should be taken in the morning approximately at the same time each day.

For participants who are unable to retain oral medications due to toxicity, dexamethasone can be administered IV.

Refer to the SRM for further details on preparation, handling, and administration contained in package inserts.

6.3. Preparation/Handling/Storage/Accountability

65. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

66. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored

(manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

67. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

68. Further guidance and information for the final disposition of unused study treatment are provided in the SRM or other specified location.

69. Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

70. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.4. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study; GSK2857916 will be administered based on actual body weight.

6.5. Study Treatment Compliance

Participants will receive study treatment at the site directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the study site will be recorded in the source documents and reported in the eCRF. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment and documented in source.

When participants self-administer oral study treatment(s) at home, dosing will be recorded in the Participant's Study Medication Diary. The entries in the Diary will be assessed through querying the participant during the site visits and documented in the source documents and eCRF. A record of the number of doses dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the eCRF.

6.6. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates

- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until the end of the study. Concomitant medications administered after the end of treatment (EOT) visit should be recorded for SAEs/AESIs. Any concomitant medication(s), including non-prescription medication(s) and herbal product(s), taken during the study will be recorded in the eCRF. Additionally, a complete list of all prior anti-myeloma therapies will be recorded in the eCRF. Please see the SRM for the list of permitted/prohibited medications.

6.6.1. Permitted Medications

Participants should receive full supportive care during the study, including transfusions of blood products, growth factors, and treatment with antibiotics, anti-emetics, antidiarrheal, and analgesics, as appropriate.

- While the participants are receiving treatment with pomalidomide, thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the participant's underlying risks, in accordance with local prescribing information.
- Herpes zoster prophylaxis is recommended in accordance with local prescribing information in participants being treated with bortezomib.
- Concomitant therapy with bisphosphonates is allowed and recommended.
- Concomitant prophylactic treatment for tumor lysis syndrome (according to local standards) in participants with high tumor load should be considered.

Participants may receive local irradiation for pain or stability control. In Japan, it is not approved to use growth factor products (except for granulocyte-colony stimulating factor) for neutropenia due to cancer chemotherapy and erythropoietin products for anemia due to cancer chemotherapy.

6.6.2. Prohibited Medications

Chronic treatment with oral steroids other than part of the study treatment is prohibited while the participant is on study, unless for treatment of acute complications related to study treatment, or pre-medication prior to GSK2857916 infusion. Steroids may be used to treat IRRs, and acute exacerbations of chronic disease (up to 7 days). Inhaled steroids are allowed for management of asthma or chronic obstructive pulmonary disease exacerbations. Chronic low dose replacement therapy (less than or equal to 10 mg prednisolone) is allowed in participants with adrenal insufficiency.

Elimination pathways for GSK2587916 or cys-mcMMAF in humans have not been characterized in humans. Cys-mcMMAF was not an inhibitor, an inducer or a good substrate of CYP450 enzymes *in vitro*. However, *in vitro*, cys-mcMMAF was shown to be a substrate of P-gp, and OATP (OATP1B1 and OATP1B3) transporters. Concomitant

administration of strong P-gp inhibitors and strong OATP1B1 and OATP1B3 inhibitors with GSK2857916 should be avoided unless considered medically necessary. Please see the SRM for a list of relevant P-gp inhibitors and OATP1B1 and OATP1B3 inhibitors.

Other prohibited therapies include:

- Growth factor products: prohibited from 14 days prior to clinical laboratory test (hematology) at Screening to first dose and prohibited to use for primary prophylaxis during DLT observation period.
- Blood products: prohibited from 7 days prior to clinical laboratory test (hematology) at Screening to first dose.
- Plasmapheresis: prohibited from 7 days prior to first dose through the end of study.
- Any other approved or investigational anti-myeloma therapy not specified in this protocol (including but not limited to immunomodulatory and antineoplastic drugs or proteasome inhibitors). This is inclusive of all medications with activity against multiple myeloma and medications used for other indications that have anti-myeloma properties.
- Investigational agents other than GSK2857916.
- In Part 2, administration of live or live-attenuated vaccines are contraindicated 30 days prior to the first dose of study treatment and while on study. Use of live or live-attenuated vaccines is further contraindicated for at least 70 days following the last dose of GSK2857916. Killed or inactivated vaccines may be administered; however, the response to such vaccines cannot be predicted.

Bortezomib is a substrate of CYP450 enzyme 3A4, 2C19 and 1A2. Caution should be exercised when bortezomib is combined with CYP3A4 or CYP2C19 substrates. Participants should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors. Co-administration with strong CYP3A4 inhibitors can increase bortezomib exposure by 35%. If bortezomib must be given in combination with a strong CYP3A4 inhibitor (e.g., ketoconazole, ritonavir), monitor participants for signs of bortezomib toxicity and consider a bortezomib dose reduction. Co-administration with strong CYP3A4 inducers may decrease bortezomib exposure by 45% or more, which may reduce bortezomib efficacy. Strong CYP3A4 inducers are therefore not recommended in combination with bortezomib. St. John's Wort (Hypericum perforatum) may decrease bortezomib exposure unpredictably and should be avoided.

Pomalidomide clearance includes hydrolysis and CYP450-mediated hydroxylation. In vitro pomalidomide was neither an inducer nor inhibitor of CYP450, nor an inhibitor of transporter proteins P-gp. Oxidative metabolism of pomalidomide was predominantly mediated by CYP1A2 and CYP3A4, and pomalidomide was shown to be a P-gp substrate. Co-administration of pomalidomide with fluvoxamine (CYP1A2 inhibitor) in the presence of ketoconazole approximately doubled pomalidomide exposure. Thus, concomitant use of strong CYP1A2 inhibitors with pomalidomide should be avoided. If a strong CYP1A2 inhibitor must be used, reduce pomalidomide dose by 50%.

For further information see the package inserts included in the SRM [Pomalyst, 2019; VELCADE, 2019].

6.6.3. Prohibited Device(s)

Contact lenses are prohibited while the participant is on study.

6.7. Dose Modification and Delay

6.7.1. Dose Modification and Delay for Part 1

After C1, participants may have their dose delayed or reduced for toxicities according to the guidance.

See Table 15 for dose modifications guidelines for GSK2857916-related AEs and Table 16 for guidelines for drug-related AEs.

See Table 17 for dose modification guidelines for cornea-related AEs associated with GSK2857916.

Permitted dose reductions for GSK2857916 are shown in Table 14.

Table 14 Permitted Dose Reductions

Starting dose level	1st reduction (25% reduction of original dose)	2nd reduction (Additional 25% reduction of reduced dose)
2.5 mg/kg	1.92 mg/kg	--
3.4 mg/kg	2.5 mg/kg	1.92 mg/kg

- Dose reduction up to 1.92 mg/kg is permitted (up to 2 dose reductions for 3.4 mg/kg and up to 1 dose reduction for 2.5 mg/kg).
- 25% dose reduction is defined as de-escalation to 1 lower dose level.
- If the participant cannot tolerate the drug after the allowed dose reductions, he or she must be withdrawn from the study for lack of tolerability.
- In case of full resolution of symptoms which lead to dose reduction, further treatment at the previous dose may be considered by the investigator.

Dosing delays are permitted in the case of medical/surgical events or for logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, participant vacation, and/or holidays, but not for participants' decision to delay treatment). If a dose is delayed, the participant should wait for the next scheduled dose to resume treatment. The reason for any dose delay must be documented in the participant's eCRF and site record.

Resuming treatment with GSK2857916 will be possible with or without dose reduction after the toxicity has resolved to Grade 1 or less.

Table 15 Dose Modification Guidelines for GSK2857916-Related Adverse Events for Part 1

Toxicity	Grade/description of toxicity	Recommendations for GSK2857916
Elevated serum creatinine which cannot be explained by concomitant sepsis, tumor lysis syndrome, other severe condition with fever, or dehydration	If absolute serum creatinine increases from baseline by >0.5 mg/dL	• Repeat serum creatinine or eGFR within 48 hours • If confirmed: withhold therapy, institute treatment and monitoring as clinically indicated, and follow for resolution • Discuss any further dosing with Medical Monitor
Serum creatinine >Grade 3	>3.0 mg/dL from baseline or 3.0-6.0xULN	• Provide appropriate medical treatment. • Permanently discontinue treatment with GSK2857916
Spot urine (albumin / creatinine ratios)	>2000 mg/g (or 224 mg/mmol)	• Re-test (at least 7 days apart) • If not confirmed, continue GSK2857916 at 100% dose • If confirmed on re-test and no clear evidence of disease progression o Interrupt treatment with GSK2857916 o Repeat testing within 4 weeks i. If spot urine <2000 mg/g (224 mg/mmol), may restart GSK2857916 with 25% dose reduction ii. If spot urine remains >2000 mg/g (224 mg/mmol) after 4 weeks, permanently discontinue GSK2857916 and withdraw participant from study; provide treatment as clinically indicated and follow for resolution[a]
Thrombocytopenia (on days of dosing)	3	• No bleeding: continue treatment with 25% dose reduction. Consider reverting to previous dose once thrombocytopenia recovered to G2 or less
		• With bleeding: withhold the dose, continue treatment after recovery with 25% dose reduction
Thrombocytopenia (On days of dosing)	4	• Withhold the dose. Consider restarting with 25% dose reduction if recovered, or transfused to ≤G3 only if there is no active bleeding at time of treatment re-start
		• If thrombocytopenia is considered disease related, is not accompanied by bleeding, and recovers with transfusion to >25x10^9/L continuing treatment at 25% dose reduction or additional 25% dose reduction of reduced dose (i.e. up to 1.92 mg/kg) may be considered after discussion with the Medical Monitor
Febrile neutropenia	3-4 (defined as: single temp of >38.3°C, or sustained ≥38°C for >1 hr AND ANC <1000/mm^3	• Withhold the dose • Implement treatment with antibiotics, antivirals and antifungals, as clinically indicated, consider growth factors • Continue treatment after resolution. Consider 25% dose reduction of GSK2857916, if neutropenia was drug related

Toxicity	Grade/description of toxicity	Recommendations for GSK2857916
Infusion-Related Reaction[b]	2	• Stop the infusion, provide medical treatment and continue at half the original infusion rate after resolution to Grade 0-1
Infusion-Related Reaction[b]	3	• Further treatment with GSK2857916 needs to be discussed with Medical Monitor. Continuation only allowed after recovery to ≤Grade 1 and with pre-medication, and extension of infusion time to 2-4 hours. Any future infusion needs to be pre-medicated
	4	• Permanently discontinue
Pneumonitis	2	• Continue treatment when toxicity resolves to Grade 0-1
	Grade 3-4	• Permanently discontinue

a. Medical Monitor may consult GSK's nephrology panel about plans to continue therapy.

b. If symptoms resolve within one hour of stopping infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant must be pre-medicated for the next scheduled dose.

Table 16 General Dose Modification and Management Guidelines for Drug-related Adverse Events Not Otherwise Specified[a] for Part 1 and Part 2

Severity	Management	Follow-up
Grade 1	• Administer symptomatic treatment as appropriate • Continue study treatment[a]	• Provide close follow-up to evaluate for increased severity, no dose modification necessary
Grade 2	• Administer symptomatic treatment • Investigate etiology • Consider consulting subspecialist, and/or diagnostic procedure	*Symptoms resolved in ≤7 days:* Continue after resolution at the current dose *Symptoms ongoing >7 days or worsening:* ○ Delay study drug[b], or consider dose reduction by 25% (or consider at the same dose level for Part 2 Arm B) If recovery takes >3 weeks- consult Medical Monitor • If symptoms continue or worsen to Grade 3-4, see below
Grade 3	• Provide appropriate medical treatment • Consider consulting subspecialist	Delay treatment till recovery to Grade 1 or less. Consider dose reduction (or consider at the same dose level for Part 2 Arm B). Consider consultation with Medical Monitor. Exceptions: Participants who develop Grade 3 toxicities which respond to standard treatment and resolve to ≤Grade 1 within 48 hours may continue treatment at scheduled or reduced dose
Grade 4	• Provide appropriate medical treatment • Consider Consulting subspecialist • Discuss with Sponsor/Medical Monitor	Interrupt treatment. Further treatment with GSK2857916 only allowed on individual basis if in the discussion with Medical Monitor it is agreed that benefits outweigh the risks for a given participant

c. Treatment-related decisions can be made based on local laboratory results if central results are not available or delayed.

d. In case a dose is delayed, the participant should wait for the next scheduled dose to resume treatment.

Table 17 Dose Modification Guidelines for GSK2857916 Treatment-Related Corneal Events for Part 1

	Grade 1 per GSK Scale[a]	**Grade 2 per GSK Scale[a]**	**Grade 3 per GSK Scale[a]**	**Grade 4 per GSK Scale[a]**
GSK2857916 Dosing Actions	Continue treatment with current dose of GSK2857916.	If **either** ophthalmic exam findings **or** visual acuity findings are **Grade 1**, continue dosing with GSK2857916 at current dose.	Hold GSK2857916. • Upon improvement of either visual acuity or ophthalmic exam findings to Grade 1 or baseline, resume with 25% dose reduction*. (* for participants receiving 1.92 mg/kg, dose continue at same dose)	Stop treatment with GSK2857916.
		If visual acuity **and** exam findings are **both** Grade 2, **HOLD** GSK2857916. • Upon improvement of either visual acuity or ophthalmic examination findings to Grade 1 or baseline, resume with current dose.	In case of recurring ≥Grade 3 events, consider consulting GSK.	Additional topical treatment may be prescribed as recommended by ophthalmologist. Treatment re-start may be possible after discussion and agreement between the treating ophthalmologist, treating physician, and possible discussions with GSK.
Corneal Management Care Regardless of Grade	**Preservative-free Artificial Tears**: • Increase to 1 drop as frequently as every 2 hours, as needed. **Cooling Eye Masks**: • At the start of each infusion, participants may apply cooling eye masks to their eyes for approximately 1 hour or as long as tolerated. **Steroid Eye Drops**: • Corticosteroid eye drops are not required but can be used if clinically indicated per discretion of an eye-care specialist. Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops (if administered).			

e. See Appendix 7 for corneal event grading scale

6.7.2. Dose Modification and Delay for Part 2 Arm A

Dose delays and reductions are permitted throughout the study as described below.

After Cycle 1 Day 1, dose modifications may be made for individual participants based on safety findings.

Dosing delays are also permitted for medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, participant vacation, and/or holidays) but not for participant's decision to delay treatment.

6.7.2.1. GSK2857916

The dose allowed for GSK2857916 may be reduced once from the starting dose (Dose Level -1) (Table 18). Participants not able to tolerate Dose Level -1 will permanently discontinue GSK2857916 treatment due to unacceptable toxicity. Detailed guidance for dose modifications are shown in Table 16, Table 19, and Table 20.

In case of full resolution of symptoms which lead to dose reduction, further treatment at the previous dose may be considered by the investigator.

Table 18 Dose Levels GSK2857916 for Part 2 Arm A

Dose Level	GSK2857916 Dose
Starting Dose	2.5 mg/kg intravenously (IV) once every 3 weeks (Q3W)
Dose Level -1	1.9 mg/kg IV Q3W

Table 19 Dose Modification Guidelines for Adverse Events Associated with GSK2857916 for Part 2 Arm A

Toxicity	Grade/Symptoms	Recommendations
Serum creatinine elevation which cannot be explained by concomitant sepsis, tumor lysis syndrome, other severe condition with fever or dehydration	If absolute serum creatinine increases from baseline of >0.5 mg/dL	Repeat within 48 hours • If confirmed: withhold therapy, initiate treatment and monitoring as clinically indicated, and follow for resolution. Discuss any further dosing with Medical Monitor[a]
Serum creatinine >Grade 3	>3.0 mg/dL from baseline or 3.0-6.0 × ULN	• Provide appropriate medical treatment • Permanently discontinue treatment with GSK2857916

Spot urine (albumin / creatinine ratios)	>2000 mg/g (224 mg/mmol)	• Re-test (at least 7 days apart)
		• If not confirmed, continue GSK2857916 at pre-held dose
		• If confirmed on re-test and no clear evidence of disease progression:
		  ○ Interrupt treatment with GSK2857916
		  ○ Repeat testing within 4 weeks
		  ○ If spot urine ≤2000 mg/g (224 mg/mmol), may restart GSK2857916 with 1 dose level reduction

Toxicity	Grade/Symptoms	Recommendations
		○ If spot urine remains >2000 mg/g (224 mg/mmol) after 4 weeks, permanently discontinue GSK2857916 and withdraw participant from study; provide treatment as clinically indicated and follow for resolution[a].
Thrombocytopenia (on days of dosing) Graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) criteria	Grade 3	• No bleeding: continue treatment with 1 dose level reduction. Consider reverting to previous dose once thrombocytopenia recovered to Grade 2, or less. • With bleeding: withhold the dose, continue treatment after recovery with 1 dose level reduction. • Consider additional supportive treatment (e.g., transfusion), as clinically indicated and per local practice.
	Grade 4	• Withhold the dose. Consider restarting with 1 dose level reduction if recovered, or transfused to ≤Grade 3 only if there is no active bleeding at time of treatment restart • If thrombocytopenia is considered disease related, is not accompanied by bleeding, and recovers with transfusion to >25x10^9/L, continuing treatment with dose reduction may be considered after discussion with the Medical Monitor
Neutropenia Graded according to NCI-CTCAE criteria	≥Grade 3 (Defined as absolute neutrophil count [ANC] <1.0x10^9/L)	• If noted on Day (D) 1 of any cycle, withhold GSK2857916 dose. • Resume GSK2857916 at pre-held dose once neutropenia recovers to ≤Grade 2 (ANC ≥1.0x10^9/L) on D1 of a subsequent cycle. • Prophylactic antibiotics, per physician discretion and local institutional guidance. Consider growth factors. • Local guidance must be followed for hematological monitoring if more conservative than the protocol schedule of activities specifications. • In cases of frequent recurrent neutropenia (ANC <1.0x10^9/L), consider dose reduction of GSK2857916.
Febrile neutropenia Graded according to NCI-CTCAE criteria	Grade 3-4 (Defined as: single temperature of >38.3°C, or sustained ≥38°C for >1 hr AND ANC <1.0x10^9/L)	• Withhold GSK2857916 and immediately hospitalize participant with appropriate management, per local institutional guidance. • Consider additional supportive treatment per local practice (e.g., growth factors). • Upon recovery, consider dose reduction of GSK2857916, if neutropenia was drug-related.
Infusion-Related Reaction[b]	Grade 2	• Stop the infusion, provide medical treatment and continue at a reduced rate after resolution to Grade 0-1

Toxicity	Grade/Symptoms	Recommendations
	Grade 3	• Further treatment with GSK2857916 needs to be discussed with Medical Monitor. Continuation only allowed after recovery to ≤Grade 1 and with premedication, and extension of infusion time to 2-4 hours. Any future infusion needs to be premedicated.
	Grade 4	• Permanently discontinue
Pneumonitis	Grade 2	• Withhold treatment with GSK2857916 • Upon recovery, restart treatment with 1 dose level reduction. • If participant is already at the lowest dose level (1.9 mg/kg), then rechallenge with the same dose must be discussed with the Medical Monitor
	Grade 3-4	• Permanently discontinue treatment with GSK2857916

f. Medical Monitor may consult GSK's nephrology panel about plans to continue therapy.

g. If symptoms resolve within 1 hour of stopping infusion, the infusion may be restarted at 1 dose level reduction of the original infusion rate (e.g., from 100 mL/h to 50 mL/h). Otherwise, dosing will be held until symptoms resolve and the participant must be pre-medicated for the next scheduled dose.

Table 20 Dose Modification Guidelines for GSK2857916 Treatment-Related Corneal Events for Part 2

Grade per GSK scale	Grade 1	Grade 2	Grade 3	Grade 4
Recommended Dosage Modifications[a]	Continue treatment at current dose.	Withhold GSK2857916 until improvement in **either** corneal examination findings **or** changes in BCVA to Grade 1 or better and resume at same dose.	Withhold GSK2857916 until improvement in **either** corneal examination findings **or** changes in BCVA to Grade 1 or better and resume at reduced dose (1 level)[b]. Consider re-escalating after at least 2 ophthalmic assessments post treatment re-initiation, for events that do not worsen after resuming at lower dose and following benefit/risk assessment and discussion with the Sponsor.	Permanently discontinue GSK2857916. Patient may be re-challenged on a case-by-case basis at a reduced dose after improvement and following benefit/risk assessment and discussion between the eye care specialist, the investigator, and the Sponsor.

BCVA = best corrected visual acuity

h. Dose modification should be based on the most severe grade. If eyes differ in severity, dose modification guideline should be applied based on the more severe eye.

i. If already on reduced dose (1.9 mg/kg), participant should resume treatment at that dose.

6.7.2.2. Bortezomib

Detailed guidance for bortezomib dose modifications is shown in Table 21 and Table 22.

If the decision is made to permanently discontinue bortezomib, but GSK2857916 continues, a participant may remain in the study and continue treatments and assessments as described in the SoA (Section 1.3).

Dose adjustments should be based on the highest grade of toxicity that is attributed to bortezomib. Bortezomib therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological toxicities excluding neuropathy. Once the symptoms of the toxicity have resolved, bortezomib therapy may be reinitiated at a reduced dose per approved labeling, as described in Table 21.

Table 21 Dose Levels for Bortezomib

Dose Level	Bortezomib Dose
Starting Dose	1.3 mg/m^2
Dose Level -1	1.0 mg/m^2
Dose Level -2	0.7 mg/m^2
Dose Level -3	Discontinue bortezomib

Table 22 Dose Modification Guidelines for Hematologic and Other Toxicities Associated with Bortezomib

Toxicity	Grade	Recommendations
Hematological toxicity	≥Grade 4	• Withhold bortezomib therapy until symptoms of toxicity have resolved. • Bortezomib may be reinitiated with 1 dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2).
Non-hematological toxicities (excluding peripheral neuropathy)	≥Grade 3	• Withhold bortezomib therapy until symptoms of toxicity have resolved. Then, bortezomib may be reinitiated with a 1 dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). • For bortezomib-related neuropathic pain and/or peripheral neuropathy, hold or modify bortezomib as outlined below and in the package inserts included in the Site Reference Manual.
Peripheral neuropathy	Grade 1	• Defined as clinical or diagnostic observations only • Grade 1 asymptomatic, without pain or loss of function – No action needed • Grade 1 with pain: 1 dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2)
	Grade 2	• Defined as moderate symptoms; limiting instrumental Activities of Daily Living (ADL)[a] • Grade 2 with no pain: 1 dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2) • Grade 2 with pain: withhold bortezomib therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 once per week
	Grade 3	• Defined as severe symptoms; limiting self-care ADL[b]

		• Grade 3: withhold bortezomib therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 once per week
	Grade 4	• Defined as life-threatening consequences; urgent intervention indicated • Discontinue bortezomib

a. Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc.
b. Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

6.7.2.3. Dexamethasone

Starting dose of dexamethasone may be reduced to 10 mg for participants older than 75 years of age, who have a body mass index (BMI) of less than 18.5, who had previous unacceptable side effects associated with glucocorticoid therapy, or who are unable to tolerate the starting dose (Table 23).

For participants with contraindications to the starting dose regimen of dexamethasone in combination with bortezomib, or who are intolerant to this regimen, the dose of dexamethasone can be reduced dose level -1. If dose level -1 is not tolerated, the dexamethasone dose can be reduced by a further 50%. If this is also not tolerated, dexamethasone should be discontinued.

If bortezomib dosing is delayed or discontinued, dexamethasone dosing could continue per investigator discretion and local institutional guidelines.

Dose modification guidelines are described in Table 24 for dexamethasone-related AEs.

Table 23 Permitted Dose Reductions for Dexamethasone for Part 2 Arm A

Dose Level	≤ 75 years of age	> 75 years of age, BMI ≤ 18.5 Kg/m^2
Starting dose	**20 mg**	**10 mg**
Dose level -1	12 mg	6 mg
Dose level -2*	8 mg	4 mg

*Dexamethasone could be reduced further than dose level -2 per Investigator discretion.

Table 24 Dose Modifications Guidelines for Dexamethasone-Related Adverse Events for Part 2

Toxicity	Dose Modification
Dyspepsia + Grade 1-2	Maintain dose and treat with histamine (H2) blockers or equivalent. Decrease by 1 dose level if symptoms persist.
Dyspepsia ≥ Grade 3	Interrupt dose until symptoms are controlled. Add H2 blocker or equivalent and decrease 1 dose level when dose restarted.
Edema ≥ Grade 3	Use diuretics as needed and decrease dose by 1 dose level.
Confusion or mood alteration ≥ Grade 2	Interrupt dose until symptoms resolve. When dose restarted, decrease dose by 1 dose level.
Muscle weakness ≥ Grade 2	Interrupt dose until muscle weakness ≤Grade 1. Restart with dose decreased by 1 level.
Hyperglycemia ≥ Grade 3	Decrease dose by 1 dose level. Treat with insulin or oral hypoglycemic agents as needed.
Acute pancreatitis	Discontinue participant from dexamethasone treatment regimen.
Other ≥ Grade 3 dexamethasone-related adverse events	Stop dexamethasone dosing until adverse event resolves to ≤Grade 2. Resume with dose reduced by 1 level.

6.7.2.4. Guidance on Dose Delays

Table 25 provides guidance on dose delays for Part 2 Arm A.

In any dosing delay scenario, Q3W assessments should continue to be carried out as described in the SoA. For treatment delays within the treatment window, subsequent treatment dates will not be adjusted.

Table 25 Dose Delays for Part 2 Arm A

Scenario	Actions for GSK2857916	Actions for Bortezomib
1. Delay of only GSK2857916	After Cycle (C) 1, a window of ±3 days is acceptable for GSK2857916 dosing. Outside this window, treatment should be given on Day (D) 1 of the next planned cycle.	Continue bortezomib according to the regimen outlined in the schedule of activities (SoA), until completion of 8 full or truncated cycles of bortezomib.
2. Delay of only bortezomib	Continue GSK2857916 according to the regimen outlined in the SoA.	Bortezomib should be administered on the planned treatment day. If treatment cannot be administered as planned, when a participant is ready to resume treatment, bortezomib may be restarted at the appropriate point in the planned dosing regimen, e.g., if the participant is unable to receive bortezomib on D1 and D4 of a given cycle, treatment could resume on D8 or D11, and missed D1 and D4 doses will not be made up.
3. Delay of both GSK2857916 and bortezomib >21 days (C1-C8)	Bortezomib can be resumed at the appropriate point in the cycle, e.g., in C1-C8, if the participant is unable to receive bortezomib on D1 and D4, resume treatment with bortezomib on D8 or D11. GSK2857916 should be administered on D1 of the next planned cycle. Visits and assessments should continue to occur as specified in the SoA until treatment is restarted.	
4. Delay of both GSK2857916 and bortezomib <21 days (C1-C8)	Follow the guidance as outlined in Scenario 1 above.	Follow the guidance as outlined in Scenario 2 above.

6.7.3. Dose Modification and Delay for Part 2 Arm B

6.7.3.1. GSK2857916

After C1, participants may have their dose delayed or reduced for toxicities according to the recommendations.

See Table 26 for dose modification guidelines for GSK2857916-related AEs, Table 16 for guidelines for drug-related otherwise specified AEs, and Table 20 for dose modification guidelines for corneal-related AEs associated with GSK2857916.

- GSK2857916 will be administered at 2.5 mg/kg on C1D1 and then followed at 1.9 mg/kg on D1 of C2+ Q4W.
- For GSK2857916, no dose reductions, except for dose delays and interruptions, will be allowed.

- If the participant cannot tolerate the drug after the allowed dose level of GSK2857916, the participant can delay or interrupt GSK2857916 treatment and can continue Pom/Dex therapy.
- In case of full resolution of symptoms which lead to dose delay or interruption, further treatment at the same dose level may be considered by the investigator.

Dosing delays are permitted in the case of medical/surgical events or for logistical reasons not related to study treatment (e.g., elective surgery, unrelated medical events, participant vacation, and/or holidays), but not simply for participants' decision to delay treatment. For dose delays or interruptions lasting more than 21 days the Medical Monitor should be contacted to discuss restarting treatment.

The reason for any dose delay must be documented in the participant's eCRF and clinic record. Where safety findings cannot be ascribed solely to 1 study treatment, follow the guidance provided in Table 16.

Resuming treatment with GSK2857916 will be possible without dose reduction after the toxicity has resolved to Grade 2 or less.

Table 26 Dose Modifications Guidelines for GSK2857916 Treatment-Related Adverse Events for Part 2 Arm B

Toxicity	Grade/Symptoms	Recommendations
Elevated serum creatinine that cannot be explained by concomitant sepsis, tumor lysis syndrome, other severe condition with fever, or dehydration	If absolute serum creatinine increases from baseline by >0.5 mg/dL	• Repeat within 48 hours. • If confirmed: withhold therapy, institute treatment and monitoring as clinically indicated, and follow for resolution. • Discuss any further dosing with Medical Monitor[a].
Serum creatinine >Grade 3	>3.0 mg/dL from baseline or 3.0-6.0 x ULN	• Provide appropriate medical treatment. • Permanently discontinue treatment with GSK2857916.
Spot urine (albumin/creatinine ratios)	>2000 mg/g (or 224 mg/mmol)	Re-test (at least 7 days apart) • If not confirmed, continue GSK2857916 at pre-held dose. • If confirmed on re-test and no clear evidence of disease progression o Interrupt treatment with GSK2857916. o Repeat testing within 4 weeks. o If spot urine <2000 mg/g (224 mg/mmol), may restart GSK2857916 at same dose level. o If spot urine remains >2000 mg/g (224 mg/mmol) after 4 weeks, permanently discontinue GSK2857916 and withdraw participant from study; provide treatment as clinically indicated and follow for resolution[a].

Toxicity	Grade/Symptoms	Recommendations
Thrombocytopenia (on days of dosing) Graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) criteria	Grade 3	• No bleeding: continue treatment with at the same dose level.
		• With bleeding: withhold the dose, continue treatment after recovery at the same dose level. • Consider additional supportive treatment (e.g., transfusion), as clinically indicated and per local practice.
	Grade 4	• Withhold the dose. Consider restarting at the same dose level if recovered, or transfused to ≤Grade 3 only if there is no active bleeding at time of treatment restart.
		• If thrombocytopenia is considered disease related, is not accompanied by bleeding, and recovers with transfusion to >25x10^9/L continuing treatment at the same dose level may be considered after discussion with the Medical Monitor.
Neutropenia Graded according to NCI-CTCAE criteria	Grade ≥3 (Defined as absolute neutrophil count [ANC] <1.0x10^9/L)	• If noted on Day (D) 1 of any cycle, withhold GSK2857916 dose. • Resume GSK2857916 at pre-held dose once neutropenia recovers to ≤Grade 2 (ANC ≥1.0x10^9/L) on D1 of the subsequent cycle. • Prophylactic antibiotics, per physician discretion and local institutional guidance. Consider growth factors. • Local guidance must be followed for hematological monitoring, if more conservative than the protocol schedule of activities specifications. • In cases of frequent recurrent neutropenia (ANC <1.0x10^9/L), consider at the same dose level of GSK2857916.

Toxicity	Grade/Symptoms	Recommendations
Febrile neutropenia Graded according to NCI-CTCAE criteria	Grade 3-4 (Defined as: single temperature of >38.3°C, or sustained ≥38°C for >1 hr AND ANC <1.0x10^9/L)	• Withhold the dose and immediately hospitalize participant with appropriate management, per local institutional guidance. • Consider additional supportive treatment per local practice (e.g., growth factors). • Upon recovery, consider at the same dose level of GSK2857916, if neutropenia was drug-related.
Infusion-Related Reaction[b]	Grade 2	• Stop the infusion, provide medical treatment and continue at a reduced rate after resolution to Grade 0-1.
	Grade 3	• Further treatment with GSK2857916 needs to be discussed with Medical Monitor. Continuation only allowed after recovery to ≤Grade 1 and with pre-medication, and extension of infusion time to 2-4 hours. Any future infusion needs to be premedicated.
	Grade 4	• Permanently discontinue.
Pneumonitis	Grade 2	• Withhold treatment with GSK2857916. • Upon recovery to Grade 1, restart treatment at the same dose level. • Rechallenge with the same dose must be discussed with the Medical Monitor.
	Grade 3-4	• Permanently discontinue treatment with GSK2857916.

j. Medical Monitor may consult GSK's nephrology safety panel about plans to continue therapy.
k. If symptoms resolve within 1 hour of stopping infusion, the infusion may be restarted at 1 dose level reduction of the original infusion rate (e.g., from 100 mL/h to 50 mL/h). Otherwise, dosing will be held until symptoms resolve and the participant must be pre-medicated for the next scheduled dose.

6.7.3.2. Pomalidomide

Pomalidomide dose reductions will be permitted in each 28-day treatment cycle (Q4W). Permitted dose level -1, level -2, and level -3 reductions for pomalidomide is shown in Table 27. Detailed dose modifications guidelines for pomalidomide-related AEs are described in Table 28.

Table 27 Permitted Dose Reductions for Pomalidomide

Starting dose level	Dose level -1	Dose level -2	Dose level -3
4 mg	3 mg	2 mg	1 mg

Table 28 Dose Modifications Guidelines for Hematologic and Other Toxicities associated with Pomalidomide

Toxicity	Dose Modification
Neutropenia	
Absolute neutrophil count (ANC) <500/μL (<0.5 x 10^9/L) or febrile neutropenia (single temperature of >38.3°C, or sustained ≥38°C for >1 hr and ANC <1,000/μL [<1 x 10^9/L])	Interrupt pomalidomide treatment, follow complete blood counts weekly
ANC return to ≥1000/μL	Resume pomalidomide treatment at 1 mg less than the previous dose
Thrombocytopenia	
Platelet count <25,000/μL (<25 x 10^9/L) Platelet count returns to ≥50,000/μL (≥50 x 10^9/L)	Interrupt pomalidomide treatment, follow complete blood counts weekly Resume pomalidomide treatment at 1 mg less than the previous dose
Cutaneous Reactions	
Grade 3	Hold pomalidomide treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to ≤Grade 1
Grade 4 or blistering	Permanently discontinue pomalidomide
Hypersensitivity	
Angioedema and anaphylaxis reactions	Permanently discontinue pomalidomide

Toxicity	Dose Modification
For other non-hematologic toxicities judged to be related to pomalidomide	
Grade 3-4	Hold pomalidomide treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to ≤Grade 2

- To initiate a new cycle of pomalidomide, the neutrophil count must be ≥500/μL, the platelet count must be ≥50,000/μL (≥50 x 10^9/L).
- In case of neutropenia, the physician should consider the use of growth factors.
- If adverse reactions occur after dose reductions to 1 mg, then pomalidomide should be discontinued.
- Concomitant use of strong CYP1A2 inhibitors (e.g., ciprofloxacin, enoxacin, and fluvoxamine) should be avoided. If strong inhibitors of CYP1A2 must be used, reduce pomalidomide dose by 2 dose levels.

6.7.3.3. Dexamethasone

Dexamethasone dose reductions will be permitted in each 28-day treatment cycle (Q4W). Permitted dose level -1 and level -2 reductions for dexamethasone are shown in Table 29. Detailed dose modification guidelines for dexamethasone-related AEs are described in Table 24. If recovery from toxicities is prolonged beyond 21 days in 28-day cycles, then the dose of dexamethasone will be decreased by 1 dose level.

Table 29 Permitted Dose Reductions for Dexamethasone

Starting dose level	Dose level -1	Dose level -2
40 mg (≤75 years of age)	20 mg	12 mg
20 mg (>75 years of age)	12 mg	8 mg

6.7.3.4. Guidance on Dose Delays

Table 30 summarizes the guidance on dose delays for Part 2 Arm B.

Table 30 Dose Delays for Part 2 Arm B

Scenario	Actions for GSK2857916	Actions for Pomalidomide and Dexamethasone (Pom/Dex)
1. Delay of only GSK2857916	After Cycle 1, a window of ±3 days is acceptable for GSK2857916 dosing. Outside this window, treatment should be given on Day (D) 1 of the next planned cycle, every 4 weeks (Q4W).	Continue Pom/Dex according to the regimen outlined in the schedule of activities (SoA).
2. Delay of only pomalidomide	Continue GSK2857916 according to the schedule, Q4W as outlined in the SoA.	If pomalidomide treatment cannot be administered as planned, when a participant is ready to resume treatment, pomalidomide may be restarted at the appropriate time in the planned dosing regimen. If the participant is unable to receive pomalidomide on D1-D21 of a given cycle, treatment could resume on D1 of next cycle, and missed pomalidomide doses will not be made up. Dexamethasone should be administered on the planned treatment day.
3. Delay of only dexamethasone	Continue GSK2857916 according to the schedule, Q4W as outlined in the SoA.	If participant is ready to resume treatment, dexamethasone may be restarted at the appropriate time in the planned dosing regimen (e.g., on D1, D8, D15, and D22 Q4W). If the participant is unable to receive dexamethasone on D22 of a given cycle, treatment could resume on D1 of next cycle, and missed dexamethasone doses will not be made up. Pomalidomide should be administered on the planned treatment day.
4. Delay of Pom/Dex components	Continue GSK2857916 according to the schedule, Q4W as outlined in the SoA if Pom/Dex are delayed.	Follow Pom/Dex delay guidelines as outlined above for pomalidomide only delay (Scenario 2) or dexamethasone only delay (Scenario 3).
5. Delay of both GSK2857916 and Pom/Dex	Follow GSK2857916 only delay guidelines as outlined above (Scenario 1).	Follow Pom/Dex delay guidelines as outlined above for pomalidomide only delay (Scenario 2) or dexamethasone only delay (Scenario 3).
6, Permanent discontinuation of GSK2857916	Not applicable	Pom/Dex will be allowed to continue according to the schedule, Q4W as outlined in the SoA.

Scenario	Actions for GSK2857916	Actions for Pomalidomide and Dexamethasone (Pom/Dex)
7. Permanent discontinuation of either pomalidomide or dexamethasone or both	Continue GSK2857916 according to the schedule, Q4W as outlined in the SoA.	If either pomalidomide or dexamethasone is permanently discontinued, the remaining drug in Pom/Dex combination will be allowed to continue.

6.7.4. Management of Hepatitis B+ participants

- Management by local hepatology or infectious disease services is required. If no subspecialist support is available, consultation with Medical Monitor is required prior to enrolment into the study for participants with positive titres to Hepatitis B.
- Participants should be monitored according to SoA Table 4.
- Participants who experience clinically significant elevations in liver chemistry should follow liver event monitoring and stopping criteria (Section 7.1.2 andAppendix 5), and careful evaluation should be immediately initiated for evaluation of etiology including HBV DNA testing.
- **Participants who develop detectable HBV DNA levels during study treatment should be reviewed by local specialist(s) immediately (within 1 week) and appropriate therapy and monitoring instituted.**
- **Study treatment should be withheld, and Medical Monitor should be contacted for any participant who develops detectable HBV DNA levels.**

Table 31 Dose Modification Guideline for Hepatitis B Reactivation

Toxicity	Grade/description of toxicity	Recommendations
Hepatitis B reactivation	Detectable HBV DNA	• Immediate consult with local specialist to institute/modify treatment • Hold study treatment • Contact Medical Monitor promptly - agreement with MM must be obtained prior to further dosing of study treatment • Follow liver monitoring/stopping guidelines per protocol for elevation in liver function tests.

6.7.5. Corneal Supportive Care Guideline

Corneal events, which commonly manifests as a superficial microcystic keratopathy, has been observed with antibody drug conjugates, including those conjugated to MMAF.

Further information regarding corneal event associated with GSK2857916, including a grading scale and prophylactic measures are in Appendix 7.

Sites are required to establish a close collaboration with an ophthalmologist who will be responsible for assessing participants and managing those who develop corneal events in close communication with Medical Monitor and possibly a GSK ophthalmologist.

Participants will be assessed by an ophthalmologist at baseline and every 3 weeks for Part 1 and Part 2 Arm A or every 4 weeks for Part 2 Arm B. If there are no corneal signs per the GSK scale at time specified in SoA, participants may have their ophthalmologic exams decreased to once every 3 months. If a participant subsequently develops ocular symptoms, the participant should be evaluated by an ophthalmologist. Intraocular pressure must be monitored if steroid eye drops are used continuously for more than 7 days.

Participants who have corneal signs per the GSK scale at EOT will continue to be followed at 3 weeks after the EOT visit and then every 6 weeks for up to 12 months, or until full resolution of findings defined as a return to participant's baseline, or deemed clinically stable by an ophthalmologist, whichever comes first.

In case a dose reduction is necessary, the study treatment will be administered as follows as shown in Section 6.7.

6.8. Continued Access to Study Intervention after the End of the Study

Study participants that continue to benefit from study intervention beyond the final analysis DCO date will continue to have access to study intervention until the EOS as defined in Section 4.4. There is no planned intervention following the EOS.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

Refer to Section 8.3.1 for follow-up assessments from the final DCO date to the EOS.

6.8.1. Continued Access to Study Intervention After Data Cut-off prior to EOS

Participants receiving study treatment at the time of the final analysis DCO date may continue to receive study treatment, if in the opinion of their treating physician, they are benefiting from continued treatment, and they do not meet any protocol-defined treatment discontinuation criteria (see Section 7.1). Study treatment will continue until a study treatment discontinuation criterion (see Protocol Section 7.1), as assessed by the investigator, has been met.

Participants who continue study treatment in the PACT phase will be cared for in accordance with local standard clinical practice, at a participant's particular site. Participants will continue to be monitored for all SAEs, AEs leading to treatment discontinuation, prespecified ocular data, overdoses and pregnancy cases while receiving study drugs. Information relating to participant care will be recorded on participant medical records, with the exception of SAEs, AEs leading to treatment discontinuation, prespecified ocular data, overdoses and pregnancy cases that must continue to be reported to GSK, will not otherwise be reported for the purposes of this study. Investigators must report all SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases until 70 days after the participant's last dose of study treatment in accordance with Section 8.3.1. Prespecified ocular data will be reported until resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up. During the PACT phase, reporting and follow up of SAEs, overdose and pregnancy cases and prespecified ocular data will be done via paper forms. All other assessments will revert to standard of care at their site.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

Participants will receive study treatment until disease progression, unacceptable toxicity, or withdrawal of consent (including but not restricted to meeting stopping criteria for significant toxicity as outlined below).

Study treatment may be permanently discontinued for any of the following reasons:

- disease progression or unacceptable toxicity
- participant has met any of the protocol defined safety stopping criteria
- deviation(s) from the protocol
- request of the participant or proxy (withdrawal of consent by participant or proxy)
- investigator's discretion
- concurrent illness that prevents further administration of study treatment.
- participant is lost to follow-up (see Section 7.3)
- pregnancy
- study is closed or terminated.

Once a participant has permanently discontinued from study treatment, the participant will not be allowed to re-enter the study. The primary reason study treatment was permanently discontinued must be documented in the participant's medical records and eCRF. If the participant voluntarily discontinues from treatment due to toxicity, AE must be recorded as the primary reason for permanently discontinuation on the eCRF.

If study treatment is permanently discontinued, the participant will remain in the study to be evaluated for safety. See the SoA for data to be collected at the time of discontinuation of study treatment.

7.1.1. Discontinuation of Individual Components of Combination Study Treatment in Part 2

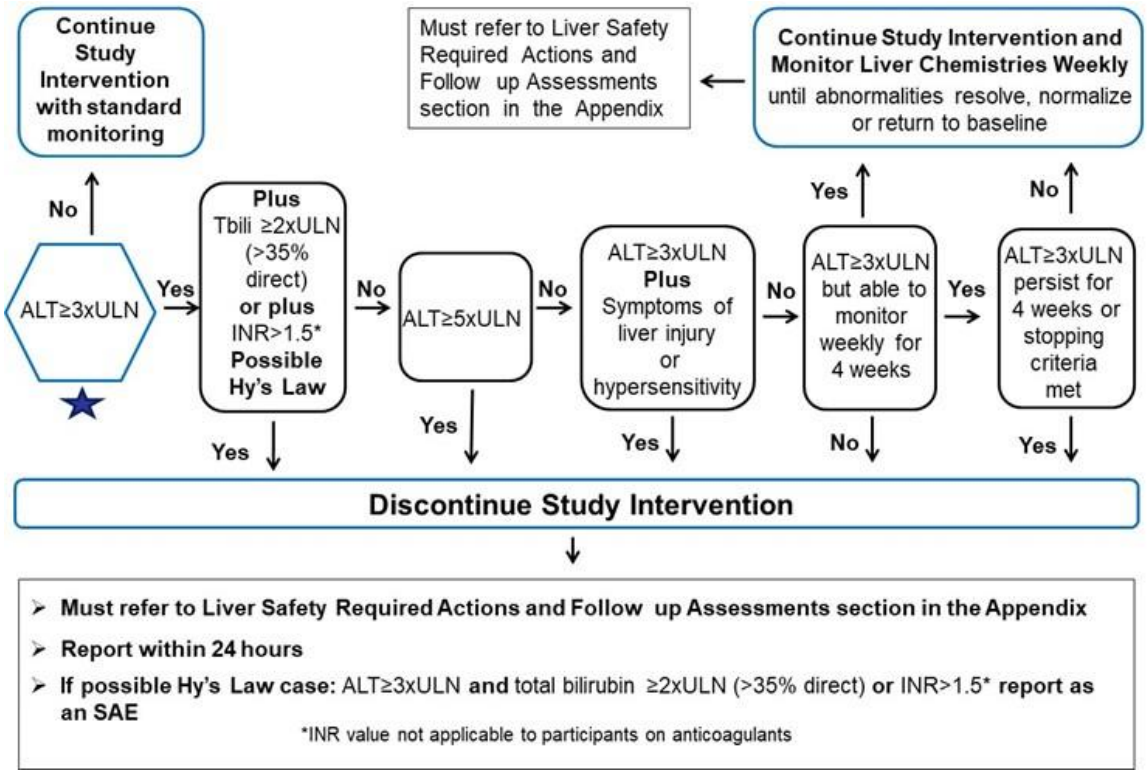
At the discretion of the investigator, participants who discontinue bortezomib and dexamethasone (Arm A) or pomalidomide and dexamethasone (Arm B) may continue GSK2857916 monotherapy until disease progression, unacceptable toxicity, or withdrawal of consent. Similarly, participants in Arm A who discontinue GSK2857916 may continue bortezomib and dexamethasone until completion of 8 cycles (after which they should attend an EOT Visit and be followed up according to the SoA), disease progression, unacceptable toxicity, or withdrawal of consent. Participants in Arm B who discontinue GSK2857916 may continue pomalidomide and dexamethasone until disease progression, unacceptable toxicity, or withdrawal of consent.

The primary reason for discontinuation of each study treatment must be documented independently in the medical record and on the eCRF.

7.1.2. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology. The diagram below illustrates Liver Stopping Event Algorithm (Figure 5).

Figure 5 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Refer to Appendix 5 for required Liver Safety Actions and Follow up Assessments and for required process for study treatment restart/rechallenge if considered for the participant.

7.1.2.1. Study Treatment Restart or Rechallenge after Liver Stopping Criteria Met

A participant who met liver chemistry stopping criteria cannot resume study treatment unless all of the following conditions are met:

- GSK approval **is granted** (as described below)
- Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval is obtained
- Separate informed consent form (ICF) for study treatment restart/rechallenge is signed by the participant and participant is informed of any associated risks

If GSK approval to restart/rechallenge the participant with study treatment **is not granted**, then the participant must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments.

7.1.3. QTc Interval Stopping Criteria

If a participant that meets the corrected QT (QTc) interval duration criteria below, study treatment(s) will be withheld.

- QT interval corrected for heart rate by Fridericia's formula (QTcF = QT / $RR^{0.33}$) >530 msec

  OR

- Increase of QTcF by ≥60 msec from baseline

If an ECG demonstrates a prolonged QT interval, obtain 2 additional ECGs over a brief period (e.g., within approximately 10 minutes of the abnormal ECG, if possible, and approximately 10 minutes apart from each other), and then use the averaged QTc values of the 3 ECGs to determine whether the participants should have study treatment(s) withheld. The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minutes) recording period.

The QT interval should be corrected for heart rate by Fridericia's formula (QTcF).

7.1.4. Left Ventricular Ejection Fraction (LVEF) Stopping Criteria

Echocardiography must be performed at Screening and the EOT visit. If an ECHO is done at any point during the study, the following stopping criteria are to be employed. Participants who have an asymptomatic absolute decrease of >10% in LVEF and the ejection fraction is below the institution's lower limit of normal (LLN) should temporarily discontinue study treatment and have a repeat evaluation of LVEF within 1 week. Echocardiogram (ECHO) should be repeated every 1 to 2 weeks for 4 weeks or until LVEF recovery to above institutional LLN and within 10% of baseline.

- If the LVEF recovers (defined as ≥ institutional LLN and absolute decrease ≤10% compared with baseline) at any time during the next 4 weeks, after consultation with and approval from the Medical Monitor, the participant may be restarted on GSK2857916 at a reduced dose. For such participants, monitoring of LVEF will be performed 2 and 4 weeks after rechallenge, then every 4 weeks for a total of 16 weeks
- If repeat LVEF does not recover within 4 weeks, treatment must be permanently discontinued. Ejection fraction must be monitored every 4 weeks for a total of 16 weeks or until resolution (whichever occurs first).

Participants with Grade 3 or 4 (symptomatic) left ventricular systolic dysfunction must interrupt treatment with GSK2857916. Ejection fraction must be monitored every 4 weeks for a total of 16 weeks or until resolution. If recovery occurs (LVEF ≥ institutional LLN and symptom resolution) within 4 weeks, then treatment with GSK2857916 may be restarted at a reduced dose in consultation with the medical monitor.

7.1.5. Corneal Event Stopping Criteria

Corneal events should be graded according to the guidelines provided in Appendix 7. The investigator must discuss the participants who develop a Grade 4 corneal event with the Medical Monitor to determine whether the participant can be allowed to continue treatment with GSK2857916 or whether GSK2857916 should be permanently discontinued. If a participant is allowed to continue on study, the dose of GSK2857916 will be reduced by at least 25%, and the treatment will only be allowed to continue upon recovery to Grade 1 or less. The decision will be documented in study files, together with individual assessment of risk-benefit. For details on re-start guidance, see Table 17 for Part 1 and Table 20 for Part 2.

7.1.6. Infusion-Related Reaction Management and Stopping Criteria

Premedication is not required prior to infusion unless deemed medically appropriate by the investigator following evaluation of IRRs. Premedication should be considered in any participant who experienced an IRR at first or any subsequent infusion with GSK2857916.

IRRs should be managed by guidelines provided in Section 6.7. A participant that experiences a Grade 4 IRR should be permanently withdrawn from the study.

7.1.7. Allergic and Anaphylactic Reaction Stopping Criteria

All participants will be monitored carefully for evidence of allergic response. A participant that exhibits signs or symptoms of severe hypersensitivity or anaphylaxis will receive appropriate medical treatment and be permanently withdrawn from the study.

In accordance with the preparedness for treatment of anaphylaxis, emergency resuscitation equipment, advanced cardiac life support equipment, and medications must be readily accessible during GSK2857916 administration.

It is important to recognize early signs of an anaphylaxis reaction and appropriate treatment must begin immediately to prevent progression to severe anaphylaxis. Participants will be closely monitored in an appropriate setting for early signs of dyspnea and edema. Antihistamines, such as diphenhydramine; and corticosteroids such as prednisone may be given to reduce symptoms.

If more severe clinical signs arise, immediate assessment of the ABC's (airway, breathing, and circulation from Basic Life Support) will be done in all suspected anaphylactic reactions. Cardio-Pulmonary Resuscitation (CPR) will be initiated if needed. Epinephrine will be given by injection without delay. Emergency interventions may include endotracheal intubation or tracheostomy. Treatment for shock will include IV fluids and medications that support the actions of the heart and circulatory system.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA for data to be collected at the time of study discontinuation follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

- Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form must be obtained from the participant prior to any study-specific procedures or assessments being performed. The timing of each assessment is listed in the SoA (Section 1.3).

A list of clinical laboratory tests is displayed in Table 32.

Whenever vital signs, 12-lead electrocardiograms (ECGs) and blood draws are scheduled for the same nominal time, blood draws must occur last. The timing of the assessments must allow the blood draw to occur at the exact nominal time. Detailed procedures for obtaining each assessment are provided in the SRM.

- Study procedures and their timing are summarized in the SoA (Section 1.3)
- Protocol waivers or exemptions are not allowed
- Demographic and baseline assessments will include year of birth, sex, race, and ethnicity.
- Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.1 and Section 5.2
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA
- Visit Window:
    - Baseline disease assessments must be completed with 21 days prior to dosing start unless otherwise specified. Refer to SoA (Section 1.3)
    - Screening assessments performed within the permitted time do not need to be repeated on C1D1 unless otherwise specified
    - Safety labs completed within 72 hours of first dose do not need to be repeated on C1D1

- Part 1 and Part 2 Arm A: Pregnancy testing may be completed within 72 hours prior to first dose
  Part 2 Arm B: Two negative serum pregnancy tests must be obtained prior to initiating treatment; the first test should be performed within 10 to 14 days of C1D1, but the second must be performed within 24 hours of C1D1.
- ECHO must be completed within 35 days prior to first dose
- Imaging may be completed within 30 days prior to first dose
- Bone marrow (BM) archival tissue from up to 60 days prior to study is acceptable
- Part 1: For C1D2 assessments, no time window is permitted. C1D8 and C1D15 assessments can be performed within ±1 day of scheduled occurrence.
  Part 2 Arm A: D4, D8, and D11 assessments of each cycle can be performed within ±1 day of scheduled occurrence. Other assessments at non-dosing days can be performed within ±3 days of scheduled occurrence unless otherwise specified.
  Part 2 Arm B: D8, D15, and D22 assessments of each cycle can be performed within ±1 day of scheduled occurrence. Other assessments at non-dosing days can be performed within ±3 days of scheduled occurrence unless otherwise specified.

Table 32 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]			
Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential only) (screening)[1]			
Pregnancy test (urine or blood per local practice)[1]			
Hepatitis B surface antigen (HBsAg)[1] Hepatitis B surface antibody (HbsAb)[1] Hepatitis B core antibody (HbcAb)[1] Hepatitis B virus DNA (HBV DNA) [1]			
Hepatitis C (Hep C antibody)[1]: Note: Hepatitis C RNA testing is optional but may be done to determine participant eligibility if hepatitis C antibody positive. Participants with positive hepatitis C antibody due to prior resolved disease may be offered hepatitis C RNA testing to determine eligibility.			
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 microglobulin[1]
Serum kappa, lambda FLC, 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]			

CCI [redacted]

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.

8.1. Efficacy Assessments

Standard disease assessments for RRMM will include the following assessments:

- UPEP, Urine Immunofixation, 24 hr collection for urine M-protein
- SPEP, Serum M-protein, Serum Immunofixation
- Calcium corrected for albumin
- IgG, IgM, IgA
- IgD, IgE (only in participants with IgD or IgE myeloma)
- Serum Kappa, lambda FLC, FLC ratio
- Bone marrow aspirate at screening and to confirm CR and biopsy for immunohistochemistry (IHC) to confirm sCR.
- Imaging of extramedullary disease (in participants with extramedullary disease)
- CT, MRI, or PET/CT is required upon achieving CR or sCR
- Skeletal surveys at screening and as clinically indicated.

Response evaluation will be performed according to the IMWG Uniform Response Criteria for Multiple Myeloma [Kumar, 2016].

Baseline serum/urine disease assessment will be completed during screening period (within 21 days prior to the first dose of study treatment) and baseline imaging within 30 days prior to the first dose of study treatment. On study serum and urine-based assessments (M-protein, FLC, immunofixation) will be performed as specified in the SoA (Section 1.3). Details for the preparation and shipment of samples for central laboratory assessments will be provided in the SRM.

In participants with extramedullary plasmacytoma, the disease assessments must include imaging (e.g., CT, MRI, or PET/CT scans- the same method should be used throughout the study) and physical examination (as indicated for palpable/superficial lesions).

For participants who are followed by imaging for extramedullary disease the imaging has to be performed as described in the SoA (Section 1.3).

All assessments on study must be performed on a calendar schedule and must not be affected by dose interruptions/delays. For post-baseline assessments, a window of ±3 days is permitted to allow for flexible scheduling.

The confirmation of progressive disease must be performed within 14 days, but NOT on the same day, and NOT from the same blood draw as the initial test documenting progressive disease. The assessments of anti-myeloma activity will be performed during the EOT Visit as described in the SoA (Section 1.3).

If the last imaging assessment was greater than or equal to 8 weeks prior to the participant's discontinuation from study treatment and progressive disease has not been documented, a new disease assessment must be obtained at the time of discontinuation from study treatment.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

At screening, on dosing days, and at EOT visit a full physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes, and extremities. Height and weight will also be measured at Screening and recorded, with weight repeated at the start of each cycle.

During the physical examinations, investigators should pay special attention to clinical signs related to previous serious illnesses and record any changes noted during study treatment, if any.

8.2.2. Ocular Examinations and Procedures

A full *baseline* ophthalmic examination for all participants must include, but is not limited to:

1. Best corrected visual acuity

2. Documentation of manifest refraction used to obtain best corrected visual acuity
3. Current glasses prescription (if applicable)
4. Pupillary light reflex
5. Extraocular muscle movements (graded from 1 to 4 with (+) sign indicating over action, (-) sign indicating under action and 0 representing normal movements
6. Intraocular pressure measurement and time checked
7. Full anterior segment examination including fluorescein staining of the cornea:
    - Anterior segment exam (slit lamp) includes: orbit/lids/adnexa, conjunctiva, sclera, cornea, anterior chamber, iris, lens and anterior vitreous.
8. Anterior segment photography of a fluorescein stained cornea
9. Dilated funduscopic exam: fundus photography with interpretation

The *on-treatment* and *follow-up* ophthalmic exam must include everything except, dilated funduscopic exam, including fundus photography, anterior segment photography, extraocular muscle movements, (which must be performed as clinically indicated) and current glasses prescription (if applicable).

The *last follow-up* visit should also include anterior segment photography of a fluorescein stained cornea.

The *EOT* ophthalmic exam should match the *baseline (screening)* exam.

Additional examinations should be performed at the discretion of the treating eye specialist.

8.2.3. ECOG Performance Status

Participant performance status will be assessed as specified in the SoA (Section 1.3), using the Eastern Cooperative Oncology Group (ECOG) scale, provided in Appendix 6.

8.2.4. Vital Signs

Vital sign measurements must include systolic and diastolic blood pressure, temperature, and pulse rate. Vital signs must be measured after resting for at least 5 minutes. Vital signs must be measured more frequently if warranted by the clinical condition of the participant. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

8.2.4.1. First Infusion

Monitoring intervals: Vital signs must be monitored at designated time points related to drug infusion as specified in the SoA (Section 1.3). In general, participants must also be monitored for at least 1 hour after the completion of the first infusion and may be discharged if considered clinically stable and all other study procedures have been completed.

8.2.4.2. Subsequent Infusions

Monitoring intervals: Vital signs must be monitored at designated time points related to drug infusion as specified in the SoA (Section 1.3). Participants may be discharged after the infusion has been completed if considered clinically stable and all other study procedures have been completed.

8.2.5. Electrocardiograms

Singlet 12-lead ECGs must be obtained at designated time points specified in the SoA (Section 1.3). The ECG machine must automatically calculate the heart rate and measure PR, QRS, QT, and corrected QT (QTc) intervals. At each assessment, a 12-lead ECG must be performed by qualified personnel at the site after the participant has at least a 5-minute rest.

8.2.6. Echocardiogram

Echocardiograms (ECHOs) must be performed at baseline to assess cardiac ejection fraction for the purpose of study eligibility, as specified in the SoA (Section 1.3). The evaluation of the echocardiographer must include an evaluation for LVEF. If an ECHO is performed on study the results must be documented in the eCRF.

8.2.7. Clinical Safety Laboratory Assessments

- Refer to Table 32 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 70 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified
- All protocol-required laboratory assessments, as defined in Table 32, must be conducted in accordance with the laboratory manual and the SoA.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 2.

Adverse events will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class. Adverse events, aside from corneal events, will be graded by the investigator according to the NCI-CTCAE, (version 4.03). Corneal events associated with GSK2857916 will be graded according to the grading scale provide in Appendix 7.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up Aes that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment or the study (see Section 7.1 and Section 7.1.1).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of treatment until 70 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study up to and including any follow-up.
- All Aes will be collected continually from the start of treatment until 70 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice at the time points specified in the SoA (Section 1.3)
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 2. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available
- Investigators are not obligated to actively seek Aes or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor
- For participants in the PACT phase of the study, GSK will continue to collect safety information including SAEs, Aes leading to treatment discontinuation, prespecified ocular data, overdose and pregnancy cases via paper forms which will be reported directly to GSK. SAEs, Aes leading to treatment discontinuation, overdose and pregnancy cases will be reported during the PACT treatment period and for up to 70 days after last dose and pre-specified

ocular data will be reported until resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up. Additionally, any SAEs that are ongoing at the time of the final DCO must be followed up to resolution unless the event is considered by the investigator unlikely to resolve, or the patient is lost to follow-up. Updates to these events will also occur via paper forms directly to GSK.

Follow up of ocular data after the start of PACT:

1) For participants continuing on GSK2857916 as part of PACT:

Ocular exam schedule during PACT treatment:

- For participants before completing the 6th dose of GSK 2857916: ophthalmic exams to be performed by an ophthalmologist every cycle prior to dosing, up to, and including, the 6th dose of GSK2857916.
- For participants completing the 6th dose of GSK 2857916: Participants without ocular (including corneal) examinations findings, symptoms or vision changes when entering the PACT phase, and up to and including the 6th GSK 2857916 dose, may have their ocular assessment decreased to at least every 3 months, or as clinically indicated, until the end of treatment. For participants who at the time of entering PACT and/or during PACT doses, have ocular (including corneal) examinations findings, symptoms or vision changes, the ocular assessment will occur (increase to) every cycle (and prior to the next GSK2857916 infusion if dosing), until resolution (GSK Grade 1 or baseline). After resolution, the ocular exam assessment frequency reduces to at least every 3 months, or as clinically indicated, until the end of treatment.

Ocular exam schedule after end of PACT treatment: Participants with treatment-related ocular (including corneal) examination findings, symptoms, or vision changes at the end of PACT treatment have ocular assessments at least every 3 months, or more frequently as clinically indicated, for up to 12 months from the end of treatment or until resolution (to GSK Grade 1 or baseline), or withdrawal of consent, whichever comes first. For participants without ocular (including corneal) examination findings, symptoms, or vision changes at the end of PACT treatment no further ocular exams are required.

2) For participants who stopped GSK2857916 prior to PACT but have ongoing ocular events at the time of final study data-cut-off/start of PACT:

- Participants with treatment-related ocular (including corneal) examination findings, symptoms, or vision changes at the start of PACT have ocular assessments at least every 3 months, or more frequently as clinically indicated, for up to 12 months from the end of treatment or until resolution (GSK Grade 1 or baseline), or withdrawal of consent, whichever comes first.

GSK retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at EOS, if judged necessary.

8.3.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 8.3.5), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 2.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements

8.3.5. Adverse Events of Special Interest

AESI for GSK2857916 are corneal events, thrombocytopenia and IRRs. The severity of corneal events associated with GSK2857916 and related ophthalmic exam findings or visual acuity will be graded using the scale provided in Table 37. The severity of corneal events and other AESI will be graded utilizing NCI-CTCAE. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment are provided in Section 6.7.

8.3.6. Pregnancy

Do not collect pregnancy information for female participants known to be pregnant during the screening phase or before exposure to study.

The need for a screening pregnancy test depends on whether a female participant is of childbearing potential or non-childbearing potential.

If a female participant in Part 1 or Part 2 Arm A is of childbearing potential, she must have a serum pregnancy test performed within 72 hours prior to the first dose of GSK2857916, and the result must be negative. For questionable cases, follicle-stimulating hormone (FSH) and estradiol (as needed) should be performed at local lab to determine childbearing potential. Subsequent pregnancy tests on dosing days may be either serum or urine. Final pregnancy test (serum or urine) must be performed at the EOT Visit. Follow up pregnancy assessment by telephone (for female participants with childbearing potential only) should be performed 4 months after the last dose of GSK2857916 or 7 months after the last dose of bortezomib (only Part 2 Arm A), whichever is longest.

If a female participant in Part 2 Arm B is of childbearing potential, she must have a serum pregnancy test at screening. Two negative serum pregnancy tests must be obtained prior to initiating treatment; the first test should be performed within 10 to 14 days of the first dose of GSK2857916, but the second must be performed within 24 hours of the first dose of GSK2857916. After the first dose, pregnancy test will be done weekly during the first month, then every cycle thereafter (or every 2 weeks in females with irregular menstrual cycles). Subsequent pregnancy test on dosing days may be either serum or urine test. Each pregnancy test must be performed within 24 hours prior to dosing. Final pregnancy test (serum or urine) must be performed in female participants of childbearing potential at the EOT visit and at 2 weeks (in case of irregular menses) and 4 weeks following treatment discontinuation. Follow up pregnancy assessment by telephone (for female participants of childbearing potential only) should be performed 4 months after the last dose of GSK2857916 or 4 weeks after the last dose of pomalidomide, whichever is longest.

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study and for 4 months following the last dose of GSK2857916, 7 months following the last dose of bortezomib (only Part 2 Arm A), and 4 weeks following the last dose of pomalidomide (only Part 2 Arm B), whichever is longest
- Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while participating in this study and for 6 months following the last dose of GSK2857916, 4 months following the last dose of bortezomib (only Part 2 Arm A), and 4 weeks following the last dose of pomalidomide (only Part 2 Arm B), whichever is longest

- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 2
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

8.3.7. Cardiovascular and Death Events

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

For any cardiovascular events detailed in Appendix 2 and all deaths, whether or not they are considered SAEs, specific Cardiovascular and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The Cardiovascular eCRFs are presented as queries in response to reporting of certain cardiovascular MedDRA terms. The cardiovascular information must be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a Cardiovascular Event data query prompting its completion.

8.3.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Disease progression does not need to be reported as a SAE. Death due to disease under study is to be recorded on the Death electronic eCRF. However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the participant, or if the investigator considers that there was a causal relationship between treatment with study treatment(s) or protocol design or procedures and the disease progression, then this must be reported as a SAE.

8.4. Treatment of Overdose

There is no specific antidote for an overdose of GSK2857916. GSK does not recommend a specific treatment for an overdose of GSK2857916.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically (at least 90 days).
3. Obtain a plasma sample for PK analysis and a blood sample for [redacted] within 24 hours of the event study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

There is no known specific antidote for pomalidomide, bortezomib, or dexamethasone overdose.

No specific information is available on the treatment of overdose with pomalidomide. Hemodialysis can remove pomalidomide from circulation [Pomalyst, 2019].

In the event of an overdose of bortezomib, the participant's vital signs should be monitored, and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or inotropic agents) and body temperature [VELCADE, 2019].

For dexamethasone, it is difficult to define an excessive dose of a corticosteroid as the therapeutic dose will vary according to indication and participant requirements. Exaggeration of corticosteroid related adverse effects may occur. Treatment should be asymptomatic and supportive as necessary [LenaDex, 2019].

For further information, see the SRM for prescribing information.

8.5. Pharmacokinetics

8.5.1. Blood Sample Collection for Pharmacokinetics

Blood samples for PK analysis of GSK2857916 (intact ADC and total mAb) and cys-mcMMAF will be collected at the time points indicated in the SoA (Section 1.3), Table 33, Table 34, and Table 35. Each PK sample must be collected as close as possible to the planned time relative to the dose (which is 0 h) administered to the participant on PK days. The actual date and time of each blood sample collection will be recorded.

Details on PK blood sample collection, processing, storage, and shipping procedures are provided in the SRM.

8.5.2. Pharmacokinetic Sample Analysis

Plasma analysis will be performed under the control of GSK Platform Technology and Sciences (PTS)-Bioanalysis Immunogenicity and Biomarkers (BIB) group, the details of which will be included in the SRM. Concentrations of GSK2857916 (intact ADC and total mAb) and cys-mcMMAF will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma has been analyzed for GSK2857916 (intact ADC and total mAb) and cys-mcMMAF, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate GSK PTS-BIB protocol.

CCI

[redacted]

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[redacted]

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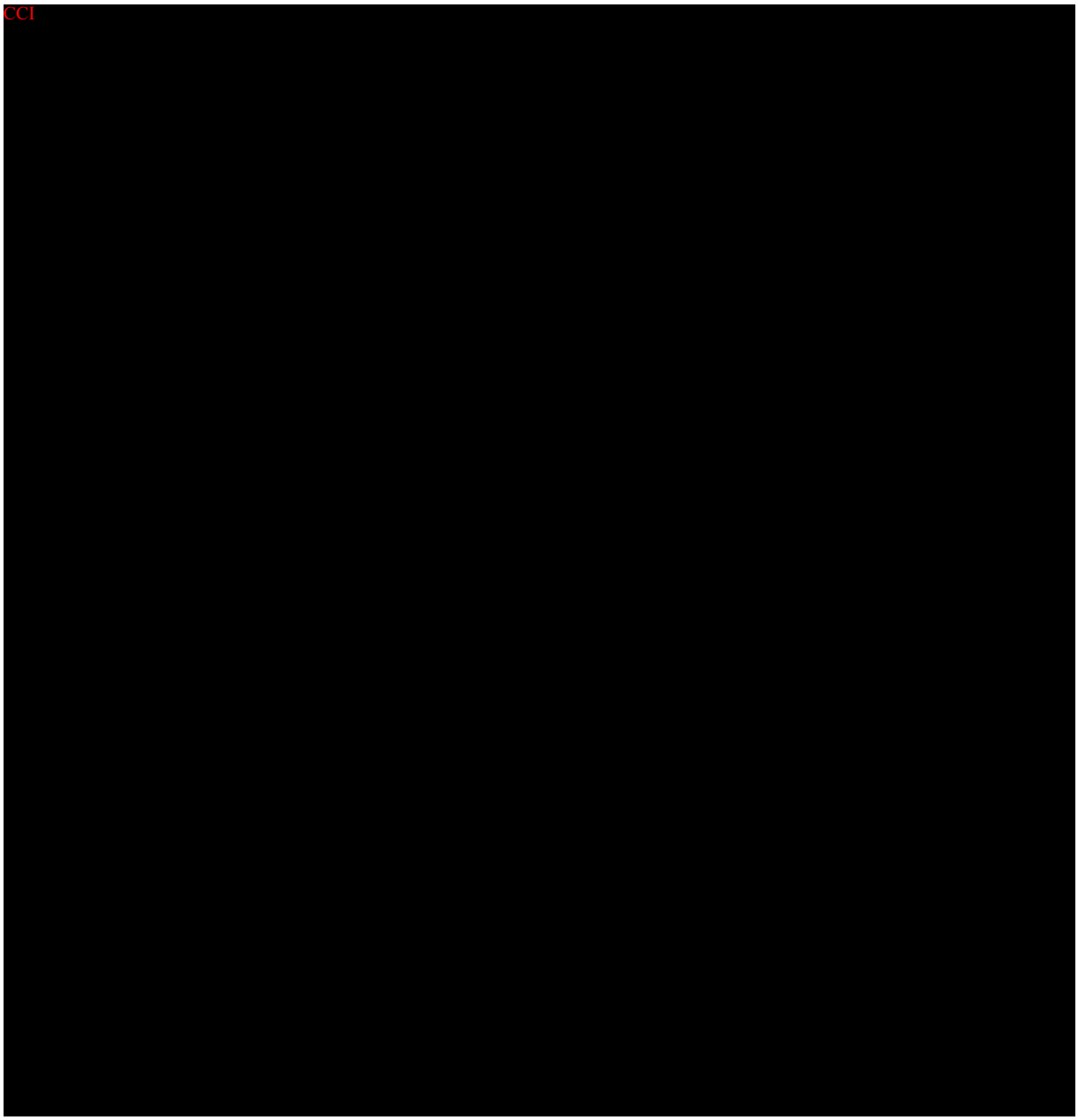


8.7. Genetics

In this study, genetics may be evaluated after review by the ethical review committee established by GSK in accordance with Japanese ethical guidelines for human genome/gene analysis research.

A 6 mL sample for blood sample for deoxyribonucleic acid (DNA) isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 4 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in study manual.

CCI

[redacted]

8.9. Immunogenicity Assessments

Immunogenicity sample analysis will be performed under control of GSK Platform Technology and Sciences (PTS)-Bioanalysis Immunogenicity and Biomarkers (BIB) group, the details of which will be included in the SRM.

In Part 1, serum samples for determination of anti-GSK2857916 antibodies will be taken from all participants in this study at the time-points specified in the SoA.

In Part 2, serum samples for the analysis of anti-GSK2857916 antibodies will be collected prior to each GSK2857916 dose on PK/PD sampling days (at the same time as the predose GSK2857916 PK/PD samples are taken); for treatment beyond 12th doses, collect samples for ADA analysis prior to every 6th dose of GSK2857916 (Dose 18, Dose 24, Dose 30, and so on, until PD). A final ADA sample will be drawn at the EOT visit.

Anti-GSK2857916 antibody samples will be tested for anti-GSK2857916 antibodies using a tiered-testing scheme consisting of validated screening, confirmation, and titration assays. Briefly, all samples will be tested in the screening assay. Samples that screen positive are considered potentially positive and will be tested for specificity in a confirmation assay. Finally, titer values will be obtained for confirmed positive samples using a titration assay. The sample results (e.g., positive or negative) and titer values (positive samples only) will be reported. Samples that test positive for anti-GSK2857916 antibodies may be further characterized in a validated neutralizing antibody assay to determine the neutralizing activity of the antibodies.

The detection and characterization of antibodies to GSK2857916 will be performed using validated assays. The anti-GSK2857916 antibody assay was designed to detect antibodies to GSK2857916, the unconjugated monoclonal antibody and the linker-payload portion of GSK2857916.

For each participant, immunogenicity results, including the incidence and titers, will be reported. Raw data will be archived at the bioanalytical site (detailed in the SRM).

8.10. Evaluation of Anti-myeloma Activity

Response will be assessed according to the IMWG criteria [Kumar, 2016] by the Investigator.

Standard disease assessments for MM will include serum and urine laboratory tests, bone marrow aspirate/biopsy at the time of CR (IHC). Evaluation will follow the guidance of IMWG Uniform Response Criteria for Multiple Myeloma [Kumar, 2016].

- Clinical efficacy measured as ORR, which is defined as the percentage of participants with confirmed sCR, CR, VGPR, or PR as assessed by 2016 recommendation of the IMWG Panel I [Kumar, 2016].
- Other efficacy measures of interest (see Section 8.1).

Disease assessment will include laboratory testing and physical examination (as indicated for palpable/superficial lesions), or imaging CT, MRI, PET/CT, or X-ray (as indicated). Laboratory-based disease assessments will be completed within 21 days prior to the first dose of GSK2857916 then testing will be performed every 3 weeks from C1D1. The imaging will be performed up to 30 days prior to the first dose and will be repeated as indicated in the SoA table. See the SoA (Section 1.3) for the schedule of anti-cancer activity.

Assessments must be performed on a calendar schedule and must not be affected by dose interruptions/delays.

8.11. Health Economics

Not applicable.

9. DATA MANAGEMENT

For this study, data will be collected using defined eCRFs, transmitted electronically to the sponsor or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable the sponsor or designee standards and data cleaning procedures to ensure the integrity of the data, e.g. removing errors and inconsistencies in the data. AEs and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSK Drug. ECRFs, including queries and audit trails, will be retained by the sponsor or designee, and copies will be sent to the investigator to maintain as the investigator copy.

When laboratory samples (i.e., hematology and clinical chemistry) are analyzed by a central laboratory the results will be stored in a database maintained by the central laboratory and transferred to the sponsor or designee at agreed times.

In all cases, participant initials will not be collected or transmitted to the sponsor or designee according to GSK policy.

10. STATISTICAL CONSIDERATIONS

This section briefly describes the planned analyses to be performed for study 207504. Analyses will be fully described in the Reporting and Analysis Plan (RAP).

For 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. 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.

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 any arm in Part 2 has completed at least one cycle of the combination treatment to support a regulatory submission. 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 collection (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 (B-Vd cohort) and Arm B (B-Pd cohort) in Part 2 will be the final analysis for the entire study.

10.1. Statistical Hypotheses

No formal statistical hypotheses are being tested in the study. Analysis of the data obtained from the study will only utilize descriptive methods. Statistical analyses will be performed separately for Part 1 and for Part 2 as well as being performed independently for Arm A and Arm B.

10.2. 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 1 will be up to 12 participants, 6 participants each for 2.5 mg/kg cohort and 3.4 mg/kg cohort based on the 3 + 3 design. 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 design.

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined. Each of the following populations will be created separately for Part 1 and for Part 2 as well as being performed independently for Arm A and Arm B.

Population	Description
All Screened	The 'All Screened' population is defined as all participants who sign the ICF to participate in the clinical study. Participants in this population will be used for screen failure summary
All Treated	All eligible participants who receive 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. Note: Participants with major deviations from the eligibility criteria affecting safety or from the treatment schedule at the DLT evaluation period (1 cycle: 21 days for once every 3 weeks schedule for Part 1 and Part 2 Arm A or 28 days for once every 4 weeks for Part 2 Arm B) for reasons other than toxicity may be presented in separate tables/listings.
DLT Evaluable	This population enables an appropriate evaluation of study DLTs. It is defined as those participants fulfilling the 'All Treated' population criteria, and those who received a complete infusion in Cycle 1 (Part 1) or received a complete infusion of GSK2857916 and at least 75% of planned doses of bortezomib/dexamethasone or pomalidomide/dexamethasone in Cycle 1 (Part 2).
Pharmacokinetic Population	Defined as those participants in the "All Treated" population from whom at least one PK sample is obtained and analyzed.
Pharmacodynamic (PD) Population	Defined as those participants in the "All Treated" population from whom at least one PD sample is obtained, analyzed, and is measurable.

10.4. Statistical Analyses

Data will be listed and summarized according to the GSK reporting standards and the Clinical Data Interchange Standards Consortium (CDISC), where applicable. Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

As the duration of treatment for a given participant will depend on efficacy and tolerability, the duration of follow-up will vary between participants. Consequently there will be no imputation for missing data.

Demographic and baseline characteristics will be summarized separately for Part 1 and for Part 2 as well as being performed independently for Arm A and Arm B.

10.4.1. Safety Analyses

The All Treated Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g. laboratory tests, vital signs, ECGs) will be summarized separately for Part 1 and for Part 2 as well as being performed independently for Arm A and Arm B, according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a "worst-case" analysis. Complete details of the safety analyses will be provided in the RAP.

Endpoint	Statistical Analysis Methods
Primary	**Adverse Events**: Events will be summarized by frequency and proportion of total participants, by system organ class and preferred term. Separate summaries for Part 1 and for Part 2 as well as for Arm A and Arm B will be given for all AEs, treatment related AEs, SAEs and AEs leading to discontinuation of study treatment. AEs, if listed in the NCI-CTCAE (version 4.03) will be summarized by the maximum grade separately for Part 1 and for Part 2 as well as being performed independently for Arm A and Arm B. Otherwise, the AEs will be summarized by maximum intensity separately for Part 1 and for Part 2 as well as being performed independently for Arm A and Arm B. Characteristics (e.g. number of occurrences, action taken, grade, etc.) of the following AEs of clinical interest will be summarized separately for Part 1 and for Part 2 as well as being performed independently for Arm A and Arm B: Corneal events, hematologic toxicities (including but not limited to thrombocytopenia and neutropenia), infusion related reaction etc. The incidence of deaths and the primary cause of death will be summarized separately for Part 1 and for Part 2 as well as being performed independently for Arm A and Arm B. **Laboratory Events**: Hematology and clinical chemistry data will be summarized separately for Part 1 and for Part 2 as well as being performed independently for Arm A and Arm B, using frequencies and proportions according to NCI-CTCAE Version 4.03. The evaluation of clinical laboratory tests will focus on selected laboratory analytes from the hematology and blood chemistry panel. Descriptive statistics (mean, standard deviation, median, range) will be used to summarize observed laboratory values and change from baseline in observed value at each scheduled visit, as appropriate. The worst-case- toxicity grade in hematology and chemistry result during the treatment will be summarized separately for Part 1 and for Part 2 as well as being performed independently for Arm A and Arm B. Shift tables from baseline to the worst toxicity grade during treatment will be provided for each laboratory analyte separately for Part 1 and for Part 2 as well as being performed independently for Arm A and Arm B. Further details will be provided in the RAP.

Endpoint	Statistical Analysis Methods
Other Safety Measures:	Data for vital signs, ECGs and ophthalmic examination findings will be summarized separately for Part 1 and for Part 2 as well as being performed independently for Arm A and Arm B, based on predetermined criteria identified to be of potential clinical concern (PCI). For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages. Further details will be provided in the RAP.

10.4.1.1. Extent of Exposure

The number of participants administered study treatment will be summarized separately for Part 1 and for Part 2 as well as being performed independently for Arm A and Arm B, according to the duration of therapy.

10.4.2. Efficacy Analyses

ORR is one of the secondary endpoints to measure clinical activity of this study.

For multiple myeloma, ORR is defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR and sCR), according to the IMWG Response Criteria [Kumar, 2016], as assessed by the investigator. In addition CBR is defined as the percentage of participants with a confirmed MR or better (i.e., MR, PR, VGPR, CR and sCR), according to the IMWG Response Criteria [Kumar, 2016], as assessed by the investigator.

The number and percentage of participants in the following response categories will be presented separately for Part 1 and for Part 2 as well as being performed independently for Arm A and Arm B: sCR, CR, VGPR, PR, MR, SD, progressive disease, and not evaluable.

sCR+CR+VGPR+PR for ORR.

sCR+CR+VGPR+PR+MR for CBR.

The corresponding 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.

Endpoint	Statistical Analysis Methods
Primary	No primary efficacy analysis is planned in the study

Endpoint	Statistical Analysis Methods
Secondary	Investigation of initial anti-tumor activity is a secondary objective in the study. The All Treated Population will be used for anti-myeloma activity analyses. Since this is a Phase I study, anti-myeloma activity will be evaluated based on clinical evidence and response criteria. If data warrant, the response data will be summarized separately for Part 1 (by dose level) and for Part 2 as well as being performed independently for Arm A and Arm B. Full details will be specified in the RAP.

10.4.3. Immunogenicity Analyses

For each participant, the results and titers of anti-GSK2857916 binding antibodies will be listed for each assessment time point. The frequency and percentage of participants with positive and negative results will be summarized for each assessment time and overall for each participant separately for Part 1 (by dose cohort) and for Part 2 as well as being performed independently for Arm A and Arm B.

10.4.4. Pharmacokinetic Analyses

10.4.4.1. Concentration-Time Data

Linear and semi-logarithmic individual plasma concentration-time profiles and mean and median profiles (when applicable) will be plotted for both GSK2857916 (intact ADC and total mAb) and cys-mcMMAF separately for Part 1 (by dose cohort) and for Part 2 by Arm.

GSK2857916 (intact ADC and total mAb) and cys-mcMMAF concentration-time data will be listed for each participant and summarized by descriptive statistics at each time point separately for Part 1 (by dose cohort) and for Part 2 as well as being performed independently for Arm A and Arm B.

10.4.4.2. Derived Pharmacokinetic Parameters

PK parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on the actual sampling times. From the plasma concentration-time data, the following GSK2857916 (intact ADC, total mAb), 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 concentration (Cmax, plasma), 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), concentration pre-dose after C3 (Ctrough), Rac (accumulation ratio) for Ceoi and Ctrough.

Pharmacokinetic parameters will be listed, and summarized descriptively (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, coefficient of variation [CV%] and 95% CI of log-transformed parameters) separately for Part 1 (by dose cohort) and for Part 2 by Arm.

To assess the extent of accumulation following GSK2857916 repeat dosing, the observed Rac for both GSK2857916 intact ADC, total mAb, and cys-mcMMAF will be determined as Ceoi and Ctrough at steady-state to Ceoi and Ctrough after the first dose, respectively.

CCI

10.4.6. Genetic Analyses

Further details on genetic analyses will be addressed in Appendix 4.

10.5. Interim Analyses

10.5.1. 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.

10.5.2. 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.

10.5.3. Data Monitoring Committee (DMC)

Data Monitoring Committee will not be established in the study.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

11.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations: The Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27 Mar 1997)" and Pharmaceuticals and Medical Devices Act
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

GSK will submit the Clinical Trial Notification to the regulatory authorities in accordance with Pharmaceuticals and Medical Devices Act before conclusion of any contract for the conduct of the study with study sites.

11.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

11.1.3. Informed Consent

Prior to participation in the study, the investigator should fully inform the potential participant and/or the participant's legally acceptable representative of the study including the written information. The investigator should provide the participant and/or the participant's legally acceptable representative ample time and opportunity to inquire about details of the study. The participant and/or the participant's legally acceptable representative should sign and personally date the consent form. The participant may consider the content of the written information at home. The person, who conducted the informed consent discussion and the study collaborator giving supplementary explanation, where applicable, should sign and personally date the consent form. If an impartial witness is required, the witness should sign and personally date the consent form. The investigator should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the participant and/or the participant's legally acceptable representative.

11.1.3.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

- Participants who are rescreened are required to sign a new ICF.

11.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.1.5. Committees Structure

Safety and Efficacy Evaluation Committee will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of participants and to protect the scientific validity of the study. GSK can request the Safety and Efficacy Evaluation Committee to assess at intervals the progress of the study, the safety data, and the efficacy endpoints, and to make a recommendation whether to continue, modify, or stop the study if necessary.

11.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy
- GSK intends to make anonymized patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

11.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations)
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available

- Definition of what constitutes source data can be found in SRM.

11.1.9. Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

11.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements

11.1.11. Study Period

Study period is included in Exhibit 3.

11.1.12. Study Administrative Structure

Sponsor information is included in Exhibit 1. List of Medical Institutions and Investigators is included in Exhibit 2.

11.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.2.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

11.2.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
Is associated with liver injury and impaired liver function defined as: • ALT ≥3 x ULN and total bilirubin* ≥2 x ULN (>35% direct), or • ALT ≥3 x ULN and INR** >1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥3 x ULN and total bilirubin ≥2 x ULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form. **Refer to Appendix 5 for liver chemistry follow-up procedures.**

11.2.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack

- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

11.2.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Corneal events associated with GSK2857916 will be graded according to the grading scale provide in Appendix 7.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

11.2.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone
- Contacts for SAE reporting can be found in SRM.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **SAE coordinator**. Detail provided in the SRM.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in SRM.

11.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

11.3.1. Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

11.3.2. Contraception Guidance:

- **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**

• **Highly Effective Methods[b] That Have Low User Dependency**
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent**
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
• Sexual abstinence *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
l. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. m. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. n. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

Of contraceptive methods defined in the protocol Appendix 3, Contraceptive Methods Approved in this Study, the followings are not approved in Japan as contraceptive method.

Highly Effective Methods That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
Highly Effective Methods That Are User Dependent

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  • intravaginal
  • transdermal
  • injectable
• Progestogen-only hormonal contraception associated with inhibition of ovulation
  • oral
  • injectable

11.3.3. Collection of Pregnancy Information:

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study and for 6 months following the last dose of GSK2857916, 4 months following the last dose of bortezomib (only Part 2 Arm A), and 4 weeks following the last dose of pomalidomide (only Part 2 Arm B), whichever is longest, by telephone for WOCBP partners only. This applies only to male participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study and for 4 months following the last dose of GSK2857916, 7 months following the last dose of bortezomib (only

Part 2 Arm A), and 4 weeks following the last dose of pomalidomide (only Part 2 Arm B), whichever is longest.

- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will discontinue study treatment or be withdrawn from the study

11.4. Appendix 4: Genetics

USE/ANALYSIS OF DNA

In this study, genetics may be evaluated after review by the ethical review committee established by GSK in accordance with Japanese ethical guidelines for human genome/gene analysis research, see Section 8.7 for further details on genetic research.

- Genetic variation may impact a participant's response to study treatment, susceptibility, severity and progression of disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a 6 mL of blood sample will be collected for DNA analysis
- DNA samples will be used for research related to Multiple Myeloma and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK2857916 or study treatments of this drug class, and Multiple Myeoloma. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate)
- DNA samples will be analyzed for describe planned analyses. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to GSK2857916 or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The results of genetic analyses will not be disclosed to each participant because they may not directly relevant to the treatment strategy and may stress out the participant and his/her family.
- Where participants withdraw the consent to participate in the genetics analysis component of the study after samples have been taken from them, the samples will not be used for new analyses and will be destroyed. Where participants' genetic data have been analyzed before they withdraw the consent to the genetics analysis component, the results will be used. In addition, where participants' genetic data have been obtained but have not been analyzed yet when they withdraw they withdraw the consent to the genetics analysis component, the data will not be used for any purposes.
- The sponsor will store the DNA samples in a secure storage space at approximately -80°C with adequate measures to protect confidentiality.

  Please refer to Gx Sample Storage Facility of Exhibit 1 for information about the storage facility.

- The samples will be retained while research on GSK2857916 (or study treatments of this class) or Multiple Myeloma continues but no longer than 15 years after the last subject last visit or other period as per local requirements.
- The samples will be destroyed appropriately according to the procedures of the storage facility (see Exhibit 1), under administration of the sponsor. The sponsor will be informed of sample destruction.

11.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Phase I liver chemistry stopping criteria have been designed to assure participant's safety and to evaluate liver event etiology.

Phase I liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT≥5xULN
ALT Increase	ALT≥3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT≥3xULN **and** bilirubin≥2xULN (>35% direct bilirubin)
INR[2]	ALT≥3xULN **and** INR>1.5
Cannot Monitor	ALT≥3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event form and complete SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING** below) **MONITORING:** **<u>If ALT≥3xULN AND total bilirubin≥2xULN or INR>1.5:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24 hrs**	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Blood sample for pharmacokinetic (PK) analysis and a blood sample for [redacted] within 70 days after last dose of GSK2857916[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH), gamma glutamyltransferase (GGT), glutamate dehydrogenase (GLDH), and serum albumin • Fractionate bilirubin, if total bilirubin≥2xULN

• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended **<u>For all other criteria (bilirubin <2xULN and INR≤1.5):</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline **<u>RESTART/RECHALLENGE:</u>** • **Restart/rechallenge is allowed per protocol but do not resume study treatment unless GSK approval is granted;** If restart/rechallenge is **not granted**, permanently discontinue study treatment and continue participant in the study for any protocol specified follow up assessments. Refer to Restart/Rechallenge guidelines in Appendix 5.	• Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter medications. • Record alcohol use on the liver event alcohol intake form **If ALT≥3xULN AND total bilirubin≥2xULN or INR>1.5** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins) • Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week. (e.g., where the participant has been resident in the clinical unit throughout) • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease; complete Liver Imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance: o In participants when serology raises the possibility of autoimmune hepatitis (AIH)

	○ In participants when suspected drug-induced liver injury (DILI) progresses or fails to resolve on withdrawal of study treatment ○ In participants with acute or chronic atypical presentation • If liver biopsy conducted complete liver biopsy form.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** total bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE** (excluding studies of hepatic impairment or cirrhosis); and the threshold value stated will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody or Hepatitis E RNA
5. PK sample and associated CCI sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK/CCI blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PKCCI sample cannot be collected in the time period indicated above, do not obtain a PK/CCI sample. Instructions for sample handling and shipping are in the SRM

Phase I liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Treatment Liver Monitoring Event	
Criteria	**Actions**
ALT≥3xULN **but** <5xULN **and** total bilirubin <2xULN or INR≤1.5, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the Medical Monitor **within 24 hours** of learning of the abnormality to discuss participant safety • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin and INR) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above

	• If, after 4 weeks of monitoring, ALT<3xULN and total bilirubin<2xULN and INR≤1.5, monitor participants twice monthly until liver chemistries resolve or return to within baseline.

11.5.1. Liver Safety Drug Restart or Rechallenge Guidelines

A participant who met liver chemistry stopping criteria cannot resume study treatment unless all of the following conditions are met:

- GSK approval **is granted** (as described below)
- IRB/IEC approval is obtained
- Separate ICF for study treatment restart/rechallenge is signed by the participant and participant is informed of any associated risks

If GSK approval to restart/rechallenge the participant with study intervention **is not granted**, then the participant must permanently discontinue study treatment and may continue in the study for protocol-specified follow-up assessments.

11.5.1.1. Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment

Following drug-induced liver injury (DILI), **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies** [Andrade, 2009]. Clinical outcomes vary by drug with nearly 50% fatality with halothane readministered within 1 month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- Hypersensitivity with initial liver injury (e.g., fever, rash, eosinophilia) [Andrade, 2009]
- Jaundice or bilirubin >2 x ULN with initial liver injury (direct bilirubin >35% of total)
- Ongoing severe liver injury defined by: ALT ≥3 x ULN, bilirubin ≥2 x ULN (direct bilirubin >35% of total), or INR >1.5

SAE or fatality has been observed with drug rechallenge [Hunt, 2010; Papay, 2009]

Evidence of drug-related preclinical liability (e.g., reactive metabolites; mitochondrial impairment) [Hunt, 2010]

Rechallenge refers to resuming study treatment following study treatment induced liver injury (DILI). Because of the risks associated with rechallenge after DILI this should only be considered for a participant for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favorable.

Approval by GSK for rechallenge with study treatment can be considered where:

- The Principal Investigator requests consideration of rechallenge with study treatment for a participant who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- IRB/IEC approval for rechallenge with study treatment must be obtained.

If the rechallenge is approved by GSK in writing

- The participant must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study file.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK for rechallenge with study treatment must return to the study site twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, participant meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- Medical Monitor and the IRB/IEC as required, must be informed of the participant's outcome following study treatment rechallenge.
- GSK to be notified of any AEs, as per Section 11.2.

11.5.1.2. Restart Following Transient Resolving Liver Stopping Events NOT Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g., biliary obstruction, pancreatic events, hypotension, and acute viral hepatitis). Furthermore, restart is not permitted following liver stopping event when the underlying cause was aoclhol-related hepatitis.

Approval by GSK for study treatment restart can be considered where:

- Principal Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3 x ULN).
- Possible study treatment-related liver injury has been excluded by the Principal Investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study treatment has an identified genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate), the presence of the marker should be

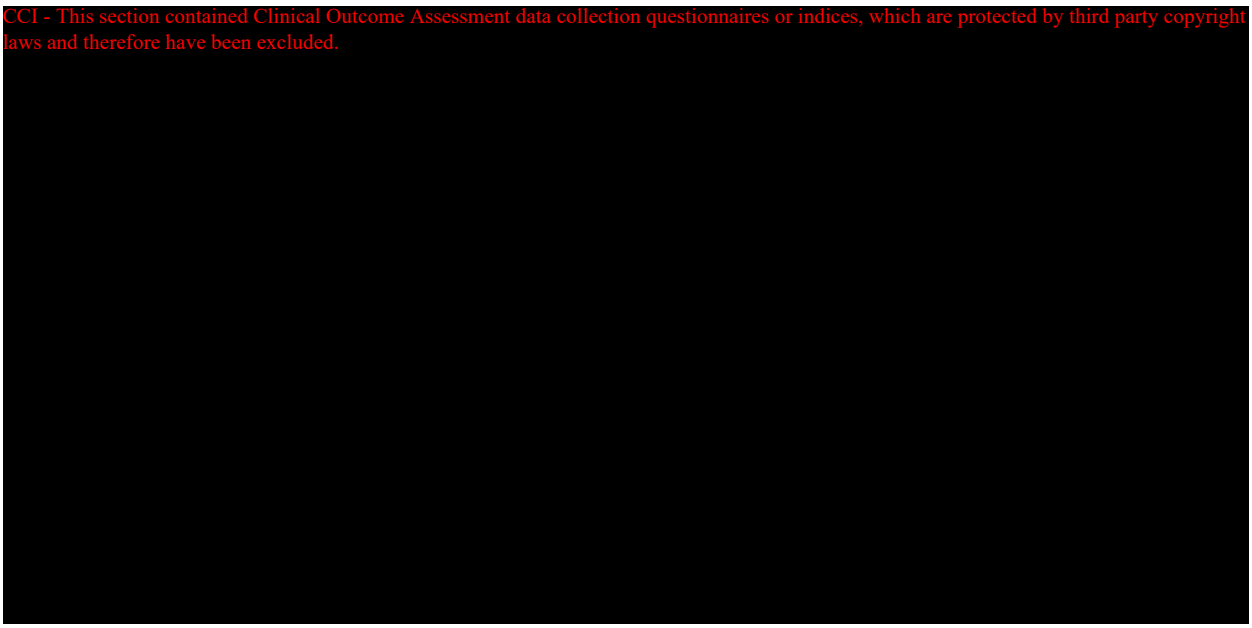
excluded. If study treatment-related liver injury cannot be excluded, the guidance on rechallenge as stated in previous section will apply.

- There is no evidence of alcoholic hepatitis.
- IRB/IEC approval of study treatment restart must be obtained, as required.

If restart of study treatment is approved by GSK in writing,

- The participant must be provided with a clear description of the possible benefits and risks of study treatment administration including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study file.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK for restarting study treatment must return to the study site once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If participant meets protocol-defined liver chemistry stopping criteria after study treatment restart, study treatment should be permanently discontinued.
- Medical Monitor and the IRB/IEC must be informed of the participant's outcome following study treatment restart.
- GSK must be notified of any AEs, as per Section 11.2.

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



11.7. Appendix 7: Corneal Event Severity Grading and Mitigation Strategy

In order to minimize the corneal toxicity, prophylactic preservative-free artificial tears should be administered in each eye at least 4 to 8 times daily beginning on C1D1 until the EOT. In the event of ocular symptoms (e.g., dry eyes), the use of artificial tears may be increased up to every 2 hours as needed. Corticosteroid eye drops are not required but can be used if clinically indicated per discretion of an eye-care specialist. Allow at least 5 to 10 minutes between administration of artificial tears and steroid eye drops (if administered together). If steroid eye drops are deemed medically necessary and prescribed, intraocular pressure must be monitored if used for more than 7 days.

While not yet clinically demonstrated, it is theoretically possible that the application of a cooling eye mask during GSK2857916 administration, and in the first few hours after infusion may subsequently decrease ocular side effects. On the day of infusion at the discretion of the participant and the investigator, the following may be considered:

- Beginning with the start of each GSK2857916 infusion, participants may apply cooling eye masks to their eyes for approximately 1 hour or as much as tolerated.
- Participants may continue using the cooling eye mask beyond the first hour for up to 4 hours. Further use beyond 4 hours is at the participant's discretion.

Participants must avoid the use of contact lenses while the participant is receiving GSK2857916. Contact lens use may be restarted after an ophthalmologist confirms there are no other contraindications. Use of bandage contact lenses is permitted during study treatment as directed by the treating eye care specialist.

An ophthalmology consult is required for all participants who develop signs or symptoms of corneal toxicity or require steroid eye drops for more than 7 days.

A summary of prophylactic interventions for corneal events associated with GSK2857916 is provided in Table 36. The severity of corneal events associated with GSK2857916 and related to ophthalmic exam findings or visual acuity will be also graded using the scale provided in Table 37. The severity of the other corneal events will be graded utilizing the NCI-CTCAE. Additional guidance on grading visual acuity changes provided in Table 38.

Table 36 Prophylactic Measures for Corneal Events Associated with GSK2857916 [a]

Prophylactic Measure[a]	Dose and Administration	Timing
Preservative-free artificial tears	Administer in each eye at least 4 to 8 times four times daily	Administer daily beginning on Cycle 1 Day 1 until EOT.
Cooling eye mask	May apply cooling eye mask to both eyes for approximately 1 hour or as much as tolerated	During GSK2857916 infusion administration in the first hour for up to 4 hours, as tolerated

a Dose modifications and treatment for ocular toxicities are discussed in Section 6.7

Table 37 Grading Scale for Corneal Events Associated with GSK2857916 [a]

Measure	Grade 1	Grade 2	Grade 3	Grade 4
Ophthalmic exam findings	Mild superficial keratopathy (change from baseline)	Moderate punctate keratopathy and/or Mild/patchy microcysts and/or Mild/patchy Epithelial or stromal edema and/or Sub-epithelial haze (peripheral) and/or Active stromal opacity (peripheral)	Severe punctate keratopathy and/or Diffuse microcysts and/or Diffuse Epithelial or stromal edema and/or Sub-epithelial haze (central) and/or Active stromal opacity (central)	Corneal ulcer
Visual Acuity [b]	Change of 1 line from baseline [c]	Change of 2-3 lines from baseline and not worse than 20/200 [c]	Change of more than 3 lines from baseline and not worse than 20/200 [c]	Worse than Vision 20/200 [c]

Note: Sites will be provided with standardized guidance for grading ophthalmic findings.

o. Grading is based on most severe finding. If eyes differ in severity, GSK grading should be based on the more severe eye.

p. Change in visual acuity should be due to corneal findings associated with GSK2857916. If change in vision is for reason other than corneal findings, ophthalmic exam findings will drive event grading.

q. The change in visual acuity by Snellen chart is shown in this table. See Table 38 for additional guidance on how to grade changes in Landolt ring visual acuity depending on baseline vision. If a participant has a baseline visual acuity of 20/200 (0.1 for Landolt ring visual acuity) or worse in an eye, ophthalmic exam findings will drive event grading.

Table 38 Additional Guidance on Grading Based on Changes in Visual Acuity (Landolt Ring Chart)

Baseline Vision (best corrected)	Grade 1	Grade 2	Grade 3	Grade 4
1.0	0.7 – 0.9	0.5 – 0.6	0.1 – 0.4	Worse than 0.1
0.9	0.6 – 0.8	0.5	0.1 – 0.4	Worse than 0.1
0.8	0.6 – 0.7	0.4 – 0.5	0.1 – 0.3	Worse than 0.1
0.7	0.5 – 0.6	0.4	0.1 – 0.3	Worse than 0.1
0.6	0.4 – 0.5	0.3	0.1 – 0.2	Worse than 0.1
0.5	0.4	0.3	0.1 – 0.2	Worse than 0.1
0.4	0.3	0.2	0.1	Worse than 0.1
0.3	0.2	NA	0.1	Worse than 0.1
0.2	NA	0.1	NA	Worse than 0.1

11.8. Appendix 8: Modified Diet in Renal Disease (MDRD) Formula

The MDRD formula for calculating the eGFR is as follows:

$$eGFR = 175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (0.808 \text{ if Japanese})$$

GFR is expressed in mL/min/1.73 m^2, SCr is serum creatinine expressed in mg/dL, and age is expressed in years.

The link below will auto-calculate the creatinine clearance: http://nephron.org/cgi-bin/MDRD_GFR/cgi

11.9. Appendix 9: International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma

Anti-tumor activity will be assessed according to the following criteria [Kumar, 2016].

Response	International Myeloma Working Group (IMWG) Criteria
sCR (stringent CR)	CR as defined below plus normal free light chain (FLC) ratio 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 [PCs]).
CR (complete response)	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% PCs in bone marrow aspirates.
VGPR (very good partial response)	• 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.
PR (partial response)	• ≥ 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 PCs is required in place of M-protein, provided baseline bone marrow PC percentage was ≥ 30%. • In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size (sum of the products of the maximal perpendicular diameters of measured lesions [SPD]) of soft tissue plasmacytomas is also required.
MR (minimal response)	• ≥ 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) of soft tissue plasmacytomas is also required.
SD (stable disease)	Not meeting criteria for CR, VGPR, PR, MR, or PD.
PD (progressive disease)	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 patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be ≥ 10 mg/dL); ➢ In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow PC percentage irrespective of baseline status (absolute increase must be ≥ 10%); • Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion > 1 cm in short axis; • ≥ 50% increase in circulating PCs (minimum of 200 cells per μL) if this is the only measure of disease.

11.10. Appendix 10: Abbreviations and Trademarks

ADA	Anti-drug antibodies
ADC	Antibody drug conjugate
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
ADL	Activity of daily living
AE	Adverse Event
AESI	Adverse event of special interest
AIH	Autoimmune hepatitis
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APRIL	A proliferation-inducing ligand
ASCT	Autologous stem-cell transplantation
AST	Aspartate aminotransferase
AUC	Area under the curve
AV	Atrioventricular
BAFF	B-cell-activating factor belonging to the TNF family
BCMA	B-cell maturation antigen
BIB	Bioanalysis Immunogenicity and Biomarkers
BM	Bone marrow
BMI	Body mass index
BNP	B-type natriuretic peptide
Bor/Dex	Bortezomib and dexamethasone
BP	Blood Pressure
BUN	Blood urea nitrogen
CBR	Clinical Benefit Rate
CDISC	Clinical Data Interchange Standards Consortium
Ceoi	Concentration at end of infusion
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council of International Organizations of Medical Sciences
CK	Creatine kinase
CL	Clearance
Cmax	Maximum observed concentration
CPR	Cardio-pulmonary resuscitation
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CR	Complete Response
CRF	Case Report Form
CRP	C-reactive protein
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Trough plasma concentration

CV	Coefficient of variation
CTFG	Clinical Trial Facilitation Group
CYP	Cytochrome P
cys-mcMMAF	Cysteine maleimidocaproyl monomethyl auristatin F
CX	Cycle X
CX+	Cycle X and beyond
DCO	Data cut-off
DILI	Drug-induced liver injury
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of Response
DRESS	Drug reaction with eosinophilia and systemic symptoms
DX	Day X
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOI	End of infusion
EOT	End of treatment
FDA	Food and Drug Administration
FISH	Fluoroscence in situ hybridization
FLC	Free light chain
FSH	Follicle stimulating hormone
FTIH	First Time in Human
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GLDH	Glutamate dehydrogenase
GSK	GlaxoSmithKline
HBV	Hepatitis B
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDT	High-dose conventional therapy
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
Hr	hour
HRT	Hormone replacement therapy
HUS	Hemolytic uremic syndrome
IB	Investigator Brochure
ICD	Immunogenic cell death
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee

IgA	ImmunoglobulinA
IgD	ImmunoglobulinD
IgE	ImmunoglobulinE
IgG	ImmunoglobulinG
IgM	ImmunoglobulinM
IHC	Immunohistochemistry
IMiD	Immunomodulatory drugs
IMWG	International Myeloma Working Group
INR	International normalization ratio
IP	Investigational product
IRB	Institutional review board
IRR	Infusion-related reaction
IUD	Intra-uterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous(ly)
LAM	Lactational amenorrhoea method
LC	Light chain
LDH	Lactate dehydrogenase
LLN	Lower limit of normal (range)
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCRN	Myeloma Canada Research Network
MDRD	Modified diet in renal disease
MHW	Ministry of Health, Labour and Welfare
MedRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MMAF	Monomethyl auristatin F
mPFS	Median progression-free survival
MR	Minimal Response.
MRI	Magnetic resonance imaging
MRP	Multidrug resistance associated protein
MSDS	Material Safety Data Sheet
NA	Not applicable
NCI	National Cancer Institute
NE	Not estimable
NHL	Non-Hodgkin lymphoma
NR	Not reached
OATP	Organic anion transporting polypeptide
ORR	Overall Response Rate
OS	Overall survival
PACT	Post analysis continued treatment
PC	Plasma cells
PCI	Potential clinical concern

PD	Pharmacodynamic(s)
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PML	Progressive multifocal leukoencephalopathy
POEMS	Polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes
Pom/Dex	Pomalidomide and dexamethasone
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PTS	Platform Technology and Sciences
QD	Once daily
Q3W	Once every 3 weeks
Q4W	Once every 4 weeks
QID	Four times a day
QTc	Corrected QT interval (ECG)
QTcF	Corrected QT interval Fridericia
Rac	Accumulation ratio
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RNA	Ribonucleic acid
RP2D	Recommended Phase II Dose
RP3D	Recommended Phase III Dose
RRMM	Relapsed / refractory multiple myeloma
SAE	Serious adverse event
CCI [redacted]	[redacted]
SC	Subcutaneous(ly)
sCR	Stringent Complete Response
SCr	Serum creatinine
SD	Stable disease
SJS	Stevens-Johnson syndrome
SoA	Schedule of activities
SoC	Standard of care
SOI	Start of infusion
SPD	Sum of the products of the maximal perpendicular diameters of measured lesions
SPEP	Serum Protein Electrophoresis
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reaction
t½	Terminal phase half-life
TEN	Toxic epidermal necrolysis
tlast	Time of last quantifiable concentration
tmax	Time of maximum observed concentration
TNF	Tumor necrosis factor
TTP	Thrombotic thrombocytopenic purpura

ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
US	United States
VGPR	Very good partial response
Vss	Volume of distribution at steady state
VZIG	Varicella-Zoster immune globulin
WBC	White blood cell
WOCBP	Woman of Childbearing Potential
λz	Terminal phase elimination rate constant

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
None

11.11. Appendix 11: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1: 07-DEC-2018

Overall Rationale for the Amendment: Action taken for the response to inquiries from Pharmaceuticals and Medical Devices Agency (PMDA) (dated 27 NOV 2018) to the initial clinical trial notification.

Section # and Name	Description of Change	Brief Rationale
Synopsis	Changed text of Synopsis to reflect changes to the text of the protocol.	See below for all significant changes.
1.3 Schedule of Activities (SoA)	Added chest X-ray imaging.	For early detection of interstitial lung disease.
4.1 Overall Design	Added the dosing interval between the first and subsequent participants in each dose cohort. Added the information that the dose-escalation will be determined considering all available information on AEs occurred in the dose-limiting toxicity (DLT) observation period.	To clearly show how to consider the safety information for dose-escalation.
5.1 Inclusion Criteria 4	Added “at least 2 regimens” to the criterion of pretreatment.	To clearly show that the target participants are the patients with no options of standard of care.
5.2 Exclusion Criteria 16, 18, and 21	Added the following exclusion criteria. Female who are interrupting lactation. Those who have positive hepatitis B surface antibody (HBsAb).	To make the exclusion criteria clearer and to add a new exclusion criterion according to the regulatory agency advice.

Section # and Name	Description of Change	Brief Rationale
	Those who were previously diagnosed with interstitial lung disease or who have current complication of interstitial lung disease.	
6.5.1 Permitted Medications(s)	Added the following information. In Japan, it is not approved to use growth factor products (except for granulocyte-colony stimulating factor) for neutropenia due to cancer chemotherapy and erythropoietin products for anemia due to cancer chemotherapy.	Some of the treatment participants may receive during the study included non-approved treatment in Japan.
6.5.2 Prohibited Medications(s)	Growth factor products: prohibited to use for primary prophylaxis during DLT observation period.	DLT may be underestimated if growth factor products are used during the DLT observation period.
8. Study Assessments and procedures Table 10	Added HBsAb.	Based on the revised exclusion criterion.
8.6 Pharmacodynamics	Added Table 11: Timing and volume of blood collection for pharmacokinetic and pharmacodynamic analyses.	To clearly show the timing and volume of blood collection for pharmacokinetic and pharmacodynamic analyses.
11.4 Appendix 4: Genetics	Added the following information. • How to store, where to store, and how to destroy blood samples. • Whether to disclose the results of genetic analyses to participants, and the reason of the action. • How to handle tissue and blood samples in case of consent withdrawal.	To clearly show how to handle samples, whether to disclose the results of analyses, and how to handle samples in case of consent withdrawal.

Amendment 2: 05-APR-2019

Overall Rationale for the Amendment: This protocol has been amended to address feedback from investigators, clarification of study assessment and procedure, and administrative change.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Changed text of synopsis to reflect changes to the text of the protocol.	See below for all significant changes.
1.3. Schedule of Activities (SoA) Footnote 1	Added the time window of Cycle (C) 1 Day (D) 2, C1D8, and C1D15.	To clarify the time window.
1.3. Schedule of Activities (SoA) Footnote 5	Clarified that corneal supportive care will be done based on Grading Scale for Corneal Events Associated with GSK2857916.	To make the description consistent and aligned throughout the protocol.
1.3. Schedule of Activities (SoA) Footnote 6	Added the time window for ocular examination during follow-up.	To clarify the time window for ocular examination.
	Changed the timing of follow-up visits for participants with corneal signs per GSK scale after the End of Treatment (EOT) visit.	To align the timing of follow-up visits after EOT visit with other GSK2857916 protocols.
	Added the definition of full resolution of ophthalmic findings.	To clarify the definition of full resolution of ophthalmic findings.
1.3. Schedule of Activities (SoA) Footnote 11	Added troponin T.	To assess troponin with troponin I or T.
1.3. Schedule of Activities (SoA) Footnotes 21, 22, and 23	Added the procedures for sample collection for [redacted], anti-drug antibodies (ADA), and pharmacokinetics (PK) assessments when a dose is delayed.	To clarify the timing and number of times for sample collection for [redacted] ADA, and PK assessments when a dose is delayed.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA) Genetics Sample and Footnote 25	Revised the timing of collecting genetics sample.	To collect it between the first opportunity after a participant has met all eligibility requirements and the EOT Visit.
1.3. Schedule of Activities (SoA) Footnote 27	Added prednisolone acetate as an example of steroid eye drops as prophylaxis.	To clarify the allowed steroid eye drops as prophylaxis.
1.3. Schedule of Activities (SoA) Adverse Events	Added adverse events assessment at Screening. Added Footnote 28 that any serious adverse events assessed as related to study participation or related to a GSK product will be recorded from the time a participant consent.	To clarify the timing of collection of adverse event information.
3. Objectives and Endpoints	Removed the requirement for pretreatment with the specific drug and for drug class from the criterion of targeting participants for this clinical study.	To align with current practice.
5.1. Inclusion Criteria #4	Removed the requirement for pretreatment with the specific drug and for drug class.	To align with current practice.
5.2. Exclusion Criteria #18	Added exemption for participants with positive HBsAb alone due to hepatitis B vaccination.	To allow participants with positive HBsAb alone due to hepatitis B vaccination to be enrolled given Guidelines for the Management of Hepatitis B Virus Infection
6.5.2. Prohibited Medications	Added strong organic anion transporting polypeptide (OATP) 1B1 and OATP1B3 inhibitors as prohibited medications.	To update information on prohibited medications.
	Added prohibition period for supportive care.	To clarify that the requirements for prohibited medications.

Section # and Name	Description of Change	Brief Rationale
6.6.2. Dose Reduction for Toxicity Table 9	Incorporated Grading Scale for Corneal Events Associated with GSK2857916 and amended dosing modifications guidelines.	To further clarify dose modifications based on the visual acuity or findings on ophthalmic examination.
6.6.3. Corneal Supportive Care Guideline	Clarified that corneal supportive care will be done based on Grading Scale for Corneal Events Associated with GSK2857916.	To make the description consistent and aligned throughout the protocol.
8. Study Assessments and procedures	Removed the requirement for the order of 12-lead electrocardiograms and vital signs.	To allow flexibility for assessments.
	Added the time window of C1D2, C1D8, and C1D15.	To clarify the time window.
8. Study Assessments and procedures Table 10	Removed total bicarbonate and added troponin T.	Total bicarbonate measurement became unnecessary. To assess troponin with troponin I or T.
8.1. Efficacy Assessments	Added computed tomography and magnetic response imaging as methods to assess complete response (CR) and stringent complete response (sCR).	To clarify additional methods to assess CR and sCR.
8.2.2. Ocular Examinations and Procedures	Revised the examination item at baseline ophthalmic examination from pupillary examination to pupillary light reflex.	To clarify the examination item.
11.1.2. Financial Disclosure	Revised information about financial disclosure.	To apply GSK's standard process of financial disclosure.

Section # and Name	Description of Change	Brief Rationale
11.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines	More classified liver chemistry stopping criteria and added follow up assessments.	To provide Liver Chemistry Stopping Criteria and Required Actions and Follow up Assessments according to GSK's standard template.
11.7. Appendix 7: Corneal Event Severity Grading and Mitigation Strategy	Added prednisolone acetate as an example of steroid eye drops as prophylaxis.	To clarify the allowed steroid eye drops as prophylaxis.
11.7. Appendix 7: Corneal Event Severity Grading and Mitigation Strategy Table 12	Added prednisolone acetate as an example of steroid eye drops as prophylaxis.	To clarify the allowed steroid eye drops as prophylaxis.
11.7. Appendix 7: Corneal Event Severity Grading and Mitigation Strategy Table 13	Revised Grade 2 and Grade 3 ophthalmic examination findings as follows: Grade 2 • Moderate keratopathy to moderate punctate keratopahy. Grade 3 • Severe keratopathy to severe punctate keratopahy.	To clarify the ophthalmic examination findings that are assessed as Grade 2 and Grade 3.
	Added how to perform corneal event grading into the footnotes.	To clarify how to perform corneal event grading.
11.7. Appendix 7: Corneal Event Severity Grading and Mitigation Strategy Table 14	Revised guidance on grading based on changes in visual acuity to use Landolt ring chart.	To provide change grading scale for visual acuity using Landolt ring chart.

Section # and Name	Description of Change	Brief Rationale
11.9 Appendix 9: International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma	Added International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma.	To clarify the response criteria.

Amendment 3: 01-JUL-2020

Overall Rationale for the Amendment: This protocol has been amended 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) evaluating the efficacy and safety of two doses of GSK2857916 monotherapy in relapsed / refractory multiple myeloma refractory to proteasome inhibitors, immunomodulatory drugs and who failed anti-CD38 antibody treatment.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Changed text of synopsis to reflect changes to the text of the protocol.	See below for all significant changes.
1.2. Schema 4.1. Overall Design Figure 2	Added Part 2 (GSK2857916 combination therapy).	To include GSK2857916 combination therapy cohorts.
1.3. Schedule of Activities (SoA) Table 1 Pregnancy test and footnote 13	Updated the pregnancy test and the follow-up period of pregnancy assessment for Part 1.	To align with Food and Drug Administration (FDA) guidance "Oncology Pharmaceuticals Reproductive Toxicity and Testing recommendations" and considering the half-life of GSK2857916.
1.3. Schedule of Activities (SoA) Table 1	Added preservative-free artificial tears and cooling eye masks (optional) instead of steroid eye drops.	To align with revised prophylactic measures for corneal events.
	Added new anticancer therapy record during follow up.	To clarify the collection of new anticancer therapy.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA) Table 1 Adverse events and concomitant medications	Added adverse event and concomitant medication assessments at the follow-up visit.	To clarify adverse event (AE) and concomitant medication assessment
1.3. Schedule of Activities (SoA) Table 1 footnote 3	Updated the timing of the end of treatment visit.	To align with program level language.
1.3. Schedule of Activities (SoA) Table 1 footnotes 7 and 21	Added time window for vital sign assessments and [redacted] blood collection.	To add clarity of the window.
1.3. Schedule of Activities (SoA) Table 1 footnote 27	Clarified the period to collect serious AEs assessed as related to study participation or related to a GSK product. Updated the period to collect non-serious and serious AEs. Added the requirement of concomitant medication record.	
1.3. Schedule of Activities (SoA)	Added Table 2: Schedule of Activities for Part 2 Arm A (GSK2857916 in combination with Bortezomib plus Dexamethasone). Added Table 3: Schedule of Activities for Part 2 Arm B (GSK2857916 in combination with Pomalidomide plus Dexamethasone).	To include assessments and procedures for Part 2.
2. Introduction	Updated the multiple myeloma (MM) information.	To reflect the latest information of MM.

Section # and Name	Description of Change	Brief Rationale
2.1. Study Rationale	Updated the results of BMA117159 study.	To reflect the latest information of BMA117159 study.
	Updated the information of other studies of GSK2857916 combination therapy.	To provide the rationale of including GSK2857916 combination therapy cohorts for this study.
2.3 Antibody-Drug Conjugate GSK2857916	Added the mechanism of action of GSK2857916.	
2.3.1. Human Experience with GSK2857916	Added Section 2.3.1.1 and updated the information of clinical studies with GSK2857916 monotherapy. Added Section 2.3.1.1.1 and updated the safety information of GSK2857916 monotherapy. Added Section 2.3.1.2 to describe the information of clinical studies with GSK2857916 combination therapy.	To provide the latest information of clinical studies with GSK2857916.
2.3.1.3. Pharmacokinetics and Pharmacodynamics in Human	Updated the pharmacokinetics (PK) and added the pharmacodynamics (PD) of GSK2857916.	To reflect the latest PK and PD of GSK2857916.
2.4.1. Risk Assessment	Added the potential overlapping toxicities of GSK2857916 when combined with bortezomib and dexamethasone (Bor/Dex) or pomalidomide and dexamethasone (Pom/Dex) and other risks related to GSK2857916, bortezomib, pomalidomide, or dexamethasone.	To provide the risks related to study treatment.

Section # and Name	Description of Change	Brief Rationale
2.4.2. Benefit Assessment	Updated the benefit assessment for GSK2857916 monotherapy.	To provide the latest benefit assessment for GSK2857916 monotherapy.
	Added the benefit assessment for GSK2857916 combination therapy.	To provide the rationale for the potential benefit of including GSK2857916 combination therapy cohorts.
2.4.3. Overall Benefit: Risk Conclusion	Added the overall benefit and risk conclusion for GSK2857916 combination therapy.	To provide the overall risk-benefit balance of including GSK2857916 combination therapy cohorts.
3. Objectives and Endpoints Table 4	Updated the endpoints for the objective of evaluating PK profile of GSK2857916 and cys-mcMMAF after IV single and repeat dose administration in Japanese participants with RRMM.	To include GSK2857916 combination therapy cohorts.
4.1. Overall Design	Added the study design and planned sample size for Part 2.	To include GSK2857916 combination therapy cohorts.
	Added Table 7: Dose Level for Part 2 Arm A and Table 8: Dose Levels for Part 2 Arm B.	To clarify the dose levels used for each part and each arm.
4.1.1. Dose-Limiting Toxicity	Added the definitions of dose-limiting toxicity (DLT) and DLT-evaluable participants and the requirement for replacement of participants during the DLT observation period for Part 2.	To include GSK2857916 combination therapy cohorts.
4.2. Scientific Rationale for Study Design	Updated the results of BMA117159 study.	To reflect the latest information of BMA117159 study.
	Added the rationale of including GSK2857916 combination therapy cohorts for this study.	To include GSK2857916 combination therapy cohorts.
4.3. Justification for Dose	Added Section 4.3.2 to provide justification for dose for Part 2.	To include GSK2857916 combination therapy cohorts.

Section # and Name	Description of Change	Brief Rationale
4.4. End of Study Definition	Added the definitions of study completion and study withdrawal.	To clarify the definition of completion of study treatment and withdrawal of study treatment.
5.1. Inclusion Criteria #4	Revised the requirement for prior therapy.	To expand target population for Part 2.
5.1. Inclusion Criteria #7	Updated the duration of contraception and of refraining from donating eggs for female participants in Part 1. Added the requirement of pregnancy test and the duration of contraception and of refraining from donating eggs for female participants for Part 2.	To align with FDA guidance "Oncology Pharmaceuticals Reproductive Toxicity and Testing recommendations" and considering the half-life of GSK2857916.
5.1. Inclusion Criteria #8	Updated the duration of contraception and of refraining from donating sperm for male participants. Updated the contraceptive requirement for male participants including those who have undergone a successful vasectomy to use a male condom.	To align with FDA guidance "Oncology Pharmaceuticals Reproductive Toxicity and Testing recommendations" and considering the half-life of GSK2857916.
5.1. Inclusion Criteria #9	Revised to enroll participants with Grade 2 peripheral neuropathy only into Part 1 and Part 2 Arm B.	To include GSK2857916 combination therapy cohorts.
5.1. Inclusion Criteria #10	Added Table 10: Criteria for Determining Adequate Organ System Function for Part 2	To provide the criteria of adequate organ system functions for Part 2.
5.2. Exclusion Criteria	Added #22 to #24 as Part 2 Arm A-specific exclusion criteria. Added #25 to #27 as Part 2 Arm B-specific exclusion criteria.	To include GSK2857916 combination therapy cohorts.

Section # and Name	Description of Change	Brief Rationale
5.3. Lifestyle Considerations 11.7. Appendix 7: Corneal Event Severity Grading and Mitigation Strategy	Updated the period of prohibiting contact lenses. Added the possibility of restarting contact lens use. Allowed bandage contact lenses during the study treatment.	To clarify lifestyle considerations.
5.3. Lifestyle Considerations	Added restrictions of blood donation for Part 2 Arm B participants.	To update lifestyle considerations due to combination with Bor/Dex or Pom/Dex.
6. Study Treatment	Added Table 12: Study Treatments Administered for Part 2 Added Section 6.2 to describe the treatments administered for Part 2.	To include GSK2857916 combination therapy cohorts.
6.1. GSK2857916 Treatments Administered for Part 1	Added how to calculate the actual dose of GSK2857916.	To simplify the structure of this protocol.
6.5. Study Treatment Compliance	Added how to assess study treatment compliance for self-administered oral study treatments at home.	Participants in Part 2 will receive study treatments orally at home.
6.6 Concomitant Therapy	Added the requirement of recording concomitant medications for serious AEs and AEs of special interest (AESIs).	To clarify the requirement of recording concomitant medications.
6.6.1. Permitted Medications	Added recommendation of thromboprophylaxis for participants treated with pomalidomide, herpes zoster prophylaxis, and prophylactic treatment for tumor lysis syndrome.	To add recommendation due to combination with Bor/Dex or Pom/Dex.

Section # and Name	Description of Change	Brief Rationale
6.6.2. Prohibited Medications	Added live or live-attenuated vaccines as a prohibited therapy for Part 2.	Addition of wording due to language associated with dexamethasone.
	Added prohibited medications for participants treated with pomalidomide or bortezomib.	To include GSK2857916 combination therapy cohorts.
6.7. Dose Modification and Delay	Added Section 6.7.1 to describe the detailed guideline of dose modification and delay for Part 1.	To simplify the structure of this protocol.
	Added Section 6.7.2 and Section 6.7.3 to provide dose modification and delay guidelines for Part 2.	To include GSK2857916 combination therapy cohorts.
6.7.4 Corneal Supportive Care Guidelines	Updated the frequency of ocular examinations.	To make the statement suitable for Part 2 Arm B.
7. Discontinuation of Study Treatment and Discontinuation/ Withdrawal	Added Section 7.1.1 to clarify the stopping criteria of each component of combination study treatment in Part 2.	To include GSK2857916 combination therapy cohorts.

Section # and Name	Description of Change	Brief Rationale
7.1.2. Liver Chemistry Stopping Criteria 7.1.2.1. Study Treatment Restart or Rechallenge after Liver Stopping Criteria Met 11.5. Appendix 5 Liver Safety: Required Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines 11.5.1.1. Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment 11.5.1.2. Restart Following Transient Resolving Liver Stopping Events Not Related to Study Treatment	Reflected the latest liver language template.	To reflect the liver language template update.
8. Study Assessments and Procedures	Updated visit window of pregnancy test, bone marrow archival tissue, and each study visit's assessments.	To include GSK2857916 combination therapy cohorts and to add clarity.
8.1. Efficacy Assessments	Updated the frequency of serum and urine-based assessments (M-protein, free light chain, immunofixation).	To make the statement suitable for Part 2 Arm B.

Section # and Name	Description of Change	Brief Rationale
8.2.7. Clinical Safety Laboratory Assessments	Updated the period to perform repeated laboratory tests for parameters with values considered clinically significantly abnormal.	
8.3.1. Time Period and Frequency for Collecting AE and SAE Information	Updated the period to collect non-serious and serious AEs.	
8.3.5. Adverse Events of Special Interest	Updated how to assess severity of corneal events and other AESIs	Corneal events will be assessed using National Cancer Institute-Common Toxicity Criteria for Adverse Events and GSK scale.
8.3.6. Pregnancy	Updated the pregnancy test and the follow-up period of pregnancy assessment for Part 1. Added the pregnancy test and the follow-up period of pregnancy assessment for Part 2.	To align with FDA guidance "Oncology Pharmaceuticals Reproductive Toxicity and Testing recommendations" and considering the half-life of GSK2857916.
8.3.6. Pregnancy 11.3.3. Collection of Pregnancy Information	Added the period to collect pregnancy information from female participant and male participant's female partner.	To clarify the period to collet pregnancy information in Part 2 and to align with FDA guidance "Oncology Pharmaceuticals Reproductive Toxicity and Testing recommendations" considering the half-life of GSK2857916,
8.4. Treatment of Overdose	A blood sample for [redacted] will also be obtained in the event of an overdose.	PK measurement needs [redacted] concentration.
	Added the information of overdose treatment for pomalidomide, bortezomib, and dexamethasone.	To include GSK2857916 combination therapy cohorts.

Section # and Name	Description of Change	Brief Rationale
8.6. Pharmacodynamics	Revised timing of blood collection for PD analyses.	To add clarity of the window.
	Added Table 32: Timing and Volume of Blood Collection for GSK2857916 Pharmacokinetic and Pharmacodynamic [redacted] Analyses (Part 2 Arm A). Added Table 33: Timing and Volume of Blood Collection for GSK2857916 Pharmacokinetic and Pharmacodynamic [redacted]) Analyses (Part 2 Arm B).	To clarify the sampling time and blood volume for PK and PD analyses of GSK2857916 in Part 2.
8.9. Immunogenicity Assessments	Added the detailed description of immunogenicity assessments and analyses.	To perform immunogenicity assessments in GSK2857916 combination therapy cohorts.
10.1. Statistical Hypotheses	Clarified that statistical analyses will be performed separately for each part and each arm.	To include GSK2857916 combination therapy cohorts.
10.2. Sample Size Determination	Added the planned sample size for Part 2.	To include GSK2857916 combination therapy cohorts.
10.3. Populations for Analyses	Updated the definitions of all treated population and DLT evaluable population. Clarified that each analysis population will be created separately for each part and each arm.	To include GSK2857916 combination therapy cohorts.

Section # and Name	Description of Change	Brief Rationale
10.4. Statistical Analyses 10.4.1 Safety Analyses 10.4.1.1. Extent of Exposure 10.4.2. Efficacy Analyses 10.4.3. Immunogenicity Analyses	Clarified that each statistical analysis will be performed separately for each part and each arm.	To include GSK2857916 combination therapy cohorts.
10.4.4.1 Concentration-Time Data 10.4.4.2 Derived Pharmacokinetic Parameters	Updated the planned analyses of PK parameters of GSK2857916.	To align with the current analysis plan and to include GSK2857916 combination therapy cohorts.
CCI [redacted]		
10.5. Interim Analyses	Added Section 10.5.1 and clarified the data cut-off for Part 1.	To perform interim analysis for Part 1 of this study.
	Added Section 10.5.2 to add interim analyses for Part 2.	To perform interim analyses for Part 2 of this study.

Section # and Name	Description of Change	Brief Rationale
11.7. Appendix 7: Corneal Event Severity Grading and Mitigation Strategy	Made steroid eye drops as prophylaxis for corneal events optional. Added the option to use corticosteroid eye drops as prophylaxis for corneal events optional.	Based on available data from overseas study, steroid eye drops were removed from mandatory prophylactic measures for corneal events.
	Updated how to assess severity of corneal events.	Corneal events will be assessed using National Cancer Institute-Common Toxicity Criteria for Adverse Events and GSK scale.
11.7. Appendix 7: Corneal Event Severity Grading and Mitigation Strategy Table 34	Deleted steroid eye drops as prophylaxis for corneal events associated with GSK2857916.	Based on available data from overseas study, steroid eye drops were removed from mandatory prophylactic measures for corneal events.
11.1.11. Study Period	Deleted the study period.	To move the study period to Exhibit 3.

Amendment 4: 15-JAN-2021

Overall Rationale for the Amendment: This protocol has been amended to address feedback from investigators, to clarify study assessment and procedures, and to reflect administrative change. Additional changes were incorporated to align with program-wide revisions and/or updates.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Changed text of synopsis to reflect changes to the text of the protocol.	See below for all significant changes.
1.3. Schedule of Activities (SoA)	Added Table 4 for additional procedures for participants with a history of Hepatitis B.	In line with program wide update.
1.3. Schedule of Activities (SoA) for Part 2 Arm A	Updated timepoint for 12-lead ECG. Updated footnote 27.	To clarify the timepoint. Administrative changes were made as described.

Section # and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria #4	Revised the requirement for most recent therapy for Part 2.	To ensure consistency in target population with DREAMM-7 / 207503 study and DREAMM-8 / 207499 study.
5.2. Exclusion Criteria #18	Updated exclusion criteria for Hep B+ participants.	In line with program wide update.
6.2.1. GSK2857916 with Bortezomib/Dexamethasone (Arm A) 21-day Cycle	Clarified language regarding dosing schedule for GSK2857916.	To clarify dosing schedule for GSK2857916.
6.2.2. GSK2857916 with Pomalidomide/Dexamethasone (Arm B) 28-day Cycle	Clarified language regarding dosing schedule for GSK2857916.	To clarify dosing schedule for GSK2857916.
6.7.2. Dose Modification and Delay for Part 2 Arm A	Updated dose modification guidelines for adverse events associated with GSK2857916 for Part 2 Arm A. Updated dose modification guideline for GSK2857916 treatment-related corneal events for Part 2. Updated dose delay scenario for GSK2857916.	To align with program level language. In line with program wide update. To clarify dosing schedule for GSK2857916.
6.7.3. Dose Modification and Delay for Part 2 Arm B	Updated dose delay scenario for GSK2857916.	To clarify dosing schedule for GSK2857916.
6.7.4. Management of Hepatitis B+ participants	Added section to clarify management of Hepatitis B+ participants	In line with program wide update.

Amendment 5: 12-NOV-2021

Overall Rationale for the Amendment: This protocol has been amended to clarify the timing and purpose of analyses.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA) Table 3	Added examination points for IgG, IgM and IgA at C2 D1 and C3 to CX D1	Corrected
2.3.1. Human Experience with GSK2857916 2.3.1.3. Pharmacokinetics and Pharmacodynamics in Human	Background information has been amended to be consistent with clarifications and updates made in the most current version of the Investigator Brochure (v9.0).	To align language with the most current version of the Investigator Brochure (v9.0).
2.4.1 Risk Assessment Risks from Study Procedures	Updated the procedure of incidental findings during image acquisition.	To align with program level language.
8.3. Adverse Events and Serious Adverse Events 8.3.1. Time Period and Frequency for Collecting AE and SAE Information	Deleted the description related to post-marketing study.	This study is not applicable.
8.3. Adverse Events and Serious Adverse Events 8.3.3. Follow-up of AEs and SAEs	Deleted the description related to post-marketing study.	This study is not applicable.
8.3. Adverse Events and Serious Adverse Events 8.3.4. Regulatory Reporting Requirements for SAEs	Deleted the description related to post-marketing study.	This study is not applicable.
10. Statistical Considerations	Added the description for primary analysis in Part 1 and for potential interim analysis and primary analysis in Part 2.	To clarify the purpose and timing for analyses.
10.5. Interim Analyses 10.5.1 Part 1 10.5.2. Part 2	Part1: Deleted the description on data cut-off. Part2: Added potential interim analysis.	To clarify the purpose and timing for analyses.

Section # and Name	Description of Change	Brief Rationale
11.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 11.2.4. Recording and Follow-Up of AE and SAE	Deleted the description related to post-marketing study.	This study is not applicable.
11.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 11.2.5. Reporting of SAE to GSK SAE Reporting to GSK via Electronic Data Collection Tool SAE Reporting to GSK via Paper CRF	Deleted the description related to post-marketing study.	This study is not applicable.

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