inside the malignant cell after binding and internalization of the antibody. The normal function of BCMA is to promote cell survival by transduction of signals from two known ligands: B-cell activating factor from the tumor necrosis factor (TNF) family (BAFF/BLyS), and APRIL, a proliferation-inducing ligand.

In addition, preclinical experiments indicate that GSK2857916 has the potential to induce immunogenic cell death (ICD) in a BCMA-expressing multiple myeloma cell line. Exposure of dendritic cells to tumor cells undergoing ICD induces an antigen-specific T cell response, which may help to exert anti-tumor effects.

Preliminary clinical data from the ongoing BMA117159 study as of 26 June 2017 (n=35 participants treated at 3.4 mg/kg) has demonstrated an ORR of 60% [95% CI: 42.1%, 76.1%], (complete response: 6%, very good partial response [VGPR] 43%, partial response [PR] 9%), with 51% of participants (N = 18/35) having deep responses of VGPR or better, in heavily pretreated participants with relapsed/refractory multiple myeloma (RRMM). The median duration of response (DoR) has not been achieved, the 25th percentile for DoR is 6.7 months; the median PFS in this population was 7.9 months [95% CI: 3.1, NA]. The number of prior therapies ranged from 1-13 with 71% of participants reporting greater than or equal to 4 prior therapies. For the 14 (40%) participants who had received prior daratumumab, the ORR was 43%, (95% CI: 17.7%, 71.1%; CR: 0, VGPR: 21%; PR: 14%).

In Study BMA117159, the maximum clinical benefit (ORR) was observed at the 3.4 mg/kg dose level, but a significant number of participants required dose delays and dose reductions to manage adverse events. In order to generate additional safety and efficacy data at a lower dose while providing participants a chance of deriving clinical benefit, the dose of 2.5 mg/kg has been selected for testing in an additional arm in this study. The two-arm design with two dose levels and a futility analysis is justified for this population because there is no approved comparator for the proposed treatment setting.

Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
To evaluate the clinical efficacy of 2 doses of GSK2857916 in participants with relapsed/refractory multiple myeloma.	ORR, defined as the percentage of participants with a confirmed partial response (PR) or better (i.e., PR, very good partial response [VGPR], complete response [CR] and stringent complete response [sCR]), according to the 2016 International Myeloma Working Group (IMWG) Response Criteria by Independent Review Committee (IRC).
Secondary Objectives	
To further evaluate the clinical measures of efficacy of GSK2857916 in participants with RRMM	ORR, defined as the percentage of participants with a confirmed partial response (PR) or better, according to the 2016 International Myeloma Working Group (IMWG) Response Criteria by investigator assessment Clinical benefit rate (CBR), defined as the percentage of participants with a confirmed minimal response (MR) or better according to the 2016 International Myeloma Working Group

Table 1 Schedule of Activities - Screening Assessments

Study Assessments[1]	Screen[1]	Notes
Informed Consent	X	1. 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. Screening Assessment do not need to be repeated on Day 1 of Cycle 1 (C1D1) unless otherwise specified. 2. All related SAEs are to be collected from consent through OS follow-up 3. Screening examination to be performed within 21 days prior to first dose. See Section 9.2.9 for the list of screening ophthalmic exam procedures. 4. Refer to Table 14 for a comprehensive list of clinical laboratory tests that must be collected for all participants. If labs are completed within 72 hours prior to the first dose, this assessment need not be repeated on C1D1 5. Albumin/Creatinine ratios (spot urine from first void) at screening, C1, and every other cycle thereafter (C3, C5, C7) (local labs or central if local not available) 6. Hepatitis: If the participant is hepatitis C virus (HCV) positive by serology, an additional Hep C RNA testing may be done to determine participant eligibility (if Hep C RNA is negative, participant is eligible). 7. Troponin I will be measured at the local lab, or by central laboratory if not available locally. If cardiac workup is required due to safety concerns during the study, troponin I should be measured as clinically indicated. 8. B-type natriuretic peptide (BNP) to be measured locally, or by a central laboratory if not available locally, at screening; if cardiac workup is required due to safety concerns during the study, BNP should be measured as clinically indicated. 9. Perform only in women of child-bearing potential. A serum pregnancy test must be performed at screening, and subsequent pregnancy tests may be either serum or urine. If test is completed within 72 hours prior to the first dose, this assessment need not be repeated on Day 1 of Cycle 1. For questionable cases of whether a participant is of non-child bearing potential, obtain follicle stimulating hormone (FSH) and estradiol. See Section 6.1, Section 9.2.8, and Appendix 5 for more details. 10. Echocardiography for LVEF performed within 35 days prior to first dose is acceptable as screening value. 11. Skeletal Survey: Imaging of bones for lytic lesions by a method aligned with the institutional guidance (ex: X-ray, CT, or MRI). Skeletal survey results within 30 days prior to C1D1 are acceptable. For sites in Germany: Only MRI is allowed to be used as imaging modality for participants. 12. 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
Medical History including disease history and characteristics	X	
Physical Exam	X	
Concomitant Medications	X	
Adverse Events [2]	X	
Safety		
Ocular Exam[3]	X	
ECOG Performance Status	X	
Vital Signs (BP, HR, Body Temperature)	X	
Weight and Height	X	
Hematology[4]	X	
Clinical chemistry[4]	X	
Urine Dipstick[4]	X	
eGFR (by MDRD formula- see Appendix 10)	X	
Spot Urine (albumin/creatinine ratio)[4, 5]	X	
CRP	X	
HBsAg, HBcAb, and hepatitis C Ab. [6]	X	
Troponin I[7]	X	
BNP[8]	X	
Pregnancy Test [9]	X	
ECHO[10]	X	
12-lead ECG	X	

Study Assessments[1]	Screen[1]	Notes
Disease Evaluation		(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). Imaging will be collected for independent review. For sites in Germany: Only MRI is allowed to be used as imaging modality for participants with extramedullary disease. 13. Only required for participants with IgD/E myeloma, where serum m-component cannot be followed otherwise. 14. FISH testing at least for: t (4;14), t (14;16), and 17p13del. FISH results from samples taken within 60 days prior to first dose are acceptable. If testing cannot be performed at a local lab, a bone marrow aspirate can be sent to central lab for analysis. If the patient is known to have high risk disease from previous FISH tests regardless of timing (i.e.: t(4;14), or t(14;16) they should be stratified as High Risk for the purpose of enrollment. 15. Minimal residual disease (MRD) to be performed by the central lab at screening, at the time of first achieving VGPR or CR, repeat MRD testing 6 mo and 12 mo after achieving VGPR or CR (provided VGPR/CR is maintained). 16. Bone Marrow (aspirate preferred) for disease assessment performed within the screening period prior to first dose is acceptable.
Beta2 microglobulin	X	
Skeletal survey[11]	X	
Imaging for Extramedullary disease[12]	X	
UPEP (Urine Protein Electrophoresis) 24 hr. urine collection	X	
Urine immunofixation	X	
SPEP (Serum Protein Electrophoresis)	X	
Serum Immunofixation	X	
Serum Kappa, Lambda free Light chain, FLC ratio	X	
Calcium corrected for albumin (serum)	X	
IgG, IgM, IgA	X	
IgD/E[13]	X	
Bone Marrow (BM) Aspiration/Biopsy		
BM for FISH [14]	X	
BM aspirate for BCMA IHC assessment	X	
BM for MRD testing[15]	X	
BM for disease assessment[16]	X	
Health Outcomes		
PRO-CTCAE	X	
NEI-VFQ-25	X	
OSDI	X	

BM = bone marrow; BNP = B-type natriuretic peptide; BP = blood pressure; C1D1 = Cycle 1 Day 1, etc. CRP = C-reactive protein; FISH = fluorescence in situ hybridization; FLC = free light chain; HR= heart rate; Ig = immunoglobulin; NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire 25; OSDI = Ocular Surface Disease Index; PRO-CTCAE = Patient Reported Outcome version of the Common Term Criteria for Adverse Events; PD = Progressive Disease; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

Study Assessments	**Cycle 1, Day 1[1]**	**Cycle 1 & Cycle 3 Day 4**	**Cycle 1 & Cycle 3, Day 8-15**	**Q3W starting Wk 4[2] (to be performed regardless of dosing)**	**Cycle 2-CX with dosing [2]**	Notes
Pharmacokinetics PK[5,]	X[11]	X[12]	X[13]		X[14]	infusion (EOI), and 1-hour (±5 minutes) post EOI. On subsequent dosing days, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), within ±5 minutes of EOI. On days where vital sign time points align with PK sampling time points, vital signs must be assessed prior to PK samples being drawn. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.
Anti-drug antibodies[5, 15]	X				X	
Disease Evaluation						
Response assessment[16]				X		7. Refer to Table 14 for a comprehensive list of lab tests that must be collected for all participants. If labs are completed within 72 hours prior to the first dose, this assessment need not be repeated on C1D1.
Skeletal Survey [17]				As clinically indicated		
Imaging for Extramedullary disease[18]				Week 13, 25, 37, 49, and then every 12 weeks within the first 12 months; thereafter only if clinically indicated		8. Albumin / creatinine ratios (spot urine from first void) at, C1, and every other cycle thereafter (C3, C5, C7, etc.) (use local labs; use central labs if local not available) 9. Perform only in women of child-bearing potential. A serum pregnancy test must be performed at screening, and subsequent pregnancy tests may be either serum or urine. If test is completed within 72 hours prior to the first dose, this assessment need not be repeated on C1D1. For questionable cases of whether a participant is of non-child bearing potential, obtain follicle stimulating hormone (FSH) and estradiol. See Section 6.1, Section 9.2.8, and Appendix 5 for more details.
PET/CT upon achieving CR or sCR[19]				Once after CR or sCR		10. ECGs on dosing days: Triplicate ECGs to be performed at predose (within 30 minutes prior to SOI) and EOI (within 5 minutes prior to EOI) at cycles 1, 2, 3, 6, 9 and 12. Additional triplicate ECGS to be performed at 24 h ± 2h after SOI on Day 1 of Cycle 1 and Cycle 3 and on Day 4 (±1 day) and on any day from Day 8 to Day 15 in Cycle 1 and Cycle 3. Single ECGs predose at all other cycles.
UPEP (Urine Protein Electrophoresis) 24 hr. urine collection				X		ECG recordings should be made after at least 10 minutes rest and collected 2 minutes apart. On days where ECG time points align with PK sampling time points, ECGs must be performed prior to PK samples being drawn. ECGs on Day 4 and Day 8-15 in Cycle 1 and Cycle 3 should

Study Assessments	EOT Visit[1]	PFS Follow-up[2]	OS Follow-Up[3]	Notes
Imaging for Extramedullary disease[11]	X [12]	Every 12 weeks if clinically indicated		7. Refer to Table 14 for a comprehensive list of lab tests that must be collected for all participants. Only serum creatinine is required at PFS visits (not a full chemistry) 8. Perform only in women of child-bearing potential. For questionable cases of whether a participant is of non-child bearing potential, obtain follicle stimulating hormone (FSH) and estradiol. See Section 6.1, Section 9.2.8, and Appendix 5 for more details. Final pregnancy test (serum or urine) must be performed in women of childbearing potential 80 days (+7 days) after last study treatment. 9. Single ECG required at End of Study. On days where ECG time points align with PK sampling time points, ECGs must be performed prior to PK samples being drawn. ECGS will be collected and stored centrally. 10. For participants who are discontinuing IP due to PD the confirmation must be performed from a different blood collection within 14 days of the original disease progression, preferably before institution of any new anti-myeloma therapy. This may be performed at the EOT visit. 11. Imaging is only required for participants with extramedullary disease (CT, MRI, or PET/CT can be applied per local guidance). 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). Imaging will be collected for independent review. 12. If the last radiographic assessment occurred ≥8 weeks prior to the participant's withdrawal from study treatment, and PD has NOT been documented, –a new assessment for extramedullary disease should be obtained at EOT. If participant continues in PFS follow-up, perform scans
PET/CT upon achieving CR or sCR[13]	Once after CR or sCR declared	Once after CR or sCR declared		
UPEP (Urine Protein Electrophoresis) 24 hr. urine collection	X	X		
Urine immunofixation (Central lab)	By central lab if UPEP is negative, at the time of first achieving CR then perform every 21 days (± 7 days) until suspected PD after CR or sCR.	By central if UPEP is negative, at the time of first achieving CR then perform every 21 days (± 7 days) until suspected PD after CR or sCR.		
SPEP (Serum Protein Electrophoresis)	X	X		
Serum Immunofixation	By central lab if SPEP is negative, at the time of first achieving CR then perform every 21 days (± 7 days) until suspected PD after CR or sCR.	By central lab if SPEP is negative, at the time of first achieving CR then perform every 21 days (± 7 days) until suspected PD after CR or sCR.		
Serum Kappa, lambda free LC, FLC ratio	X	X		
Calcium corrected for albumin (serum)	X	X		
IgG, IgM, IgA	X	X		
IgD/E[14]	X	X		
Bone Marrow (BM) Aspiration/Biopsy				
BM for MRD testing[15]		X		
BM for disease assessment	Only if CR has been achieved by this visit, or suspected PD not evident otherwise	Only if CR has been achieved by this visit, or suspected PD not evident otherwise		

3. INTRODUCTION

Multiple myeloma (MM) is an incurable malignancy and accounts for 1% of all cancers and for 10% of all hematologic malignancies. Worldwide, approximately 103,000 new cases are diagnosed annually, and an estimated 30,330 new cases and 12,650 deaths will occur in the US in 2016 [Siegel, 2016]. There have been significant advances in treatment for MM, including novel therapies like second and third -generation proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and recent addition of monoclonal antibodies (mAbs). Those advances have contributed to incremental gains in PFS and OS, but most MM patients still relapse and ultimately develop resistance to existing therapies. Therefore, there is an urgent need to develop treatments with novel MOA which could potentially prevent the cross resistance to existing therapies [Kumar, 2004]. Details of the characteristics of GSK2857916, nonclinical, and clinical activity are provided in the Investigator's Brochure (IB) [GSK2857916 GlaxoSmithKline Document Number 2013N175128_04].

3.1. Study Rationale

Before the introduction of daratumumab, patients with disease that is refractory to both immunomodulatory drugs and proteasome inhibitors (PIs) had a median overall survival (OS) ranging from 9 months [Kumar, 2012] to 12 months [Kumar, 2004; Kumar, 2003].

Daratumumab [DARZALEX, 2017], is a human IgG*k* monoclonal antibody that 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% ORR and mPFS 3.7 months in patients with relapsed or refractory multiple myeloma. The median number of prior lines of treatment reported in this study was 5.

Later, daratumumab has been approved in combination with lenalidomide/dexamethasone, bortezomib/dexamethasone for patients who were previously treated with at least one prior line, and in combination with pomalidomide and dexamethasone for patients previously treated with at least 2 prior lines [DARZALEX, 2017; Janssen-Cilag International NV, 2016].

While the data with daratumumab indicate that further prolongation of PFS can been 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. Patients with MM who relapse after daratumumab therapy, have few treatment options available and could benefit from treatment with a novel drug such as GSK2857916.

GSK2857916 is a first in class, ADCC enhanced, humanized immunoglobulin G1 (IgG1) antibody-drug conjugate (ADC) that binds specifically to B-cell maturation antigen (BCMA), a target present on mature B cells and on tumor cells in patients with MM [Tai, 2015; Tai, 2006]. The antibody is conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF), and is produced as an afucosylated form that generates an enhanced antibody-dependent cellular cytotoxicity (ADCC) response. As demonstrated

In Part 2, there were no serious corneal events and no participants permanently discontinued study treatment due to a corneal event. In Part 1, there was one SAE of Grade 3 limbal stem cell deficiency (in a participant at the 1.92 mg/kg dose) that was characterized by blurred vision and dry eyes. The events resolved after treatment was discontinued, and the participant's vision returned to baseline. Another participant in Part 1 (4.6 mg/kg) discontinued treatment due to the feeling of a foreign object in the eye (Grade 2). The mean time to onset of corneal AEs was 28 days after first dose for Part 2 MM; most participants developed events within 42 days of first dose though 20% of those who reported these events developed them after Day 43.

In addition to the AEs describing corneal events, 89% of participants in Part 2 had corneal findings upon examination. These findings were generally characterized by a superficial punctate keratopathy/keratitis which was often associated with epithelial (microcystic) edema and occasional stromal edema or opacities. Visual acuity declined during treatment in most participants experiencing these clinical findings, but improved on average to near baseline in participants completing end of study treatment visits (n=13). Eleven of these 13 participants (84.6%) had corneal clinical signs at the end of study treatment visit, with most cases (9/11 or 81.8%) considered as having "mild" changes.

3.4.3. Pharmacokinetics

The pharmacokinetics of GSK2857916 (antibody-drug conjugate), the parent antibody, total antibody (including the complex), and cys-mcMMAF were investigated in 70 participants after IV administration at doses of 0.03 to 4.60 mg/kg in a preliminary analysis. Maximum concentrations of GSK2857916, parent antibody, and total antibody were observed at end of infusion (EOI), whereas maximum cys-mcMMAF concentrations peaked approximately 24 hours after dosing. There was limited accumulation of GSK2857916 or cys-mcMMAF during subsequent cycles.

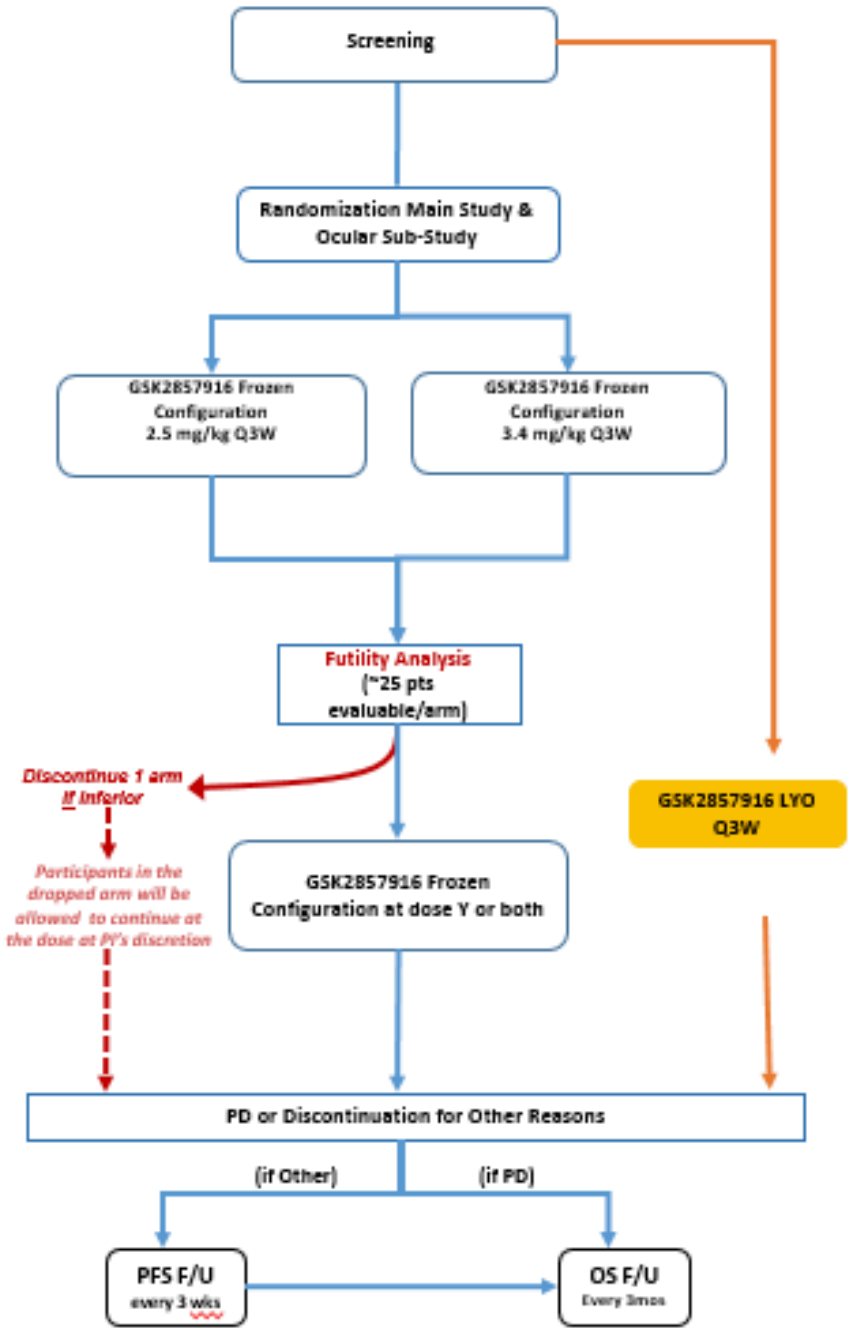
The pharmacokinetics of GSK2857916 were linear over the range of doses tested, with exposure of all analytes increasing proportionately with increasing dose, and were well-described in a preliminary population PK analysis using conventional allometry. Total plasma clearance of GSK2857916 was 0.37 L/day, and the mean steady-state volume of distribution was 4.2 L. The model-predicted terminal phase elimination half-life of GSK2857916 was 8.2 days (95% CI: 6.4 to 10.1), in keeping with the log-linear model estimate (8.7 days). On a molar basis, the levels of cys-mcMMAF were <1% of GSK2857916, and the half-life of free cys-mcMMAF was <2 hours.

3.4.4. Clinical Activity

Preliminary clinical data from the ongoing BMA117159 study as of 26 June 2017 (n=35 participants treated at 3.4 mg/kg) has demonstrated an ORR of 60% [95% CI: 42.1%, 76.1%], (complete response: 6%, very good partial response [VGPR] 43%, partial response [PR] 9%), with 51% of participants (N = 18/35) having deep responses of VGPR or better, in heavily pretreated participants with relapsed/refractory multiple myeloma (RRMM). The median duration of response (DoR) has not been achieved, the 25th percentile for DoR is 6.7 months; the median PFS in this population was 7.9 months [95% CI: 3.1, NA]. Although no responses were observed at the 2.5 mg/kg dose in Study

Objectives	Endpoints
	better. Time to response, defined as the time between the date of randomization and the first documented evidence of response (PR or better). Progression-free survival, defined as the time from randomization until the earliest date of documented disease progression (PD) per IMWG, or death due to any cause. Time to progression, defined as the time from randomization until the earliest date of documented PD per IMWG, or death due to PD. Overall survival, defined as the time from randomization until death due to any cause.
To evaluate the safety of GSK2857916 in participants with RRMM.	The safety profile of GSK2857916 will be evaluated in participants with RRMM as assessed through: standard clinical and laboratory tests (hematology and chemistry, physical examination, vital sign measurements, and diagnostic tests) through the collection of adverse events (AEs) and serious adverse events (SAEs) AEs of special interest ocular findings on ophthalmic exam
To evaluate the pharmacokinetic profile of GSK2857916	Plasma concentrations of GSK2857916 (ADC, total mAb, and cys-mcMMAF) Derived pharmacokinetic parameter values (e.g., AUC, Cmax, tmax, t½), as data permit.
To assess anti-drug antibodies (ADAs) against GSK2857916	Incidence and titers of ADAs against GSK2857916
Participant self-reported symptomatic adverse effects by evaluation of tolerability of GSK2857916	Symptomatic adverse effects and related impacts as measured by the PRO-CTCAE, NEI-VFQ-25 and OSDI
To evaluate disease and treatment related symptoms and impact on function and health-related quality-of-life	Health-related quality-of-life as measured by the EORTC QLQ-C30 and EORTC QLQ-MY20
Exploratory Objectives	
To explore the relationship between clinical response and other biologic characteristics including BCMA expression on tumor cells and sBCMA concentrations	Determine BCMA expression levels and other markers on malignant cells, serum sBCMA levels, and evaluate the relationship of these factors to clinical response
To investigate the relationship between genetic variants in the host and response to GSK2857916	Possible relationship between host genetic variation and response to GSK2857916
To evaluate disease and treatment related symptoms and impact on function and health-related quality-of-life	Qualitative telephone interview(s)
To explore exposure-response relationships between GSK2857916 exposure and clinical endpoints	Explore relationships between GSK2857916 exposure (e.g., dose, dose intensity, concentration, Cmax, or AUC) and clinical endpoints (e.g., response, corneal event), if data permit
To assess Minimal Residual Disease (MRD) in participants who achieve ≥VGPR or better	Minimal Residual Disease (MRD) negativity rate, defined as: the percentage of participants who are MRD negative by Next Generation Sequencing (NGS).
To assess the safety, efficacy, immunogenicity, and pharmacokinetics of GSK2857916 in a lyophilized configuration (approximately 25 participants)	AEs, clinical and laboratory assessments; descriptive analyses of ORR, duration of response, time to response, time to progression, overall response; incidence and titers against GSK2857916; plasma concentrations of GSK2857916 (ADC, total mAb, and cys-mcMMAF)

Figure 1 Study 205678 Schematic



Abbreviations: OS = overall survival; PD = progressive disease; PFS = progression-free survival; F/U = follow-up; lyo = lyophilized; DP = drug product; pts = participants.

The two-arm design with two dose levels and a futility analysis is justified for this population because there is no approved comparator for the proposed treatment setting. In Study BMA117159, the maximum clinical benefit (ORR) was observed at the 3.4 mg/kg dose level, but a significant number of participants required dose delays and dose reductions. At lower dose levels, the results were variable, with wide confidence intervals. In order to generate additional safety and efficacy data at a lower dose while providing participants a chance of deriving clinical benefit, the dose of 2.5 mg/kg has been selected for additional testing (see Section 5.5 for dose justification).

This design is appropriate for the selected patient population, since there is no approved standard of care in patients failing daratumumab. As shown in earlier studies on a similar population, the response rate is low and the mPFS is short in those patients. For example, in the pomalidomide + dexamethasone (PomDex) vs pomalidomide (Pom) study that enrolled patients with median of 5 prior lines, among whom 61% have been refractory to the mainstay of treatment, lenalidomide and bortezomib had an ORR of 18%, and mPFS of 2.7 months on Pom monotherapy arm [Richardson, 2013]. A similar Phase3 study of Pom with low dose dexamethasone (Pom/loDex) vs high dose dexamethasone (HiDex) has demonstrated an ORR of 3.9%, mPFS of 1.8 months, and mOS of 8 months in the HiDex arm where patients had a median of 5 prior lines, and 74% of them were double refractory to lenalidomide and bortezomib [Weisel, 2013].

Further, a randomized, phase III study which compared carfilzomib monotherapy against low-dose corticosteroids and optional cyclophosphamide in relapsed and refractory multiple myeloma has demonstrated an ORR of 11%, and OS of 10 months in populations previously treated with 5 lines of therapy and 63% of patients were double refractory to bortezomib and IMiD [Hájek, 2017]. In summary, these examples provide indirect evidence that the prognosis of patients eligible for this protocol is poor, and that selected threshold for claiming success (33%) is appropriate since it doubles the expected ORR for those patients when treated with available agents.

5.5. Dose Justification

GSK2857916 is currently being studied in the Phase I FTIH study, BMA117159. As of the clinical cut-off date of 26 June 2017, a total of 73 participants with RRMM have received at least 1 dose of GSK2857916.

Participants in Study BMA117159 were enrolled into the dose-escalation phase of the study (Part 1) at the following dose levels: 0.03 mg/kg (n=1), 0.06 mg/kg (n=1), 0.12 mg/kg (n=4), 0.24 mg/kg (n=4), 0.48 mg/kg (n=4), 0.96 mg/kg (n=3), 1.92 mg/kg (n=4), 2.50 mg/kg (n=8), 3.40 mg/kg (n=3), and 4.60 mg/kg (n=6). Based on the data from Part 1 of the study, 35 participants were treated in the Dose Expansion portion (Part 2) at 3.4 mg/kg Q3W.

Clinical activity in Study BMA117159
Clinical activity at the tested dose levels in Part 1 is summarized in Table 7. There were no dose-limiting toxicities (DLTs) observed during dose escalation; however, there was limited tolerability of the 4.6 mg/kg dose (prolonged fever, headache, severe fatigue).

Table 8 Summary of Predicted Mean Response and Mean ≥Grade 2 Corneal Event* and 95% Credible Intervals (Parts 1 and 2, Study BMA117159)

Dose (mg/kg)	Predicted response rate (%) (95% credible interval)	Predicted ≥G2 corneal AE rate (%) (95% credible interval)
1.92	25.3 (9.4, 42.2)	33.7 (18.3, 49.0)
2.5	37.0 (22.3, 51.6)	43.4 (30.2, 56.9)
3.4	53.7 (40.3, 66.9)	55.7 (42.3, 68.7)

*Predicted values are based on the posterior distribution of response rate and corneal event rate per CTCAE 4.03

In summary, based on the safety, tolerability, and clinical activity observed to date, 2.5 mg/kg and 3.4 mg/kg were selected as the appropriate dose levels of GSK2857916 to be further studied in this phase 2 study. The dose may be further individually adjusted in participants experiencing adverse events, according to the guidance in the protocol.

6. STUDY POPULATION

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

6.1. 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, 18 years or older (at the time consent is obtained)
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 (Appendix 8)
4. Histologically or cytologically confirmed diagnosis of MM as defined according to IMWG, [Rajkumar, 2014] criteria, and

    a) Has undergone stem cell transplant or is considered transplant ineligible, and

    b) Has failed at least 3 prior lines of anti-myeloma treatments, including an anti-CD38 antibody (e.g., daratumumab) alone or in combination, and is refractory to an IMiD (i.e., lenalidomide or pomalidomide), and to a proteasome inhibitor (e.g., bortezomib, ixazomib or carfilzomib). The number of prior lines of therapy will be determined according to the guidelines in Rajkumar, 2015.

    Refractory myeloma is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve at least minimal response or development of progressive disease (PD) while on therapy [Rajkumar, 2011]

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 FLC assay: Involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum free light chain 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(s)
   c. participant meets the remainder of the eligibility criteria outlined in this protocol
7. Adequate organ system functions as defined in Table 9.

Table 9 Criteria for Determining Adequate Organ System Function

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[a] Spot urine (albumin/creatinine ratios (spot urine)	≥30 mL/min/ 1.73 m^2 <500 mg/g (56 mg/mmol)
Cardiac	
LVEF (Echo)	≥45%

a. As calculated MDRD equation (Appendix 10)
Note: Laboratory results obtained during Screening must be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may retest the participant and the subsequent within range screening result may be used to confirm eligibility.

8. Female Participants: Contraceptive use by men or 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

   - 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 intervention period and for at least 80 days after the last dose of study

Toxicity	Grade/description of toxicity	Recommendations for GSK2857916
		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 nephrotoxicity 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 12 General Dose Modification and Management Guidelines for Drug-related Adverse Events Not Otherwise Specified[a]

Severity	Management	Follow-up
Grade 1	• Administer symptomatic treatment as appropriate • Continue study drug(s)[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% If recovery takes >3 weeks- consult GSK MM • 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 G1 or less. Consider dose reduction. Consider consultation with GSK MM. Exceptions: Participants who develop G3 toxicities which respond to standard treatment and resolve to ≤G1 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 MM it is agreed that benefits outweigh the risks for a given participant

a. Treatment-related decisions can be made based on local laboratory results if central results are not available or delayed.
b. In case a dose is delayed, the participant should wait for the next scheduled dose to resume treatment.

Table 13 Dose Modification Guidelines for GSK2857916 Treatment-Related Corneal Events

	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. If visual acuity **and** exam findings are **both** Grade 2, **HOLD** GSK2857916. • Upon improvement of either visual acuity or ophthalmic exam findings to Grade 1 or baseline, resume with 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 1.92 mg/kg) In case of recurring ≥Gr3 events, consult GSK Medical monitor	Stop treatment with GSK2857916. 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, the GSK Medical Monitor and possibly a GSK ophthalmologist *or optometrist, if an ophthalmologist is not available
Corneal Management Care Regardless of Grade[b]	**Steroid Eye Drops:** • If symptoms occur within the 7-day steroid eye drop prophylaxis window, increase the frequency to 1 drop every 2-4 hours (6-12 times daily) and continue until symptom resolution. • If symptoms occur after the 7-day prophylaxis window is complete, re-start ocular steroid drops at 4x daily until symptom resolution. **Preservative-free artificial tears**: • Increase to 1 drop as frequently as every 2 hours, as needed			

a. See Appendix 9 for GSK Scale for GSK2857916 Corneal Events

b. In the sub-study of approximately 30 participants will receive monocular topical corticosteroids for the first 4 cycles, (or every 3 weeks in the case of dose delays) treatment of both eyes (in case of worsening symptoms in the untreated eye) with topical corticosteroids will be at the discretion of the Investigator.

7.2.3. Corneal Supportive Care Guidelines

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 GSK corneal event scale and prophylactic measures are in Appendix 9.

Sites are required to establish a close collaboration with an ophthalmologist (or optometrist, if an ophthalmologist is not available) who will be responsible for assessing participants and managing those who develop a corneal event in close communication with GSK Medical Monitor and possibly a GSK ophthalmologist.

Participants will be assessed by ophthalmologists (or optometrist, if an ophthalmologist is not available) at baseline and every three weeks. If there are no corneal events at time of the Cycle 4 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 (or optometrist, if an ophthalmologist is not available). 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 for corneal events present at end of study will continue to be followed at 3 and 6 weeks after the EoT visit and then every 6 weeks for up to 12 months, or until full resolution of ophthalmic changes, or deemed clinically stable by an ophthalmologist/optometrist, whichever comes first.

At the selected sites, participants in the ocular sub-study will undergo additional ophthalmic exams (see Section 9.2.10).

7.3. Method of Treatment Assignment

The Sponsor will supply a range of unique numbers to each site and participants eligible for enrolment will be assigned a unique Participant Number by the site.

Before the study is initiated, log-in directions for the central Interactive Response Technology (IRT) system will be provided to each site to be used to for study drug supply.

Participant numbers are unique will not be reassigned to another participant if a participant assigned a number is found to be a Screen Failure.

Participants will be assigned to study treatment in accordance with the randomization schedule.

Participants will be identified by a unique participant number that will remain consistent for the duration of the study.

Upon completion of all the required screening assessments, eligible participants will be registered into the Registration and Medication Ordering System (RAMOS), the GSK

- Increase of QTcF by ≥60 msec from baseline

  Based on average QTcF value of triplicate electrocardiograms (ECGs) to include manual over-read. For example, 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 minute) recording period.

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

8.2.4. Left Ventricular Ejection Fraction (LVEF) Stopping Criteria

Echocardiography must be performed at Screening. 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 GSK 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 re-challenge, 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.

8.2.5. Corneal Event Stopping Criteria

All GSK2857916 dose modifications and stopping criteria are to be based on the GSK Scale for GSK2857916 Corneal Events (Appendix 9). Corneal events will be graded according to both CTCAE criteria for eye disorders (see Section 9.2) and the guidelines provided in Appendix 9. The treating physician or ophthalmologist (or optometrist, if an ophthalmologist is not available) must discuss the participants who develop a Grade 4 corneal event according to the GSK scale with the GSK Medical Monitor or a GSK ophthalmologist to determine whether the participant can be allowed to restart treatment

with GSK2857916 or whether GSK2857916 should be permanently discontinued. The decision will be documented in study files, together with individual assessment of risk-benefit. For details on re-start guidance (Table 13).

8.2.6. Infusion-Related Reaction Management and Stopping Criteria

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

IRRs should be managed by guidelines provided in Table 11. A participant that experiences a Grade 4 IRR should be permanently withdrawn from the study.

8.2.7. 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 treatment.

8.3. 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.

8.4. Lost to Follow Up

The following actions must be taken in relation to a participant who fails to attend the clinic for a required study visit:

- The site must attempt to contact the participant and re-schedule the missed visit as soon as possible.
- The site must counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to continue or if the investigator believes that the participant should continue in the study.

- Survival follow-up can be conducted by phone call.
- Baseline disease assessments must be completed with 21 days prior to dosing start unless otherwise specified. Refer to SOA.
- 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.
- Pregnancy testing must be completed within 72 hours prior to first dose.
- ECHO must be completed within 35 days prior to first dose.
- Imaging must be completed within 30 days prior to first dose.
- On-study visits have a ±3-day window
- PFS follow-up visits have a ±7-day window.
- Survival follow-up visits have a ±14-day window.

- Bone marrow (aspirate preferred) at screening and to confirm CR. Additional BM testing for MRD testing in case of VGPR or CR is achieved, and BM biopsy for immunohistochemistry (IHC) to confirm sCR.
- Imaging of extramedullary disease (in participants with extramedullary disease)
  - Germany: Only MRI is allowed to be used as imaging modality for participants with extramedullary disease.
- PET/CT is required upon achieving CR or sCR
  - Germany: no PET/CT to confirm CR or sCR will be performed until approval by the German Federal Office for Radiation Protection until further notice.
- Skeletal surveys at screening
  - Germany: Only MRI is allowed to be used as imaging modality of bones for lytic lesions.

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 every 3 weeks. Details for the preparation and shipment of samples for central laboratory assessments will be provided in the SRM.

In participants with extramedullary myeloma, 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 must be performed as described in the SOA (Section 2).

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.

For participants who are discontinuing IP due to PD the confirmation must be performed from a different blood collection performed either on the same day, or within 14 days of the original disease progression, preferably before initiation of any new anti-myeloma therapy.

The assessments may be performed during End of Treatment Visit (Table 3) for the Schedule of Activities of anti-cancer activity

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.

considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

- 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 4.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.3. 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 clinical interest, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.4). Further information on follow-up procedures is given in Appendix 4.

9.2.4. 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, Institutional Review Boards (IRB)/Independent Ethics Committees (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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. 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 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) 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 CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information must be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

9.2.6. Disease-Related Events and/or Disease-Related

Disease progression does not need to be reported as a serious adverse event (SAE). Death due to disease under study is to be recorded on the Death electronic case report form (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.

9.2.7. Adverse Events of Special Interest

Adverse events of special interest (AESI) for GSK2857916 are corneal events, thrombocytopenia and infusion related reactions. The severity of all AESI will be graded utilizing the National Cancer Institute- Common Toxicity Criteria for Adverse Events. Severity of corneal events will also be graded using the GSK scale for corneal events provided in Table 22. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in Table 11. Dose modifications for GSK2857916 corneal events will be based on the GSK scale for corneal events in Table 22.

9.2.8. 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 is of childbearing potential, she must have a serum β-human chorionic gonadotropin (β –HCG) pregnancy test performed within 72 hours prior to the first dose of study treatment. Participants with positive pregnancy test result must be excluded from the study. Participants with negative pregnancy test result must agree to use an effective contraception method as described below during the study until 80 days following the last dose of study treatment.

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until approximately 80 days.
- If a pregnancy is reported, the investigator must inform GSK within 24 hours of learning of the pregnancy and must follow the procedures outlined in Appendix 5.

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAE.

9.2.9. 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 exam
5. Extraocular muscle movements (graded from one to four with (+) sign indicating over action, (-) sign indicating under action and 0 representing normal movements
6. Tear film examination: Schirmer's test with anesthesia and tear breakup time
7. Intraocular pressure measurement & time checked
8. Full anterior segment examination including fluorescein staining of the cornea:
9. Anterior segment exam (slit lamp) includes: orbit/lids/adnexa, conjunctiva, sclera, cornea, anterior chamber, iris, lens and anterior vitreous
10. Anterior segment photography of a fluorescein stained cornea
11. Dilated funduscopic exam: fundus photography with interpretation.
12. Pachymetry

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 ophthalmic visit should also include anterior segment photography of a fluorescein stained cornea. Representative images will be collected and stored centrally.

The *end of study treatment visit* ophthalmic exam should match the *baseline (screening)* exam.

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

9.2.10. Ocular Sub-Study Examinations

Refer to Table 4 for the schedule of assessments for ocular sub-study of participants

Although ocular corticosteroids have been used in both published studies (Tannir, 2014; Moskowitz, 2015; Thompson, 2015; Reardon, 2016; Macsai, 2016) and BMA117159 to ameliorate the frequency and severity of MMAF-associated corneal events, this has yet to

participant. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

9.4.3.1. First Infusion

Monitoring intervals: Vital signs must be monitored at designated time points related to drug infusion as specified in the Schedule of Activities (Section 2). 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.

9.4.3.2. Subsequent Infusions

Monitoring intervals: Vital signs must be monitored at designated time points related to drug infusion as specified in the Schedule of Activities (Section 2). Participants may be discharged after the infusion has been completed if considered clinically stable and all other study procedures have been completed.

9.4.4. Electrocardiogram

12-lead electrocardiogram (ECGs) must be obtained in triplicate at designated time points specified in the Schedule of Activities (Section 2). 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 10-minute rest.

At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicate ECGs should be completed in 4 minutes or less.

The QT interval must be corrected for heart rate by Fridericia's formula (QTcF). Refer to Section 8.3 for QTc withdrawal criteria. Refer to the SRM for details regarding ECG procedures.

9.4.5. Echocardiogram

Echocardiograms (ECHOs) must be performed at baseline to assess cardiac ejection fraction for the purpose of study eligibility, as specified in the SOA. The evaluation of the echocardiographer must include an evaluation for left ventricular ejection fraction (LVEF). If an ECHO is performed on study the results must be documented in the e-CRF.

9.4.6. Laboratory Assessments

All protocol-required laboratory assessments, as defined in Table 14, must be performed according to the SOA (Section 2). Details for the preparation and shipment of samples for central laboratory assessments will be provided in the SRM.

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 that are significantly abnormal during participation in the study or within 45 days after the last dose of study treatment must be repeated until the values return to normal or baseline.

If such values do not return to normal within a period judged reasonable by the investigator, the etiology must be identified and the sponsor notified.

Hematology, clinical chemistry, urinalysis, and additional parameters to be tested are listed, with detailed instructions and timing, in the SRM.

9.4.7. Patient-Reported Outcome Version of the Common Term Criteria for Adverse Events (PRO-CTCAE)

The Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a patient-reported outcome measure developed to evaluate symptomatic toxicity in patients on cancer clinical trials [Basch, 2014]. The PRO-CTCAE was designed to be used as a companion to the Common Terminology Criteria for Adverse Events (CTCAE), the standard lexicon for adverse event reporting in cancer trials. The PRO-CTCAE includes an item library of 124 items representing 78 symptomatic toxicities drawn from the CTCAE. PRO-CTCAE provides a systematic yet flexible tool for descriptive reporting of symptomatic treatment side effects in cancer clinical trials. In the present study, a sub-study of items selected from the PRO-CTCAE Version 1.0 Item library will be administered. The PRO-CTCAE will be administered to participants in different regions based on the availability of translated versions.

9.4.8. Visual Function Questionnaires

The impact of potential ocular toxicity on function and health-related quality-of-life will be assessed with the use of two visual function questionnaires, the NEI-VFQ-25 and OSDI. All participants will use the Self-Administered version of the questionnaires, unless their vision prevents them from being able to complete the questionnaire on their own. Participants who are not able to complete the questionnaire on their own and require assistance must use an Interviewer Administered format. If the Interviewer Administered format is being used, it must be read to the participants verbatim, and participant responses must be recorded directly without any interpretation. For any additional assessments conducted via telephone (either during participation in the treatment period or during Follow-up), the Interviewer Administered format must be used.

The NEI-VFQ-25 and OSDI will be administered to participants in different regions based on the availability of translated versions.

9.4.8.1. National Eye Institute Visual Function Questionnaire-25

The NEI-VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question [Orr, 2011; Kirwan, 2012; Mangione, 2001]. These include a global vision rating (1 item); difficulty with near vision activities (3 items); difficulty with distance vision activities (3 items); limitations in social functioning due to vision (2 items); role limitations due to vision (2 items); dependency on others due to vision (3 items); mental health symptoms due to vision (4 items); driving difficulties (3 items); limitations with peripheral vision (1 item), limitations with color vision (1 item); and Ocular pain (2 items). In addition to the core items from the NEI-VFS-25, select questions from the Appendix of Optional Additional Questions will also be administered to further assess the impact of ocular toxicity on visual function.

9.4.8.2. The Ocular Surface Disease Index

The Ocular Surface Disease Index (OSDI) is a 12-item questionnaire designed to assesses both the frequency of dry eye symptoms and their impact on vision-related functioning [Schiffman, 2000; Dougherty, 2011]. The OSDI has demonstrated good reliability, validity, sensitivity, and specificity, and can be used as a complement to other clinical and subjective measures of dry eye disease by providing a quantifiable assessment of dry eye symptom frequency and the impact of these symptoms on vision-related functioning.

9.5. Pharmacokinetics

9.5.1. Blood Sample Collection for Pharmacokinetics

Blood samples for pharmacokinetic (PK) analysis of GSK2857916 (ADC and total antibody) and cys-mcMMAF will be collected at the time points indicated in the Schedule of Activities table (Section 2). 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.

9.5.2. 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 (ADC and total antibody) 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 (ADC and total antibody) 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.

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 Cycle 1 Day 1 (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 for the Schedule of Activities of anti-cancer activity.

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

MRD negativity rate (defined as the percentage of participants who are MRD negative by clonoSEQ). Testing will be performed at: Screen for all participants; and at the time of achieving VGPR or CR. The testing will be repeated 6 months and 12 months after achieving VGPR or CR.

9.11. Health-Related Quality-of-Life

Three Health-Related Quality-of-Life (HRQoL) assessments will be performed in this study. More details about all patient questionnaires can be found in the SRM.

The following assessments will be administered to participants in different regions based on the availability of translated versions.

9.11.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module (EORTC QLQ-C30)

The EORTC QLQ-C30 is a 30-item questionnaire containing both single- and multi-item measures [Aaronson, 1993]. These include five functional scales (Physical, Role, Cognitive, Emotional, and Social Functioning), three symptom scales (Fatigue, Pain, and Nausea/Vomiting), a Global Health Status/QoL scale, and six single items (Constipation, Diarrhea, Insomnia, Dyspnea, Appetite Loss, and Financial Difficulties). Scores for each scale and single-item measure are averaged and transformed linearly to a score ranging from 0–100. A high score for functional scales and for Global Health Status/QoL represent better functioning ability or HRQoL, whereas a high score for symptom scales and single items represents significant symptomatology [Proskorovsky, 2014].

9.11.2. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma module (EORTC QLQ-MY20)

The EORTC QLQ-MY20 is a supplement to the QLQ-C30 instrument used in patients with multiple myeloma [Aaronson, 1993; Cocks, 2007]. The module comprises 20 questions that address four myeloma-specific HRQoL domains: Disease Symptoms, Side Effects of Treatment, Future Perspective, and Body Image. Three of the four QLQ-MY20 domains are multi-item scales: Disease Symptoms (includes bone aches or pain, back pain, hip pain, arm or shoulder pain, chest pain, and pain increasing with activity); Side Effects of Treatment (includes drowsiness, thirst, feeling ill, dry mouth, hair loss, upset by hair loss, tingling hands or feet, restlessness/agitation, acid indigestion/heartburn, and burning or sore eyes); and Future Perspective (includes worry

about death and health in the future, and thinking about illness). The Body Image scale is a single-item scale that addresses physical attractiveness. As with the QLQ-C30, QLQ-MY20 domain scores are averaged and transformed linearly to a score ranging from 0–100. A high score for Disease Symptoms and Side Effects of Treatment represents a high level of symptomatology or problems, whereas a high score for Future Perspective and Body Image represents better outcomes [Proskorovsky, 2014].

9.11.3. Qualitative Telephone Interviews (Patient Interviews)

To further evaluate disease and treatment related symptoms and associated impacts on function and health-related quality of life, participants will participate in qualitative interviews conducted via telephone. The interview will be conducted by a trained interviewer in the participant's native language and will be audio recorded for transcription and analysis.

The patient interview (PRO) should be conducted via telephone within 21(±7 days) days following Day 1 of the fourth treatment cycle (C4D1). The PRO interview should also be conducted within 21 days (±7 days) of the participants end of treatment visit, unless the participant has already completed their interview following C4D1 within the prior 30 days.

10. STATISTICAL CONSIDERATIONS

10.1. Hypothesis Testing

This is a two-arm study. The primary objective of this study is to establish the efficacy of BCMA over historical control with respect to ORR for participants with RRMM for each of the two dose levels (frozen liquid solution) studied.

The study is designed to provide evidence with respect to ORR to either support the null hypothesis, H_0: ORR ≤15%, or reject H_0 in favor of the alternative hypothesis, H_1: ORR≥33%. The hypothesis testing will be performed within each arm separately. No hypothesis testing for comparing ORR between the two arms will be performed.

All randomized participants will be included in the final analysis to test the hypotheses of interest regardless of length of follow-up or whether or not they receive the treatment or whether or not they have a post-baseline assessment (i.e., participants will not be replaced).

An interim analysis (IA) will be conducted after approximately 25 randomized participants per arm are evaluable (i.e., received at least two doses of study treatment and have completed at least one disease assessment after the second dose, or progressed or died or discontinued treatment due to reasons other than PD).

The Final analysis will be performed based on a data cutoff 6 months after the last participant (in the frozen liquid solution) is randomized in the study to allow sufficient data maturity of all efficacy endpoints. Time from first-subject-first visit (FSFV) to primary ORR analysis will be approximately 12 months. The timeline is subject to change based on the actual enrollment rate.

Endpoint	Statistical Analysis Methods
	and Efficacy population. In addition, ORR based on confirmed response from investigator assessment will be performed in both ITT and Efficacy population. ORR at IA will be analyzed based on investigator-assessed confirmed responses if available. However, in case a participant has achieved a response of PR or better at data cut, which was not confirmed due to the time constraints (too short timeframe for the next assessment) but with a potential to be confirmed through subsequent assessments after interim, the participant will also be considered as a responder. More details will be provided in the RAP.
Secondary	Secondary efficacy endpoints of this study are CBR, DoR, TTR, PFS, TTP, and OS. CBR, TTR, and DoR as assessed by IRC and investigator will be analyzed using both ITT and Efficacy population. Other TTE endpoints will be analyzed using ITT population only. **CBR** is defined as the percentage of participants with a confirmed minimal response (MR) or better, according to the IMWG Response Criteria [Kumar, 2016]. CBR at interim and final will be summarized in the same way as the primary endpoint ORR. No hypothesis testing will be performed for CBR **DoR** is defined as the time from first documented evidence of PR or better until the earliest date of disease progression (PD) per IMWG, or death due to PD among participants who achieve a response (i.e., confirmed PR or better). Responders without disease progression will be censored at the censoring time point for TTP. DoR will be analyzed at the time of final ORR analysis. **TTR** is defined as the time between the date of randomization and the first documented evidence of response (PR or better), among participants who achieve a response (i.e., confirmed PR or better). TTR will be analyzed at the time of final ORR analysis. **PFS** is defined as the time from randomization until the earliest date of PD per IMWG, or death due to any cause. Determination of dates of PFS event and dates for censoring will be described in the RAP. PFS will be analyzed at the time of final ORR analysis, also at study close out if applicable. **TTP** is defined as the time from randomization until the earliest date of PD per IMWG, or death due to PD. Determination of dates of TTP event and dates for censoring will be described in the RAP. TTP will be analyzed at the time of final ORR analysis, also at study close out if applicable. **OS** is defined as the time from randomization until death due to any cause. Participants who withdraw consent from the study or are lost to follow-up will be censored at the time of withdrawal or lost to follow-up. Participants who are still alive at the clinical cut-off date for the analysis will be censored at the last known alive date or last contact date. The last contact date will be determined by the maximum collection/assessment date from among selected data domains within the clinical database. OS, including 12- and 18-month survival rates, will be analyzed for the safety population. An OS analysis will be performed at the time of final ORR analysis if there is a sufficient number of death events. An updated OS analysis will be performed at the end of study as defined in Sec 5.3 of the protocol. For all the TTE endpoints described above, median TTE with 95% CI will be estimated employing the Kaplan-Meier method. A Kaplan-Meier survival curve will be generated. The number and percentage of participants who had the event or were censored will also be reported. In addition, the survival rate with 95% CI at 12 and 18 months will be estimated using Kaplan-Meier methods for the OS endpoint.

10.5.3. Analyses of Health-Related Quality of Life Data

Descriptive statistics will be used to summarize scores derived from different questionnaires and change from baseline at each scheduled visit. Additional details will be provided in the reporting and analysis plan.

10.5.4. Pharmacokinetic Analyses

10.5.4.1. Pharmacokinetic Data Analyses

Concentration-Time Data: Linear and semi-logarithmic individual concentration-time profiles and mean and median profiles (when appropriate) will be plotted for GSK2857916 (ADC and total mAb) and cys-mcMMAF. Concentrations of GSK2857916 (ADC and total mAb) and cys-mcMMAF will be listed for each participant and summarized (when appropriate) by planned time point and dose level.

Derived Pharmacokinetic Parameters: Pharmacokinetic analyses will be the responsibility of Clinical Pharmacokinetics/Modelling and Simulation, GSK.

Plasma GSK2857916 (ADC, total mAb) and cys-mcMMAF concentration-time data will be analyzed by non-compartmental methods using WinNonlin. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following PK parameters will be determined for GSK2857916 (ADC and total mAb) as data permit, for each participant after each dose of GSK2857916:

- maximum observed plasma concentration (Cmax), time to Cmax (tmax), predose plasma concentration (Ctrough)
- For Cycle 1 and Cycle 3: area under the plasma concentration-time curve [AUC(0-t), AUC (0-tau) and/or AUC(0-∞)], 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)

For cys-mcMMAF, Cmax, tmax, AUC [AUC(0-t), AUC (0-tau) and/or AUC(0-∞)], tlast, λz, and t½ will be computed at Cycle 1 and Cycle 3, as data permit.

Plasma GSK2857916 concentration-time data may be combined with data from other studies and will be analyzed using a population pharmacokinetic approach. A nonlinear mixed effects model will be used to determine population pharmacokinetic parameters (clearances, CL and volumes of distribution, V) and identify important covariates (e.g., age, weight, or disease-related covariates). Summary exposure measures (e.g., Cmax, AUC) will also be computed. For the data from the lyophilized configuration, individual pharmacokinetic parameters may be obtained using a Bayesian approach and the population PK model. Results of this analysis may be provided in a separate report.

Scenarios	Participants per arm	Response Rate		Futility Stopping Boundary Crossing Probabilities at IA [1]		Probabilities of Claiming Efficacy at Final [1]	
		Arm 1 [2]	Arm 2 [2]	Arm 1 [2]	Arm 2 [2]	Arm 1 [2]	Arm 2 [2]
8 [4]	65	15%	15%	68.22%	68.22%	**1.23%**	1.24%
9	100	33%	60%	53.59%	0.01%	46.11%	99.99%
10	100	33%	45%	16.95%	0.47%	82.09%	99.53%
11 [3]	100	33%	33%	6.33%	6.33%	**92.38%**	92.39%
12	100	33%	25%	5.09%	23.83%	93.57%	53.93%
13	100	33%	20%	4.97%	44.59%	93.68%	15.46%
14	100	33%	15%	4.96%	69.99%	93.70%	0.94%
15	100	33%	10%	4.96%	90.85%	93.70%	0.003%
16 [4]	100	15%	15%	68.22%	68.22%	**0.97%**	0.97%

Note:

[1] The Boundary Crossing Probabilities are calculated based on 10,000,000 simulations using R program.

[2] Arm 1 and Arm 2 in the table just represent two different treatment arms and are not necessarily refers to 3.4 mg/kg and 2.5 mg/kg, respectively.

[3] The power is shown in Scenario 3, and 11 as **86.90%** and **92.38%** for sample size of 65, and 100 respectively.

[4] The type I error is shown in Scenario 8, and 16 as **1.23%,** and **0.97%** for sample size of 65, and 100 respectively.

The IA to assess futility will be reviewed by an Independent Data Monitoring Committee (IDMC). Additional details of the IA are provided in Section 10.5.9 and will be provided in an IDMC Charter. The stopping rules described above are guidelines for decision-making and the totality of the data will be considered when making a final decision.

Participants will continue to be enrolled, dosed, and followed as planned at the time of IA.

CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DAMPs	Danger-associated molecular patterns
DCs	Dendritic cells
DICOM	Digital Imaging and Communications in Medicine
DILI	Drug-induced liver injury
DLT	Dose limiting toxicities
DNA	Deoxyribonucleic acid
DOR	Duration of Response
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EORTC	European Organization for Research and Treatment of Cancer
EOT	Endo of treatment
EQ-5D-5L	EuroQOL Group EQ-5D 5 Level
FISH	Fluorescence in situ hybridization
FLC	Free light chain
FSFV	First subject first visit
FSH	Follicle stimulating hormone
FTIH	First Time in Human Trial
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GSK	GlaxoSmithKline
HBV	Hepatitis B
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte antigen
HR	Hazard ratio
HRT	Hormone replacement therapy
HSCT	Hematopoietic stem cell transplantation
IB	Investigator Brochure
ICD	Immunogenic cell death
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Institutional Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IMiD	Immunomodulatory drugs

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.

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 must 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 (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	**For bilirubin or INR criteria:** • 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 HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]) **Note: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

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** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required 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
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. Record the date/time of the PK 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 PK sample cannot be collected in the time period indicated above, do not obtain a PK sample.

paradigm, participants generally showed improvement in both corneal examination findings and visual acuity over time. Therefore, the dosing guideline has been adjusted to allow dosing with GSK2857916 if only one component on the GSK corneal event scale indicates Grade 2 corneal event.

Table 21 Prophylactic Measures for Corneal Events Associated with GSK2857916 [a, b]

Prophylactic Measure[a]	Dose and Administration	Timing
Steroid eye drops[b]	Prednisolone acetate 1.0%, Prednisolone phosphate 1%, or dexamethasone 0.1%, or equivalent, 1 drop QID	Begin 1 day prior to each dose of GSK2857916 infusion, and continuing for a total of consecutive 7 days
Preservative-free artificial tears	Administer in each eye at least 4 to 8 times daily	Administer daily beginning on Cycle 1 Day 1 until EOT. Allow 5-10 minutes between administration of artificial tears and steroid eye drops
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 7.2

b Omission or discontinuation of prophylactic steroid eye drops may be allowed under certain circumstances (e.g., in the setting of intolerability, contraindication, or toxicity secondary to steroid eye drops) upon discussion with the Medical Monitor.

Table 22 GSK Scale for Corneal Events Associated with GSK2857916[a]

Measure	Grade 1 per GSK Scale	Grade 2 per GSK Scale	Grade 3 per GSK Scale	Grade 4 per GSK Scale
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, c]	Change of 1 line from baseline	Change of 2-3 lines from baseline and not worse than 20/200[b]	Change of more than 3 lines from baseline and not worse than 20/200[b]	Worse than Vision 20/200[b]

Note: Standardized guidance for grading ophthalmic findings associated with GSK2857916 is provided to sites in the ophthalmology SRM. Ophthalmic exam findings as described must be present in a participant to utilize GSK's scale.

a. Grading is based on most severe finding. If eyes differ in severity, GSK grading should be based on the more severe eye.
b. Change in visual acuity should be due to corneal events. If change in vision is for reason other than corneal events, ophthalmic exam findings will drive event grading.
c. See Table 23 for additional guidance on how to grade changes in visual acuity depending on baseline vision. If a participant has a baseline visual acuity of 20/200 or worse in an eye, ophthalmic exam findings will drive event grading.

Table 23 Guidance on GSK Scale Grading Based on Changes in Visual Acuity

Baseline Vision (best corrected)	Grade 1 per GSK scale	Grade 2 per GSK scale	Grade 3 per GSK scale	Grade 4 per GSK scale
20/20	20/25	20/30 – 20/40	20/50 –20/200	Worse than 20/200
20/25	20/30	20/40 – 20/50	20/60 –20/200	Worse than 20/200
20/30	20/40	20/50 – 20/60	20/70 –20/200	Worse than 20/200
20/40	20/50	20/60 – 20/70	20/80 –20/200	Worse than 20/200
20/50	20/60	20/70 – 20/80	20/100 – 20/200	Worse than 20/200
20/60	20/70	20/80 – 20/100	20/125 – 20/200	Worse than 20/200
20/70	20/80	20/100 – 20/125	20/200	Worse than 20/200
20/80	20/100	20/125 – 20/200	N/A	Worse than 20/200
20/100	20/200	20/200	N/A	Worse than 20/200

Objectives	Endpoints
	(IMWG) Response Criteria Duration of response (DoR), defined as: the time from first documented evidence of PR or better until the earliest date of documented disease progression (PD) per IMWG; or death due to PD occurs among participants who achieve an overall response, i.e., confirmed PR or better. Time to response, defined as the time between the date of randomization and the first documented evidence of response (PR or better). Progression-free survival, defined as the time from randomization until the earliest date of documented disease progression (PD) per IMWG, or death due to any cause. Time to progression, defined as the time from randomization until the earliest date of documented PD per IMWG, or death due to PD. Overall survival, defined as the time from randomization until death due to any cause.
To evaluate the safety of GSK2857916 in participants with RRMM.	The safety profile of GSK2857916 will be evaluated in participants with RRMM as assessed through: standard clinical and laboratory tests (hematology and chemistry, physical examination, vital sign measurements, and diagnostic tests) through the collection of adverse events (AEs) and serious adverse events (SAEs) AEs of special interest ocular findings on ophthalmic exam
To evaluate the pharmacokinetic profile of GSK2857916	Plasma concentrations of GSK2857916 (ADC, total mAb, and cys-mcMMAF) Derived pharmacokinetic parameter values (e.g., AUC, Cmax, tmax, t½), as data permit.
To assess anti-drug antibodies (ADAs) against GSK2857916	Incidence and titers of ADAs against GSK2857916
Participant self-reported symptomatic adverse effects by evaluation of tolerability of GSK2857916	Symptomatic adverse effects and related impacts as measured by the PRO-CTCAE, NEI-VFQ-25 and OSDI
To evaluate disease and treatment related symptoms and impact on function and health-related quality-of-life	Health-related quality-of-life as measured by the EORTC QLQ-C30 and EORTC QLQ-MY20
Exploratory Objectives	
To explore the relationship between clinical response and other biologic characteristics including BCMA expression on tumor cells and sBCMA concentrations	Determine BCMA expression levels and other markers on malignant cells, serum sBCMA levels, and evaluate the relationship of these factors to clinical response
To investigate the relationship between	Possible relationship between host genetic variation and

Table 2 Schedule of Activities – On Study Assessments

Study Assessments	**Cycle 1, Day 1[1]**	**Cycle 1 & Cycle 3 Day 4**	**Cycle 1 & Cycle 3, Day 8-15**	**Q3W starting Wk 4[2] (to be performed regardless of dosing)**	**Cycle 2-CX with dosing [2]**	Notes
Physical Exam	X			X		(**Important: Every participant will complete Cycle 1 Day 1 on study assessments. Then, they will complete 'Q3W' assessments starting at week 4' AND the 'Cycle 2-CX with dosing' assessments during the treatment phase). If dosing is not completed only perform the "Q3W starting at Week 4" assessments at the scheduled visit.** 1. Assessments scheduled on days of dosing must be done prior to drug administration, unless otherwise specified. All other assessments can be done ±3 days unless otherwise specified. 2. GSK2857916 will be administered intravenously on Day 1 (D1) of every 21-day cycle (Q3W) until disease progression, unacceptable toxicity, death or withdrawal of consent. 3. All related SAEs are to be collected from consent through OS follow-up 4. On-study ophthalmic exams to be performed by an ophthalmologist (or an optometrist if an ophthalmologist is not available) predose every 3 weeks. See Section 9.2.9 for the list of ophthalmic exam procedures. If there are no corneal signs per the GSK Scale for corneal events at time of the cycle 4 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 (an optometrist if an ophthalmologist is not available). Intraocular pressure must be monitored if steroid eye drops are used continuously for more than 7 days. Additional exams may be performed by the ophthalmologist (an optometrist if an ophthalmologist is not available), as clinically indicated. At selected sites, participants will undergo additional ophthalmic exams. If you are a selected site, see Section 9.2.9 for full list of ocular sub-study exam procedures. 5. If a participant's GSK2857916 dose is not administered at a given visit, the following activities do not need to be performed at that visit unless clinically indicated: Vitals, weight, spot urine, pregnancy test, ECG, PK sample, ADA sample, and soluble BCMA sample. 6. On initial (first infusion) dosing day, vital signs must be assessed at pre-dose (within 30 minutes prior to start of infusion(SOI)), +10 minutes after SOI, within ±5 minutes of end of
Adverse Events[3]	Ongoing			Ongoing	Ongoing	
Concomitant Medications	Ongoing			Ongoing	Ongoing	
Safety						
Ocular Exam[4]				X		
ECOG Performance Status				X		
Vital Signs (BP, HR, Body Temperature)[5, 6]	X				X	
Weight[5]	Weight Only				Weight Only	
Hematology [7]	X			X		
Clinical chemistry [7]	X			X		
Urine Dipstick [7]	X			X		
eGFR (by MDRD formula- see Appendix 10)	X			X		
Spot urine for albumin/creatinine ratio[5, 7, 8]	X				X	
CRP				X		
Pregnancy Test [5, 9]					X	
ECHO				As clinically indicated		
12-lead ECG [5,10]	X	X	X		X	

Study Assessments	**Cycle 1, Day 1[1]**	**Cycle 1 & Cycle 3 Day 4**	**Cycle 1 & Cycle 3, Day 8-15**	**Q3W starting Wk 4[2] (to be performed regardless of dosing)**	**Cycle 2-CX with dosing [2]**	Notes
Urine Immunofixation				By central lab if UPEP is negative, at the time of first achieving CR then perform every 3 weeks until suspected PD after CR or sCR.		be collected at a similar time of day as the SOI on Cycle 1 Day 1 (±2 h). ECGs will be collected and stored centrally and may be reviewed by an independent central reviewer. See SRM for details on collection regarding ECGs. 11. PK samples to be taken in all participants for GSK2857916 measurement **during Cycle 1, Day 1 and Cycle 3, Day 1** at the following study times: predose (within 30 minutes prior to SOI), at EOI (±5 min), at 2 h (±15 min) after SOI, and at 24 h (±2 hrs) after SOI. 12. PK samples to be taken for GSK2857916 measurement C1D4 and C3D4 (±1 day): one sample after ECG collection. 13. One PK sample to be taken for GSK2857916 measurement in Cycle 1 and Cycle 3 after ECG collection on any day from Day 8 to Day 15. **If dosing is delayed at Cycle 2 or Cycle 4**, a PK sample should be drawn 21 days post dose (Day 22 ±2 days) in Cycle 1 and Cycle 3. 14. PK samples to be taken on Cycle 3, Day 1 at the following study times: predose (within 30 minutes prior to SOI), at EOI (±5 min), at 2 h (±15 min) after SOI, and at 24 h (±2 hrs) after SOI. At C2, C4, C6, C9, and C12, PK samples to be taken at predose (within 30 minutes prior to SOI) and at EOI (±5 min). Every 6 subsequent cycles (e.g., C18, C24, etc.) at predose (within 30 minutes prior to SOI). 15. Anti-drug antibodies should be collected prior to the dose at C2, C6, C9, C12, and every 6 cycles thereafter (C18, C24, etc.) until end of treatment (dosing days only) with the PK sample 16. Response assessment must be conducted every 3 weeks based on disease laboratory tests and imaging (if applicable) as outlined in this table. Response evaluation will be performed according to the IMWG (Uniform Response Criteria for Multiple Myeloma 2016). Central laboratory results for all disease response assessments will be shared with the Independent Review Committee (IRC) 17. Only if clinically indicated or if worsening clinical symptoms suggest skeletal PD. 18. Imaging is only required for participants with extramedullary disease (CT, MRI, or PET/CT can
SPEP (Serum Protein Electrophoresis)				X		
Serum Immunofixation				By central lab if SPEP is negative at the time of first achieving CR then perform every 3 weeks until suspected PD after CR or sCR.		
Serum Kappa, Lambda free Light chain, FLC ratio				X		

Study Assessments	EOT Visit[1]	PFS Follow-up[2]	OS Follow-Up[3]	Notes
Bone marrow biopsy to assess sCR by IHC[16]	Only if CR has been achieved on this visit	Only if CR have been achieved on this visit		for extramedullary disease as clinically indicated. 13. Germany: no PET/CT to confirm CR or sCR will be performed until approved by the German Federal Office of Radiation Protection until further notice. 14. Only required for participants with IgD/E myeloma, where serum m-component cannot be followed otherwise. 15. Performed by a central lab at the time of first achieving VGPR or CR. And repeated at 6 months and 12 months after achieving the VGPR or CR (provided VGPR/CR is maintained). 16. In participants achieving a CR, bone marrow biopsy to confirm sCR by IHC. 17. Upon PD- Optional tumor sample (BM aspirate clot, or fresh tissue, or tissue block from extramedullary tumor) for BCMA expression analysis by IHC. To be submitted to central lab for analysis 18. Participants who discontinue participation in the study will continue to be assessed during follow-up until resolution of visual symptoms. Continue to follow up with participants via telephone who are still experiencing visual symptoms even after discontinuation 19. Patient Interview (PRO) must be conducted via telephone within 21 days (±7 days) of the end of treatment visit, unless the participant has already completed their interview following C4D1 within the prior 30 days.
Biomarkers				
Soluble BCMA (serum)	X			
cfDNA (plasma)	X			
Optional				
Optional tissue sample at PD for BCMA[17]	At time of PD	At time of PD		
Health Outcomes				
PRO-CTCAE	X			
NEI-VFQ-25[18]	X	X	X	
OSDI[18]	X	X	X	
EORTC-QLQ-C30	X			
EORTC-QLQ-MY20	X			
Patient Interview (PRO) [19]	X			
Survival Status phone call			X	
Subsequent Treatment Information		X	X	

Abbreviations:
BM = bone marrow; BP = blood pressure; cfDNA = Circulating free DNA; CRP = C-reactive protein; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module; EORTC QLQ-MY20 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma module; FISH = fluorescence in situ hybridization; FLC = free light chain; ; HR= heart rate; Ig = immunoglobulin; NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire 25; OSDI = Ocular Surface Disease Index; PRO-CTCAE = Patient Reported Outcome version of the Common Term Criteria for Adverse Events; PD = Progressive Disease; PK = Pharmacokinetics; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

in the FTIH study this novel mechanism of action can be reasonably expected to overcome cross resistance to existing therapies.

GSK2857916 has shown strong single-agent activity in the currently ongoing FTIH study BMA117159.

Among the 35 participants receiving GSK2857916 at the RP2D of 3.4 mg/kg IV, Q3W, the following results were observed:

- Overall response rate (ORR) of 60% (95% CI: 42.1%, 76.1%)
- Median progression-free survival (PFS) was 7.9 months (95% CI: 3.1, - months).
- The ORR in 14 participants who failed prior daratumumab treatment was 43% (95% CI: 17.7%, 71.1%), and the PFS in this subgroup was 6.8 mo.
- Overall, GSK2857916 was well tolerated and adverse events were manageable.

This data supports further development of GSK2857916 as monotherapy in patients who failed an anti-CD38 antibody and are refractory to PI and IMiD.

3.2. 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 first time in human (FTIH) study demonstrating single-agent activity of GSK2857916 in heavily pre-treated MM participants. Chimeric Antigen Receptor T-Cells (CAR-T) based therapies targeting BCMA have also demonstrated powerful activity against MM, with substantial albeit reversible risks [Cohen, 2016]. Other approaches utilizing bispecific antibodies (BiTe) have also entered development, but clinical results have not been reported at the time of writing this protocol.

3.3. Antibody-Drug Conjugate GSK2857916

GSK2857916 is a first in class, ADCC-enhanced, humanized immunoglobulin G1 (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 antibody moiety of GSK2857916 is produced as an afucosylated form that generates an enhanced antibody-

BMA117159 (0 in 8 participants), one response was noted at each of the lower doses of 0.96 mg/kg (1 in 3 participants) and 1.92 mg/kg, and (1 in 4 participants). In addition, estimated receptor binding saturation was seen at doses 1.92 mg/kg.

3.5. Benefit / Risk Assessment

3.5.1. Risk Assessment

Additional information about the known and expected benefits and risks, detailed information of nonclinical and clinical findings information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on GSK2857916 that may impact participant eligibility is provided in the Investigator's Brochure [GSK2857916 (IB) GlaxoSmithKline Document Number 2013N175128_04].

Table 5 Risk Assessment and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (GSK2857916)		
Corneal events	Reversible corneal events have been observed with various ADCs (specific corneal changes with ADCs conjugated to MMAF). Cornea-related AEs such as blurred vision, dry/watery eyes, decreased visual acuity, and photophobia are among the most common AEs associated with GSK2857916 in the clinic. The majority of events have been non-serious and transient, some requiring dose delays/reductions. Time to recovery is variable, and in some instances the resolution may take several weeks.	Active monitoring for corneal events according to the Schedule of Activities (Table 1). Preventive use of steroid eye drops as outlined in Table 21 in Appendix 9. Timely evaluation and management by an ophthalmologist (an optometrist if an ophthalmologist is not available) upon developing corneal related events. Recommendations for dose delays/reductions are provided in Section 9.4.8 and Appendix 9.
Infusion related reaction	Without pre-medication, the majority of IRRs observed in the clinic to date have been G1-2 and non-serious; however, there have also been serious IRRs. Overall, participants who experienced an IRR during the initial infusion were pre-medicated prior to subsequent infusions and IRRs did not recur.	Participants will be closely monitored for signs of IRR. Premedication prior to first infusion of GSK2857916 is not mandatory but may be considered based on investigator judgment. If an infusion-related reaction occurs during GSK2857916 administration, the infusion rate may be reduced or halted depending on the severity of the symptoms. The participant will receive appropriate medical treatment. When the participant's condition is stable, the infusion may be restarted. Upon restart, the infusion rate must be half of the infusion rate at the time the infusion was paused.
Thrombocytopenia	Thrombocytopenic events of all grades (1-4) are among the most common AEs	A hematologic panel is assessed frequently. Supportive therapy (including

Objectives	Endpoints
	and derived pharmacokinetic parameters, if data permit
Ocular sub-study objective	
To evaluate the effect of topical corticosteroids on corneal findings in approximately 30 participants who will receive monocular topical corticosteroids for the first 4 cycles	Description of differences in corneal findings in each eye based on ophthalmic examinations (participant-level).

Abbreviations: IV = intravenous; Q3W: once every 3 weeks; RRMM = relapsed refractory multiple myeloma; BCMA = B-cell maturation antigen; MMAF = monomethyl auristatin-F; MRD = minimal residual disease; NGS = Next Generation Sequencing; ORR = overall response rate; CI = confidence interval; CR = complete response; VGPR = very good partial response; PR = partial response; PFS = progression free survival; AUC = area under the curve; Cmax = maximum concentration; tmax = time to maximum; t½ = half-life; PRO-CTCAE = Patient Reported Outcomes-Common Terminology Criteria for Adverse Events; NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire 25; OSDI = Ocular Surface Disease Index; EORTC = European Organisation for Research and Treatment of Cancer; QLQ-C30 = Quality of Life Questionnaire 30-item Core module; FLC = free light chain; SCT = stem cell transplant; QLQ-MY20 = ; Quality of Life Questionnaire 20-item module for MM; QTcF = QT interval corrected by Fridericia's formula; HIV = human immune deficiency virus; RNA = ribose nucleic acid.

5. STUDY DESIGN

5.1. Overall Design

This is a Phase II, open-label, two-arm, randomized, multicenter study to evaluate the efficacy and safety of GSK2857916 monotherapy at the dose of 2.5 mg/kg or 3.4 mg/kg IV, Q3W, in participants with RRMM. Participants will be treated until disease progression or unacceptable toxicity and will be followed for PFS and OS. An ocular sub-study will evaluate the effectiveness of steroid eye drops in approximately 30 participants (~15 on each dose arm) who sign an optional ICF.

The study will use frozen solution of GSK2857916 for those participants enrolled into 2 dose arms.

The design includes an independent cohort of approximately 25 participants who will receive a lyophilized configuration of GSK2857916. Those participants will follow the same assessments and procedures as the main study and will be analyzed separately from participants randomized to the frozen solution.

The lyophilized cohort will be initiated when the lyophilized configuration becomes available. It will evaluate the 3.4 mg/kg dose level, unless the results of the IA indicate that it should not be continued. In that case, the lyophilized cohort will have a dose of 2.5 mg/kg.

The study consists of a screening/baseline period, a treatment period, and a post-treatment follow-up period (schematic is displayed in Figure 1)

Participants eligible for screening will be assigned a unique Participant Number by their investigational site. Upon completion of all the required screening assessments, eligible participants will be registered into the Registration and Medication Ordering System (RAMOS), GSK's Interactive Response Technology (IRT) system, by the investigator or authorized site staff. Following randomization, eligible participants will begin Cycle 1 treatment in the assigned treatment arm. Assessments will be performed as illustrated in the Schedule of Activities (Section 2).

Selected investigative sites will participate in the ocular sub-study and will conduct additional ocular examinations on approximately 30 participants who sign an additional consent to receive monocular treatment with corticosteroid eye drops. In this specific subgroup, the ophthalmic examinations will occur pre-dose every 3 weeks and on Day 10 after a treatment dose for the first 4 cycles. Additional treatments and examinations will be at the discretion of the treating ophthalmologist (an optometrist if an ophthalmologist is not available). See the SOA for the scheduling (Section 2).

Additional details of the individual assessments are provided in Section 9.

An interim analysis (IA) for futility is planned for ORR based on investigator's assessment after approximately 25 participants per arm are evaluable for response (defined as having received at least 2 doses of study treatment and having completed at least 1 disease assessment after the second dose, or progressed or died or discontinued treatment due to reasons other than PD).

At the IA, given that 25 participants are evaluable for each arm, treatment arm/s will be dropped from the study if there are ≤4 responses. If both arms have 5 or more responses at IA, in addition to the futility rule described above, the posterior probability of observing a better RR in one arm than the other will be calculated. If such a probability is at least 97.5%, then the treatment arm with lower RR will be dropped due to lack of efficacy.

The IA to assess futility will be performed by an Independent Data Monitoring Committee (IDMC). Additional details of the IA are provided in Section 10.5.9 and will be provided in an IDMC Charter. At the time of the IA, additional participants will continue to be enrolled, treated, and followed as described in the SOA (Section 2). Efficacy and safety results from the interim analysis will not be shared with investigators or other site/study personnel.

If one arm is selected based on the results of the IA, enrollment to the futile arm will be stopped and ongoing participants from the futile arm will have the possibility upon additional consent to either continue at their current dose level or to have their dose adjusted to the dose in the selected arm based on the following rules:

If the 2.5 mg/kg dose is discontinued, participants have the option to switch to 3.4 mg/kg dose if they:

- Did not experience an SAE, or a ≥ Grade 3 non-corneal AE
- Provide informed consent for the 3.4 mg/kg dose.

Table 7 Summary of Investigator-Assessed Best Response (with Confirmation; Study BMA117159 Part 1)

Dose level (mg/kg)	ORR (%)	95%CI
0.03	0	(0.0, 97.5)
0.06	0	(0.0, 97.5)
0.12	0	(0.0, 60.2)
0.24	0	(0.0, 60.2)
0.48	0	(0.0, 60.2)
0.96	33	(0.8, 90.6)
1.92	25	(0.6, 80.6)
2.5	0	(0.0, 36.9)
3.4	100	(29.2, 100.0)
4.6	50	(11.8, 88.2)

Preliminary clinical data from Part 2 of Study BMA117159 (3.4 mg/kg Q3W) indicated an Overall Response Rate (ORR) of 60% (95% CI: 42.1, 76.1) in an RRMM population (57% of participants had 5 or more lines of prior therapy, n=35). The median progression-free survival (mPFS) was 7.9 months (95% CI: 3.1, NA). The ORR was 43% (95% CI: 17.7, 71.1) in the 14 participants who had received prior daratumumab.

Clinical safety and tolerability in Study BMA117159
In general, GSK2857916 has been well tolerated; the most frequent AEs were corneal events and thrombocytopenia/platelet count decrease, which were manageable following protocol-defined dose modification guidelines. Most participants in Study BMA117159 experienced dose reduction and/or dose delays; all events were graded using CTCAE Version 4.03.

In the All Treated population (n=73), 35 participants (48%) had AEs that led to dose reduction. The most common AEs (frequency ≥5%) that led to dose reductions were vision blurred (18%), thrombocytopenia (8%), dry eye (5%), and keratitis (5%). In the Part 2 group (n=35), 23 participants (66. %) had AEs that led to dose reduction. The most common AEs (frequency ≥5%) that led to dose reductions were vision blurred (31%), thrombocytopenia (11%), keratitis (9%), photophobia (6%), platelet count decreased (6%), and infusion-related reactions (6%).

Dose delays due to AEs were experienced by 38 participants (52%) in the All Treated population. The most common AEs (≥5%) leading to dose delays were vision blurred (22%), thrombocytopenia (8%), dry eye (7%), and keratitis (5%). Dose delays due to AEs were experienced by 25 participants (71%) in Part 2. The most common AEs (frequency ≥5%) leading to dose delays were vision blurred (34%), thrombocytopenia (11%), dry eye (9%), keratitis (9%), lung infections (6%), and photophobia (6%).

Rationale for evaluating 2.5 mg/kg in addition to 3.4 mg/kg in the current study
A substantial number of participants treated at 3.4 mg/kg dose required a dose delay and/or dose reduction due to an AE. Responders in the 3.4 mg/kg dose group in Part 2 maintained their responses with dose reductions and delays. Based on the available data, evaluation of a lower dose level in addition to the 3.4 mg/kg dose is being done to ensure that the appropriate dose of GSK2857916 has been selected for monotherapy treatment.

intervention 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 intervention.

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 intervention.

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.

9. Male Participants: Contraceptive use by men or women 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 during the intervention period and for at least 140 days:

   - 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 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 who is not currently pregnant.

10. 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 and Grade 2 peripheral neuropathy.
11. (France only) A participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

Interactive Response Technology (IRT, by the investigator or authorized site staff. RAMOS allows study sites to register and randomize participants, and also records stratification information.

The following information for stratification must be entered into the system to obtain the treatment assignment:

- number of prior lines of therapy (≤4 vs >4);
- cytogenetic risk categories (high risk defined as t(4;14), t(14;16), and 17p13del vs non-high risk - all others);

Randomization will be done centrally using a randomization schedule generated by the GSK Clinical Statistics Department, which will assign participants in a 1:1 ratio to:

- Arm 1: 3.4 mg/kg IV Q3W
- Arm 2: 2.5 mg/kg IV Q3W

Once a randomization number has been assigned it must not be re-assigned even in cases of errors.

In the lyophilized cohort participants will be assigned the 3.4 mg/kg dose level, unless the results of the IA indicate that it should not be continued. In that case, the 2.5 mg/kg dose level will be assigned to participants.

RAMOS Study Specific User Guide and Clinical Support Helpdesk contact information will be provided to the study site in the SRM.

7.4. Blinding

This will be an open-label, 2-arm monotherapy study with an additional independent cohort enrolled after lyophilized product is available. Therefore, sponsor will have access to the participant level data throughout the study. However, there will be no intention to summarize and interpret data from the ongoing study at any time point except the pre-defined analyses.

In the ocular sub-study of participants (Section 9.2.10 and Appendix 9), the treating ophthalmologist will remain blinded as to which eye receives the prophylactic corticosteroid treatment.

7.5. Preparation/Handling/Storage/Accountability

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.

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 cases where the 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, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up."

9. 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 Schedule of Activities (Table 1).

A list of clinical laboratory tests is displayed in Table 14.

Whenever vital signs, 12-lead electrocardiograms (ECGs) and blood draws are scheduled for the same nominal time, the assessments must occur in the following order: 12-lead ECG, vital signs, blood draws. 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 (Table 1 – Table 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 6.1 and Section 6.2.
- Immediate safety concerns must 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.

Table 14 List of Clinical Laboratory Tests

Hematology[1]			
Platelet Count	*RBC Indices*:		*Automated WBC Differential:*
Red blood cell (RBC) Count	MCV		Neutrophils
White blood cell (WBC) Count (absolute)	MCH		Lymphocytes
Reticulocyte Count	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	Total bicarbonate	Gamma glutamyl transferase (GGT)	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
Magnesium	Phosphorous	Creatine kinase (CK)	LDH
eGFR	Spot urine (albumin / creatinine ratio)[5, 8]		
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[5]			
B-type natriuretic peptide (BNP)[5]			
Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-child bearing potential only) (screening)[1]			
Pregnancy Test (urine or blood- per local practice)[1]			
Hepatitis B surface antigen (HBsAg)[1] Hepatitis B core antibody (HBcAb)[1]			
Hepatitis C (Hep C antibody)[1]: Note: Hep C RNA testing is optional but may be done to determine participant eligibility if Hep C antibody positive). Participants with positive Hepatitis C antibody due to prior resolved disease may be offered hepatitis C RNA testing to determine eligibility.			

9.1.1. Independent Review Committee

An Independent Review Committee (IRC) will be utilized to assess efficacy endpoints of the study. All laboratory parameters and lesion measurements used to assess participant response will be shared with the IRC. Additional information can be found in Appendix 3 and in the IRC Charter.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

Adverse events will be coded using the standard MedDRA and grouped by system organ class. Adverse events will be graded by the investigator according to the NCI-CTCAE, (version 4.03). Corneal events associated with GSK2857916 will also be graded according to the GSK corneal event scale provide in Appendix 9. Dose modifications as a result of corneal events will be based on the GSK scale for corneal events (Table 22).

The investigator and any 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 (see Section 8).

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

- All SAEs will be collected from the start of treatment until 45 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 (Table 1, Table 2, and Table 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 from the start of treatment until 45 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.
- 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 electronic case report form (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 4. 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 in former study participants. 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

be investigated systematically. Furthermore, the effect of MMAF-conjugated ADCs on the eye has not been fully delineated in studies to date. Therefore, Study 205678 will include a sub-study of approximately 30 participants (~15 participants each dose) to evaluate the effect of ophthalmic topical corticosteroids on GSK2857916-associated corneal findings and to further characterize these findings. This sub-study of participants will be recruited at selected investigational sites associated with ophthalmologists with subspecialty training/expertise in the cornea. These participants will undergo additional ophthalmic examinations during the first 4 cycles of treatment at a minimum or as clinically indicated as determined by the treating ophthalmologist. A separate informed consent (in addition to the main study ICF) will be obtained from these participants.

9.2.10.1. Monocular prophylaxis

Figure 4 summarizes the prophylaxis administration schedule in the ocular sub-study of participants.

The treating ophthalmologist, but not the participant, will be blinded as to which eye has received the prophylactic steroid treatment.

Randomization will be done within each treatment arm centrally using a randomization schedule, which will assign participants in a 1:1 ratio to:

- receive topical corticosteroids in right eye only
- receive topical corticosteroids in left eye only.

The participants of the sub-study will administer prophylactic corticosteroid eye drops (prednisolone acetate 1%, prednisolone phosphate 1%, dexamethasone 0.1%, or equivalent, 1 drop four times daily starting one day prior to dosing for a total of 7 days). They will be instructed to administer the steroid drops in **only one eye**.

Corticosteroid treated eye

- Participant should administer 1 drop of topical corticosteroid followed by 1 drop of preservative-free artificial tears 5-10 minutes later, four times daily. This should start one day prior to dosing for a total of 7 days.

Other Eye

- Participants should administer 1 drop of preservative-free artificial tears followed by another 1 drop of preservative-free artificial tears 5-10 minutes later, 4-8 times daily. This should start one day prior to dosing for a total of 7 days. Outside the 7-day prophylaxis period, preservative-free artificial tears should be administered in each eye at least 4-8 times daily as needed (See Appendix 9, Section 12.9).

9.6. Immunogenicity

Immunogenicity sample analysis will be performed under control of GSK PTS BIB group, the details of which will be included in the SRM.

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. Details of sample preparation, storage, and analysis will be provided in the SRM.

Samples will be analyzed for the presence of anti-GSK2857916 antibodies by a validated electrochemiluminescent immunoassay. First, all samples will be tested in a screening assay to identify potentially positive samples. Next, samples that screen positive will be further characterized for specificity in a confirmation assay, and, finally, for samples that test positive in the confirmation assay, the antibody titer values will be determined. 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).

9.7. Translational Research

See Section 9.9.

9.8. Genetics

Participation in this part of the study is optional and all enrolled participants will be given the opportunity to contribute samples. Participation may be declined without effect on medical care during the clinical study. Separate consent signature is required for participation in genetic research.

Information regarding genetic research is included in Appendix 6. In approving the clinical protocol, the IEC/IRB and, where required, the applicable regulatory agency, are also approving the genetic research described in Appendix 6 unless otherwise indicated. Where required by regulatory authorities, approval of the genetic assessments can occur after approval is obtained for the rest of the study. In that case, written approval will indicate that approval of the genetic assessments is being deferred and the study, except for genetic assessments, can be initiated. If genetic assessments are not approved, they will not be conducted.

9.9. Tumor Biomarker Analysis

9.9.1. sBCMA Sample Analysis

The BCMA receptor undergoes gamma-secretase mediated cleavage, leading to release of the BCMA extracellular domain as soluble BCMA (sBCMA) into the circulation [Laurent, 2015].

Samples will be collected to measure concentrations of sBCMA at the time points specified in the SOA using a validated assay. Details of sample preparation, storage, and analysis will be provided in the SRM.

An updated analysis for OS will be performed at end of study as defined in Section 5.3.

10.2. Sample Size Determination

The sample size calculation was initially performed using East 6.4 software as a starting point, based on the ORR comparison between the GSK2857916 arm and the historical control in order to choose a final refined study design. The following assumptions were made in the estimation of the required sample size:

- Normal approximation of binomial proportion
- A response rate of ≥33% in the BCMA arm and ≤15% for the historical control
- A 1.25%, one-sided risk of erroneously claiming superiority of the BCMA arm, in the presence of no true underlying improvement
- A ~90% chance of rejecting the null hypothesis when the alternative hypothesis is true

An IA after approximately 38% of information is available (i.e., approximately after 25 participants out of originally planned 65 participants per arm are evaluable for IA), with a futility rule based on a gamma spending function.

The operating characteristics were refined using simulation to account for both within arm futility rule and the comparative futility rule. Based on the simulation results with the originally planned sample size of 65 participants per arm, there is 86.90% power to reject the null hypothesis within each arm with a 1-sided type I error of 1.23%.

Due to over enrollment, it is estimated that approximately 200 participants (~100 per arm) will be randomized to the frozen liquid solution. At the Final analysis, the null hypothesis will be rejected if the lower bound of 2-sided 97.5% exact C.I. exceeds the historical control rate of 15%.

With no change to planned IA (i.e., approximately after 25 participants/arm are evaluable for IA, and same futility boundary), simulation results show that there is 92.38% power to reject the null hypothesis within each arm with a 1-sided type I error of 0.97% for 100 participants per arm as specified in Section 10.3 and Section 10.5.

The study will also include an independent cohort of approximately 25 additional participants who will receive the lyophilized configuration of GSK2857916. The sample size for this cohort was chosen based on feasibility in order to gain clinical experience with the lyophilized configuration. The probability of observing a >=20% RR was retrospectively calculated. If the true RR is 33% there is a 95% probability of observing at least a 20% RR with 25 participants. This cohort will be analyzed separately from participants enrolled to the frozen liquid solution formulation.

10.3. Sample Size Sensitivity

Table 15 shows the various power scenarios at the final ORR analysis under different assumption of the ORR given the sample size of 65, and 100 participants per arm and stopping rules based on group sequential design as specified in Section 10.5.9.1.

Endpoint	Statistical Analysis Methods
Exploratory	MRD negative rate is defined as the proportion of participants who are negative for MRD at any time point after first dose as determined by the protocol defined testing procedure. For analysis purposes, participants in the safety population without MRD assessment will be considered as having positive MRD. The MRD negative rate will be calculated based on the ITT population. The corresponding 95% exact CI will be provided. Other exploratory endpoints will be described in the reporting and analysis plan (RAP)

CBR: clinical benefit rate; CI: confidence interval; CR: complete response; DoR: duration of response; Minimal Response MR; SD: stable disease; MRD: Minimal Residual Disease; NE: non-evaluable; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; RAP: report analysis plan; sCR: stringent complete response; TTP: time-to-progression; TTR: time-to-response; VGPR: very good partial response.

10.5.2. Safety Analyses

All safety analyses (Table 18) will be performed on the Safety Population.

Table 18 Statistical Analysis Methods for Safety Endpoints

Endpoint	Statistical Analysis Methods
Secondary	Adverse Events: All adverse events whether serious or non-serious, will be reported from the start of treatment until 45 days after the last dose of study treatment, until the participant withdraws consent for study participation, or until the participant starts subsequent anticancer therapy, whichever occurs first. AEs will be recorded using standard medical terminology and graded according to the NCI-CTCAE, Version 4.03. For AE reporting, the verbatim term used in the CRF by investigators to identify adverse events will be coded using the latest version of MedDRA coding dictionary [NCI, 2010]. Adverse events will be summarized by frequency and proportion of total participants, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs, and AEs leading to discontinuation of study treatment. Adverse events, if listed in the NCI-CTCAE (version 4.03,) will be summarized by the maximum grade. Characteristics (e.g., number of occurrences, action taken, grade, etc.) of the following AEs of clinical interest will be summarized separately: • The incidence of deaths and the primary cause of death will be summarized. • Clinical Laboratory Evaluation: 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, and range) will be used to summarize observed laboratory values and change from baseline in observed value at each scheduled visit or worst-case post baseline, as appropriate. • The worst-case- toxicity grade in hematology and chemistry result during the treatment will be summarized. • Corneal events associated with GSK2857916 will be summarized using the GSK scale Other Safety Measures: Data for vital signs, electrocardiograms (ECGs), echocardiograms (ECHOs), and ophthalmic examination findings will be summarized. 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 Reporting and Analysis Plan (RAP).
Exploratory	Exploratory analyses will be described in the RAP

10.5.4.2. Statistical Analysis of Pharmacokinetic Data

Statistical analyses of the pharmacokinetic (PK) parameters data will be the responsibility of Clinical Statistics, GSK.

GSK2857916 (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 (when appropriate) by planned time point and dose level as needed.

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

10.5.5. Pharmacokinetic/Pharmacodynamic Analyses

If deemed appropriate and if data permit, exposure-response relationships between GSK2857916 exposure (e.g., dose, dose intensity, concentration, Cmax, or AUC) and clinical activity and/or toxicity (e.g., response, corneal event, AESIs) may be explored using population methods. If data permit, the effects of covariates may be explored. Results of this analysis may be provided in a separate report.

10.5.6. Translational Research Analyses

The results of translational research investigations will be reported either within or separately from the main clinical study report (CSR). All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Further details on the translational research analyses will be addressed in the RAP.

10.5.6.1. Analysis of Novel Biomarker Data

The results of these biomarker investigations may be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Additional exploratory analyses may be performed to further characterize the novel biomarker.

10.5.6.2. Analysis of Genetic Data

Further details on genetic analyses are addressed in Appendix 6.

10.5.6.3. Exploratory Analyses of DNA and Protein Data

Exploratory analyses may be performed on remaining study samples for analyses of DNA, RNA and protein to understand changes in response to the combination treatment with GSK2857916.

11. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Institute. 1993 Mar 3;85(5):365-76.

Afifi S, Michael A, Lesokhin A. Immunotherapy: A New Approach to Treating Multiple Myeloma with Daratumumab and Elotuzumab. Ann Pharmacother. 2016;50(7):555-68.

Alley SC, Zhang X, Okeley NM, Anderson M, Law CL, Senter PD, et al. The pharmacologic basis for antibody-auristatin conjugate activity. J Pharmacol Exp Ther. 2009;330(3):932-8.

Basch E, Reeve BB, Mitchell SA, Clauser SB, Minasian LM, Dueck AC, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst. 2014;106(9).

Belnoue E, Pihlgren M, McGaha TL, Tougne C, Rochat AF, Bossen C, et al. APRIL is critical for plasmablast survival in the bone marrow and poorly expressed by early-life bone marrow stromal cells. Blood. 2008;111(5):2755-64.

Cocks K, Cohen D, Wisløff F, Sezer O, Lee S, Hippe E, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-MY20) in assessing the quality of life of patients with multiple myeloma. European Journal of Cancer. 2007 Jul 31;43(11):1670-8.

Cohen AD, Garfall AL, Stadtmauer EA, Lacey SF, Lancaster E, Vogl DT, et al., editors. B-Cell Maturation Antigen (BCMA)-Specific Chimeric Antigen Receptor T Cells (CART-BCMA) for Multiple Myeloma (MM): Initial Safety and Efficacy from a Phase I Study. Abstract 1147. American Society of Hematology (ASH) 58th Annual Meeting & Exposition December 3rd to 6th, 2016; 2016 05December 2016; San Diego, CA. https://ash.confex.com/ash/2016/webprogram/Paper92775.html.

DARZALEX (daratumumab) injection, for intravenous use Full Prescription Information. In: Janssen Biotech I, editor. https://wwwdarzalexhcpcom/shared/product/darzalex/darzalex-prescribing-informationpdf. Horsham, PA 19044 2017. p. 9.

de Weers M, Tai YT, van der Veer MS, Bakker JM, Vink T, Jacobs DC, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. J Immunol. 2011;186(3):1840-8.

Dougherty BE, Nichols JJ, Nichols KK. Rasch analysis of the Ocular Surface Disease Index (OSDI). Invest Ophthalmol Vis Sci. 2011;52(12):8630-5.

GSK2857916 IB [GlaxoSmithKline Document Number 2013N175128_04] Report Date 26-APRIL-2018

IMWG	International Myeloma Working Group
INR	International normalization ratio
IP	Investigational product
IRB	Institutional review board
IRC	Independent Review Committee
IRR	Infusion related reaction
IRT	Interactive Response Technology
IUD	Intra-uterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
LC	Light chain
LDH	Lactate dehydrogenase
LLN	Lower limit of normal (range)
LSFV	Last subject's first visit
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MDRD	Modified diet in renal disease
MM	Multiple myeloma
MMAF	Monomethyl auristatin-F
MOA	Mechanism of Action
MR	Minimal Response.
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
NCI	National Cancer Institute
NE	Not evaluable
NEI-VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
NGS	Next Generation Sequencing
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall survival
OSDI	Ocular Surface Disease Index
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PR	Partial response
PRO	Patient reported outcome
PRO-CTCAE	Patient-Reported Outcome Version of the Common Term Criteria for Adverse Events
PTS	Platform Technologies and Science
Q21D	Once every 21 days
Q3W	Once every 3 weeks
QID	Four times a day

Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment must 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 must 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 7 for liver chemistry follow-up procedures.**

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

Phase I/II Oncology liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the GSK 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, bilirubin) until they resolve, stabilize 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 bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

12.7.1. Liver Safety Drug Restart or Re-Challenge Guidelines

If participant meets liver chemistry stopping criteria do not restart/re-challenge participant with study treatment unless all the following conditions are met:

- GSK Medical Governance approval is granted (as described below)
- IRB/IEC approval is obtained, if required
- Separate consent for treatment restart/re-challenge is signed by the participant

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

12.7.1.1. Re-challenge Following Liver Stopping Events that are Possibly Related to Study Treatment

Re-challenge refers to resuming study treatment following drug-induced liver injury (DILI). Because of the risks associated with re-challenge 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 re-challenge is considered to be favorable.

Following DILI, drug re-challenge is associated with a 13% mortality across all drugs in prospective studies [Andrade, 2009]. Clinical outcomes vary by drug with nearly 50%

12.10. Appendix 10: Modified Diet in Renal Disease (MDRD) Formula

The MDRD formula for calculating the estimated glomerular filtration rate (eGFR) is as follows:

eGFR (mL/min/1.73 m^2) = 175 × $(S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American)

GFR is expressed in mL/min/1.73 m^2, S_{cr} 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