TITLE PAGE

Protocol Title: A Phase II, Open Label, Randomized, Two-Arm Study to Investigate the Efficacy and Safety of Two Doses of the Antibody Drug Conjugate GSK2857916 in Participants with Multiple Myeloma Who Had 3 or More Prior Lines of Treatment, Are Refractory to a Proteasome Inhibitor and an Immunomodulatory Agent and Have Failed an Anti-CD38 Antibody (DREAMM 2)

Protocol Number: 205678/ Amendment 07

Compound Number: GSK2857916

Brief Title: Open-label, randomized study of two doses of GSK2857916 in participants with relapsed/refractory multiple myeloma who have failed prior treatment with an anti-CD38 antibody

Study Phase: Phase 2

Sponsor Name and Legal Registered Address:

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

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Document	**Date**	**Document Identifier**
Amendment 7	*06 Jul 2023*	TMF-16142696
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Amendment 5	*08-Oct-2020*	2017N330177_06
Amendment 4	*21-Oct-2019*	2017N330177_05
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Amendment 2	*30-Aug-2018*	2017N330177_02
Amendment 1	*02-Apr-2018*	2017N330177_01
Original Protocol	*18-Jan-2018*	2017N330177_00

Amendment 07: 06 Jul 2023

Overall Rationale for the Amendment:

This protocol has been amended to update the already existing Post Analysis Continued Treatment (PACT) language across the protocol as per the current Sponsor standards.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Deleted content related to End of Treatment and End of Study Definition	End of Treatment and End of Study Definition has changed as per the latest PACT template language.
Section 1.2 Schedule of Activities (SoA)	Added additional content to clarify visit schedule for PACT phase	The PACT wording has been updated as per the latest GSK PACT template language.
Section 4.1 Overall Design	Added definitions for final analysis and EoS.	The PACT wording has been updated as per the latest GSK PACT template language.
Section 4.6 End of Study Definition	Updated the definitions for EoS.	The PACT wording has been updated as per the latest GSK PACT template language.
Section 6 Treatments	Added additional content to dosage form of belantamab mafodotin as a lyophilized powder.	To allow continued treatment of study participants who continue to derive clinical benefit post final analysis

Section # and Name	Description of Change	Brief Rationale
Section 6.1 Belantamab Mafodotin Treatments Administered	Added additional content to dosage form of belantamab mafodotin as a lyophilized powder.	To allow continued treatment of study participants who continue to derive clinical benefit post final analysis
Section 6.8 Treatment after the End of the Study	This section was deleted and it is replaced with a section on Continued Access to Study Intervention after the End of the Study	The old PACT language was deleted with the new section.
Section 6.8 Continued Access to Study Intervention after the End of the Study	Clarification around treatment following end of the study	The PACT wording has been updated as per the latest GSK PACT template language.
Section 6.8.1 Continued Access to Study Intervention after the Data Cut-off prior to EOS (PACT Phase)	New section is added as per PACT	Added as per the latest GSK PACT template language.
Section 8.2.1 Time Period and Frequency for collecting AE and SAE Information	Included additional content to align with implementation of PACT phase	The PACT wording has been updated as per the latest GSK PACT template language.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase II, Open Label, Randomized, Two-Arm Study to Investigate the Efficacy and Safety of Two Doses of the Antibody Drug Conjugate GSK2857916 in Participants with Multiple Myeloma Who Had 3 or More Prior Lines of Treatment, Are Refractory to a Proteasome Inhibitor and an Immunomodulatory Agent and Have Failed an Anti-CD38 Antibody (DREAMM 2)

Short Title: Open-label, randomized study of two doses of GSK2857916 in participants with relapsed/refractory multiple myeloma who have failed prior treatment with an anti-CD38 antibody.

Rationale: 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. Despite significant advances in treatment options, including hematopoietic stem cell transplant (HSCT), and novel therapies like second- and third-generation proteasome inhibitors (PIs), immunomodulatory agents, and recent addition of monoclonal antibodies (mAbs), most MM patients will ultimately develop resistance to existing therapies and die of relapse.

One such novel therapy, daratumumab, is a human IgG$_k$ monoclonal antibody that was granted first approval in the US in November 2015. Daratumumab binds with high affinity to the CD38 molecule, which is highly expressed on the surface of MM cells. It is believed to induce rapid tumor cell death through apoptosis, and multiple immune-mediated mechanisms, including complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis and antibody-dependent cellular cytotoxicity.

Daratumumab is approved by the FDA for the treatment of MM in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone in patients who have received at least one prior therapy, in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI), and as monotherapy for the treatment of patients who have received at least three prior lines of therapy, including a PI and an immunomodulatory agent, or who are double-refractory to a PI and an immunomodulatory agent.

In Europe, daratumumab is approved for the treatment of MM in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients who have received at least one prior therapy and as monotherapy for the treatment of patients with relapsed and refractory MM, whose prior therapy included a PI and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. Patients with MM who have proven refractory to daratumumab mono- and combination therapy, have few treatment options available, and could benefit significantly from treatment with a next-generation regimen, such as GSK2857916, belantamab mafodotin.

Belantamab mafodotin is a humanized (IgG1) antibody-drug conjugate (ADC) which binds to BCMA, a target widely expressed on malignant plasma cells in MM. The parent anti-BCMA antibody is conjugated to the microtubule inhibitor, MMAF, which is released 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 belantamab mafodotin 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 belantamab mafodotin 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 belantamab mafodotin 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

Objectives	Endpoints
	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 (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 belantamab mafodotin in participants with RRMM.	The safety profile of belantamab mafodotin 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 belantamab mafodotin	Plasma concentrations of belantamab mafodotin (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 belantamab mafodotin	Incidence and titers of ADAs against belantamab mafodotin
Participant self-reported symptomatic adverse effects by evaluation of tolerability of belantamab mafodotin	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	Determine BCMA expression levels and other markers on malignant cells, serum sBCMA levels, and evaluate the relationship of these factors to clinical response

Objectives	Endpoints
expression on tumor cells and sBCMA concentrations	
To investigate the relationship between genetic variants in the host and response to belantamab mafodotin	Possible relationship between host genetic variation and response to belantamab mafodotin
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 belantamab mafodotin exposure and clinical endpoints	Explore relationships between belantamab mafodotin 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 belantamab mafodotin in a lyophilized configuration (n= 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 belantamab mafodotin; plasma concentrations of belantamab mafodotin (ADC, total mAb, and cys-mcMMAF) 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.

Overall Study Design: This is a Phase II, open-label, two-arm, randomized, multicenter study to evaluate the efficacy and safety of belantamab mafodotin monotherapy at the dose levels of 2.5 mg/kg and 3.4 mg/kg administered intravenously (IV), Q3W, in participants with RRMM. Participants will be treated until disease progression or unacceptable toxicity. The study consists of a screening/baseline period, a treatment period, and a post-treatment follow-up period.

The design includes an independent cohort of approximately 25 additional participants who will receive a lyophilized configuration of belantamab mafodotin. Participants in the main study will receive a frozen liquid solution of belantamab mafodotin. Assessments

will be performed during Screening, prior to the first dose of Cycle 1, and during each cycle of treatment as illustrated in the Schedule of Activities.

The study will include 1 interim analysis for futility. If one arm is discontinued as a result of the interim analysis, participants will be offered the opportunity to receive treatment at the dose that is continuing, or at the original dose upon re-consenting.

As part of an ocular sub-study, approximately 30 participants (~15 per dose level) will be evaluated to study the effect of ophthalmic topical corticosteroids on belantamab mafodotin-associated corneal findings and to further characterize these findings.

Following 39 months post last subject first dose (LSFD), the study will move into the post analysis continued treatment (PACT) phase where the study remains open only to provide continued access to treatment for study participants who are continuing to derive clinical benefit. At that time, the collection of new data for participants who no longer receive study treatment will stop and the clinical trial database will be closed. Participants in survival follow-up will be considered to have completed the study. Those participants still benefiting from study drug in the opinion of their treating physician may continue to receive study drug and only SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases, and pre-specified ocular data will be reported directly to GSK using paper forms. The end of study (EOS) is defined as the date of the last visit of the last participant in the study.

Number of Participants: The sample size calculation was performed using East 6.4 software as a starting point, based on the ORR comparison between the belantamab mafodotin arm and the historical control. Based on the simulation results with the planned sample size of 65 participants there is 86.90% power to reject the null hypothesis within each arm with a 1-sided type I error of 1.23%.

Approximately 170 participants were initially planned to be screened to enroll a minimum of 155 participants at approximately 60 investigational sites globally. A minimum of 130 participants (65/arm) were planned to be enrolled to 2 arms receiving frozen liquid solution of belantamab mafodotin, which includes ~30 participants from the ocular sub-study. Approximately 200 participants will be enrolled onto the frozen liquid portion of the study.

Approximately, twenty-five additional participants will be enrolled into the independent lyophilized drug product cohort.

Treatment Groups and Duration: In this two-arm randomized study, belantamab mafodotin will be administered at 2 dose levels (2.5 mg/kg or 3.4 mg/kg) to participants by IV infusion on the Q3W schedule at the study site. The dose will be based on actual body weight calculated at baseline and may be reduced to address toxicities according to protocol guidelines.

Belantamab mafodotin will be administered on Day 1 of each cycle. Premedication is not required unless deemed medically necessary by the investigator, in which case it should

be administered according to institutional recommendations. If an infusion-related reaction (IRR) occurs during administration, the infusion rate may be reduced or halted at the discretion of the investigator depending on the severity of the symptoms.

Participants will be treated until disease progression or until unacceptable toxicity.

Inclusion Criteria: Participants are eligible to be included in the study only if all 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
4. Histologically or cytologically confirmed diagnosis of MM as defined in IMWG, 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 immunomodulatory agent (i.e., lenalidomide or pomalidomide), and to a proteasome inhibitor (e.g., bortezomib, ixazomib or carfilzomib).
    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.
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 function.
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 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. In France, a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

Exclusion Criteria: Participants satisfying any of these criteria are not eligible for assignment to treatment:

1. Systemic anti-myeloma therapy within ≤14 days or 5 half-lives, whichever is shorter, or plasmapheresis within 7 days prior to the first dose of study drug
2. Systemic treatment with high dose steroids (equivalent to ≥60 mg prednisone daily for ≥4 days) within the past 14 days if administered to treat MM or non- MM disease
3. Symptomatic amyloidosis, active POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes), active plasma cell leukemia at the time of screening.
4. Prior allogeneic stem cell transplant (SCT)
5. Current corneal epithelial disease except mild punctate keratopathy
6. Use of an investigational drug within 14 days or five half-lives, whichever is shorter, preceding the first dose of study drug. Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study drugs. Prior BCMA targeted therapy.
7. Evidence of active mucosal or internal bleeding
8. Any major surgery within the last four weeks
9. Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect participant's safety). Participants with isolated proteinuria resulting from MM are eligible, provided they fulfil entry criteria.
10. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions (including lab abnormalities) that could interfere with participant's safety, obtaining informed consent or compliance to the study procedures.
11. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. Note: Stable chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) or hepatobiliary involvement of malignancy is acceptable if participant otherwise meets entry criteria.
12. Malignancies other than disease under study are excluded, except for any other malignancy from which the participant has been disease-free for more than 2 years and, in the opinion of the principal investigators and GSK Medical Monitor, will not affect the evaluation of the effects of this clinical trial treatment on the currently targeted malignancy (MM). Participants with curatively treated non-melanoma skin cancer may be enrolled.
13. Evidence of cardiovascular risk including any of the following:
    a. QTcF interval QTcF > 480 msec (the QT interval values must be corrected for heart rate by Fridericia's formula [QTcF])

b. Evidence of current clinically significant uncontrolled arrhythmias, including clinically significant ECG abnormalities such as 2nd degree (Type II) or 3rd degree atrioventricular (AV) block.

c. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within six months of Screening.

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

e. Uncontrolled hypertension

14. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to belantamab mafodotin, or any of the components of the study treatment.
15. Pregnant or lactating female.
16. Active infection requiring antibiotic, antiviral, or antifungal treatment.
17. Known HIV infection.
18. Presence of hepatitis B surface antigen (HBsAg), or hepatitis B core antibody (HBcAb at screening or within 3 months prior to first dose of study treatment)
19. Positive hepatitis C antibody test result or positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment.
    Note: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.
    Note: Hepatitis RNA testing is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.

1.2. Schedule of Activities (SoA)

All assessments planned for participants in Study 205678 are shown in Table 1 (Screening), Table 2 (On Study Assessments), and Table 3 (End of Treatment and Follow Up Assessments).

Assessments for participants in the ocular sub-study are shown in Table 4. Participants who are enrolled into the lyophilized configuration cohort of belantamab mafodotin (Figure 1) will follow the same assessments and procedures as the main study.

The details of these assessments are provided in footnotes to the table, with more details provided in Section 8.

PACT Phase: Participants who continue to receive study treatment during the PACT phase will be monitored and receive follow-up care in accordance with standard local clinical practice at the participant's particular study site. Only SAEs, AEs leading to discontinuation of study treatment, overdoses, prespecified ocular data, and pregnancy cases will be reported directly to the Sponsor via paper forms (see Section 8.2.1 and refer to the SRM). For participant discontinuing treatment in the PACT phase, no end of treatment visit is required.

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 8.2.9 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 5.1, Section 8.2.8, 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). Digital copies of all scans must be maintained at the investigator site as source document. For sites in Germany: Only MRI is allowed to be used as imaging modality for participants with extramedullary disease.
Beta2 microglobulin	X	
Skeletal survey[11]	X	
Imaging for Extramedullary disease[12]	X	
UPEP (Urine Protein Electrophoresis) 24 hr. urine collection	X	13. Only required for participants with IgD/E myeloma, where serum m-component cannot be followed otherwise.
Urine immunofixation	X	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.
SPEP (Serum Protein Electrophoresis)	X	
Serum Immunofixation	X	
Serum Kappa, Lambda free Light chain, FLC ratio	X	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).
Calcium corrected for albumin (serum)	X	16. Bone Marrow (aspirate preferred) for disease assessment performed within the screening period prior to first dose is acceptable.
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.

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.**
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		

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. Belantamab mafodotin 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 8.2.9 for the list of ophthalmic exam procedures. If there are no corneal signs per the GSK/KVA Scale for treatment related 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 8.2.9 for full list of ocular sub-study exam procedures.
5. If a participant's belantamab mafodotin 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.

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
12-lead ECG [5,10]					As clinically indicated	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 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, it is recommended that vital signs 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. 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. More frequent hematologic monitoring is recommended for subjects with thrombocytopenia and/or neutropenia who are receiving treatment. See Table 11 for further details. 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 5.1, Section 8.2.8, and Appendix 5 for more details. 10. ECGs previously collected and stored centrally may be reviewed by an independent central reviewer. ECGs performed as clinically indicated will be kept locally. See SRM for details on collection regarding ECGs. 11. PK samples to be taken in all participants for belantamab mafodotin 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.
Pharmacokinetics PK[5,]	X[11]	X[12]	X[13]		X[14]	
Anti-drug antibodies[5, 15]	X				X	
Disease Evaluation						
Response assessment[16]				X		
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		
PET/CT upon achieving CR or sCR[19]				Once after CR or sCR		
UPEP (Urine Protein Electrophoresis) 24 hr. urine collection				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.		12. PK samples to be taken for belantamab mafodotin measurement C1D4 and C3D4 (±1 day) 13. One PK sample to be taken for belantamab mafodotin measurement in Cycle 1 and Cycle 3 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 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
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.		

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
Serum Kappa, Lambda free Light chain, FLC ratio				X		(SPD). Digital copies of all scans must be maintained at the investigator site as source document. For sites in Germany: Only MRI is allowed to be used as imaging modality for participants with extramedullary disease.
Calcium corrected for albumin (serum)				X		19. 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.
IgG, IgM, IgA				X		
IgD/E[20]				X		20. Only required for participants with IgD/E myeloma, where serum m-component cannot be followed otherwise
Bone Marrow (BM) Aspiration/Biopsy						
BM for MRD testing[21]				X		21. Minimal residual disease (MRD) to be performed by the central lab 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). If MRD sample is drawn after date of achieving VGPR or CR the repeat testing should take place 6 months and 12 months from the time of initial MRD testing.
BM for disease assessment (aspirate, preferred)				At the time of CR (always) or at time of suspected PD (only if not evident otherwise)		22. In participants achieving a CR, bone marrow biopsy to confirm sCR by IHC.
Bone marrow biopsy to assess sCR by IHC[22]				Only if CR have been achieved on this visit		23. sBCMA samples to be taken in all participants for belantamab mafodotin 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, on Cycle 1 Day 4 (±1 days) and one sample at any time between Cycle 1 Day 8 & Day 15, with the PK samples. Pre-infusion sBCMA samples are collected prior to belantamab mafodotin infusion during each of the first 18 cycles: after which, sBCMA sample should be collected every 3 cycles, i.e. pre-infusion C18D1, C21D1, C24D1, etc.
Biomarker						
Soluble BCMA (serum)[5, 23]	X	X	X		X	24. 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.
cfDNA (plasma)	X					
Optional						
Optional tissue sample at PD for BCMA[24]				X		25. Belantamab mafodotin administration: Study drug administration ±3-day window. In case a dose is delayed, the participant should wait for the next scheduled dose to resume treatment. Please refer to Section 6.2.2

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
Genetics sample (optional)	X					26. Corneal management information: **a)** Prophylactic preservative-free artificial tears must be administered in each eye at least 4-8 times daily beginning on Cycle 1 Day 1 until end of treatment. **b)** At the start of each infusion, participants may apply cooling eye masks to their eyes for approximately 1 hour or as long as tolerated. **b)** Selected sites will participate in an ocular sub-study. 27. NEI-VFQ-25 and OSDI will be administered every 3 weeks even if dose is delayed. Additional assessments may be conducted for those participants who are experiencing a worsening in visual function. 28. EORTC- QLQ-C30 and EORTC QLQ-MY20 should start at week 7 and continue every 6 weeks. 29. Patient Interview (PRO) must be conducted via telephone within 21 days (±7 days) following Day 1 of the fourth treatment cycle (C4D1). The second patient Interview must be completed 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
Treatment						
Premedication if needed	X				X	
Belantamab mafodotin administration[25]	X				X	
Preservative-free artificial tears [26]	X			X	X	
Health Outcomes						
PRO-CTCAE	X			X		
NEI-VFQ-25[27]	X			X		
OSDI[27]	X			X		
EORTC QLQ-C30[28]	X			every 6 weeks		
EORTC QLQ-MY20[28]	X			every 6 weeks		
Patient Interview (PRO) [29]					X (within 21 days after C4 Day 1)	

ADA = Anti-drug Antibody; ALP = alkaline phosphatase BM = bone marrow; BP = blood pressure; C1D1 = Cycle 1 Day 1, etc.; cfDNA = Circulating free DNA; CK = creatine kinase; CRP = C-reactive protein; EM = extramedullary; EOI = End of Infusion; 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; KVA = Keratopathy Visual Acuity; 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; QID = 4 times a day; SOI = start of infusion; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

Table 3 Schedule of Activities: End of Treatment (EOT) and Follow-Up Assessments

Study Assessments	EOT Visit[1]	PFS Follow-up[2]	OS Follow-Up[3]	Notes
Physical Exam	X	X		1. The EOT visit is to assess any residual AEs or toxicities associated with treatment. The visit should occur within 45 days after last dose or before the start of any new anti-cancer therapy. 2. PFS follow-up every 21 days (±7 days) for participants who discontinue IP for a reason other than PD. Disease evaluations will continue until confirmed PD, death, start of a new anticancer treatment, withdrawal of consent, or end of the study whichever occurs first. 3. Survival follow-up every 3 months (±14-day window): After PD is documented, participants will be followed for survival and subsequent anticancer therapy by chart review, phone call, or any form of communication every 3 months. Record participant's survival status and whether subsequent treatment for disease was given. Participant does not need to come in for visit unless they are being followed for corneal signs that are present at the end of study treatment. 4. All related SAEs are to be collected from consent through OS follow-up. 5. End of treatment ophthalmic exam to be performed by an ophthalmologist (or an optometrist if an ophthalmologist is not available). See Section 8.2.9 for the list of ophthalmic exam procedures. 6. Participants with corneal events per the GSK/KVA Scale for treatment related corneal events present at the end of study will continue to be followed at 3 and 6 weeks after the EOT visit and then every 6 weeks (±7 days) for up to 12 months, or until full resolution of ophthalmic changes or deemed clinically stable by ophthalmologist (an optometrist if an ophthalmologist is not available, whichever comes first. Clinically stable is defined as any GSK/KVA Grade 1 exam finding (mild keratopathy) and a one-line change in vision when compared to baseline or no exam findings
Safety				
Adverse Events[4]	X	Related SAEs only	Related SAEs only	
Concomitant Medications	X	X		
Ocular Exam	X[5]	X[6]	X[6]	
ECOG Performance Status	X			
Vital Signs (BP, HR, Body Temperature)	X			
Weight and Height	Weight only			
Hematology[7]	X			
Clinical chemistry[7]	X	X		
Urine Dipstick[7]	X	X		
eGFR (by MDRD formula- see Appendix 10)	X			
Spot urine for albumin/creatinine ratio	X			
CRP	X			
Pregnancy Test[8]	X	X		
Pharmacokinetics PK	X			
Anti-drug antibodies	X			
Disease Evaluation				
Response Assessment[9]	X	X		

Study Assessments	EOT Visit[1]	PFS Follow-up[2]	OS Follow-Up[3]	Notes
Imaging for Extramedullary disease[10]	X [11]	Every 12 weeks if clinically indicated		and a one-line change in vision when compared to baseline or a GSK/KVA Grade 1 exam finding (mild keratopathy) and no change in vision since baseline. Once clinically stable the event will not be followed up further; therefore, no repeat exam necessary. Corneal exams to be performed by an ophthalmologist (an optometrist if an ophthalmologist is not available). See Section 8.2.9 for the list of ophthalmic exam procedures). 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-childbearing potential, obtain follicle stimulating hormone (FSH) and estradiol. See Section 5.1, Section 8.2.8, and Appendix 5 for more details. Final pregnancy test (serum or urine) must be performed in women of childbearing potential at the EOT visit and 4 months after the last dose of study treatment (may be via a urine pregnancy kit mailed to the participant's home with results reported by telephone). 9. For participants who are discontinuing IP due to PD the confirmation based on laboratory parameters 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. For participants with PD due to extramedullary disease, confirmatory scans are not required. The laboratory parameters do not need to be repeated only if the extramedullary disease is the singular site of progression. 10. Imaging is only required for participants with extramedullary disease (CT, MRI, or PET/CT can be applied per local guidance). The same modality
PET/CT upon achieving CR or sCR[12]	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[13]	X	X		
Bone Marrow (BM) Aspiration/Biopsy				
BM for MRD testing[14]		X		

Study Assessments	EOT Visit[1]	PFS Follow-up[2]	OS Follow-Up[3]	Notes
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		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). Digital copies of all scans must be maintained at the investigator site as source document.
Bone marrow biopsy to assess sCR by IHC[15]	Only if CR has been achieved on this visit	Only if CR have been achieved on this visit		
Biomarkers				
Soluble BCMA (serum)	X			
cfDNA (plasma)	X			
Optional				11. 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 for extramedullary disease as clinically indicated.
Optional tissue sample at PD for BCMA[16]	At time of PD	At time of PD		
Health Outcomes				
PRO-CTCAE	X			
NEI-VFQ-25	X	X	X[17]	12. 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.
OSDI	X	X	X[17]	
EORTC-QLQ-C30	X			
EORTC-QLQ-MY20	X			
Patient Interview (PRO)[18]	X			13. Only required for participants with IgD/E myeloma, where serum m-component cannot be followed otherwise.
Survival Status phone call			X	

Study Assessments	EOT Visit[1]	PFS Follow-up[2]	OS Follow-Up[3]	Notes
Subsequent Treatment Information		X	X	14. 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). If MRD sample is drawn after date of achieving VGPR or CR the repeat testing should take place 6 months and 12 months from initial MRD testing 15. In participants achieving a CR, bone marrow biopsy to confirm sCR by IHC. 16. 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 17. Participants who discontinue participation in the study will continue to be assessed during follow-up for up to 12 months from EOT, or until resolution of visual symptoms and/or resolution of ophthalmic changes to baseline or deemed clinically stable by ophthalmologist (an optometrist if an ophthalmologist is not available, whichever comes first. Continue to follow up with participants via telephone who are still experiencing visual symptoms even after discontinuation 18. 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.

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; KVA = Keratopathy Visual Acuity; 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.

Table 4 Ocular Sub-Study Schedule of Activities (Selected Sites Only)

Study Assessments	Screen	Cycle 1-Cycle 4	C1-C4 10 days post Dose exam	Every 3 weeks starting at week 4 (to be completed regardless of dose given)	C5-CX	End of Treatment	PFS Follow-up	OS Follow-up
Informed Consent [1]	X							
Steroid eye drops [2]		X			X[6]			
Preservative-free artificial tears [3]		X[3]	X[3]	X[3]	X[3]			
Full Ocular exams [1,4]	X	X	X	X	X[6]	X	X[6]	X[6]
Specialty Ocular Exams[1, 5, 6]	X	X	X	X		X		

1. Informed consent obtained for inclusion into the ocular sub-study population. Consent must be obtained prior to performing any sub-study protocol-related procedures. All Screening assessments must be performed within 21 days prior to first dose unless otherwise specified. There is no need to repeat screening ocular assessments at C1D1 if they have been done within 21 days of first dose.
2. Steroid eye drops administered as prophylaxis (such as: prednisolone acetate 1.0%, prednisolone phosphate 1%, dexamethasone 0.1%, or equivalent) 1 drop QID starting 1 day prior to each belantamab mafodotin infusion and continuing for a total of 7 consecutive days. Steroid eye drops are to be administered in only one eye as assigned (randomized) centrally by the Sponsor and the site staff will instruct the participant which eye will be treated. The ophthalmologist will remain blinded to this decision. The treating ophthalmologist has discretion to begin steroid drops in the both eyes should the participant develop symptoms requiring intervention as clinically indicated. Intraocular pressure should be monitored if steroid eye drops are used for more than 7 consecutive days. ***Based on data from the primary analysis the use of prophylactic steroid eye drops is no longer required for main study participants. Determination for use of steroid eye drops will be up to the discretion of the treating ophthalmologist for the ocular sub-study participants.
3. Prophylactic preservative-free artificial tears will be administered starting 1 day prior to C1D1 according to Section 8.2.10.1. Outside of the 7-day prophylaxis period they should be administered at least 4-8 times daily as needed, at least one drop in each eye, until end of treatment or as clinically indicated.
4. Participants will undergo 'full' ocular exams as outlined in Section 8.2.9 within 3 days prior to day 1 and on day 10 (±3 days) of Treatment Cycles 1, 2, 3 and 4 (4 doses of study medication). Day 10 exam is only necessary after participant receives study medication.
5. Participants could undergo 'specialty' ocular exams as outlined in Section 8.2.10 on Day 10 (±3 days) of Treatment Cycles 1, 2, 3 and 4 (4 doses of study medication) and within 3 days prior to day 1 of cycles 2,3, and 4. A Day 10 exam is only necessary if participant receives study medication.
6. After Cycle 4 Day 10, participants who have no signs/symptoms should revert to the ocular activities of the general participant population (see main SOA tables), treatment with steroid eye drops, and specialty ocular exams should continue at the discretion of the treating ophthalmologist. If a participant subsequently develops ocular signs/symptoms, or they require additional treatment, participant must be evaluated by an ophthalmologist (an optometrist if an ophthalmologist is not available) and treated as clinically indicated.

2. 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 agents, 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 belantamab mafodotin, nonclinical, and clinical activity are provided in the Investigator's Brochure (IB) [GSK2857916 GlaxoSmithKline Document Number 2013N175128_09, 2021].

2.1. Study Rationale

Before the introduction of daratumumab, patients with disease that is refractory to both immunomodulatory agents 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 belantamab mafodotin.

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

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

Among the 35 participants receiving belantamab mafodotin 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, belantamab mafodotin was well tolerated and adverse events were manageable.

This data supports further development of belantamab mafodotin as monotherapy in patients who failed an anti-CD38 antibody and are refractory to PI and immunomodulatory agent.

2.2. Background – BCMA and Multiple Myeloma

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

2.3. Antibody-Drug Conjugate Belantamab Mafodotin

Belantamab mafodotin 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 belantamab mafodotin is produced as an afucosylated form that generates an enhanced antibody-dependent cellular cytotoxicity (ADCC) response upon binding to FcγRIIIa receptors on the surface of human immune effector cells. The antibody is conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF).

Upon binding to the cell surface, belantamab mafodotin is rapidly internalized and the active drug (cys-mcMMAF) is released inside the cell. The cys-mcMMAF moiety disrupts microtubule networks, leading to cell cycle arrest and apoptosis (ADC mechanism) [Alley, 2009; Pettit, 1998]. This dual mechanism of action of belantamab mafodotin (ADCC and microtubule disruption) enables anti-tumor activity on both dividing and non-dividing cells. In addition, when MM cell lines expressing BCMA are exposed to belantamab mafodotin, it may act as an inducer of immunogenic cell death (ICD) [Kroemer, 2013; Krysko, 2012], representing a potential third mechanism of action. Exposure of dendritic cells to tumor cells undergoing ICD induces an antigen-specific T-cell response, and if it acts similarly in humans could induce the patient's own immune response against the MM tumor. Expression of the target of belantamab mafodotin (BCMA) is restricted to B cells at later stages of differentiation. The target is also present on tumor cells of all patients with MM [Tai, 2015; Tai, 2006].

2.4. Human Experience with Belantamab Mafodotin

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

FTIH study BMA117159/DREAMM-1

In the FTIH DREAMM-1 study, which consisted of a dose escalation phase (Part 1, n=38) and a dose expansion phase (Part 2, n=35), as of the primary analysis cut-off date of 31 August 2018, a total of 73 participants with RRMM received at least 1 dose of belantamab mafodotin [GSK2857916 GlaxoSmithKline Document Number 2013N175128_09, 2021; Trudel, 2019].

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

Phase II study 205678/DREAMM-2

The ongoing Phase II study 205678/DREAMM-2 is evaluating these two IV single agent doses (2.5 and 3.4 mg/kg) administered Q3W until disease progression in participants who have failed at least 3 prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and who are refractory to an immunomodulatory agent and a proteasome inhibitor. A total of 194 participants received frozen drug product in the main cohort and 24 participants received 3.4 mg/kg lyophilized drug product. Primary analysis data from this study indicated no new safety signals, and the profile of adverse events was similar to the experience in the DREAMM-1 study for both arms. Both dose levels, 2.5 and 3.4 mg/kg, were shown to have a positive benefit/risk profile [Li, 2017; Lonial, 2020].

As of the cut-off date of 31 January 2020, the study met its primary endpoint for ORR in both the 2.5 mg/kg [ORR 31% (97.5% CI 21.7, 43.6)] and 3.4 mg/kg [ORR 35% (97.5%CI 24.8, 47.0)] frozen treatments, and the benefit of belantamab mafodotin was supported by the secondary endpoints. The median DoR was 11.0 months (95% CI: 4.2, NR) at 2.5 mg/kg and 6.2 months (95% CI: 4.8, NR) at 3.4 mg/kg. The mPFS in this population was 2.8 months (95% CI: 1.6, 3.6) and 3.9 months (95% CI: 2.0, 5.8), respectively and the median Overall Survival (mOS) was 13.7 months (95% CI: 9.9, NR) at 2.5 mg/kg and 13.8 months (95% CI: 10.0, NR) at 3.4 mg/kg. Positive clinical activity was also demonstrated at the 3.4 mg/kg lyophilised dose [ORR 52% (97.5% CI 28.9, 74.5)].

Safety

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

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

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

2.4.1. Thrombocytopenia

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

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

2.4.2. Corneal Events

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

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

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

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

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

2.4.3. Infusion-related reactions

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

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

2.4.4. Pharmacokinetics and Pharmacodynamics

The pharmacokinetics and pharmacodynamics of belantamab mafodotin (antibody-drug conjugate, including complex with soluble BCMA (sBCMA)) and total monoclonal antibody (total mAb; including complex), and cys-mcMMAF were investigated in 291 participants with RRMM following IV administration at doses from 0.03 to 4.6 mg/kg Q3W in Study BMA117159 (n=73) and at doses of 2.5 or 3.4 mg/kg Q3W in Study 205678 (n=218).

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

Belantamab mafodotin pharmacokinetics were well described by a linear, two-compartment population model, with a time-varying decrease in clearance in a population pharmacokinetic analysis. At Cycle 1, belantamab mafodotin had a systemic clearance of 0.92 L/day, steady-state volume of distribution of 10.8 L, and an elimination half-life of 12 days in participants with RRMM in Study 205678. Over time, clearance was reduced by 28%, resulting in an elimination half-life of 14 days. The time to 50% change in clearance was approximately 50 days.

No clinically significant differences in the pharmacokinetics of belantamab mafodotin or cys-mcMMAF were observed based on age (34 to 89 years), sex, race (African American/Black and White), body weight (42 to 130 kg), mild or moderate renal impairment (eGFR≥30 mL/min/1.73m^2) or mild hepatic impairment (NCI-ODWG classification). Higher serum levels of β_2-microglobulin, IgG, and soluble BCMA (sBCMA) and lower levels of albumin are associated with more advanced multiple myeloma or a higher multiple myeloma disease burden. Higher baseline IgG and sBCMA levels, and lower baseline albumin levels were associated with higher belantamab mafodotin clearance leading to lower average and trough concentrations (Ctau) of belantamab mafodotin. Higher baseline IgG and sBCMA levels were associated with higher cys-mcMMAF central volume of distribution leading to lower cys-mcMMAF Cmax.

In nonclinical studies, cys-mcMMAF had limited metabolic clearance. *In vitro* data suggested that belantamab mafodotin and cys-mcMMAF are unlikely to perpetrate a drug-drug interaction or to be a victim of a drug-drug interaction with inhibitors or inducers of cytochromes (CYP) P450. Cys-mcMMAF was an *in vitro* substrate of organic anion transporting polypeptides (OATP)1B1 and OATP1B3, multidrug resistance associated proteins (MRP)1, MRP2, and MRP3, a borderline substrate of bile salt export pump (BSEP), and a possible substrate of P-glycoprotein (P-gp). Following the administration of belantamab mafodotin to participants with RRMM, only intact cys-mcMMAF was detected in pooled human urine, with no evidence of other MMAF-related urinary metabolites.

Free sBCMA levels were measured in Study BMA117159 and Study 205678. All participants exhibited reductions in free sBCMA concentration at end of infusion compared to baseline at Cycle 1, with a return to near-baseline level by seven days after dosing, reflecting binding of belantamab mafodotin to sBCMA. Maximum decreases ranged from 2% to 97%, which were qualitatively dose-dependent, with larger reductions in free sBCMA at higher doses.

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

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

2.5. Benefit / Risk Assessment

2.5.1. 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 belantamab mafodotin that may impact participant eligibility is provided in the Investigator's Brochure [GSK2857916 (IB) GlaxoSmithKline Document Number 2013N175128_09, 2021].

Table 5 Risk Assessment and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (Belantamab Mafodotin)		
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 belantamab mafodotin in the clinic. Corneal erosions and corneal ulcers (associated with infective keratitis) have also been reported.	Active monitoring for corneal events according to the Schedule of Activities (Table 1). Timely evaluation and management by an ophthalmologist (an optometrist if an ophthalmologist is not available) upon developing corneal related events. Recommendations for dose

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 weeks to months.	delays/reductions are provided in Section 6.2.2 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 belantamab mafodotin is not mandatory but may be considered based on investigator judgment. If an infusion-related reaction occurs during belantamab mafodotin 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 associated with belantamab mafodotin in the clinic.	A hematologic panel is assessed frequently. Supportive therapy (including transfusions) is provided according to standard medical practice, and dose reductions or treatment discontinuations are outlined in Section 6.2.
Neutropenia	Non-serious and serious neutropenia has been observed in the clinic with belantamab mafodotin.	A hematologic panel is assessed frequently. Supportive therapy (growth factors, antibiotics, and treatment of active infections) is provided according to standard medical practice, and dose reductions or treatment discontinuations are outlined in Section 6.2.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential for cardiotoxicity related to an inflammatory response	Preclinical inflammatory findings were seen in the rat mandibular and mesenteric lymph nodes, brachial/sciatic nerves, epididymides, lung, thymus, and atrial epicardium. In the monkey, microscopic effects in spleen and bone marrow at ≥3 mg/kg/week were reflective of a systemic inflammatory response. Electrocardiograms (ECG) were monitored in monkeys for up to 24 hours following repeat dosing and did not produce any evidence of test-article induced electrocardiographic waveform abnormalities, arrhythmias or QTc changes. Serum cardiac troponin I was also measured in the rat and monkey 3-week studies and no treatment-related effects were observed. This potential risk was based on described preclinical findings, however to date there is no evidence of systemic inflammatory response or cardiotoxicity in the clinic.	Monitoring of ECG. Treatment as medically indicated. Monitoring of other cardiac parameters as clinically indicated.
Laboratory abnormalities	Report of non-serious, asymptomatic elevations in LDH / CK levels have been observed in the clinic.	Monitoring of LDH and CK levels will be performed.
Hepatotoxicity	Non-clinical safety experiments demonstrated increased liver weight and elevated at doses of ≥10 mg/kg in rats. Elevations in liver enzymes, and increased mitotic figures in Kupffer cells were observed in monkeys ≥3 mg/kg. These changes were associated with minimal hepatocellular necrosis with cellular infiltrates which were reversible. Extramedullary hematopoiesis was observed in livers of monkeys and rats given ≥10 mg/kg. Non-serious elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST) have been observed in the clinical trials.	Only participants with well-preserved liver function per the inclusion/exclusion criteria will be enrolled. Participants with chronic Hepatitis B (HBV) and C will be excluded from the trial. Liver function tests will be monitored. In case of liver abnormalities, management will be implemented according to clinical practice. Participants that meet liver stopping criteria (Section 7.2.1) will be withdrawn from the study.
Potential for Other Laboratory Abnormalities	Increased skeletal troponin I was observed in the single dose monkey study and increased skeletal troponin I and/or creatine kinase and aldolase in the rat studies. Cases of elevated aspartate aminotransferase (AST), lactic dehydrogenase (LDH) and creatine kinase (CK) alone or concomitant with no clear	Monitoring of laboratory values will be continued as outlined in the protocol. In case of elevations of ≥ x3 ULN, participants should (where possible) have a sample sent for central testing of LDH and CPK isoenzyme levels.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	clinical correlate have been observed in clinical studies.	Participants with contemporaneous constitutional symptoms should be discussed with the Medical Monitor.
Nephrotoxicity	Non-clinical safety experiments have demonstrated primary glomerular injury and tubular degeneration (in rat and monkey). The morphologic changes were accompanied by large molecular proteinuria (albuminuria). The renal changes were dose dependent and reversible.	During the study, participants will be monitored for kidney function by assessing creatinine, estimated glomerular filtration rate (eGFR), electrolytes, and albumin / creatinine ratios (spot urine). Participants will be educated about the need of maintaining adequate urinary output. Management will be implemented according to clinical practice. Dose reductions and treatment stopping criteria will be applied according to Section 6.2 and Section 7.2
Pulmonary toxicity (pneumonitis)	Preliminary nonclinical safety experiments have demonstrated the presence of microscopic changes in the lungs (prominent alveolar macrophages associated with flocculent eosinophilic material; mixed perivascular inflammation) in rats at all doses tested. To date no pneumonitis has been observed in the clinic.	Monitoring for clinical signs and symptoms potentially related to pulmonary toxicity. Further diagnostic tests and management will be implemented immediately according to recommendations provided in Section 6.2.2.
Immunosuppression	In nonclinical studies belantamab mafodotin has been associated with decrease in immunoglobulins in monkeys. An increase in immunoglobulins was seen in rats (rats are not an antigen specific species for belantamab mafodotin).	Participants will be monitored for infections. Participants will receive immediate treatment according to standard practice.
Potential for overdose specific to the preparation of study drug	A frozen liquid configuration of belantamab mafodotin will be used to **initiate** this trial. An independent cohort of approximately 25 additional participants will be enrolled and administered a lyophilized configuration of compound (upon availability). A separate set of preparation instructions will need to be followed in order to prevent potential overdose.	Proactive communication and training will be provided to the sites ahead and at the time that the lyophilized configuration is introduced at the site. There is no specific antidote for overdose with belantamab mafodotin. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care should be instituted, as dictated by the participant's clinical status.
Embryo-Fetal Toxicity	Nonclinical reproductive studies with belantamab mafodotin have not been conducted. Embryo-fetal toxicity is expected due to the cytotoxic component, cys-mcMMAF via nonspecific uptake and/or BCMA-mediated toxicity (due to reports of BCMA expression in human placental cells [Langat, 2008]). Use of belantamab mafodotin in pregnant women may cause fetal harm.	See contraception requirements in Section 11.5

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Impaired Male Fertility	In animal studies, belantamab mafodotin treatment has resulted in testicular toxicity and adverse effects on spermatogenesis. Reversibility of testicular toxicity is unknown at this time.	Men will be advised to have sperm samples frozen and stored before treatment. See contraception requirements in Section 11.5
Risks from Study Procedures		
Bone marrow aspiration/biopsy	Pain, infection, bleeding may occur after the procedure	Participants will be treated according to institution's practice
Incidental findings during image acquisition:	During the acquisition of imaging data (e.g., MRI, CT, PET, ECHO), non-MM disease or drug related clinically relevant abnormalities could be found by the radiographer or echocardiographer performing the exams.	Copies of all medical images that include non-disease, clinically relevant abnormalities will be shared with the site for storage

TCR = T-cell receptor; mAb = Monoclonal antibody; AEs = Adverse Events

2.5.2. Benefit Assessment

Belantamab mafodotin has demonstrated strong single-agent activity in 2 clinical studies conducted in heavily pre-treated participants with RRMM (Q3W schedule via IV administration). Based on the available data for the FTIH study BMA117159, as of the efficacy cut-off of 31 August 2018, participants receiving belantamab mafodotin at 3.4 mg/kg had an ORR of 60% (95% CI: 42.1, 76.1) and a median PFS of 12.0 (95% CI: 3.1, NR) in a heavily pre-treated population (57% ≥5 prior lines of therapy) [Trudel, 2019; Trudel, 2018]. For participants refractory to both immunomodulators and proteasome inhibitors (N=32), the confirmed overall response rate was 56% (95% CI: 37.7%, 73.6%). In 205678/ DREAMM 2, both dose levels evaluated, 2.5 and 3.4 mg/kg, had a positive benefit/risk profile [Li, 2017; Lonial, 2020].

Based on this profile, it is reasonable to hypothesize that the use of belantamab mafodotin as a single agent will provide an improved benefit compared to the combination regimen of pom/dex in this patient population.

2.5.3. Overall Benefit-Risk Conclusions

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

3. OBJECTIVES AND ENDPOINTS

The purpose of this Phase II study is to evaluate the safety and efficacy of belantamab mafodotin in participants with RRMM who have received at least 3 prior lines of anti-myeloma therapy, have failed an anti-CD38 antibody, and are refractory to PI and

immunomodulatory agents. See Table 6 for the primary, secondary, exploratory, and other objectives, along with the corresponding endpoints.

Table 6 Objectives and Endpoints for Study 205678 - Belantamab Mafodotin in RRMM Participants Previously Treated with an Anti-CD38 Antibody

Objectives	Endpoints
Primary Objective	
To evaluate the clinical efficacy of 2 doses of belantamab mafodotin 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 belantamab mafodotin 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 (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 belantamab mafodotin in participants with RRMM.	The safety profile of belantamab mafodotin 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 belantamab mafodotin	Plasma concentrations of belantamab mafodotin (ADC, total mAb, and cys-mcMMAF) Derived pharmacokinetic parameter values (e.g., AUC, Cmax, tmax, t½), as data permit.

Objectives	Endpoints
To assess anti-drug antibodies (ADAs) against belantamab mafodotin	Incidence and titers of ADAs against belantamab mafodotin
Participant self-reported symptomatic adverse effects by evaluation of tolerability of belantamab mafodotin	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 belantamab mafodotin	Possible relationship between host genetic variation and response to belantamab mafodotin
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 belantamab mafodotin exposure and clinical endpoints	Explore relationships between belantamab mafodotin 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 belantamab mafodotin 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 belantamab mafodotin; plasma concentrations of belantamab mafodotin (ADC, total mAb, and cys-mcMMAF) 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.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase II, open-label, two-arm, randomized, multicenter study to evaluate the efficacy and safety of belantamab mafodotin 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.

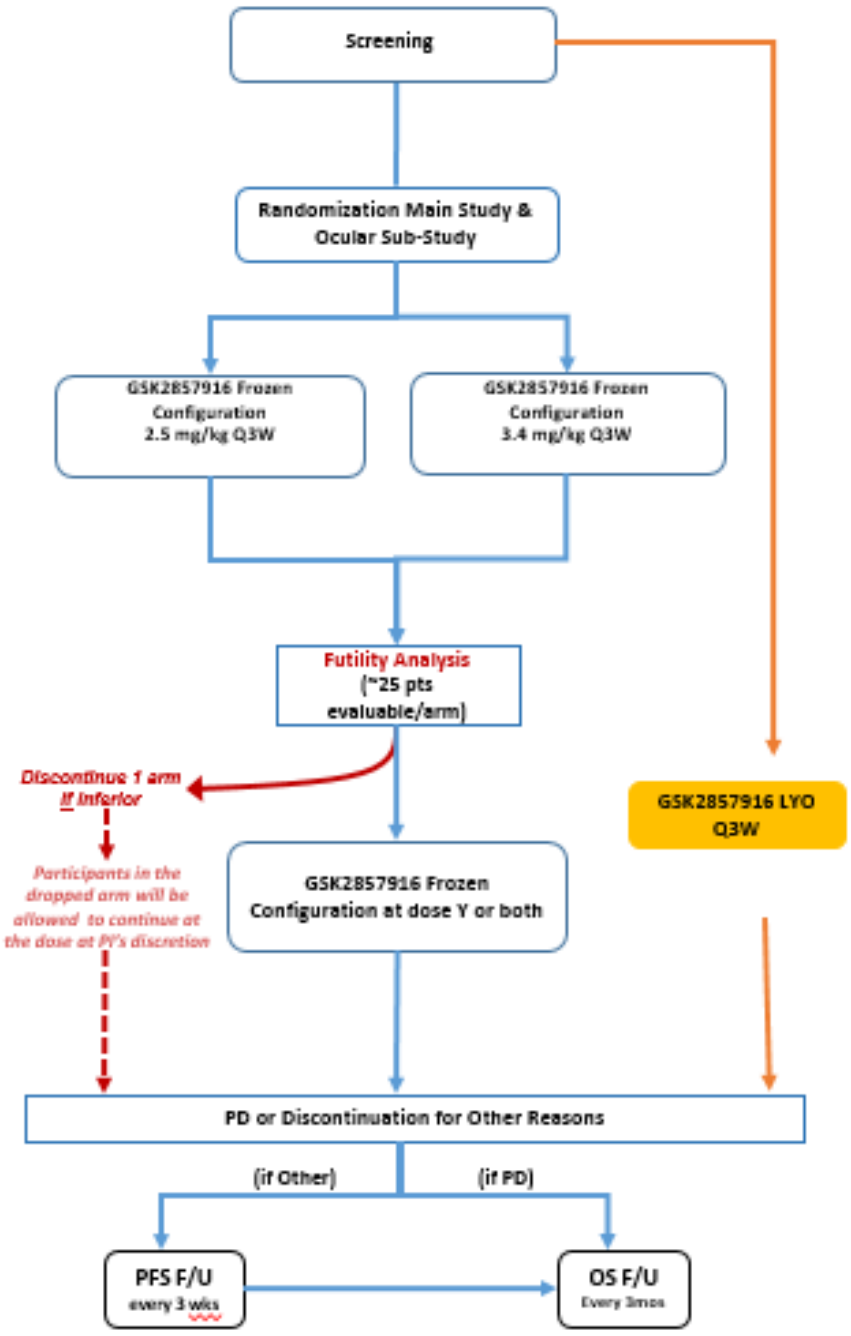
The study will use frozen solution of belantamab mafodotin for those participants enrolled into 2 dose arms.

The design includes an independent cohort of approximately 25 participants who will receive a lyophilized configuration of belantamab mafodotin. 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)

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.

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 1.2).

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 1.2).

Additional details of the individual assessments are provided in Section 8.

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 9.5.9 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 1.2). 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.

If the 3.4 mg/kg dose is discontinued, participants who are currently treated at this dose will have the option to switch to 2.5 mg/kg:

- In cases when the participant has not achieved a maximum benefit of CR or sCR, did not experience toxicity requiring a dose reduction, and is willing to continue at the higher dose level, the participant will have the option to stay on their original dose upon signing an additional informed consent informing them that a lower dose level has been selected for the remaining participants.

The final analysis of the primary endpoint (ORR) will be performed 6 months after the last participant is randomized. The study will continue and participants will remain on treatment and continue to be followed.

For participants who discontinue study treatment for reasons other than PD, disease evaluations will continue to be performed at 3-week intervals until confirmed PD, death, start of a new anticancer treatment, withdrawal of consent, or end of the study whichever occurs first. After PD is documented, participants will be followed for survival and subsequent anticancer therapy every 3 months until study ends.

Pharmacokinetic samples will be collected from all participants. The collection of PK samples for determination of belantamab mafodotin plasma (ADC and total antibody) and cys-mcMMAF concentrations will allow characterization of the PK profile and support investigation of its pharmacology.

Genetic testing (in consenting participants) and biomarker research samples will also be conducted on samples from all participants prior to the first dose. Patient-Reported Outcomes (PRO) data will be collected at each clinic visit.

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the SOA (Table 1 to Table 4) is essential.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Reference Manual (SRM). The SRM will provide the site personnel with administrative and detailed technical information that does not affect participant safety.

Following 39 months post LSFD, the study will move into the PACT phase where the study remains open only to provide continued access to treatment for study participants who are continuing to derive clinical benefit. At that time, the collection of new data for participants who no longer receive study treatment will stop and the clinical trial database will be closed. Participants in survival follow-up will be considered to have completed the study. Those participants still benefiting from study drug in the opinion of their treating physician may continue to receive study drug and only SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases, and pre-specified ocular data will be reported directly to GSK using paper forms. The end of study (EOS) is defined as the date of the last visit of the last participant in the study.

4.2. Number of Participants

Approximately 170 participants were initially planned to be screened to enroll a minimum of 155 participants at approximately 60 investigational sites globally. A minimum of 130 participants (65/arm) were planned to be enrolled to 2 arms receiving frozen liquid solution of belantamab mafodotin which includes ~30 participants from the ocular sub-study. Approximately 200 participants will be enrolled in the frozen liquid portion of the study. Approximately twenty-five additional participants will be enrolled into the independent lyophilized drug product cohort.

4.3. Participant Completion

A participant will be considered to have completed the study if he or she has received at least one dose of the study treatment and is in follow-up, or has died when the study is closed, and has not withdrawn consent from study participation.

4.4. Scientific Rationale for Study Design

Patients with RRMM who have relapsed after prior treatment with an anti-CD38 antibody and are refractory to a PI and an immunomodulatory agent represent a population of unmet medical need, for whom there is no approved treatment option. Given the clinical activity demonstrated in the BMA117159 study, treatment with belantamab mafodotin may offer a benefit to this patient population. It is also expected that due to its unique mechanism of action, belantamab mafodotin may be able to overcome the resistance to previously used drugs in the MM population.

Belantamab mafodotin is the first-in-class ADC targeting BCMA. Preliminary clinical data for belantamab mafodotin monotherapy from Study BMA117159 among 35 participants indicate an ORR of 60% [95% CI: 42.1%, 76.1%], with 51% of participants (n=18) having deep responses of VGPR or better. The median 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]. Of note, the ORR for participants previously treated with daratumumab (n=14) was 43% (95% CI: 17.7, -71.1). Fifty nine percent of the treated population had 5 of more prior treatments.

The response rate observed in this population is higher than response rates observed in similarly defined patient populations treated with other recently approved drugs (ORR ranging from 23.7% to 33.1% for Carfilzomib, pomalidomide and daratumumab) [Siegel, 2012; Usmani, 2016; Kumar, 2008]. Given the evidence of clinical activity and manageable safety/tolerability profile demonstrated to date, the current evidence supports further development.

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 4.5 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, 2014]. 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 immunomodulatory agent [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.

4.5. Dose Justification

Belantamab mafodotin 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 belantamab mafodotin.

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 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, belantamab mafodotin 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 belantamab mafodotin has been selected for monotherapy

treatment. Although no responses were observed at the 2.5 mg/kg dose in Study BMA117159, 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.

The next highest dose level to 3.4 mg/kg is 2.5 mg/kg, a dose reduction of ~25%. The preliminary population pharmacokinetic analysis estimated that the between-participant variability in belantamab mafodotin clearance was ~50%, and the variability in Cmax values was ~20%; therefore, some overlap in exposure is expected between the two dose levels. Despite this pharmacokinetic overlap, the Bayesian logistic regression modeling based on the full clinical dataset (see below) indicated that a dose level of 2.5 mg/kg had a lower predicted response rate as well as a lower predicted rate of ≥Grade 2 corneal event. The next lower dose level, 1.92 mg/kg, had a much lower predicted response rate and was not considered suitable for further exploration. Therefore, 2.5 mg/kg was selected as the second dose level for evaluation in this study. The interim analysis will help to minimize exposure to a potentially less effective dose level.

Bayesian logistic regression model of dose-response for ORR and corneal event rate
To further explore the dose selection, Bayesian logistic regression model (BLRM) was used to determine the dose-response relationships for both ORR and ≥Grade 2 corneal event rate (as determined by NCI CTCAE grading) separately using all 73 participants with RRMM in Study BMA117159 (Figure 2). Table 8 displays the predicted response rate and predicted ≥Grade 2 corneal event rate at dose levels of 3.4, 2.5, and 1.92 mg/kg. The model showed that the posterior probability of observing an ORR ≥30% is 100% in the 3.4 mg/kg dose group, 83% in the 2.5 mg/kg dose group, and 29% in the 1.92 mg/kg dose group. Similarly, the posterior probability of observing ≥Grade 2 corneal event rate is also higher in the 3.4 mg/kg dose group.

Figure 2 Fitted Dose-Response Plot for ORR and ≥ Grade 2 Corneal Event Rate

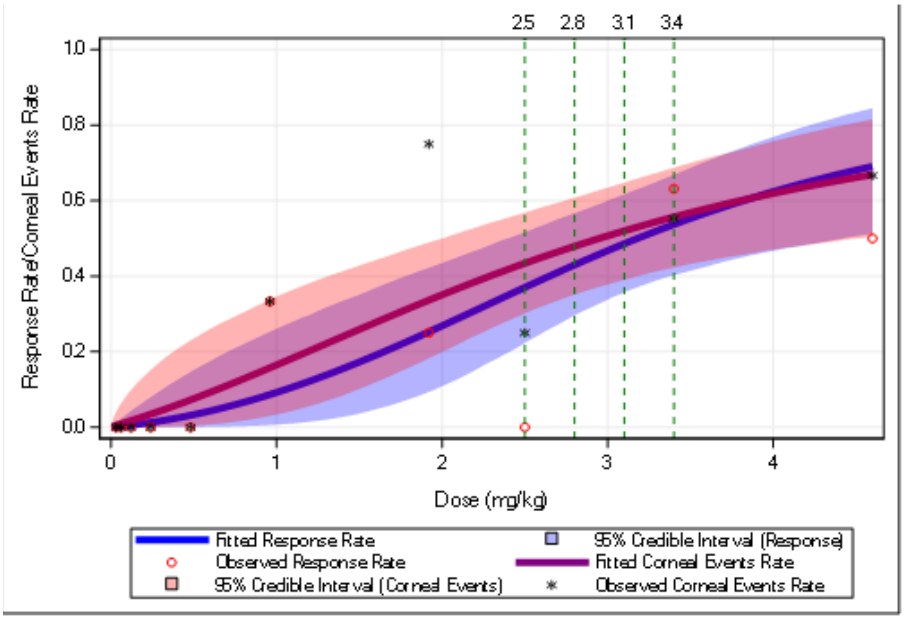


Table 8 Summary of Predicted Mean Response and Mean ≥Grade 2 Corneal Event* and 95% Credible Intervals (Parts 1 and 2, Study BMA117159)

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 belantamab mafodotin 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.

Overall, there were no new safety signals identified in the 205678 study, and the profile of adverse events was similar to the experience in BMA117159 for both arms. The dose of 2.5 mg/kg appears to have a lower incidence of adverse events and less frequent dose delays and reductions, and it results in similar efficacy with 3.4 mg/kg dose as measured by ORR.

In summary, the selection of the dose of 2.5 mg/kg Q3W for future single agent studies with belantamab mafodotin is based on the available data with single agent belantamab mafodotin in heavily pretreated patients with relapsed/refractory MM from 2 studies: BMA117159 and 205678, which showed clinically meaningful efficacy with a manageable safety profile in a heavily pre-treated patient population.

4.6. End of Study Definition

The study will end when all participants including the participants in PACT phase have either died, progressed, or have withdrawn consent.

A final DCO representing the end of data collection, prior to the EOS, is defined as 39 months post LSFD. Following the final DCO date the study will move into the PACT phase and the clinical study database will be closed to new data. Participants who are receiving belantamab mafodotin may continue to receive belantamab mafodotin if they are gaining clinical benefit as assessed by the investigator until they meet any protocol-defined treatment discontinuation criteria. Participants in survival follow-up at the time of the final DCO date will be considered to have completed the study. Although the clinical study database will be closed at the time of the final DCO date, the study remains open until all participants discontinue study treatment and complete the 70-day safety follow-up and the EOS is reached.

The EOS is defined as the date of the last visit of the last participant in the study. A participant is considered to have completed the study if he/she has completed all periods of the study including the last visit.

5. STUDY POPULATION

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

5.1. 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 immunomodulatory agent (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 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.

5.2. Exclusion Criteria

Participants satisfying any of these criteria are not eligible for assignment to treatment:

1. Systemic anti-myeloma therapy within ≤14 days or 5 half-lives, whichever is shorter, or plasmapheresis within 7 days prior to the first dose of study drug
2. Systemic treatment with high dose steroids (equivalent to ≥60 mg prednisone daily for ≥4 days) within the past 14 days if administered to treat MM or non-MM disease
3. Symptomatic amyloidosis, active 'polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes' (POEMS) syndrome, active plasma cell leukemia at the time of screening.
4. Prior allogeneic stem cell transplant
5. Current corneal epithelial disease except mild punctate keratopathy
6. Use of an investigational drug within 14 days or five half-lives, whichever is shorter, preceding the first dose of study drug. Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study drugs. Prior BCMA targeted therapy.
7. Evidence of active mucosal or internal bleeding
8. Any major surgery within the last four weeks

9. Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect participant's safety). Participants with isolated proteinuria resulting from MM are eligible, provided they fulfil criteria given in Table 9.
10. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions (including lab abnormalities) that could interfere with participant's safety, obtaining informed consent or compliance to the study procedures.
11. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. Note: Stable chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) or hepatobiliary involvement of malignancy is acceptable if participant otherwise meets entry criteria.
12. Malignancies other than disease under study are excluded, except for any other malignancy from which the participant has been disease-free for more than 2 years and, in the opinion of the principal investigators and GSK Medical Monitor, will not affect the evaluation of the effects of this clinical trial treatment on the currently targeted malignancy (MM). Participants with curatively treated non-melanoma skin cancer may be enrolled.
13. Evidence of cardiovascular risk including any of the following:
    a. QTcF interval QTcF > 480 msec (the QT interval values must be corrected for heart rate by Fridericia's formula [QTcF])
    b. Evidence of current clinically significant uncontrolled arrhythmias, including clinically significant ECG abnormalities such as 2nd degree (Type II) or 3rd degree atrioventricular (AV) block.
    c. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within six months of Screening.
    d. Class III or IV heart failure as defined by the New York Heart Association functional classification system [NYHA, 1994]
    e. Uncontrolled hypertension
14. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to belantamab mafodotin, or any of the components of the study treatment.
15. Pregnant or lactating female.
16. Active infection requiring antibiotic, antiviral, or antifungal treatment.
17. Known HIV infection.
18. Presence of hepatitis B surface antigen (HBsAg), or hepatitis B core antibody (HBcAb at screening or within 3 months prior to first dose of study treatment
19. Positive hepatitis C antibody test result or positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment.

Note: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.
Note: Hepatitis RNA testing is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.

5.3. Lifestyle Restrictions

Contact lenses are prohibited while the participant is on study.

5.4. Screen Failures

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

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

6. TREATMENTS

Study treatment is defined as any investigational treatment intended to be administered to a study participant according to the study protocol. Belantamab mafodotin will be administered intravenously.

Belantamab mafodotin will be administered intravenously, at the study sites, as either 2.5 mg/kg or 3.4 mg/kg calculated dose.

Product name:	**Belantamab mafodotin**
Dosage form:	Frozen liquid, 30 mg/vial solution in single-use vial or Lyophilized powder, 100 mg/vial in single-use vial for reconstitution (independent cohort with approximately 25 participants) (Participants continuing treatment in PACT phase after final analysis may receive lyophilized study drug.)
Unit dose strength(s)/Dose Level(s):	30 mg/vial / 2.5 or 3.4 mg/kg (Frozen liquid) or 100 mg/vial / 2.5 or 3.4 mg/kg (Lyophilized powder)
Route of Administration	Delivered as IV solution over at least 30 minutes*.
Dosing instructions:	Dilute belantamab mafodotin in normal 0.9% saline to the appropriate concentration for the dose. Doses of belantamab mafodotin are to be administered as an IV infusion via an infusion pump. See Investigator's Brochure for compatible administration materials. *For lyophilized powder only:* Reconstitute belantamab mafodotin lyophilized powder 100 mg/vial 2.0mL of water for injection (WFI); dilute with saline before use.
Manufacturer/ Source of Procurement:	GSK/Baxter

*Infusions may be prolonged in the event of an infusion reaction. If multiple participants experience clinically significant infusion reactions, the infusion rate may be slowed for all future administrations of study treatment(s) for all participants. Should this global change in infusion rate be required, it will be communicated to the sites in writing.

6.1. Belantamab Mafodotin Treatments Administered

Belantamab mafodotin is to be administered at a calculated dose of 2.5 mg/kg or 3.4 mg/kg as an IV infusion, via an infusion pump. Administration of belantamab mafodotin will be documented in the clinic source documents and reported in the electronic case report form (eCRF). The time of start and end of infusion will be documented in eCRF.

Belantamab mafodotin will be administered on Day 1 of each cycle. Premedication is not required prior to infusion unless deemed medically necessary by the investigator, in which case it should be administered according to institutional recommendations.

Any participant experiencing an IRR must receive appropriate medical treatment. When the participant's condition is stable, the infusion may be restarted at a slower rate. For details on restarting the belantamab mafodotin infusion after interruption for IRR, please see Table 11.

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

Participants will be treated until disease progression, or until death, or until unacceptable toxicity (including but not restricted to meeting stopping criteria as outlined in Section 7.1).

Participants continuing treatment during PACT phase after final analysis may receive lyophilized study drug. Lyophilized belantamab mafodotin 100 mg/vial is supplied as a white to yellow powder in a single-dose vial for reconstitution and further dilution.

6.2. Dose Modification

Dose modifications will be managed according to Dose Reduction Criteria and Guidance provided in Table 11 and Table 12.

6.2.1. Adjustments Due to Body Weight

The actual body weight in kg at baseline (assessed on Cycle 1 Day 1 prior to dosing) will be used for dose calculation of belantamab mafodotin in all participants during the treatment period. However, if the change of body weight is greater than 10%, the dose must be recalculated based on the actual body weight at the time of dosing.

6.2.2. Dose Reductions for Toxicity

After Cycle 1, participants may have their dose delayed or reduced for toxicities according to the recommendations.

See Table 11 for dose modifications guidelines for belantamab mafodotin for specific toxicity related AEs and Table 12 for guidelines for drug-related toxicities, not otherwise specified AEs.

See Table 13 for dose modification guidelines for cornea-related AEs associated with belantamab mafodotin.

Permitted dose reductions for belantamab mafodotin are shown in Table 10.

Table 10 Permitted Dose Reductions

Starting dose	1st reduction	2nd reduction
3.4 mg/kg	2.5 mg/kg	1.92 mg/kg
2.5 mg/kg	1.92 mg/kg	--

- If the participant cannot tolerate the drug after the allowed dose reductions, he or she must be withdrawn from the study for lack of tolerability.
- Only 1 dose reduction (to 1.92 mg/kg) is permitted for the lower starting dose of 2.5 mg/kg.
- In case of full resolution of symptoms which lead to dose reduction, further treatment at the previous dose may be considered by the investigator.

Dosing delays are permitted in the case of medical/surgical events or for logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, participant vacation, and/or holidays, but not for participants' decision to delay treatment). If a dose is delayed, the participant should wait for the next scheduled dose to resume treatment. In individual cases where in the judgement of an investigator waiting a full cycle to resume treatment after delay (skipping dose) related to toxicity which has resolved would be detrimental to patient's health- the Principal Investigator should contact Medical Monitor to discuss an earlier re-start. An earlier re-start may be considered only for patients who have recovered from toxicity to at least G1 or less. The

dosing with belantamab mafodotin cannot occur more frequently than every 21 days (± 3-day window). In such cases efficacy and safety assessments must continue to be conducted every 3 weeks in line with initial efficacy and safety assessments on study, which may result in 2 separate visits (1 for dosing, 1 for disease assessments) (Table 2).

Evaluations associated with a Dose (Table 2) would be entered into the eCRF under the next scheduled cycle.

The reason for any dose delay must be documented in the participant's eCRF and clinic record.

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

Table 11 Dose Modification Guidelines for Belantamab Mafodotin-Related Adverse Events

Toxicity	Grade/description of toxicity	Recommendations for belantamab mafodotin
Elevated serum creatinine which cannot be explained by concomitant sepsis, TLS, other severe condition with fever, or dehydration	If absolute serum creatinine increases from baseline by >0.5 mg/dL	• Repeat serum creatinine within 48 hours • If confirmed: withhold therapy, institute treatment and monitoring as clinically indicated, and follow for resolution • Discuss any further dosing with Medical Monitor[a]
Serum creatinine >Grade 3	>3.0 mg/dL from baseline or 3.0-6.0xULN	• Provide appropriate medical treatment. • Permanently discontinue treatment with belantamab mafodotin
Spot urine (albumin / creatinine ratios)	>2000 mg/g (or 224 mg/mmol)	• Re-test (at least 7 days apart). • If not confirmed, continue belantamab mafodotin at 100% dose • If confirmed on re-test and no clear evidence of disease progression ○ Interrupt treatment with belantamab mafodotin ○ Repeat testing within 4 weeks i. If spot urine <2000 mg/g (224 mg/mmol), may restart belantamab mafodotin with a dose reduction ii. If spot urine remains >2000 mg/g (224 mg/mmol) after 4 weeks, permanently discontinue belantamab mafodotin and withdraw participant from study; provide treatment as clinically indicated and follow for resolution[a]
Thrombocytopenia (on days of dosing	3 or 4	• Withhold treatment until thrombocytopenia recovered to Grade 2 or less (≤G2). • If Grade 3-4 thrombocytopenia is considered disease-related, treatment may be continued with more frequent hematology monitoring, until recovery to Grade 2 or less. Dose reduction should be considered in those patients • Implement supportive treatment (e.g. transfusion) as clinically indicated and per local practice.

Toxicity	Grade/description of toxicity	Recommendations for belantamab mafodotin
Febrile neutropenia	Defined as: single temp of 38.3°C, or sustained 38°C for >1 hr. AND ANC <1.0 x 10^9/L	• Withhold belantamab mafodotin and immediately hospitalize participant with appropriate management, per local institutional guidance. • Consider additional supportive treatment per local practice (e.g. growth factors). • Upon recovery consider a dose reduction of belantamab mafodotin, if neutropenia was drug related
Neutropenia	Grade ≥3 (Defined as ANC <1.0x10^9/L	• If noted on Day 1 of any cycle, withhold belantamab mafodotin. Consider more frequent hematology (CBC) monitoring as clinically indicated, until recovery to Grade 2 or less. • Resume belantamab mafodotin at pre-held dose once neutropenia recovers to Grade ≤ 2 (ANC ≥ 1.0x10^9/L) • Implement supportive care as clinically indicated and per local practice.
	In case of recurrence of frequent episodes of neutropenia <1.0 × 10^9 /L	• Consider dose reduction of belantamab mafodotin, if it was drug-related.
Infusion Reaction[b]	2	• Stop the infusion, provide medical treatment and continue at half the original infusion rate after resolution to Grade 0-1
	3	• Further treatment with belantamab mafodotin needs to be discussed with Medical Monitor. Continuation only allowed after recovery to ≤Grade 1 and with pre-medication, and extension of infusion time to 2-4 hours. Any future infusion needs to be pre-medicated
	4	• Permanently discontinue
Pneumonitis	2	• Continue treatment when toxicity resolves to Grade 0-1
	Grade 3-4	• Permanently discontinue

a. Medical Monitor may consult GSK's 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 belantamab mafodotin 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 Belantamab Mafodotin Treatment-Related Corneal Events

Grade per GSK/KVA scale	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
***Recommended** **Dosage Modifications**	Continue treatment at current dose.	Withhold belantamab mafodotin until improvement in **both** corneal examination findings and changes in BCVA to Grade 1 or better and resume at same dose.	Withhold belantamab mafodotin until improvement in **both** corneal examination findings and changes in BCVA to Grade 1 or better and resume at reduced dose. If already on lowest dose, participant should continue treatment after recovery to Grade 1 or better with the same dose.	Consider permanent discontinuation of belantamab mafodotin. If based on benefit risk assessment, treatment of belantamab mafodotin is being considered, withhold treatment until improvement in **both** corneal examination findings and change in BCVA to Grade 1 or better and resume at reduced dose. If already on lowest dose, participant should continue treatment after recovery to Grade 1 or better with the same dose.
Corneal Management Care Regardless of Grade	**Preservative-free artificial tears:** Increase to 1 drop as frequently as every 2 hours, as needed			

Grade per GSK/KVA scale	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
	Based on exam findings and symptoms the treating ophthalmologist may prescribe additional treatments (e.g. steroid eye drops, bandage contact lens, topical treatments, etc.)			

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

6.2.3. 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 belantamab mafodotin, including a GSK/KVA (Keratopathy Visual Acuity) scale for treatment related corneal toxicities 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/KVA Scale 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 (an optometrist if an ophthalmologist is not available), whichever comes first. Clinically stable is defined as:

- Any GSK/KVA Grade 1 exam finding (mild keratopathy) and a one-line change in vision when compared to baseline or,
- No exam findings, and a one-line change when compared to baseline or,
- Any GSK/KVA Grade 1 exam finding (mild keratopathy) and no change in vision from baseline

At the selected sites, participants in the ocular sub-study will undergo additional ophthalmic exams (see Section 8.2.10).

6.3. 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 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.

6.4. 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 8.2.10 and Appendix 9), the treating ophthalmologist will remain blinded as to which eye receives the prophylactic corticosteroid treatment.

6.5. 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 a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

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

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

In the case of unintentional occupational exposure notify the monitor, Medical Monitor, or GSK study contact.

6.6. Treatment Compliance

Belantamab mafodotin will be administered intravenously to participants at the site. Administration will be documented in the source documents and reported in the eCRF. Study treatment is based on body weight calculation and may be reduced for toxicity for individual participants according to protocol guidelines.

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

6.7. Concomitant Therapy

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

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

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

Participants will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until the end of the study (Final Study Visit). Any concomitant medication(s), including non-prescription medication(s) and herbal product(s), taken during the study will be recorded in the electronic case report form (eCRF). Additionally, a complete list of all prior anti-cancer therapies will be recorded in the eCRF.

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by GSK and stored in the study file. The SRM will be updated to include this information. Any such changes will be communicated to the investigative sites in the form of a letter.

6.7.1. Permitted Medication(s)

Participants should receive full supportive care during the study, including transfusions of blood products, growth factors, and treatment with antibiotics, anti-emetics, antidiarrheal, and analgesics, as appropriate. Concomitant therapy with bisphosphonates is allowed. Participants may receive local irradiation for pain or stability control.

6.7.2. Prohibited Medication(s)

Chronic treatment with oral steroids is prohibited while the participant is on study, unless for treatment of acute complications related to study treatment, or pre-medication prior to belantamab mafodotin infusion. Steroids may be used to treat infusion-related reactions. Inhaled steroids are allowed for management of asthma or COPD exacerbations. Chronic low dose replacement therapy (less than or equal to 10 mg prednisolone) is allowed in participants with adrenal insufficiency.

Elimination pathways for belantamab mafodotin and cys-mcMMAF have not been characterized in humans. Cys-mcMMAF was not an inhibitor, an inducer, or a good substrate of cytochrome P450 enzymes *in vitro*. Cys-mcMMAF was shown to be a substrate of P-glycoprotein (P-gp) and Organic Anion Transporting Proteins (OATP) 1B1 and 1B3 transporters *in vitro*. Caution should be exercised when belantamab mafodotin is combined with strong inhibitors of P-gp, and strong inhibitors of OATP1B1 and OATP1B3 should be avoided unless considered medically necessary. See the SRM for more information.

Other prohibited therapies include:

- Plasmapheresis: prohibited from 7 days prior to first dose through the end of study.
- Any other anti-cancer therapy not specified in this protocol, and any investigational agents other than belantamab mafodotin.

6.7.3. Prohibited Device(s)

Contact lenses are prohibited while the participant is on study.

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

Study participants that continue to benefit from study intervention beyond the DCO date will continue to have access to study intervention until the EOS as defined in Section 4.6. There is no planned intervention following the EOS.

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

Refer to the SoA (Table 3) for follow-up assessments of participants who are to be followed for disease progression and survival after they permanently discontinue from study drug until DCO date.

6.8.1. Continued Access to Study Intervention After Data Cut-off prior to EOS (PACT Phase)

Participants receiving belantamab mafodotin following 39 months post LSFD, may continue to receive belantamab mafodotin, if in the opinion of their treating physician, they are benefiting from continued treatment, and they do not meet any protocol-defined treatment discontinuation criteria (see Section 7). Study treatment will continue until a study treatment discontinuation criterion (see Protocol Section 7), as assessed by the investigator, has been met.

Participants who continue study treatment in the PACT phase will be cared for in accordance with local standard clinical practice. Additional guidance on treatment with the study drug, patient management, dispensing of study treatment and maintaining study

drug accountability in the PACT phase is provided in the SRM. Information relating to participant care will be recorded on their medical records. Participants will continue to be monitored for all SAEs, AEs leading to treatment discontinuation, overdoses, pregnancy cases and pre-specified ocular data that must be reported to GSK on paper form until 70 days after the participant's last dose of study treatment in accordance with Section 8.2 (Reporting of Serious Adverse Events). Pre-specified ocular data will also be reported until resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up. For dispensing of study treatment and maintaining study drug accountability in the PACT phase please refer to the SRM. All other assessments will revert to standard of care at their site.

7. DISCONTINUATION CRITERIA

7.1. Discontinuation of Study Treatment

Participants will receive study treatment until disease progression, unacceptable toxicity, or death (including but not restricted to meeting stopping criteria for significant toxicity as outlined in Section 7.1).

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

- disease progression or unacceptable toxicity.
- participant has met any of the protocol defined safety stopping criteria (Section 6.2).
- deviation(s) from the protocol
- request of the participant or proxy (withdrawal of consent by participant or proxy)
- investigator's discretion
- concurrent illness that prevents further administration of study treatment(s)
- pregnancy
- participant is lost to follow-up
- study is closed or terminated

The primary reason study treatment was permanently discontinued must be documented in the participant's medical records and electronic case report form (eCRF)

If the participant voluntarily discontinues from treatment due to toxicity, AE (adverse event) must be recorded as the primary reason for permanently discontinuation on the eCRF.

Once a participant has permanently discontinued from study treatment, the participant will not be allowed to re-enter the study.

All participants who discontinue from study treatment for any reason other than confirmed progression or death will complete safety assessments, and will be followed up for PFS, OS, and subsequent anti-cancer therapy after study as specified in the SOA (Table 1).

PFS Follow-up:

All participants who permanently discontinue study treatment in the absence of disease progression will remain in the study and will be followed for progression according to the protocol schedule until:

- New anti-cancer therapy is initiated
- Progression is documented, or
- Death occurs

OS Follow-up:

All participants who permanently discontinue study treatment will be followed for survival and new anti-cancer therapy until the end of study as described in Section 4.3.

Withdrawal from Study Treatment:

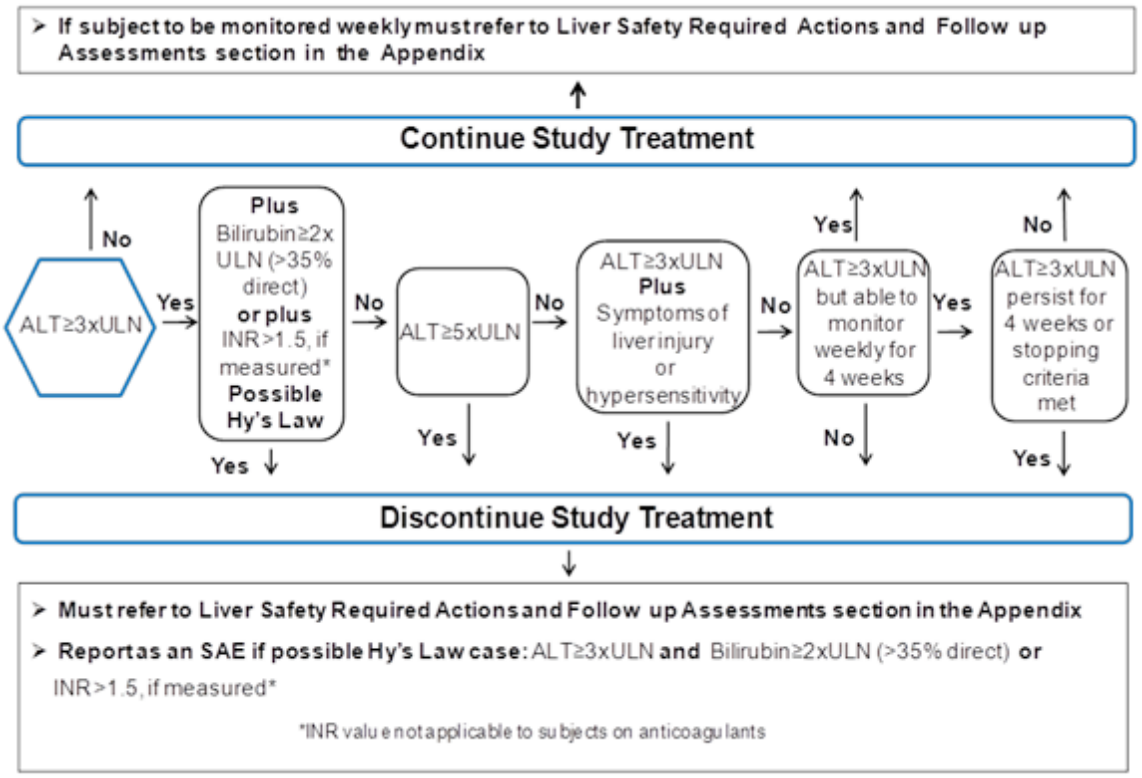
A participant may withdraw from study treatment at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral or administrative reasons. If a participant withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

7.2. Safety Stopping Criteria

7.2.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event. The diagram below illustrates Liver Stopping Event Algorithm (Figure 3)

Figure 3 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



The details on follow up procedures are outlined in Appendix 7.

7.2.2. Study Treatment Restart or Rechallenge

If participant meets liver chemistry stopping criteria do not restart/rechallenge participant with study treatment unless:

- GSK Medical Governance approval is granted (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the participant

If GSK Medical Governance approval to restart/rechallenge 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.

7.2.3. 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 belantamab mafodotin 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 belantamab mafodotin. 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 belantamab mafodotin may be restarted at a reduced dose in consultation with the medical monitor.

7.2.4. Corneal Event Stopping Criteria

All belantamab mafodotin dose modifications and stopping criteria are to be based on the GS/KVA Scale for treatment related corneal toxicities (Appendix 9). Corneal events will be graded according to both CTCAE criteria for eye disorders (see Section 8.2) 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/KVA scale with the GSK Medical Monitor or a GSK ophthalmologist to determine whether the participant can be allowed to restart treatment with belantamab mafodotin or whether belantamab mafodotin 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).

7.2.5. 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 belantamab mafodotin.

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.

7.2.6. 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.

7.3. 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.

7.4. 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.
- 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."

8. STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form must be obtained from the participant prior to any study-specific procedures or assessments being performed. The timing of each assessment is listed in the Schedule of Activities (Table 1).

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

Whenever vital signs, and blood draws are scheduled for the same nominal time, it is recommended that the assessments occur in the following order: vital signs, followed by

the 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 5.1 and Section 5.2.
- 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.
- 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.

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.			

Table 14 List of Clinical Laboratory Tests (cont.)

PK/ADA			
Pharmacokinetics (PK)[2, 3]			
Anti-Drug Antibodies (ADA)[2, 3]			
Optional Testing			
PGx[2]			
Optional tissue sample at PD for BCMA (BM aspirate clot, or fresh tissue, or tissue block from extramedullary tumor)[2]			
Disease Evaluation Laboratory Tests			
Urine Protein Electrophoresis (UPEP)[2]	urine Immunofixation[2]	24-hour urine collection for M-protein[2]	Calcium corrected for albumin (serum)[2]
Serum Protein Electrophoresis (SPEP)[2]	Serum M-protein calculation [2]	Serum Immunofixation[2]	Beta2 microglobulin[2]
Serum Kappa, lambda free LC, FLC ratio[2]	IgG, IgA, IgM, IgD[4]), IgE[4])[2]		
Bone Marrow Aspiration/Biopsy			
Bone marrow for MRD testing[2]			
Bone marrow (aspirate preferred) for disease assessment[1]			
Bone marrow biopsy to confirm sCR by IHC[1,7]			
Bone marrow for FISH testing[5,6]			
Bone marrow aspirate for BCMA IHC assessment[2]			
Biomarker Measurements			
Soluble BCMA (sBCMA) (Serum)[2]	cfDNA (plasma)[2]		

1. To be performed at local laboratory.
2. To be performed at central laboratory.
3. Not needed at screening
4. Only for participants with IgD/E myeloma
5. If not available from local laboratory, it can be performed at central laboratory.
6. FISH testing at least for: t(4;14), t(14;16), 17p13del. BM samples from within 60 days prior to first dose are acceptable for FISH analysis. If not available from local laboratory, a bone marrow aspirate can be sent to central lab for analysis. If the participant 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.
7. Results from tests to confirm sCR will be collected and stored by third party vendor and reviewed by IRC.
8. Obtained from first void

8.1. Efficacy Assessments

Standard disease assessments for RRMM will include the following assessments:

- UPEP, Urine Immunofixation, 24 hr. collection for urine M-protein
- SPEP, Serum M-protein, serum immunofixation
- Calcium corrected for albumin
- IgG, IgM, IgA
- IgD, IgE (only in participants with IgD or IgE myeloma)
- Serum Kappa, lambda free LC, FLC ratio

- 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 1.2).

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 of laboratory parameters must be performed from a different blood collection performed either on the same day, or within 14 days of the original date of suspected disease progression, preferably before initiation of any new anti-myeloma therapy. For participants with PD due to extramedullary disease, confirmatory scans are not required. The laboratory parameters do not need to be repeated only if the extramedullary disease is the single site of progression. 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.

8.1.1. 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.

8.2. 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 belantamab mafodotin will also be graded according to the GSK/KVA scale provided in Appendix 9. Dose modifications as a result of corneal events will be based on the GSK/KVA 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 7).

8.2.1. 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 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.
- Investigator need not update tick-box in InForm to confirm review of the causality assessment for the SAE within 72 hours. It is enough to record the same in source notes.
- For participants in the PACT phase of the study, GSK will continue to collect safety information including SAEs, AEs leading to treatment discontinuation, overdose, pregnancy cases and pre-specified ocular data via paper forms which will be reported directly to GSK (see SRM for details) for up to 70 days after last dose. Pre-specified ocular data will be reported until resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up. Additionally, any SAEs that are ongoing at the time of the final DCO must be followed up to resolution unless the event is considered by the investigator unlikely to resolve, or the patient is lost to follow-up. Updates to these events will also occur via paper forms directly to GSK (see SRM for details). GSK retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at EOS, if judged necessary.
- **Ocular FU:**

For participants continuing on belantamab mafodotin-containing study treatment as part of PACT:

- Ocular exam schedule during PACT treatment:
    - Participants without ocular (including corneal) examinations findings, symptoms or vision changes when entering the PACT phase will be required to have an ocular assessment at least every 3 months, or more often as clinically indicated, until the end of treatment.
    - For participants who at the time of entering PACT have ocular (including corneal) examinations findings, symptoms or vision changes (or develop these during PACT treatment), the ocular assessment will occur (increase to) every 3 weeks (and prior to the next belantamab mafodotin infusion if dosing), until resolution (KVA Grade 1 or baseline). After resolution, the ocular exam assessment frequency may revert to at least every 3 months intervals, or as clinically indicated, until the end of treatment.
- Ocular exam schedule after end of PACT treatment:
    - Participants with treatment-related ocular (including corneal) examination findings, symptoms, or vision changes at the end of PACT treatment will have ocular assessments at least every 3 months, or more often as clinically indicated, for up to 12 months from the end of treatment or until resolution (to KVA Grade 1 or baseline), or withdrawal of consent, whichever comes first.

- For participants without ocular (including corneal) examination findings, symptoms, or vision changes at the end of PACT treatment no further ocular exams are required.

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

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

8.2.2. 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.

8.2.3. 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 7.4). Further information on follow-up procedures is given in Appendix 4.

8.2.4. 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.

8.2.5. 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.

8.2.6. 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.

8.2.7. Adverse Events of Special Interest

Adverse events of special interest (AESI) for belantamab mafodotin 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/KVA 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 belantamab mafodotin corneal events will be based on the GSK/KVA scale for corneal events in Table 22.

8.2.8. 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 4 months following the last dose of study treatment.

- Details of all pregnancies for female partners of male participants will be collected after the start of study treatment to 6 months following last dose of study treatment.
- 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.

8.2.9. 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 maintained at the investigator site as source data.

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.

8.2.10. 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 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 belantamab mafodotin-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.

8.2.10.1. 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**. *** Based on data from the primary analysis the use of prophylactic steroid eye drops is no longer required for the main study participants. Determination for use of steroid eye drops will be up to the discretion of the treating ophthalmologist for the ocular sub-study participants.

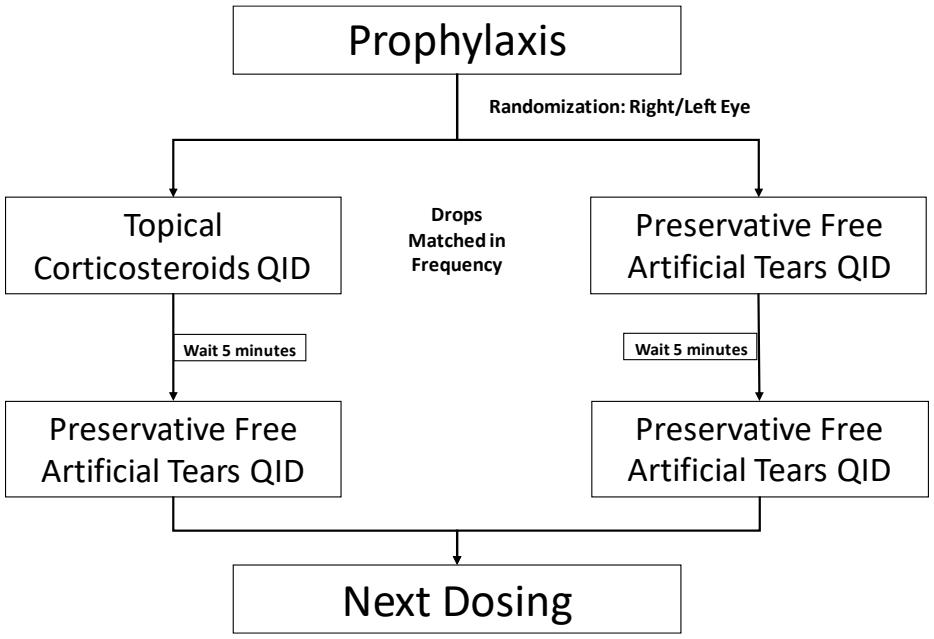
Corticosteroid treated eye

- 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 11.9).

Figure 4 Ocular prophylaxis schematic



***Based on data from the primary analysis the use of prophylactic steroid eye drops is no longer required for the main study participants. Determination for use of steroid eye drops will be up to the discretion of the treating ophthalmologist for the ocular sub-study participants.

8.2.10.2. Monocular treatment

If a participant in the ocular sub-study develops a corneal event outside the 7-day prophylaxis period, steroid eye drops may be restarted in only one eye at the discretion of the treating ophthalmologist. If steroid treatment is started in only one eye refer to Table 13 and treat the contralateral eye with an equal number of preservative-free artificial tears.

Alternatively, the treating ophthalmologist may start topical corticosteroid treatment in both eyes at any time if clinically indicated and beneficial to the participant (Table 13). If such decision is made at any time between treatment cycles 1 to 4, the participant will receive further prophylaxis and treatment as any other participant on the study according to Section 8.2.9 but will continue to undergo additional imaging as described below.

The treating ophthalmologist may unblind themselves at any time if they believe it to be in the best interest of the participant. This may be done by asking the clinical site staff.

After Cycle 4, monocular steroid treatment will be performed at the discretion of the treating ophthalmologist

Based on data from the primary analysis the use of prophylactic steroid eye drops is no longer required for the main study participants. Determination for use of steroid eye drops will be up to the discretion of the treating ophthalmologist for the ocular sub-study participants.

8.2.10.3. Sub-Study Exams

Participants will be assessed by the treating ophthalmologist at baseline, every 3 weeks or prior to each dose, and on Day 10 of Cycles 1, 2, 3, and 4. After Cycle 4, the Day 10 exam may be omitted.

In addition to the full ophthalmic exam (Section 8.2.9), the participants at these selected sites will undergo the following additional studies during screening (baseline), at the first instance of corneal changes attributable to belantamab mafodotin, end of study treatment visit, last follow-up visit and as clinically indicated by the treating ophthalmologist:

1. Anterior segment OCT (optical coherence tomography)
2. Anterior segment/corneal slit lamp photography
3. Confocal microscopy (if available at the site)
4. Lissamine green staining

Given that these evaluations are exploratory, the treating ophthalmologist has the discretion to perform them more frequently as they believe appropriate for the optimal care of the individual participant. Representative images will be collected and maintained at the investigator site as source data.

8.3. Treatment of Overdose

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

In the event of an overdose of belantamab mafodotin, the investigator must:

- contact the GSK Medical Monitor immediately
- monitor the participant closely for AEs/ SAEs and laboratory abnormalities until they have resolved and belantamab mafodotin concentrations are predicted to be within the anticipated range in absence of the overdose.

8.4. Safety Assessments

Planned time points for all safety assessments are provided in the SOA (Table 1).

8.4.1. Physical Examinations

At screening, on dosing days, and at end of study treatment visit a full physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes, and extremities. Height (once at screening only) and weight must also be measured and recorded.

8.4.2. ECOG Performance Status

Participant performance status will be assessed at Screening, every 3 weeks starting at Week 4 and End of Treatment using the Eastern Cooperative Oncology Group (ECOG) scale, provided in Appendix 8.

8.4.3. Vital Signs

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

8.4.3.1. 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 1.2). 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.

8.4.3.2. 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 1.2). Participants may be discharged after the infusion has been completed if considered clinically stable and all other study procedures have been completed.

8.4.4. 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.

8.4.5. Laboratory Assessments

All protocol-required laboratory assessments, as defined in Table 14, must be performed according to the SOA (Section 1.2). 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.

8.4.6. 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. Participants who are not able to complete the questionnaire on their own and require assistance may have the interview conducted verbally or by telephone. The interview must be read to the participants verbatim, and participant responses must be recorded directly without any interpretation.

The PRO-CTCAE will be administered to participants in different regions based on the availability of translated versions.

8.4.7. 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.

8.4.7.1. 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.

8.4.7.2. The Ocular Surface Disease Index

The Ocular Surface Disease Index (OSDI) is a 12-item questionnaire designed to assess 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.

8.5. Pharmacokinetics

8.5.1. Blood Sample Collection for Pharmacokinetics

Blood samples for pharmacokinetic (PK) analysis of belantamab mafodotin (ADC and total antibody) and cys-mcMMAF will be collected at the time points indicated in the Schedule of Activities table (Section 1.2). 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. All PK, sBCMA, and ADA samples once collected (regardless of dosing) may be analyzed if the sample date and time have been recorded.

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

8.5.2. Pharmacokinetic Sample Analysis

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

8.6. Immunogenicity

Serum samples for the analysis of anti-belantamab mafodotin antibodies will be collected from all participants according to the SoA. Additionally, serum samples should be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

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

The detection and characterization of antibodies to belantamab mafodotin will be performed using validated assays. The anti-belantamab mafodotin antibody assay was designed to detect antibodies to belantamab mafodotin, the unconjugated monoclonal antibody, and the linker-payload portion of belantamab mafodotin. Additionally, plasma samples will be collected at the same time points (see SoA) as the immunogenicity samples and analyzed to determine the belantamab mafodotin and total monoclonal antibody plasma concentrations. The plasma concentration results will enable interpretation of the anti-drug antibody data. Anti-drug antibody samples will be disposed of three months after final approved results are provided to the Clinical Study Team or its designee or upon documented study termination.

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

8.7. Translational Research

See Section 8.9.

8.8. 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.

8.9. Tumor Biomarker Analysis

8.9.1. 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.

Serum analysis for sBCMA will be performed under control of GSK PTS-BIB group, the details of which will be included in the SRM. Raw data will be archived at the bioanalytical site (detailed in the SRM).

8.9.2. Potential Tumor Related Biomarkers

While BCMA expression is present in multiple myeloma, there is some variability in its expression, as well as its membranous/cytosolic expression pattern. Therefore, it is important to determine if there is any association between the expression levels of BCMA on multiple myeloma cells and clinical responses.

Additionally, any blood, serum, and bone marrow samples collected during this study may be used to measure novel biomarkers to identify factors associated with the biological and clinical responses to belantamab mafodotin. If relevant, this approach may be extended to include the identification of biomarkers associated with AEs. Unless stated otherwise, these investigations may be performed irrespective of whether a response to belantamab mafodotin is observed.

Samples will be collected at the time points indicated in the SOA. The sample collection strategy may be adjusted on the basis of emerging data from this study or other studies involving belantamab mafodotin in order to ensure optimal evaluation of any potential biomarkers. Additionally, novel biomarkers may also be incorporated, as data warrants. These analyses may include but not be limited to:

- Bone marrow BCMA expression by IHC performed on bone marrow aspirate
- Measurements of the serum levels of soluble BCMA (sBCMA)

- Soluble factors, including circulating plasma cell-free DNA (cfDNA).

8.10. Evaluation of Anti-Cancer Activity

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

Standard disease assessments for MM will include serum and urine laboratory tests, bone marrow biopsy at the time of CR (IHC), and MRD testing at the time of VGPR, CR, and baseline. Evaluation will follow the guidance of International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma 2016.

- Clinical efficacy measured as Overall Response Rate (ORR), which is defined as the percentage of participants with confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) as assessed by 2016 recommendation of the IMWG Panel I [Kumar, 2016].
- Other efficacy measures of interest (see Section 8.1)
- The percentage of participants achieving MRD negativity.

Disease assessment will include laboratory testing and physical examination (as indicated for palpable/superficial lesions), or imaging CT, MRI, PET CT, or X-ray (as indicated). Laboratory-based disease assessments will be completed within 21 days prior to the first dose of belantamab mafodotin 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. If MRD sample is drawn after date of achieving VGPR or CR the repeat testing should take place 6 months and 12 months from time of initial MRD testing

8.11. 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.

8.11.1. 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].

8.11.2. 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].

8.11.3. 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.

9. STATISTICAL CONSIDERATIONS

9.1. 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.

An updated analysis for OS will be performed at end of study as defined in Section 4.3.

9.2. 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 belantamab mafodotin 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 9.3 and Section 9.5.

The study will also include an independent cohort of approximately 25 additional participants who will receive the lyophilized configuration of belantamab mafodotin. 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.

9.3. 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 9.5.9.1.

Table 15 Statistical Power Scenarios

ORR		Number of Participants per arm	Power (%)
BCMA Monotherapy (%)	Historical Data (%)		
40	15	65	96.05
35	15	65	91.52
30	15	65	75.13
25	15	65	43.18
20	15	65	12.81
40	15	100	96.50
35	15	100	94.62
30	15	100	85.08
25	15	100	55.21
20	15	100	15.92

Note: The power for each arm is calculated based on 10,000,000 simulations using R, assuming both arms have the same assumptions of ORR

9.4. Populations for Analysis

Six specific populations have been defined for this study, as shown in Table 16.

Table 16 Analysis Populations Defined for the Study

Population	Description
All Screened	The All Screened Population will consist of all participants who sign the ICF to participate in the clinical trial. Participants in this population will be used for screen failure summary.
Intent-to-Treat (ITT)	ITT Population will consist of all randomized participants whether or not randomized treatment was administered. This population will be based on the treatment to which the participant was randomized and will be the primary population for the analysis of efficacy data. Any participant who receives a treatment randomization number will be considered to have been randomized.
Efficacy	Efficacy population will consist of first 130 randomized participants whether or not randomized treatment was administered. This population will be based on the treatment to which the participant was randomized and will be used for sensitivity analysis of primary and selected secondary efficacy endpoints.
Safety	The Safety population will consist of all participants who receive at least 1 dose of study treatment. This population will be used for the analysis of clinical safety data
Evaluable	The Evaluable Population will consist of all participants who have at least two doses of study treatment and have completed at least one disease assessment after the second dose. This population will be the primary population for summarizing ORR to compare with stopping boundaries in interim analysis only. Refer to IDMC charter for more details.
Pharmacokinetic	The Pharmacokinetic Population will consist of those participants in Safety Population from whom at least one PK sample has been obtained and analyzed. This population will be the primary population for PK analyses.

9.5. Statistical Analyses

Statistical analyses (both interim and final) will be performed by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the RAP.

9.5.1. Efficacy Analyses

Primary analysis of the primary endpoint ORR will be based on the responses assessed by the Independent Review Committee (IRC). Investigator-assessed ORR will also be reported. Analysis of secondary endpoints will include TTR, DoR, TTP, and PFS as assessed by both investigator and IRC.

Primary analysis for all efficacy endpoints will be based on the ITT population.

In addition, sensitivity analysis for ORR, DoR, and TTR as assessed by both investigator and IRC will be performed using efficacy population; other endpoint-specific sensitivity analyses will be described in the RAP. At interim analysis, investigator-assessed ORR will be analyzed based on the Evaluable Population. In case that one dose arm is dropped based on interim analysis (IA), and some participants in that arm switch to the remaining dose arm, a sensitivity analysis of ORR based on participants who did not switch may be performed.

Appropriate subgroup analyses may be performed if data permits, e.g. the primary endpoint ORR may be analyzed by age (<65 years, >=65 years), gender (Female, Male), ethnicity (Hispanic, non-Hispanic) and race groups (American Indian or Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Mixed Race), prior anti-cancer therapy and other baseline characteristics. The estimates along with 95% exact confidence interval (CI) will be provided. In subgroup analyses, no hypothesis testing will be performed.

The analytical methods planned for each endpoint are described in Table 17.

Table 17 Statistical Analysis Methods for Efficacy Endpoints

Endpoint	Statistical Analysis Methods
Primary	Overall Response Rate is the primary endpoint of this study; it is defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR and sCR), according to the IMWG Response Criteria [Kumar, 2016]. The number and percentage of participants in the following response categories will be presented sCR, CR, VGPR, PR, MR, SD, PD, and NE sCR+CR+VGPR+PR for ORR The corresponding 97.5% exact CI for ORR will also be provided. Participants with unknown or missing response will be treated as non-responders, i.e., these participants will be included in the denominator when calculating percentages of response. The null hypothesis related to ORR against a historical control will be tested by comparing the number of responders with the pre-specified stopping boundaries in the ITT and efficacy population. The boundaries will be adjusted as needed based on the final sample size. ORR will be analyzed at interim and final analysis. A participant with best confirmed response of PR or better will be considered as a responder. ORR at final analysis will be based on the confirmed responses from IRC assessment in both ITT 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.

Endpoint	Statistical Analysis Methods
	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.
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.

9.5.2. 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 belantamab mafodotin will be summarized using the GSK/KVA 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

9.5.3. 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.

9.5.4. Pharmacokinetic Analyses

9.5.4.1. 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 belantamab mafodotin (ADC and total mAb) and cys-mcMMAF. Concentrations of belantamab mafodotin (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 belantamab mafodotin (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 belantamab mafodotin (ADC and total mAb) as data permit, for each participant after each dose of belantamab mafodotin:

- 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 belantamab mafodotin 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.

9.5.4.2. Statistical Analysis of Pharmacokinetic Data

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

belantamab mafodotin (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.

9.5.5. Pharmacokinetic/Pharmacodynamic Analyses

If deemed appropriate and if data permit, exposure-response relationships between belantamab mafodotin 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.

9.5.6. 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.

9.5.6.1. 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.

9.5.6.2. Analysis of Genetic Data

Further details on genetic analyses are addressed in Appendix 6.

9.5.6.3. 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 belantamab mafodotin.

The results of exploratory investigations will be reported separate from the main CSR. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

9.5.7. Analyses of Immunogenicity Data

For each participant, the results and titers of anti-belantamab mafodotin binding antibodies will be listed for each assessment time point, along with the time-matched belantamab mafodotin plasma concentration. The frequency and percentage of participants with positive and negative results will be summarized for each assessment time and overall for each participant by dose cohort. The detailed information will be included in the RAP.

9.5.8. Other Analyses

Participant disposition, treatment status, demographics, medical history, prior and concomitant medications, prior anti-cancer therapies, and study treatment exposure will be summarized descriptively and listed by participant.

In addition, the impact of COVID-19 will be evaluated at the end of study analysis. Details of such analysis will be provided in the updated reporting and analysis plan.

9.5.9. Interim Analyses

9.5.9.1. Futility Stopping Rule Based on Group Sequential Design

For each arm (2.5 mg/kg or 3.4 mg/kg of frozen liquid solution), one single futility IA is planned for ORR based on investigator's assessment, after approximately 25 participants (~38% information fraction of initially planned 65 participants) per arm are evaluable. A user-defined gamma spending function (γ=*1.1*) [Hwang, 1990] was used as a beta-spending function to determine the non-binding futility boundary (as implemented in East 6.4). With this β-spending function, the stopping boundary in IA is identified as 0.16 on the proportion scale (≤4 responders out of 25 participants), which is close to the historical control of 0.15. The spending function and associated boundary were chosen to ensure good operating characteristics, specifically, the type 1 error and power are well controlled.

A two-step approach is used to identify the futility stopping rule based on a group sequential design under the assumption of exact binomial distribution.

First, as described in Section 9.2, an initial design based on the assumption of normal approximation of binomial proportion is identified by East 6.4.

The interim futility and final efficacy analysis boundaries were then converted to number of responders needed in 25 participants who are evaluable at IA and the 65 participants initially planned at the final analysis.

With a total sample size of 100 participants per arm and an IA with approximately 25 participants per arm, the same futility boundary (≤ 4 responders out of 25 participants) will still apply with a user-defined gamma spending function (γ=*5.4*). For the final analysis, the boundary for claiming efficacy is the minimum number of responders required for the lower bound of the two-sided 97.5% C.I. to exceed 15% (i.e. 24 responders for sample size of 100 per arm).

Statistical properties of the group sequential design with sample sizes of 65, and 100 per arm are summarized in Table 19.

Table 19 Probabilities of Crossing Boundaries at the Interim or Final ORR Analysis based on Group Sequential Design

Look	Sample Size (per arm)	Boundaries	Cumulative Boundary Crossing Probabilities	
		# of Responders	Under H_0	Under H_1
Interim (futility)	25	≤4	68.21%	4.96%
Final (Efficacy)	65	≥17	1.23%	88.00%
	100	≥24	0.97%	93.70%

Note: The Cumulative Boundary Crossing Probabilities are calculated based on exact binomial distribution theoretically.

9.5.9.2. Additional Comparative Futility Stopping Rule Based on Bayesian Approach

If both arms pass the futility boundaries based on group sequential design described above, posterior probability of observing a better RR in one arm relative to 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. This additional guidance was put in to allow for dropping an arm with substantially inferior response rates (e.g. absolute difference > 28%).

To calculate the posterior probability, a non-informative Beta prior (0.025, 0.1) will be used for each arm. Details about calculating the posterior probabilities are provided in Appendix 12.

Statistical properties for different scenarios based on both futility rules are summarized in Table 20.

Table 20 Probabilities of Stopping for Futility at the Interim or Claiming Efficacy at the Final ORR Analysis based on Both Futility Rules

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]
1	65	33%	60%	53.59%	0.01%	44.83%	99.99%
2	65	33%	45%	16.95%	0.47%	77.94%	99.49%
3 [3]	65	33%	33%	6.33%	6.33%	**86.90%**	86.92%
4	65	33%	25%	5.09%	23.83%	87.89%	42.39%
5	65	33%	20%	4.97%	44.59%	87.98%	12.52%
6	65	33%	15%	4.96%	69.99%	87.99%	1.20%
7	65	33%	10%	4.96%	90.85%	87.99%	0.01%
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 9.5.9 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.

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11. APPENDICES

11.1. Appendix 1: Abbreviations and Trademarks

ADA	Anti-drug antibodies
ADC	Antibody drug conjugate
ADCC	Antibody dependent cellular cytotoxicity
ADL	Activities of daily living
AE	Adverse Event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
Anti-CD38	Anti-CD38 antibody
APRIL	A proliferation-inducing ligand
AST	Aspartate aminotransferase
AUC	Area under the curve
AV	Atrioventricular
BAFF	B-cell-activating factor belonging to the TNF family
BCMA	B-cell maturation antigen
BCVA	Best corrected visual acuity
BIB	Bioanalysis Immunogenicity and Biomarkers
BiTe	Bispecific antibodies
BLRM	Bayesian Logistic Regression Model
BM	Bone marrow
BNP	B-type natriuretic peptide
BP	Blood Pressure
BUN	Blood urea nitrogen
C1D1	Cycle 1 Day 1
CAR-T	Chimeric antigen receptor T-Cell
CBR	Clinical Benefit Rate
cfDNA	Circulating cell-free deoxyribonucleic acid
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council of International Organizations of Medical Sciences
CK	Creatine kinase
CL	Clearance
Cmax	Maximum observed concentration
CO_2	Carbon dioxide
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine phosphokinase
CR	Complete Response
CRF	Case Report Form
CRP	C-reactive protein
CSR	Clinical study report

CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
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
EOI	End of infusion
EOS	End of study
EORTC	European Organization for Research and Treatment of Cancer
EOT	End 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
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
KVA	Keratopathy Visual Acuity Scale
LC	Light chain
LDH	Lactate dehydrogenase
LLN	Lower limit of normal (range)
LSFD	Last subject first dose
LSFV	Last subject's first visit
LSLV	Last subject last 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
mOS	Median overall survival
mPFS	Median progression free survival
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
NR	Not reported
NYHA	New York Heart Association
OATP	Organic Anion Transporting Proteins
ORR	Overall Response Rate
OS	Overall survival
OSDI	Ocular Surface Disease Index
PACT	Post Analysis Continued Treatment
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
QLQ-C30	Quality of Life Questionnaire 30-item Core module
QLQ-MY20	Quality of Life Questionnaire 20-item Multiple Myeloma module
QTc	Corrected QT interval (ECG)
QTcF	Corrected QT interval Fridericia
RAMOS	Registration and Medication Ordering System
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RNA	Ribonucleic acid
RP2D	Recommended Phase II Dose
RRMM	Relapsed / refractory multiple myeloma
SAE	Serious adverse event
sBCMA	Soluble B-cell maturation antigen
sCR	Stringent Complete Response
SCT	Stem cell transplant
SD	Stable disease
SOA	Schedule of activities
SOI	Start of infusion
SOP	Standard operating procedure
SPD	Sum of the products of the maximal perpendicular diameters of measured lesions
SPEP	Serum Protein Electrophoresis
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardized uptake value
t½	Terminal phase half-life
TCR	T-Cell receptor
TLS	Tumor Lysis syndrome
tmax	Time of maximum observed concentration
TNF	Tumor necrosis factor
TTP	Time to progression
TTR	Time to (best) Response
TTR	Time to response
UK	United Kingdom
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
US	United States
USP	United States Pharmacopeia

V	Volume of distribution
VA	Visual Acuity
VGPR	Very good partial response
WBC	White blood cell
WFI	Sterile water for injection
WOCBP	Woman of Childbearing Potential
β-HCG	Beta human chorionic gonadotropin

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
NONE

11.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 14 are identified as being performed at either local or central laboratory.
- For response assessments, local laboratory results are only required in the event that the central laboratory results are not available in time for response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing (see Section 5.1 [Inclusion Criteria] for screening pregnancy criteria)
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure plus an additional 30 days and correspond with the time frame for female participant contraception in Section 5.1 (Inclusion Criteria).

11.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

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

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

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

Data Protection

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

Committees Structure

An IRC will be utilized to assess response and progression and primary endpoint of the study. Digital copies of all scans must be maintained at Investigator site as source document. Further details on the IRC process will be defined in the IRC charter Results from the IRC will not be provided to the investigative sites during the study.

Participant data to be shared with the IRC may include the following:

- Scans (CT, MRI, or PET CT- whichever applicable)
- SPEP, UPEP, M-protein in 24 hr. urine collection immunoelectrophoresis-urine and serum, serum calcium, and albumin (unless reported as albumin corrected),
- Serum kappa, serum lambda FLC, FLC Ratio
- MRD results

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

For studies conducted in the EU under Regulations EU 536/2014: Consider whether submission of results of the clinical study will be delayed more than one year after the end of trial and provide substantiated reasons. Provide justification if a single summary of results report will not be submitted for all study treatments used in the clinical study.

- Disclosure of CSRs, periodic safety reports, and clinical study summary reports after review by regulatory authorities. This includes access to CSRs from studies with negative outcomes and from terminated development programs.
- The posting of company-sponsored study information and tabular study results on the US National Institutes of Health's website www.ClinTrials.gov and other publicly-accessible sites.
- Publication planning and other activities related to non-promotional, peer-reviewed publications, to ensure the scientific integrity and credibility of publication activities performed by or on behalf of the company. The granting of access to analyzable datasets from clinical studies through a secure system, following an independent assessment of the scientific merit of a rigorously defined research question from a third party.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

Data Quality Assurance

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

Source Documents

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

Study and Site Closure

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

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

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

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

11.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

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

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

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

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

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.
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
- Deep venous thrombosis/pulmonary embolism
- Revascularization

Recording AE and SAE

AE and SAE Recording

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

Assessment of Intensity

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

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

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

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

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

Grade 5: Death related to AE.

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

Assessment of Causality

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

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

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

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

11.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP

1 Premenarchal

2 Premenopausal females with ONE of the following:

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

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

3 Postmenopausal females

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency**
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent**

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

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  • oral
  • injectable

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating

in this study and for 6 months following last dose of study treatment. This applies only to male participants who receive study intervention.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study and for 4 months following last dose of study treatment.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will discontinue study intervention.

11.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a 6-mL blood sample will be collected from participants who have consented to participate for DNA analysis.
- DNA samples will be used for research related to belantamab mafodotin or Multiple Myeloma and related diseases. They may also be used to develop tests/assays including diagnostic tests related to belantamab mafodotin or study treatments of this drug class, and Multiple Myeloma. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analyzed for described planned analyses. Additional analyses will be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to belantamab mafodotin or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on belantamab mafodotin (or study treatments of this class) or Multiple Myeloma continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

11.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Phase I/II liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

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

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to language within this Appendix) • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue participant in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for pharmacokinetic (PK) analysis, if it can be obtained within 45 days after last dose • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake case report form

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.

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.

11.7.1. 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.

11.7.1.1. 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%

fatality with halothane re-administered within 1 month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug re-challenge outcome include the following:

- Hypersensitivity1 with initial liver injury (e.g., fever, rash, eosinophilia)
- Jaundice or bilirubin >2 x ULN with initial liver injury (direct bilirubin >35% of total)
- Participant currently exhibits severe liver injury defined by ALT >3 x ULN, bilirubin >2 x ULN (direct bilirubin >35% of total), or INR >1.5
- SAE or fatality has been observed with drug rechallenge [Papay, 2009; Hunt, 2010]
- Evidence of drug-related preclinical liability (e.g., reactive metabolites; mitochondrial impairment) [Hunt, 2010]

Approval by GSK for re-challenge with study treatment can be considered under the following conditions:

- Investigator requests consideration of re-challenge with study treatment for a participant who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- IRB/IEC approval for re-challenge with study treatment must be obtained, as required.
- If the re-challenge is approved by GSK Medical Governance in writing, the participant must be provided with a clear description of the possible benefits and risks of study treatment administration including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the re-challenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for re-challenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment re-challenge, participant meets protocol-defined liver chemistry stopping criteria, study treatment must be permanently discontinued.
- GSK medical monitor, and the IRB/IEC as required, must be informed of the participant's outcome following study treatment re-challenge.
- GSK must be notified of any AEs as per Section 8.2.4.

11.7.1.2. Re-challenge Following Transient Liver Stopping Events Not Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g., biliary obstruction, pancreatic events, hypotension, and acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with human leukocyte antigen (HLA) markers of liver injury.

Approval by GSK for study treatment restart can be considered under the following conditions:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3 x ULN).
- Possible study treatment-related liver injury has been excluded by the investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study treatment has an identified genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate), the presence of the marker should be excluded. If study treatment-related liver injury cannot be excluded, the guidance on re-challenge in Section 11.7.1.1 will apply.
- There is no evidence of alcoholic hepatitis.
- IRB/IEC approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the participant must be provided with a clear description of the possible benefits and risks of study treatment administration including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment restart, participant meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- GSK medical monitor, and the IRB/IEC as required, must be informed of the participant's outcome following study treatment restart.
- GSK must be notified of any AEs, as per Section 8.2.4.

11.7.2. References

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.

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Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

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11.8. Appendix 8: ECOG Performance Status

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Oken,1982

11.9. Appendix 9: GSK/KVA Scale and Mitigation Strategy for Belantamab Mafodotin Treatment-Related Corneal Events

In order to minimize corneal events associated with belantamab mafodotin prophylactic preservative-free artificial tears should be administered in each eye at least 4 to 8 times daily beginning on Cycle 1 Day 1 until the EOT. In the event of ocular symptoms (e.g., dry eyes), the use of artificial tears may be increased up to every 2 hours as needed.

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

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

Participants must avoid the use of contact lenses during the study.

An ophthalmology (or optometry, if ophthalmology is not available) consult is required for all participants who develop signs or symptoms of corneal events or require steroid eye drops for more than 7 days.

Following discussions with regulatory agencies, GSK developed a grading scale for corneal events to capture both corneal findings and visual acuity changes in participants treated with belantamab mafodotin. This GSK/KVA scale is different from CTCAE criteria for eye disorders which relies mainly on patient's symptoms and patient's ability to attend to 'activities of daily living' for grading of events.

A summary of prophylactic interventions for corneal events associated with belantamab mafodotin is provided in Table 21. In addition to reporting eye disorders using CTCAE 4.03 criteria, corneal events associated with belantamab mafodotin must be graded according to the guidelines provided in Table 22. Additional guidance on visual acuity changes is provided in Table 23.

In the FTIH study (BMA117159), eye examinations showed that most participants continued to receive belantamab mafodotin dose when either a GSK/KVA Scale Grade 2 corneal examination finding ***or*** a 2-3-line decrease in visual acuity was reported. With this dosing 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 belantamab mafodotin if only one component on the GSK/KVA scale indicates Grade 2 corneal event.

Table 21 Prophylactic Measures for Corneal Events Associated with Belantamab Mafodotin [a]

Prophylactic Measure[a]	Dose and Administration	Timing
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.
Cooling eye mask	May apply cooling eye mask to both eyes for approximately 1 hour or as much as tolerated	During belantamab mafodotin infusion administration in the first hour for up to 4 hours, as tolerated

a. Dose modifications and treatment for ocular toxicities are discussed in Section 6.2

Table 22 GSK/KVA Scale for Corneal Events Associated with Belantamab Mafodotin [a]

Measure	Grade 1 per GSK/KVA Scale	Grade 2 per GSK/KVA Scale	Grade 3 per GSK/KVA Scale	Grade 4 per GSK/KVA 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 belantamab mafodotin 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/KVA 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
20/15 - 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

11.10. 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

11.11. Appendix 11: Protocol Amendment History

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

Amendment 06: 19-Nov-2021

Overall Rationale for the Amendment:

The protocol has been amended to provide updates including the addition of the end of study definition section (Section 4.6) and continued access to study intervention after the end of the study (Post Analysis Continued Treatment [PACT]) (Section 6.9).

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Additional content to the overall study has been added which includes PACT implementation and End of Study definition	To introduce the approved standard language for belantamab mafodotin studies implementing PACT
Section 2.4.4 Pharmacokinetics and Pharmacodynamics	Revision of pharmacokinetics and pharmacodynamics section as per latest information available in IB	Section updated as per latest information available in IB
Section 4.1 Overall Design	Additional content added to align to PACT implementation	To introduce the approved standard language for belantamab mafodotin studies implementing PACT
Section 4.6 End of Study Definition	New section added to align to PACT implementation and additional content added related to PACT	To introduce the approved standard language for belantamab mafodotin studies implementing PACT
Section 6.9 Continued Access to Study Intervention after the End of the Study	New section added to align to PACT implementation and additional content added related to PACT	To introduce the approved standard language for belantamab mafodotin studies implementing PACT
Section 8.2.1 Time Period and Frequency for Collecting AE and SAE Information	Additional content added to align to PACT implementation	To introduce the approved standard language for belantamab mafodotin studies implementing PACT

Amendment 5: 08-Oct-2020

Overall Rationale for the Amendment:

The protocol has been amended to provide updates based on analyses of data from the DREAMM-1, DREAMM-2 and the exposure QTc. The updates include the removal of ECG collection, unless clinically indicated, and updated contraception timeframe. The dose modification guidelines for belantamab mafodotin related corneal events was updated to align with the approved label and an appendix on Home Healthcare and Telemedicine Approaches was introduced as a result of the COVID-19 pandemic to ensure sites and participants had alternate approaches to assist participants to continue receiving care while maintaining protocol adherence.

Section # and Name	Description of Change	Brief Rationale
Section 2 Schedule of Activities	Study Assessment ECG and associated footnotes with mention of ECGs (footnote 10, 12, 13) amended to remove ECG unless clinically indicated.	Triplicate ECGs were removed because the exposure-QTc analysis demonstrated that the likelihood of a QTc prolongation >10 msec is very low following administration of belantamab mafodotin.
	Table 2, footnote 27 – deletion of text related to discontinuation	Duplication of text found in Table 3, schedule of activities for end of treatment and follow up
	Table 3, footnote 6 – clarified	Clarified for consistency with Section 7.2.3 Corneal Supportive Care Guidelines
	Table 3, footnote 8, updated pregnancy timeframe	To align with current investigator brochure
	Table 3, ECG assessment and footnote 9 removed	ECGs are to be performed as clinically indicated
		Updated to align with ocular examination timeframe.

Section # and Name	Description of Change	Brief Rationale
	Table 3, footnote 17, clarification of timeframe collection of NEI-VFQ-25 and OSDI.	
Section 3.4 Human Experience with belantamab mafodotin Section 3.4.1 Thrombocytopenia Section 3.4.2 Corneal Events Section 3.4.3 Infusion Related Reactions Section 3.4.4 Pharmacokinetics and Pharmacodynamics	Update to Human Experience Sections	To align with the most recent data from the analysis of the DREAMM-1 (117159) and DREAMM-2 (current study, 205678)
Section 3.5 Benefit/Risk Assessment	Table 5 Risk Assessment and Mitigation Strategy: Corneal events updated to include additional corneal risks Nephrotoxicity – correction of abbreviated term	To align with current Investigator brochure Administrative
Section 3.5.2 Benefit Assessment and Section 3.5.3 Overall Benefit/Risk Conclusions	Updated entire benefit assessment section	To align with the most recent data from the analysis of the DREAMM-1 (117159) and DREAMM-2 (current study, 205678) and current investigator brochure
Section 5.3 Participant and Study Completion	Clarification of end of study definition	Aligned with Section 7.2.3, Corneal Supportive Care Guidelines of follow up timeframe of corneal events.
Section 7.2 Dose Modifications	Table 13 Dose modification guidelines for belantamab mafodotin treatment	Updated to match the current approved label

Section # and Name	Description of Change	Brief Rationale
	related corneal events amended to remove symptoms	
Section 8.2.3 QTc Interval Stopping Criteria	Section removed	Based on the exposure-QTc analysis results, the likelihood of a meaningful QTc prolongation (>10 msec) is very low following administration of belantamab mafodotin.
Section 9 Study Assessments and procedures	Removal of ECGs as a study assessment	Based on the exposure-QTc analysis results, the likelihood of a meaningful QTc prolongation (>10 msec) is very low following administration of belantamab mafodotin.
Section 9.3 Treatment of Overdose	Updated timeframe for resolution of AEs/SAEs and concentrations of belantamab mafodotin.	Removed restriction of timeframe of 3 months as the timeframe can vary.
Section 9.4.4 Electrocardiogram	Section removed	Triplicate ECGs were removed because the exposure-QTc analysis demonstrated that the likelihood of a QTc prolongation >10 msec is very low following administration of belantamab mafodotin.
Section 9.4.6 Patient Reported Outcome Version of the Common Term Criteria for Adverse Events (PRO-CTCAE)	Updated to allow options for participants to complete by phone or verbal interview	Updated to provide options for PRO CTCAE completion
Section 10.5.8 Other Analyses	Addition of COVID-19 analysis	Due to the pandemic an analysis will be completed and outlined in the reporting and analysis plan.
12.5 Appendix 5: Contraception Guidance and Collection of	Updated timeframe for contraception usage in males and females.	To align with current investigator brochure

Section # and Name	Description of Change	Brief Rationale
Pregnancy Information and Section 9.2.8 Pregnancy		
Section 12.13 Appendix 13 Home Healthcare and Telemedicine Approaches	Addition of Appendix	As a result of COVID-19 pandemic, alternate approaches were introduced to allow participants to adhere to the protocol.
Editorial/Document Formatting Changes		
Whole Document	GSK2857916 or GSK'916 replaced with belantamab mafodotin	Use generic name
Whole Document	GSK Scale replace with GSK/KVA Scale	To align with belantamab mafodotin label which notes the KVA scale

Amendment 4: 21-Oct-2019

Overall Rationale for the Amendment:

The protocol has been amended to provide updates based on data from the primary analysis and address feedback from regulatory agencies.

Section # and Name	Description of Change	Brief Rationale
Section 2 Schedule of Activities	Table 2, Footnote 7 added reference to increase monitoring for hematologic events	Based on percentage of Grade (Gr) 3-4 hematologic events it was determined that more frequent monitoring should be recommended
	Table 2, Footnote 10 clarification of timeframe to perform triplicate electrocardiograms (ECGs)	To align with Section 9.4.4
	Table 2, Footnote 21: clarification	Clarification of bone marrow (BM) collection for Minimal Residual disease (MRD) testing timeframe.

Section # and Name	Description of Change	Brief Rationale
	Table 2, treatment for steroid eye drops deleted, footnote 26a updated	Removed prophylactic use of steroid eye drops based on based on data from the primary analysis
	Table 3, Footnote 6 correction of timeframe for follow up of corneal toxicity	Aligned with Section 7.2.3
	Table 3, Footnote 8 increased timeframe for contraception usage in males and females.	In May 2019, FDA released updated reproductive toxicity recommendations for oncology pharmaceuticals, including guidance on labelling the duration of contraception following cessation of therapy, to minimize any potential risk to a developing embryo or fetus Inclusion criteria 8&9 not updated to align as enrollment has closed
	Table 3, Footnote 10 Updated language on requirements for disease assessments required to be completed when confirming disease progression.	Clarification of confirmatory disease progression assessments
	Table 3, Footnote 15; Clarification	Clarification of BM collection for MRD testing timeframe

Section # and Name	Description of Change	Brief Rationale
	Table 3 reference to Footnote 18 for OSDI and NEI-VFQ-2; Clarification	Clarification of OSDI and NEI-VFQ-25 follow-up questionnaire timepoints
	Table 4, footnote 2; ophthalmologist discretion to utilize steroid eye drops	Clarification that ophthalmologist has discretion to continue utilizing steroid eye drops or may discontinue
Section 3.5.1 Risk Assessment	Table 5 Risk Assessment and Mitigation Strategy Removed preventative use of steroid eye drops Updated potential risk of Hepatotoxicity Added Potential for Other Lab Abnormalities, Embryo Fetal Toxicity and Impaired Male Fertility.	To Align with Current Investigator Brochure.
Section 5.5 Dose Justification	Addition of the dose selection and the rationale for the decision.	Updated based on data from the primary analysis
Section 7.1 GSK2857916 Treatments Administered	Correction of text related to when treatment will be discontinued.	To align with Section 8.1
Section 7.2.2 Dose Reductions for Toxicity	Table 11 Dose Modification Guidelines for GSK2857916 – Related Adverse Events • removed footnote 'c' from table	Administrative - no associated footnote related to spot urine
	• Added frequent monitoring of platelet count and/or neutrophils in the event of a Gr3/4 toxicity	Based on percentage of Gr3-4 hematologic events it was determined that frequent monitoring should be recommended

Section # and Name	Description of Change	Brief Rationale
	Table 13 Dose Modification Guidelines for GSK2857916 Treatment Related Corneal Events: • Guideline for dose modifications amended to include symptoms • Updated to remove use of prophylactic steroid eye drops • Added statement on prescribing additional treatment based on ophthalmologist discretion	Updated based on data from the primary analysis and determination that a participants symptoms should also be a factor in the determination of a dose delay/reduction, and not asymptomatic corneal changes. Removed prophylactic use of steroid eye drops based on data from the primary analysis Allow flexibility for ophthalmologist to prescribe appropriate treatment based on findings and symptoms reported by participant.
7.2.3 Corneal Supportive Care Guidelines and Table 3 Schedule of Activities	Defined clinically stable relation to eye examinations	To provide additional clarification
7.7.2 Prohibited Medications	Updated guidance on prohibited medications	Changes based on emerging *in vitro* data
9.1 Efficacy Assessments	Updated language on requirements for disease assessments required to be completed when confirming disease progression.	Clarification of confirmatory disease progression assessments
9.2.8 Pregnancy	Increased timeframe for contraception usage in males and females.	In May 2019, FDA released updated reproductive toxicity

Section # and Name	Description of Change	Brief Rationale
		recommendations for oncology pharmaceuticals, including guidance on labelling the duration of contraception following cessation of therapy, to minimize any potential risk to a developing embryo or fetus. Inclusion criteria 8&9 not updated to align as enrollment has closed
9.2.10.1 Monocular Prophylaxis Figure 4 Ocular Prophylaxis Scheme 9.2.10.2 Monocular Treatment	Ophthalmologist discretion to utilize steroid eye drops added	Clarification that ophthalmologist has discretion to continue utilizing steroid eye drops or may discontinue
9.6 Immunogenicity	Updated text to include requirement for PK sample with every ADA sample	Clarification to emphasize existing PK sample requirement
9.10 Evaluation of Anti-Cancer Activity	Updated timeframe of MRD testing	Clarification of bone marrow (BM) collection for Minimal residual disease (MRD) testing timeframe.
12.5 Appendix 5: Contraception Guidance and Collection of Pregnancy Information	Increased timeframe for contraception usage in males and females.	In May 2019, FDA released updated reproductive toxicity recommendations for oncology pharmaceuticals, including guidance on labelling the duration of contraception following cessation of therapy, to minimize any potential risk to a developing embryo or fetus. Inclusion criteria 8&9 not updated to align as enrollment has closed
12.9 Appendix 9: GSK Corneal Event Severity Scale and		

Section # and Name	Description of Change	Brief Rationale
Mitigation Strategy for GSK2857916 Treatment Related Corneal Events	Table 21: Updated to remove use of prophylactic steroid eye drops	Removed prophylactic use of steroid eye drops based on data from the primary analysis
	Table 23: Added 20/15 as a baseline vision	The visual acuity scale did not reference vision better than 20/20.

Amendment 3: 17-DEC-2018

DOCUMENT HISTORY	
Document	**Date**
Amendment 3-2017N330177_04	17-DEC-2018
Amendment 2- (Republishing)- 2017N330177_03	04-SEP-2018
Amendment 2- 2017N330177_02	30-AUG-2018
Amendment 1- 2017N330177_01	02-APR-2018
Original Protocol-2017N330177_00	18-Jan- 2018

Overall Rationale for the Amendment:

The protocol has been amended to address over-enrollment in the frozen liquid solution portion of the study.

Due to the over-enrollment, the primary analysis will be based on all randomized participants (anticipated ~200) enrolled into the frozen liquid solution arms. In addition, a sensitivity analysis based on the first 130 participants will be performed to account for the original design.

Section # and Name	Description of Change	Brief Rationale
All Sections	Removed references of precise number of participants for enrollment	To align with actual enrollment
Section 2 Schedule of Activities	Table 1, footnote 14 Correction of FISH testing Table 2, Footnote 29 and Table 3 Footnote 19 window added for patient interviews Table 4, Footnote 5 clarified	Typographical error To allow greater flexibility for interview to occur Clarification of ocular assessment timing
Section 4 Objectives and Endpoints Section 1 Protocol Synopsis Objectives and Endpoints	Addition of Investigator assessed ORR as a secondary objective and endpoint. Removed the specification that clinical benefit rate (CBR) will be performed by IRC assessment	The primary analysis for the endpoint ORR is based on IRC assessment. Therefore, a secondary analysis for ORR based on investigator assessment is added and are

Section # and Name	Description of Change	Brief Rationale
		described in Section 10.5.1, Efficacy Analyses
Section 5 Study Design	Figure 1 – Study 205678 Schematic revised to remove enrollment references Additional clarification that IA for futility is planned for ORR based on investigator's assessment Clarification that lyophilized cohort will be analyzed separately from participants randomized to the frozen solution Clarification that the final analysis of the primary endpoint (ORR) will be performed 6 months after the last participant is randomized	To account for possible under/over enrollment. Clarification of ORR analysis at IA and final analysis
Section 6.1 Inclusion Criteria Section 1 Protocol Synopsis Inclusion Criteria	Changed e.g. to i.e. for the immunomodulatory agent listed under Inclusion criteria 4b	The Latin abbreviation of e.g. which translates to "for example" and is commonly confused with the Latin abbreviation of i.e. which translates to "in other words". The intent was that participants need to be refractory to the immunomodulatory agents lenalidomide or Pomalidomide ONLY (not thalidomide) and therefore the correct abbreviation is "i.e."
Section 7 Treatments	Added Infusion Time Removed text to specify the lyophilized cohort will be initiated when enrollment has completed in the frozen arms	To address regulatory comments To more accurately reflect study conduct
Section 9 Study Assessments and Procedures	Table 14 Correction of FISH testing results	Typographical error to align with Section 7.3, method of treatment assignment

Section # and Name	Description of Change	Brief Rationale
Section 9.11.3 Qualitative Telephone Interview (Patient Interviews)	Window added for patient interviews	Updated to align with Section 2, Schedule of Activities
Section 10.1 Hypothesis Testing	Update the timing of final ORR analysis Clarification that lyophilized cohort will be analyzed separately from participants randomized to the frozen solution	To reflect shortened enrolment period Clarification of ORR analysis at IA and final analysis
Section 10.2 Sample Size Determination	Provide updated language on IA and final analysis based on sample size of 100 participants per arm.	To reflect actual enrollment onto the frozen liquid solution arms of the study
Section 10.3 Sample Size Sensitivity	Update Table 15 to include power scenarios for sample size of 100 participants per arm.	To accommodate increase in sample size due to over enrolment.
Section 10.4 Populations for Analysis	Add a new analysis population (Efficacy), which consist of the first 130 randomized patients	To evaluate the effect of over-enrollment with respect to the original planned sample size for primary and key secondary endpoints.
Section 10.5.1 Efficacy Analyses	Clarifying the analysis population for efficacy endpoints at Final analysis Clarification that IA for futility is planned for ORR based on investigator's assessment.	To accommodate increase in sample size due to over enrolment. ORR based on IRC assessment is planned for the final primary analysis and the IA will be performed based on investigator assessment.
Section 10.5.9 Interim Analyses	Provide updated language on stopping rule/boundary crossing probability for IA	

Section # and Name	Description of Change	Brief Rationale
	and final analysis based on sample size of 100 participants per arm.	To accommodate increase in sample size due to over enrolment.

Amendment 2: 04-SEP-2018

Overall Rationale for the Amendment:

The protocol has been amended to address feedback from regulatory agencies, EC/IRB, and investigators. The updates include the addition of Exclusion Criteria defining the use of high dose steroids, clarification of specific timeframe from last treatment required for systemic anti-myeloma therapy, and increase of QTcF criteria. Additional PK sampling timepoints were added to capture the Cmax of the free cytotoxic drug (cys-mcMMAF) and to better define the kinetics of cys-mcMMAF and the elimination phase of ADC and cys-mcMMAF. Soluble BCMA collection timepoints were also added to capture the effect of GSK2857916 administration on soluble BCMA concentrations over time as a marker of pharmacodynamic effect. The dose modifications guidelines for GSK2857916 related Corneal Events clarify dose adjustments for GSK Scale Grade 2 events.

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 2 (Republishing)	*04-Sep-2018*
Amendment 2	*30-Aug-2018*
Amendment 1	*02-Apr-2018*
Original Protocol	*18-Jan-2018*

Section # and Name	Description of Change	Brief Rationale
All Sections	Replaced ophthalmologist with ophthalmologist (or an optometrist if an ophthalmologist is not available) Updated Investigator Brochure Version	To allow for either an optometrist or ophthalmologist to perform eye examinations.
Section 1 Synopsis	Changed text in Synopsis to reflect changes to the text of the protocol	See below for all significant changes

Section # and Name	Description of Change	Brief Rationale
Section 2 Schedule of Activities (SOA)	Table 1-Table 3: Footnote numbering corrected and text made applicable for each schedule Table 1-Table 3: Abbreviations updated Table 1: Screening SOA – addition of FISH results that are classified as high risk beyond the 60-day timepoint. Table 2: Clarifications of timings for vital sign, ECG collections and PK sample collection, Table 2: Triplicate ECG measurements changed from 5 minutes apart to 2 minutes apart; additional timepoints added Table 2: Additional PK timepoints added Table 2 & Table 3: Clarifications of timings for imaging added Table 2 & Table 3: Clarifications of serum and urine immunofixation added Table 2: Removed requirement for German MRI collection for skeletal survey Table 2: Additional sBCMA sample collection timepoints added Table 4: Removed requirement for mandatory exams in ocular substudy	Administrative changes and clarifications of timepoints Acceptability of positive results for high risk abnormalities by FISH have been extended beyond 60-days, as those are myeloma defining abnormalities and do not change in the course of the disease. Additional ECG timepoints added to assess at the Cmax of the free cytotoxic drug (cys-mcMMAF) and to detect any delayed effects on QTc. Additional PK timepoints added to capture the Cmax of the free cytotoxic drug (cys-mcMMAF) and to better define the kinetics of cys-mcMMAF and the elimination phase of ADC and cys-mcMMAF. Additional sBCMA timepoints added to capture the effect of GSK2857916 administration on soluble BCMA concentrations over time as a marker of pharmacodynamic effect.
Section 3.4.2 Corneal Events	Added CTCAE grading	Provides clarity that CTCAE scale was utilized to report all corneal events in the FTIH study.
Section 4 Objectives and Endpoints	Secondary endpoint for Clinical benefit rate added to align with Section 1, synopsis	Resolves Discrepancy and aligns section to Synopsis

Section # and Name	Description of Change	Brief Rationale
	Secondary endpoint for Time to Response, Progression Free Survival, Time to Progression and Overall Survival updated to align with Section 1, Synopsis and Section 10, Statistical Considerations. Plasma concentrations of GSK2857916 clarified as ADC, total mAb, and cys-mcMMAF. Exploratory Endpoint for MRD negativity testing clarified	Align with Section 10, which states all randomized participants will be included in analyses Clarification on how analyses will be performed
Section 5 Study Design	Study Schema revised to remove description of start of lyophilized cohort.	Lyophilized cohort will not open until the drug configuration is available and the enrollment is complete under the frozen configuration.
Section 5.5 Dose Justification	Added CTCAE grading	Aligned with Section 3.4.2 to clarify that the CTCAE scale was utilized in the FTIH study
Section 6.1 Inclusion Criteria	Changed i.e. to e.g. for prior lines Table 9 footnote cross-reference corrected	Clarification and Prior Lines of therapy updated to clarify it is any proteasome inhibitor or immunomodulatory agent.
Section 6.2 Exclusion Criteria	Systemic anti-myeloma therapy clarified as excluded if administered within ≤14 days or 5 half-lives, whichever is shorter Added Exclusion criteria #2 for high dose steroids Modified Exclusion criteria #12 to accept malignancy of non-melanoma skin cancers QTcF increase to 480 msec from 470 msec	Exclusion Criteria #1 - Clarification of timeframe required from last treatment of systemic anti-myeloma therapy Exclusion Criteria #2 added to define high dose steroid usage that may have anti myeloma activity though not given to treat the disease Exclusion Criteria #13 - QTcF increased to align with GSK internal standards for oncology

Section # and Name	Description of Change	Brief Rationale
		trials determined by GSK Cardiac Safety Panel.
Section 7 Treatments	Removed Infusion Time	Administrative change
Section 7.2 Dose Modifications, Table 13 Dose Modification Guidelines for GSK2857916 Treatment-Related Corneal Events	Table edited for clarity. GSK Scale for corneal events incorporated and Dosing modifications amended	Changes to dose modifications guidelines for GSK2857916 related Corneal Events further clarify dose modifications based on the visual acuity or findings on ophthalmic examination
Section 7.2.2 Dose Reductions for Toxicity	Dosing delay and restarting language added	Updated to allow for restart prior to next cycle in cases where the treating physician feels it is necessary for participants well-being.
Section 7.2.3 Corneal Supportive Care Guidelines	Clarified that corneal supportive care is based on GSK Corneal Scale (Table 22)	To provide consistency and alignment throughout the protocol.
Section 7.7.2 Prohibited Medications	Caution statement for CYP inhibitors/inducers added	For alignment with IB version 05, Section 6.4
Section 7.8 Treatment after the End of Study	Cross-reference corrected from Table 1 to Table 3	Administrative change
Section 8.1 Discontinuation of Study Treatment	Pregnancy added to the list of reasons for discontinuation	To align with Section 9.2.8 and Appendix 5 as animal reproductive studies have not been conducted with GSK2857916
Section 8.2.5 Corneal Event Stopping Criteria	Added Clarity on use of GSK scale and CTCAE scale for reporting purposes and dose modifications.	Alignment throughout protocol. Both the CTCAE and GSK Scale are to be utilized for reporting of corneal events and clarify that the GSK scale to be utilized for dose modification decisions.
Section 9 Study Assessments and Procedures	On study visits and PFS follow-up visits separated to aligned with SOA Tables	Alignment with Section 2, Schedule of Activities

Section # and Name	Description of Change	Brief Rationale
	Table 14 – addition of spot urine instructions; and clarification of FISH results to align with Section 2, Schedule of activities	
Section 9.1 Efficacy Assessments	Clarified language regarding collection of PD blood sample	Language modified to allow for confirmation sample to occur on the same day as original collection.
Section 9.2 Adverse Events	Added clarity on use of GSK Scale and CTCAE Added clarity that all AEs will be graded using CTCAE and that corneal events will also be graded using the GSK scale. GSK2857916 dosing decisions related to GSK2857916 corneal events are to be made using the GSK Scale for corneal events.	Revised to provide clear guidance for dose modifications due to GSK2857916 corneal events. CTCAE scale will be utilized to harmonize data with FTIH study results
Section 9.2.1 Time Period and Frequency for collecting AE and SAE information	Updated AE reporting timeframe from 30 days to 45 days	Revised to align with 5 half-lives of GSK2857916
Section 9.2.6 Disease Related Events and/or Disease Related	Clarified disease progression does not need to be reported as an SAE	Updated to align with GSK internal standards for oncology trials.
Section 9.2.7 Adverse Events of Special Interest	Added that corneal AESI should be graded by CTCAE and GSK Scale for corneal events	Revised to align with Section 9.2 Adverse Events.
Section 9.2.9 Ocular Exams and Procedures	Added statement to clarify representative images will be collected and stored centrally.	Revised to align with all GSK2857916 protocols
Section 9.2.10.1 Monocular Prophylaxis	Preservative free artificial tear requirements updated to align with Table 21, Prophylactic measures for corneal events associated with GSK2857916	Clarification to align with Table 21.

Section # and Name	Description of Change	Brief Rationale
Section 9.2.10.3 Sub-Study Exams	Clarification of exam requirements	Updated information regarding confocal exams.
Section 9.4.2 ECOG Performance Status	Timepoints updated to perform to align with Section 2, Schedule of Activities	Clarification to align with Section 2.
Section 9.4.4 Electrocardiogram	Triplicate ECG measurements changed to 2 minutes apart	Allows time for EOI PK sample collection
Section 10.2 Sample Size Determination	Update the type-1 error and power due to the change in boundary for claiming efficacy at final ORR analysis.	To address EMA's comments on maintaining overall type-1 error (1-sided 2.5%) adjusting for multiplicity (two dose arms), the boundary for claiming efficacy at final ORR analysis was modified.
Section 10.3 Sample Size Sensitivity	Update scenarios due to change in boundary for claiming efficacy at final ORR analysis.	To address EMA's comments on maintaining overall type-1 error (1-sided 2.5%) adjusting for multiplicity (two dose arms), the boundary for claiming efficacy at final ORR analysis was modified.
Section 10.4 Populations for Analysis	Provide reference for detailed definition of Evaluable Population, which will be used for ORR analysis at interim	To ensure consistency with IDMC charter
Section 10.5.1 Efficacy Analyses	Update language regarding ORR (confirmed vs. unconfirmed) at interim analysis.	Clarify that the ORR analysis at interim should be based on confirmed response if available.
Section 10.5.2 Safety Analysis Table 18	Addition of summarizing corneal events using GSK Scale for corneal events	To clarify that AESI of corneal events will also be summarized using the GSK Scale for corneal events.
Section 10.5.4.1Pharmacokinetic Data Analyses	Creation of subsections in Section 10.5.4 to separate pharmacokinetic and statistical analyses	For clarity Added noncompartmental analysis based on revised PK sampling schedule

Section # and Name	Description of Change	Brief Rationale
	Addition of non-compartmental analysis, data permitting	
Section 10.5.4.2 Statistical Analysis of Pharmacokinetic Data	Creation of subsections in Section 10.5.4 to separate pharmacokinetic and statistical analyses	For clarity
Section 10.5.9 Interim Analyses	Modify boundary of claiming efficacy at final ORR analysis, and associated operating characteristics.	To address EMA's comments on maintaining overall type-1 error (1-sided 2.5%) adjusting for multiplicity (two dose arms), the boundary for claiming efficacy at final ORR analysis was modified.
Section 11 References	GSK2857916 IB version updated from 03 to 05	Updated to include most recent version of IB
Section 12.5 Contraception Guidance	New template language added to elective termination description	Clarifies notification needed "for medical reasons"
Section 12.7 Liver Chemistry Stopping Criteria	Removed non-applicable PK sample statements in footnote 6 PK collection interval updated to 5 half-lives	Comparator language removed since monotherapy study Clarification Updated timeframe during which drug concentrations should be measured
12.9 Corneal Event Severity Grading and Mitigation Strategy Table 22	Added clarification that Grading is a GSK Scale Footnotes updates	To align with Section 9.2 Adverse Events and to indicate the GSK Scale for corneal events is not a CTCAE scale
12.10 Modified Diet in Renal Disease (MDRD) Formula	MDRD formula for calculating the estimated glomerular filtration rate was clarified to show superscript values	Provides instruction for calculation of eGFR
12.12 Appendix 12	Table 24 clear version inserted Modified description of simulation studies for evaluating operating characteristics	The numbers in the Table 24 in previous version were not legible. To clarify the objectives and conduct of simulation studies

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

Amendment 1: 02 April 2018

Overall Rationale for the Amendment:

The protocol has been amended to address regulatory agency advice. The original single-arm design with 1 dose level (3.4 mg/kg GSK2857916 Q3W) was amended to an open-label, randomized, 2-arm study with 2 dose levels by including the 2.5 mg/kg Q3W dose. In addition, a new exploratory cohort of 25 participants, who will receive a lyophilized configuration of GSK2857916, has been added to gain clinical experience with the lyophilized configuration. To accommodate these main changes, the overall sample size and related analytical methods have been changed.

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1	*02-Apr-2018*
Original Protocol	*18-Jan-2018*

Section # and Name	Description of Change	Brief Rationale
Cover Page	Study title updated A Phase II, Open Label, Randomized, Two-Arm Study to Investigate the Efficacy and Safety of Two Doses of the Antibody Drug Conjugate GSK2857916 in Participants with Multiple Myeloma Who Had 3 or More Prior Lines of Treatment, Are Refractory to a Proteasome Inhibitor and an Immunomodulatory Agent and Have Failed an Anti-CD38 Antibody (DREAMM 2).	Title updated to reflect the design change (see below)
Synopsis	Changed text of Synopsis to reflect changes to the text of the protocol	See below for all significant changes
All sections	Replaced the word 'patient' with 'participant' and 'subset' replaced with 'sub-study'. New references added	
Section 2 Schedule of Activities	Separate schedule tables for Screening assessments, on study assessment, 'end of treatment assessment and follow-up assessment have been included. Deletion of coagulation criteria (INR) for determining adequate organ system function Removal of aspirate for flow cytometry Added PET/CT to confirm CR, sCR German exceptions to PET/CT	The tables have been separated to clarify activities. Current liver event management guidelines do not require INR. Flow cytometry is not used in IMWG Kumar, 2016. Based on Kumar, 2016. Germany: approval by the German Federal Office for Radiation Protection is required prior to PET/CT or other x-rays can be performed.

Section 3.1 Study Rationale	Ongoing FTIH study number has been changed from BMA117158 to BMA117159	Editorial changes
Section 3.4.2 Corneal Events	Additional information regarding corneal toxicity included	
Section 3.4.3 Pharmacokinetics	Included new section 'Pharmacokinetics; with section number 3.4.3	To support the additional arm that includes dose level 2.5mg/kg
Section 3.5.3 Overall Benefit- Risk Conclusions	Overall Benefit-Risk conclusions is updated to reflect the additional dose.	Updated to reflect the change in study design.
Section 4 Objectives and Endpoints, Primary Objective	Primary objective has been modified: to evaluate the clinical efficacy of 2 doses of GSK2857916 in participants with relapsed/refractory multiple myeloma by overall response rate	Updated to reflect the change in study design.
Exploratory Objective	New exploratory endpoint has been included: To assess the safety, efficacy, immunogenicity, and pharmacokinetics of GSK2857916 in a lyophilized configuration (n=25)	To gain clinical experience with the lyophilized configuration.
Ocular Sub-Study Objective	Number of participants to evaluate the effect of topical corticosteroids on corneal findings has been increased to 30 (15 in each dose arm).	Number increased to reflect the additional arm and increased study sample size.
Section 5 Study Design	Study design description and the Study Schema revised.	Language and the schema modified to clarify changes in study design have been added, including the addition of a second arm, change to the total number of participants, IA to assess futility, IDMC to review IA results, and an additional cohort of participants (n=25) who will receive the lyophilized configuration.
	Efficacy and safety results from the interim analysis will not be shared with investigators or other study/site personnel	

Section 5.2 Number of Participants	Number of participants to be screened has been changed from 100 to 170, to be enrolled changed from 90 to 155 and number of recruitment centers changed from 30 to 60 investigational sites. Number of participants in the ocular sub-study increased to 30	Study design has changed from 1 arm to 2 arms, thus the sample size is increased. Ocular sub-study sample size is increased for same reason.
Section 5.3 Participant and Study Completion	Definition of the study-completed participant has been modified New criteria have been added: If a participant remains on treatment at the time end of study is achieved, they will be offered an option to extend treatment on this or another protocol.	Language to offer participants this option was inadvertently omitted.
Section 5.4: Scientific Rationale of Study Design Section 5.5: Dose Justification	Scientific rationale and dose justification sections are updated.	Scientific rationale and dose justification updated to address new design and additional dose level.
Section 6.2 Exclusion Criteria	Deletion of exclusion criterion #3 regarding best corrected visual acuity New #2 Exclusion criteria for symptomatic amyloidosis, active 'polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes' (POEMS) syndrome, active plasma cell leukemia at the time of screening and Prior allogeneic stem cell transplant has been added.	#3 Per regulatory agency suggestion, the criterion related to visual acuity limitations deleted. Requirement for preexisting conditions has been revised according to feedback for regulatory agencies. New # 2 Included to avoid unpredictable toxicity.
Section 7 Treatments	Table listing the study treatments.	To provide details of how the lower dosage form and the lyophilized form are supplied to the sites.
Section 7.2.2 Dose Reductions for Toxicity Table 10	Permitted dose reductions have been included. Table 10 updated.	Dose reductions updated per design change to 2 dose levels.

Section 7.2.2 Dose Reductions for Toxicity Table 13	Modified grading of corneal events by deleting the presence of asymptomatic corneal findings on ophthalmic exam not observed at baseline (grade 1) Modified management of corneal events, i.e. dosage of preservative free artificial tears has been increased for G4 corneal events. Footnote 'c' regarding patients with prior allogenic transplant with corneal toxicity has been deleted:	As the AE grading scale is now based on corneal clinical symptoms and visual acuity, this situation (asymptomatic findings) is no longer applicable as all findings will be considered AEs. Changes made due to regulatory agency recommendations. Editorial changes to clarify that artificial tears are to be increased for other AE grades. Editorial changes to reflect prior allogenic transplants are now excluded, thus footnote is unnecessary.
Section 7.3 Method of Treatment Assignment	Section 7.3 updated for randomization and stratification information for treatment assignment.	7.3 changes address randomizing to 2 arms.
Section 8.1 Discontinuation of Study Treatment	Deletion of language that allowed participants who have achieved CR to discontinue treatment.	Decision made to treat all patients until PD
Section 8.2.5 Corneal Supportive Care Guidelines	Management guidelines for corneal events updated.	Guidelines updated according to feedback from regulatory agency.
Section 8.2.6	Language added to reference Table 11	Added to reinforce the actions based on a Grade 4 IRR.

Section 9 Study Assessments and Procedures Section 9.2 Adverse Events	Baseline demographic assessment and medical family history assessment included General language corrections made for clarity. Adverse event coding by MedDRA and grading by NCI-CTCAE included	Editorial updates: demographics and medical history were added.
Section 9.1 Efficacy Assessment	IgG, IgM and IgA assessments and additional bone marrow testing included	To provide additional clarification
Section 9.2.10 Ocular Sub-Study Examination	The language in the Ocular Sub-Study Examinations section has been updated for increased clarity The language in Ocular Sub-study examinations now modified to remove confrontation of visual fields, evaluation of optic nerve and retina. Tear film examination, anterior segment photography, and pachymetry were added. Fundus and anterior segment photography are now included at baseline, end of study, and last follow-up visit.	Language modified to clarify the required examinations and palliative treatment for participants in this cohort. Recommendations from independent corneal experts.
9.2.10.1 Monocular Prophylaxis 9.2.10.2 Monocular Treatment 9.2.10.3 Sub-Study Exams	Registration into RAMOS after assessment completion deleted. Additional information and schematic for prophylactic eye drops included.	The section for monocular prophylaxis has been updated to clarify the treatment.
9.2.9 (old)	The section on assessment of sentinel events deleted.	Removed as this information is specific to a GSK process rather than something the sites must do. This will be captured in the SRM.

Section 9 Table 14 List of Clinical Laboratory Tests	Total carbon dioxide replaced with bicarbonate Bone marrow to confirm stringent complete response by flow cytometry deleted and an additional footnote included	Editorial changes to reflect the correct parameter Editorial changes to reflect IMWG criteria 2016.
9.9.1 sBCMA Sample Analysis	Specific assay used for sample collection, i.e. electrochemiluminescent immunoassay deleted	
9.10 Evaluation of Anti-Cancer Activity	Testing for evaluation of anti-cancer activity at 6 months included	Clarification to state this should be performed at the 6-month timepoint.
Section 10.1 Hypothesis Testing	The sample size and hypothesis testing is updated to reflect a 2-arm study. Updated enrollment duration and number of evaluable participants for interim analysis.	Section updated to reflect revised design and operating characteristics based on interactions with regulatory agency.
Section 10.2 Sample Size Determination	Included information on independent cohort for lyophilized configuration.	Section updated to reflect revised design and operating characteristics based on interactions with regulatory agency.
Section 10.3 Sample Size Sensitivity Section 10.5.9.1 Futility Stopping Rule based on Group Sequential Design	Updated IA futility stopping rules	Section updated to reflect revised design and operating characteristics based on interactions with regulatory agency.
Section 10.4 Population for Analysis Section 10.5.1 Efficacy Analysis	Safety population has been replaced with ITT population as a primary population of analysis of efficacy data and safety population updated to be used for analysis of clinical safety data	
Section 10.5.1 Efficacy Analysis	Updated statistical analysis methods for efficacy endpoints	

Section 10.5.9.2	New section heading “Additional Comparative Futility Stopping Rule Based on Bayesian Approach” added	Clarification of the posterior probability calculations are added
Section 12.4 Adverse Events: Definition and Procedures for Recording, Evaluating, Follow-up and Reporting	AE reporting corrected. .	Reporting based on CT-CAE grading.
Section 12.7.1.2 References	Additional relevant references included	
Section 12.8	Appendix 8 deleted	IMWG response criteria are referenced directly. Further interpretation is not needed.
12.10 Corneal Event Severity Grading and Mitigation Strategy	Table 21, Table 22 and Table 23 updated	Reporting based on CT-CAE grading. Table 22 (Corneal events AE grading scale) is now based on best corrected visual acuity.

11.12. Appendix 12: Statistical Considerations for Section 10.5.9.2 Additional Comparative Futility Stopping Rule Based on Bayesian Approach

Introduction

This document provides details about the additional comparative futility stopping rule based on the Bayesian approach at interim analysis (IA) for Study 205678.

As described in Section 9.5.9.2, the additional comparative rule based on the Bayesian approach will be used to further facilitate the decision of early stopping for futility. The arm deemed inferior to the other will be dropped. In practice, if both arms pass the futility boundaries based on group sequential design described above, posterior probability of observing a better RR in one arm relative to the other will be calculated. If such a probability is at least 90%, then the treatment arm with lower RR will be dropped due to lack of efficacy. To calculate the posterior probability, a non-informative beta prior (0.025,0.1) will be used for each arm.

Statistical Modeling

In the Bayesian approach,

let P_1 denote the response rate for arm 1; m_1 and X_1 denote the number of participants and number of responders at IA for arm 1;

let P_2 denote the response rate for arm 2; m_2 and X_2 denote the number of participants and number of responders at IA for arm 2;

We assume P_1 and P_2 are independent.

We assume the prior distributions of response rates $\pi_1(p_1)$ and $\pi_2(p_2)$ follow a beta distribution *beta* (α,β). The beta distribution represents the prior knowledge or belief about the efficacy of the new drug. The quantity $\frac{\alpha}{\alpha+\beta}$ reflects the prior mean response rate, while the quantity $\alpha + \beta$ reflects the amount of information contained in the prior. The larger value of $\alpha + \beta$, the stronger belief the prior has. In both simulations and actual IA, a non-informative beta prior (0.025,0.1) will be used for each arm.

We assume $X_1|m_1,p_1 \sim binomial(m_1,p_1)$ and $X_2|m_2,p_2 \sim binomial(m_2,p_2)$.
Consequently, the posterior distributions of the response rates P_1 and P_2 follow beta distributions:

$P_1|x_1 \sim beta(\alpha + x_1, \beta + m_1 - x_1)$, $P_2|x_2 \sim beta(\alpha + x_2, \beta + m_2 - x_2)$. $P_1|x_1$ and $P_2|x_2$ are also independent.

The comparative futility stopping rules are defined as:

If the posterior probability $P\ (P_1 > P_2|x_1, x_2) > 97.5\%$, then arm 2 is considered inferior to arm 1 and will stop for futility.

If the posterior probability $P\ (P_2 > P_1|x_1, x_2) > 97.5\%$ $P(P_2 > P_1|x_1, x_2) > 90\%$, then arm 1 is considered inferior to arm 2 and will stop for futility.

Let $\alpha_1^* = \alpha + x_1$, $\beta_1^* = \beta + m_1 - x_1$, $\alpha_2^* = \alpha + x_2$, $\beta_2^* = \beta + m_2 - x_2$,

Following the methods of [Dmitrienko, 2006], the posterior probabilities $P\ (P_1 > P_2|x_1,x_2)$ and $P\ (P_2 > P_1|x_1, x_2)$ will be computed as

$$P(p_1 > p_2|x_1,x_2) = \frac{1}{B(\alpha_1^*,\beta_1^*)}\int_0^1 p^{\alpha_1^*-1}(1-p)^{\beta_1^*-1}F_{B(\alpha_2^*,\beta_2^*)}(p)dp$$

$$P(p_2 > p_1|x_1,x_2) = \frac{1}{B(\alpha_2^*,\beta_2^*)}\int_0^1 p^{\alpha_2^*-1}(1-p)^{\beta_2^*-1}F_{B(\alpha_1^*,\beta_1^*)}(p)dp$$

Where $F_{B(\alpha_1^*,\beta_1^*)}$ and $F_{B(\alpha_2^*,\beta_2^*)}$ are the cumulative distribution functions of B(α1*,β1*) andB(α2*,β2*) distributions, respectively. The integral on the right-hand side of this equation was computed using the integrate function in R.

Determination of the Cutoff for Posterior Probabilities.

The cutoff for posterior probabilities was chosen as 97.5%, to allow for dropping an arm with substantially inferior response rates (e.g absolute difference > 28%). The posterior probabilities of (Arm 1 Response Rate > Arm 2 Response Rate) for all possible scenarios of the comparative rule at IA are shown in Table 24.

Table 24 Posterior Probabilities of (Arm 1 Response Rate > Arm 2 Response Rate) at Interim Analyses

Posterior Probabilities of (Arm 1 RR > Arm 2 RR)		Arm 1, Number of Responders at IA (Observed Response Rates)																				
		5 (20%)	6 (24%)	7 (28%)	8 (32%)	9 (36%)	10 (40%)	11 (44%)	12 (48%)	13 (52%)	14 (56%)	15 (60%)	16 (64%)	17 (68%)	18 (72%)	19 (76%)	20 (80%)	21 (84%)	22 (88%)	23 (92%)	24 (96%)	25 (100%)
Arm 2, Number of Responders at IA (Observed Response Rates)	5 (20%)	50.0%	63.8%	75.3%	84.1%	90.3%	94.4%	97.0%	98.5%	99.3%	99.7%	99.9%	99.9%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
	6 (24%)	36.2%	50.0%	63.0%	74.1%	82.9%	89.3%	93.7%	96.5%	98.2%	99.1%	99.6%	99.8%	99.9%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
	7 (28%)	24.7%	37.0%	50.0%	62.4%	73.2%	82.0%	88.6%	93.2%	96.2%	98.0%	99.0%	99.6%	99.8%	99.9%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
	8 (32%)	15.9%	25.9%	37.6%	50.0%	62.0%	72.6%	81.4%	88.1%	92.8%	96.0%	97.9%	99.0%	99.6%	99.8%	99.9%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
	9 (36%)	9.7%	17.1%	26.8%	38.0%	50.0%	61.7%	72.2%	80.9%	87.7%	92.6%	95.9%	97.9%	99.0%	99.6%	99.8%	99.9%	100.0%	100.0%	100.0%	100.0%	100.0%
	10 (40%)	5.6%	10.7%	18.0%	27.4%	38.3%	50.0%	61.5%	71.9%	80.7%	87.6%	92.5%	95.9%	97.9%	99.0%	99.6%	99.9%	100.0%	100.0%	100.0%	100.0%	100.0%
	11 (44%)	3.0%	6.3%	11.4%	18.6%	27.8%	38.5%	50.0%	61.3%	71.8%	80.6%	87.6%	92.6%	96.0%	98.0%	99.1%	99.7%	99.9%	100.0%	100.0%	100.0%	100.0%
	12 (48%)	1.5%	3.5%	6.8%	11.9%	19.1%	28.1%	38.7%	50.0%	61.3%	71.8%	80.7%	87.7%	92.8%	96.2%	98.2%	99.3%	99.7%	99.9%	100.0%	100.0%	100.0%
	13 (52%)	0.7%	1.8%	3.8%	7.2%	12.3%	19.3%	28.2%	38.7%	50.0%	61.3%	71.9%	80.9%	88.0%	93.2%	96.5%	98.4%	99.4%	99.8%	100.0%	100.0%	100.0%
	14 (56%)	0.3%	0.9%	2.0%	4.0%	7.4%	12.4%	19.4%	28.2%	38.7%	50.0%	61.5%	72.1%	81.3%	88.6%	93.7%	96.9%	98.7%	99.6%	99.9%	100.0%	100.0%
	15 (60%)	0.1%	0.4%	1.0%	2.1%	4.1%	7.5%	12.4%	19.3%	28.1%	38.5%	50.0%	61.7%	72.6%	82.0%	89.3%	94.4%	97.5%	99.1%	99.8%	100.0%	100.0%
	16 (64%)	0.1%	0.2%	0.4%	1.0%	2.1%	4.1%	7.4%	12.3%	19.1%	27.9%	38.3%	50.0%	61.9%	73.2%	82.6%	90.2%	95.2%	98.1%	99.5%	99.9%	100.0%
	17 (68%)	0.0%	0.1%	0.2%	0.4%	1.0%	2.1%	4.0%	7.2%	12.0%	18.7%	27.4%	38.1%	50.0%	62.4%	74.0%	84.0%	91.4%	96.3%	98.8%	99.8%	100.0%
	18 (72%)	0.0%	0.0%	0.1%	0.2%	0.4%	1.0%	2.0%	3.8%	6.8%	11.4%	18.0%	26.8%	37.6%	50.0%	62.9%	75.2%	85.5%	93.0%	97.5%	99.5%	100.0%
	19 (76%)	0.0%	0.0%	0.0%	0.1%	0.2%	0.4%	0.9%	1.8%	3.5%	6.3%	10.7%	17.2%	26.0%	37.1%	50.0%	63.7%	76.7%	87.5%	94.9%	98.8%	100.0%
	20 (80%)	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.3%	0.7%	1.6%	3.1%	5.6%	9.8%	16.0%	24.8%	36.3%	50.0%	64.8%	78.3%	90.3%	97.3%	99.9%
	21 (84%)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.3%	0.6%	1.3%	2.5%	4.8%	8.6%	14.5%	23.3%	35.2%	50.0%	66.5%	82.2%	94.1%	99.8%
	22 (88%)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.2%	0.4%	0.9%	1.9%	3.7%	7.0%	12.5%	21.5%	33.5%	50.0%	69.2%	87.6%	99.4%
	23 (92%)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.2%	0.5%	1.2%	2.5%	5.1%	9.7%	17.8%	30.8%	50.0%	74.6%	98.3%
	24 (96%)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.2%	0.5%	1.2%	2.7%	5.9%	12.4%	25.4%	50.0%	94.2%
	25 (100%)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.2%	0.6%	1.7%	5.8%	50.0%

Note: For both Arm 1 and Arm 2, the IA sample sizes are assumed to be 25. The green cells represent scenarios with posterior probabilities greater than 97.5%.

Evaluating Probabilities of Stopping for Futility Using Simulations

Simulation studies are conducted to evaluate probabilities of stopping for futility at the interim and claiming efficacy at final using both futility rules (group sequential design and Bayesian approach). Scenarios of simulation studies tested are listed in Table 25.

Table 25 Scenarios of Simulation Studies to Evaluate Probabilities of Stopping for Futility

Scenarios	Response Rate	
	Arm 1	Arm 2
1	33%	60%
2	33%	45%
3	33%	33%
4	33%	25%
5	33%	20%
6	33%	15%
7	33%	10%
8	15%	15%

For each scenario, K=10,000,000 trials are simulated based on the assumed response rates (RR) for each arm (assuming number of responders for both arms follow binomial distribution). IA and final sample sizes are fixed as 25 and 65, respectively. For each simulate trial, the posterior probabilities $P(P_1 > P_2|x_1, x_2)$ and $P(P_2 > P_1|x_1, x_2)$ are compute as specified above. For each simulated trial, both futility rules will be used to determine whether the trial should stop for futility at IA or claim efficacy at final. Such probabilities will be computed based on K=10,000,000 simulated trials. The simulation results are summarized in Table 20 in Section 9.5.9.2.

References

Dmitrienko A, Wang MD. Bayesian predictive approach to interim monitoring in clinical trials. Statistics in Medicine. 2006 July 15;25(13):2178-2195.

11.13. Appendix 13: Home Healthcare and Telemedicine Approaches

Home Healthcare (General Visit):

Where applicable country and local regulations and infrastructure allow, home healthcare may be permitted. Home healthcare is defined as a remote visit(s) that is/are performed at the participant's home by qualified personnel (e.g. nurse).

Activities that may be done as part of a home healthcare visit must follow the schedule provided in the SoA (Section 1.2) and include:

- Collection of blood and urine samples including:
  - Safety assessments which may include routine blood and urine sampling
  - Efficacy assessments to be sent to central lab
- Measurement of vital signs (BP, heart rate, body temperature).
- Identification and reporting of concomitant medications.
- Patient reported signs and symptoms, or abnormalities noted based on vital signs are reported to the Principal Investigator to determine if they meet the definition of an AEs/SAEs.

Note: The investigator or other qualified medical professional must ensure reporting of AEs and SAEs is completed in accordance with the protocol and applicable regulations and that the appropriate medical intervention, therapeutic intervention, and/or support measures are instituted, as necessary.

The participant should be informed of any potential risks associated with Home Healthcare and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

Home Healthcare (Ophthalmologic Exam)

Where applicable country and local regulations and infrastructure allow, protocol-required eye exams may be done in the participant's home or specified alternative eye care specialist clinic.

All protocol specific assessments should be completed by the alternative eye care specialist at the clinic. Activities that may be done as part of in-home eye exams, must follow the schedule provided in the SoA (Section 1.2) and include:

- Best Corrected Visual Acuity, or Visual Acuity (VA) by near-chart visual acuity/pinhole.
- Slit lamp exam
- Intraocular pressure measurement & time checked
- Dilated funduscopic exam

The participant should be informed of any potential risks associated with Home Healthcare Ophthalmologic exams and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

Telemedicine

Where applicable country and local regulations and infrastructure allow, telemedicine visits may be permitted. Telemedicine visits are defined as online (virtual) visits which will use secure video conference, phone calls, a web portal and/or mobile application as a way of communicating with and monitoring the participant's progress. Telemedicine visits are conducted by an investigator or other qualified medical professional and may be done in combination with visits from Home Healthcare personnel (see above).

Activities that may be done as part of a telemedicine visit include:

- Medical evaluation of the participant
- Identification and reporting of concomitant medications.
- Identification, management, and reporting of AEs and SAEs.

Note: The investigator or other qualified medical professional must ensure reporting of AEs and SAEs is completed in accordance with the protocol and applicable regulations and that the appropriate medical intervention, therapeutic intervention, and/or support measures are instituted, as necessary. Participants utilizing telemedicine can report AEs at any time via an app, phone call or videoconference with site staff.

The participant should be informed of any potential risks associated with the virtual medium and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

Remote Patient Reported Outcomes (PRO) Administration

Where applicable country and local regulations and infrastructure allow, remote PRO administration may be permitted. Remote PRO administration is defined administration of protocol PROs by a qualified third party over the telephone. The remote PRO Administrator will use the versions of the PROs designed for verbal administration. The remote PRO Administrator will create a data change form with the participants' responses and send to the third party vendor for the study to add to the study portal.

The participant should be informed of any potential risks associated with the remote PRO administration and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 06-Jul-2023 16:46:15 GMT+0000

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