TITLE PAGE

Protocol Title: A Phase I Open-label, Dose Escalation Study to Investigate the Safety, Tolerability, Pharmacokinetics, Immunogenicity and clinical activity of the Antibody Drug Conjugate belantamab mafodotin in Chinese Participants with Relapsed/Refractory Multiple Myeloma Who Have Failed At Least Two Lines of Previous Treatment, Containing an alkylator, a Proteasome Inhibitor and an Immunomodulatory Agent

Protocol Number: 208465/Amendment 3

Compound Number: GSK2857916

Study Phase: Phase 1

Short Title: Phase I dose escalation study of belantamab mafodotin in Chinese participants with relapsed/refractory multiple myeloma

Acronym: CDREAMM 1

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Medical Monitor Name and Contact Information

This information will be provided in the Study Reference Manual (SRM).

Regulatory Agency Identifying Number(s): Not applicable

Approval Date: 26-OCT-2021

SPONSOR SIGNATORY:

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Beulah Ji **Date**

VP & Head of Development, GSK China

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY List dates of original protocol and all amendments in reverse chronological order.		
Document	**Date**	**DNG Number**
Amendment 3	*26-Oct-2021*	*TMF-14065056*
Amendment 2	*30-Oct-2020*	*2018N359597_02*
Amendment 1	*02-Nov-2019*	*2018N359597_01*
Original Protocol	*01-Apr-2019*	*2018N359597_00*

Amendment 3: 26-OCT-2021

Overall Rationale for the Amendment:

The protocol has been amended to accommodate the updates based on latest information available through investigator's brochure. The study period was extended to maintain the study treatment of two ongoing participants who are benefitting from the Belantamab mafodotin treatment as judged by investigator.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.1. Synopsis Section 5.1. Inclusion criteria	Inclusion criteria 8 and 9: Updated the period to use contraception (Female: 4 months after last dose of belantamab mafodotin; Male: 6 months after last dose of belantamab mafodotin)	Updated based on current safety information
Section 1.3. Schedule of Activities (SoA)	Updated footnote 19 and 33 - Samples for pharmacokinetics will be collected for the interpretation of ADA results one year after the first dose of last subject - Samples for CCI [redacted] will be collected up to one year after last subject first dose	As the sample for pharmacokinetic analysis and CCI [redacted] will not be collected further.
Section 2.2. Background	Current treatment landscape for treating Relapsed/Refractory Multiple Myeloma (RRMM) in China	Updated based on latest information available
Section 2.3.3. Pharmacokinetics and Pharmacodynamics	Pharmacokinetic and Pharmacodynamic information updated	Updated to align with current IB information
Section 2.4.1. Risk Assessment	Update in explanation of risks	To align with IB update
Section 2.4.3. Overall benefit: Risk conclusion	Removed the clinical experience available from the study BMA117159	Based on current safety information
Section 3. Objectives and Endpoints	Added exploratory objective and endpoint for CCI [redacted] assessment	To align with Schedule of activities table

Section # and Name	Description of Change	Brief Rationale
Section 4.1. Overall Design Section 4.4. End of study	Updated or added the definition of End of study (EOS)	To make it align with other study protocols in oncology
Section 6.6. Dose modification	Updated Table 5 Dose Modification Guidelines for Belantamab Mafodotin-Related Adverse Events. - Added row for 'Urine Dipstick'. - For thrombocytopenia separate recommendations are made for Belantamab Mafodotin during grade 3 and grade 4 toxicity - For Neutropenia, recommendations for Belantamab Mafodotin are updated according to current available information - For Pneumonitis, recommendations for Belantamab Mafodotin for Grade 2 and Grade 3-4 toxicities are updated according to current available information	Updated based on current information on BCMA
Section 7.1. Dose modification	Added a point that study treatment may be permanently discontinued at 'Investigator's discretion'.	Added for clarity
Previous Sections 7.1.2. QTc Stopping Criteria	Deleted	Based on available data, cardiac risk was determined to be low and stopping criteria were removed
Previous Sections 7.1.4. Left Ventricular Ejection Fraction (LVEF) Stopping criteria	Deleted	Based on available data, cardiac risk was determined to be low and routine monitoring was removed
Section 8.3.1. Time Period and Frequency for Collecting AE and SAE Information	SAE and AE collection period has been updated from 45 days to 70 days after the participant is discontinued from the study treatment.	Updated as per current safety information
Section 9.4.9. Clinical Activity Analyses	Added CCI assessment	To align with updated objective and endpoint
Section 9.5. Interim Analyses	Updated end of study definition	To align with updated EOS definition in Section 4.4
Section 11.2. Appendix 2. Clinical Laboratory Tests	Added point number 6, on use of urine dipstick to assess for presence of urine protein	Added for clarity
Section 11.4. Appendix 4. Contraceptive Guidance and Collection of Pregnancy Information	Under heading: Collection of Pregnancy Information. The duration is updated from 5 months to 6 months for pregnancy information of a female partner of a male study participant following last dose of study treatment.	Updated according to current safety information

Section # and Name	Description of Change	Brief Rationale
	The duration is updated from 8 months to 4 months for pregnancy information of a female study participant following last dose of study treatment.	
Whole document	Minor editorial, alignment for consistency and document formatting revisions	Minor, therefore not been summarized

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase I Open-label, Dose Escalation Study to Investigate the Safety, Tolerability, Pharmacokinetics, Immunogenicity and clinical activity of the Antibody Drug Conjugate belantamab mafodotin in Chinese Participants with Relapsed/Refractory Multiple Myeloma Who Have Failed At Least Two Lines of Previous Treatment, Containing an alkylator, a Proteasome Inhibitor and an Immunomodulatory Agent

Short Title: Phase I dose escalation study of belantamab mafodotin in Chinese participants with relapsed/refractory multiple myeloma

Rationale:

This is the first study for belantamab mafodotin in China to assess the safety, tolerability, pharmacokinetics (PK), immunogenicity and clinical activity of belantamab mafodotin in Chinese participants with multiple myeloma (MM). Belantamab mafodotin is a humanised (IgG1) antibody-drug conjugate (ADC) that binds to B-cell maturation antigen (BCMA), a target widely expressed on malignant plasma cells in MM. The parent anti-BCMA antibody is conjugated to the microtubule inhibitor, monomethyl auristatin-F (MMAF), which is released inside the malignant cell after binding and internalisation 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 tumour necrosis factor (TNF) family (BAFF/BLyS), and a proliferation-inducing ligand (APRIL). Belantamab mafodotin induces immunogenic cell death (ICD) in a BCMA-expressing multiple myeloma cell line. Exposure of dendritic cells to tumour cells undergoing ICD induces an antigen-specific T cell response.

Preliminary clinical data from the global ongoing BMA117159 study as of the data cut off of 31 Aug 2018, a total of 73 participants with RRMM have been treated with at least one dose of belantamab mafodotin. The Part 1 dose-escalation phase enrolled 38 participants at doses ranging from 0.03 mg/kg IV up to 4.6 mg/kg IV. Belantamab mafodotin was well tolerated with no DLTs up to 4.6 mg/kg q3w; MTD was not reached. The Part 2 dose expansion phase has enrolled 35 participants with MM at the recommended Phase 2 dose (RP2D) of 3.4 mg/kg IV, Q3W and has demonstrated an objective response rate (ORR) of 60% [95% confidence interval (CI): 42.1%, 76.1%], in heavily pre-treated participants with relapsed/refractory multiple myeloma (RRMM). The median duration of response (DOR) was 14.3 months [95% CI: 10.6, NA]; the median progression free survival (PFS) in this population was 12.0 months [95% CI: 3.1, not evaluable [NE]. Overall, belantamab mafodotin has a manageable safety profile with thrombocytopenia/platelet count decreased and corneal events as the most commonly reported events. Based on these data, GSK has initiated Study 205678, a global phase II study evaluating the safety and efficacy of belantamab mafodotin monotherapy (3.4 and 2.5 mg/kg administered once every 3 weeks) in participants with relapsed / refractory multiple myeloma previously treated with at least 3 classes of drugs, including PIs, IMIDs and an anti-CD38 antibody, and who have demonstrated disease progression on or within 60 days of completion of the last therapy.

Study 208465 is designed to evaluate the safety, tolerability, PK, immunogenicity and clinical activity of belantamab mafodotin in Chinese participants with RRMM who have received at least 2 prior line of anti-myeloma therapy including an alkylator, a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD).

Objectives and Endpoints:

Objectives	Endpoints
Primary Objectives	
• To determine safety and tolerability of belantamab mafodotin in Chinese Participants with RRMM	• Adverse events (AE), i.e., number (%) of participants with DLTs, number (%) of participants with AEs
Secondary Objectives	
• To evaluate PK profile of belantamab mafodotin in Chinese Participants with RRMM	• ADC, total antibody and cys-mcMMAF PK parameters following IV single and repeat dose administration during dose escalation as data permit (e.g., AUC, Cmax, tmax)
• To evaluate safety and tolerability of belantamab mafodotin	• Changes in clinical signs and laboratory parameters, ocular findings on ophthalmic exam
• To evaluate the clinical measures of efficacy of belantamab mafodotin	• ORR, defined as the percentage of participants with a confirmed partial response (PR) or better (i.e., VGPR, CR and stringent complete response [sCR]), according to the International Myeloma Working Group (IMWG) Response Criteria.
• To assess anti-drug antibody (ADA) formation after IV single and repeat dose administration of 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 OSDI

Abbreviations: IV = intravenous; BCMA = B-cell maturation antigen; MMAF = monomethyl auristatin-F; ORR = overall response rate; CR = complete response; VGPR = very good partial response; PR = partial response ; AUC = area under the curve; C_{max} = maximum concentration; T_{max} = time to maximum; FLC = free light chain; SCT = stem cell transplant; OSDI = Ocular Surface Disease Index.

Overall Design:

This is a Phase I, open-label study to explore safety, tolerability, PK, immunogenicity and clinical activity of belantamab mafodotin monotherapy in Chinese participants with RRMM. Projected dose levels are 2.5 mg/kg and 3.4 mg/kg. De-escalation to 1.9 mg/kg will be allowed in case of ≥2 DLT at dose 2.5 mg/kg. The sample size planned is based on predefined dose escalation criteria for dose selection and is not driven by statistical considerations.

As per current available safety and efficacy information of belantamab mafodotin studies, the 3.4 mg/kg dose cohort is converted to an optional cohort in the dose-escalation study design. Escalation may not proceed if not supported by emerging clinical data from other belantamab mafodotin studies.

Based on the 3+3 dose escalation design the anticipated size will be up to 6 evaluable participants for each dose level.

Belantamab mafodotin will be administered via 30-60 min intravenous (IV) infusion once every three weeks (21 days = 1 cycle). Extensive PK sampling will be collected at first cycle to characterize belantamab mafodotin exposures for each dose level.

Disclosure Statement:

This is an open-label, single arm, no masking study.

Number of Participants: No formal statistical hypotheses are being tested. Analysis of the data obtained will only utilise descriptive methods. The sample size planned arises from the predefined dose escalation criteria for dose selection and is not driven by statistical considerations. Based on the 3+3 dose escalation design the anticipated size will be up to 6 evaluable participants for each dose level. The dose escalation decisions will be based on the recommendation from the Dose Escalation Meeting as well as the totality of the safety, tolerability and pharmacokinetics.

Intervention Groups and Duration:

Belantamab mafodotin will be administered via 30-60 min intravenous (IV) infusion once every three weeks on day 1. Participants will be treated until disease progression, intolerable toxicity, end of study or informed consent withdrawal.

Treatment Arms

Dose escalation will characterize the safety, tolerability and immunogenicity of escalating doses of belantamab mafodotin. The following dose levels of belantamab mafodotin are planned to be studied: 2.5 mg/kg and 3.4 mg/kg.

Data Monitoring Committee: No

Dose Escalation Meeting: Yes

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 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. Histological or cytologically confirmed diagnosis of MM as defined according to IMWG, 2014 criteria and
    a. Has undergone autologous stem cell transplant or transplant is considered not feasible by local assessment.
    b. Has failed at least 2 prior lines of anti-myeloma treatments, containing ALL of the following classes of drugs: alkylating agent, IMID and PI.
    c. In addition, eligible participants needs to be refractory to an IMiD (i.e., lenalidomide or pomalidomide), and to a proteasome inhibitor (i.e., bortezomib, ixazomib or carfizomib) as defined by IMWG criteria.
    d. Participants who failed with CD38 antibody (i.e., daratumumab) in previous clinical trials can also be considered to include if they meet the remainder of inclusion criteria in this protocol.
    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 functions

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.0 X 10^9/L
Hemoglobin	≥8.0 g/dL
Platelets	≥50 X 10^9/L
Hepatic	
Total bilirubin	≤1.5X ULN (Isolated bilirubin ≥1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
ALT	≤2.5 X ULN
Renal	
eGFR[1] Spot urine (albumin/creatinine ratios (spot urine)	≥30 mL/min/ 1.73 m^1 <500 mg/g (56 mg/mmoL)
Cardiac	
LVEF (Echo)	≥25%[2]

1. As calculated MDRD equation
2. It is acceptable to use an existing ECHO result, if performed within three months of screening. For participants with abnormal LVEF (per institutional standards), the participant is to follow-up with a cardiologist. For participants with low LVEF (per institutional standards), consider referring to cardiology per local standards of care.

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 4 months after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.

     A WOCBP must have a negative highly sensitive serum pregnancy test within 72 hours of dosing on C1D1 and agree to use effective contraception during the study and for 4 months after the last dose of study treatment.

     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 from the time of first dose of study until 6 months after the last dose of study treatment to allow for clearance of any altered sperm:

- Refrain from donating sperm
  PLUS either:
- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
  OR
- Must agree to use contraception/barrier as detailed below:
  Agree to use a male condom, even if they have undergone a successful vasectomy and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year 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 5.0 must be ≤Grade 1 at the time of enrolment except for alopecia and Grade 2 peripheral neuropathy.

Exclusion Criteria

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

1. Systemic anti-myeloma therapy within <14 days, or plasmapheresis within 7 days prior to the first dose of study drug
2. Symptomatic amyloidosis, active POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes), active plasma cell leukemia at the time of screening.
3. Prior allogeneic stem cell transplant (SCT)
4. Current corneal epithelial disease except mild punctate keratopathy.
5. 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.
6. Evidence of active mucosal or internal bleeding
7. Any major surgery within the last four weeks

8. 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.

9. 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.

10. 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.

11. 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.

12. Evidence of cardiovascular risk including any of the following:

    a. QTcF interval >480 msecs (the QT interval values must be corrected for heart rate by Fridericia's formula [QTcF])
    b. Evidence of current clinically significant untreated arrhythmias, including clinically significant ECG abnormalities such as 2nd degree (Mobitz 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 three months of Screening.
    d. Class III or IV heart failure as defined by the New York Heart Association functional classification system
    e. Uncontrolled severe hypertension, e.g. 170/110

13. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to belantamab mafodotin, or any of the components of the study drug.

14. Pregnant or lactating female.

15. Active infection requiring antibiotic, antiviral, or antifungal treatment.

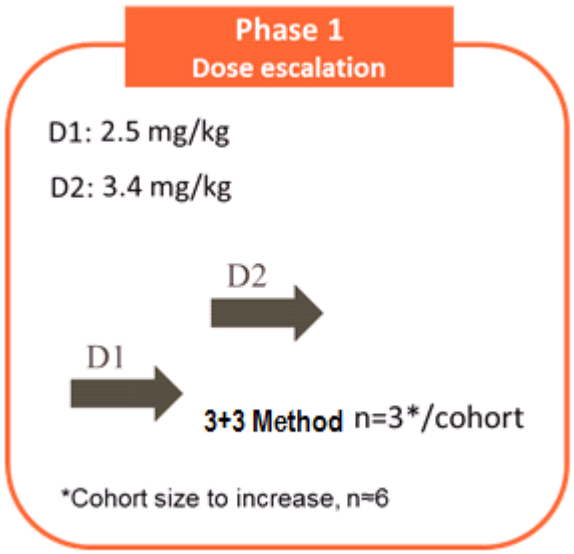
16. Known HIV infection.

17. 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)

18. 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. Schema

Figure 1 Study Design



Note: De-escalation to 1.9 mg/kg will be allowed in case of ≥2 DLT at dose 2.5 mg/kg
As per current available safety and efficacy information of belantamab mafodotin studies, the 3.4 mg/kg dose cohort is converted to an optional cohort in the dose-escalation study design. Escalation may not proceed if not supported by emerging clinical data from other belantamab mafodotin studies.

1.3. Schedule of Activities (SoA)

Table 1 Schedule of Activities for belantamab mafodotin Study 208465 - Every 3 Weeks Dosing Schedule for RRMM

Study Assessments	Screen[1]	Cycle 1 Day 1[2]	Cycle 1 Day 2	Cycle 1 Day 4	Cycle 1 Day 8	Cycle 1 Day 15	Treatment Period[3] Cycle = 21 days D1 of C2 - CX	End of Treatment Follow-up[4]	PD Follow-up[5]
Informed Consent	X								
Baseline Demographics	X								
Medical History including disease history and characteristics	X								
Physical Exam	X	X					X every 3 weeks	X	X
Safety									
Ocular Exam	X[6]						X[7]	X[7]	X[8]
ECOG Performance Status	X						X every 3 weeks	X	
Vital Signs (BP, HR, Body Temperature) [9, 10]	X	X			X	X	X	X	
Weight[9] and Height	X	Weight only					Weight only	Weight only	
Hematology[11]	X	X		X	X	X	X every 3 weeks	X	
Clinical chemistry[11]	X	X	X	X	X	X	X every 3 weeks	X	X[11]
Urine Dipstick[11]	X	X					X every 3 weeks	X	X
eGFR (by MDRD formula- see Appendix 8)	X	X					X every 3 weeks	X	
Spot urine for creatinine/albumin ratio[12]	X	X					Cycle: 3, 5, 7 and Every other cycle thereafter	X	
CRP	X						X every 3 weeks	X	

Study Assessments	Screen[1]	Cycle 1 Day 1[2]	Cycle 1 Day 2	Cycle 1 Day 4	Cycle 1 Day 8	Cycle 1 Day 15	Treatment Period[3] Cycle = 21 days D1 of C2 - CX	End of Treatment Follow-up[4]	PD Follow-up[5]
HBsAg, HBcAb, and hepatitis C Ab.[13]	X								
Troponin I[14]	X								
BNP[15]	X								
Pregnancy Test[9, 16]	X	X					X	X	X[16]
ECHO[17]	X						as clinically indicated		
12-lead ECG[9, 18]	X	X[18]	X[18]	X[18]	X[18]	X[18]	X.	X	
PK and ADA									
PK[19]		X[19]	X[19]	X[19]	X[19]	X[19]	X[19]	X[20]	
ADA[21]		X[21]					X[21]	X[21]	
Disease Evaluation									
β_2 Microglobulin	X								
Response assessment[22]							X every 3 weeks	X[23]	X
Skeletal survey[24]	X						As clinically indicated [25]		
Imaging for Extramedullary disease[26]	X						C5, C9, C13 and C17, every12 weeks then as clinically indicated [26]	X [27]	X
UPEP (Urine Protein Electrophoresis) 24 hr urine collection	X						X every 3 weeks	X	X
Urine Immunofixation	X						At time of first achieving CR or suspected PD after CR or sCR	At time of first achieving CR or suspected PD after CR or sCR	At time of first achieving CR or suspected PD after CR or sCR
SPEP (Serum Protein Electrophoresis)	X						X every 3 weeks	X	X

Study Assessments	Screen[1]	Cycle 1 Day 1[2]	Cycle 1 Day 2	Cycle 1 Day 4	Cycle 1 Day 8	Cycle 1 Day 15	Treatment Period[3] Cycle = 21 days D1 of C2 - CX	End of Treatment Follow-up[4]	PD Follow-up[5]
Serum immunofixation	X						At time of CR or suspected PD after CR or sCR	At time of CR or suspected PD after CR or sCR	At time of CR or suspected PD after CR or sCR
Serum Kappa, lambda free LC, FLC ratio	X						X every 3 weeks	X	X
Calcium corrected for albumin (serum)	X						X every 3 weeks	X	X
IgG, IgM, IgA	X	X					X every 3 weeks	X	X
IgD/E[28]	X	X					X every 3 weeks	X	X
Bone Marrow Aspiration / biopsy									
FISH testing on bone marrow[29]	X								
CCI									
BM for disease assessment[31]	X						At the time of CR (always) or at time of suspected PD (only if not evident otherwise)	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
Bone marrow to assess sCR by (IHC)[32]							X[32]	Only if CR has been achieved on this visit.	Only if CR have been achieved on this visit
Biomarker									
CCI									
Study treatment									
Premedication if needed		X					X		
Belantamab mafodotin administration[34]		X					X		
Preservative-free artificial tears[35]		X					Everyday until end of Study treatment		
Adverse Events[36]		X	X	X	X	X	X		

Study Assessments	Screen[1]	Cycle 1 Day 1[2]	Cycle 1 Day 2	Cycle 1 Day 4	Cycle 1 Day 8	Cycle 1 Day 15	Treatment Period[3] Cycle = 21 days D1 of C2 - CX	End of Treatment Follow-up[4]	PD Follow-up[5]
Concomitant Medications	X	X	X		X	X	X		
Health Outcomes									
OSDI[37]	X	X					X every 3 weeks	X	X

Abbreviations:
ADA = Anti-drug Antibody; ALP = alkaline phosphatase; BM = bone marrow; BNP = B-type natriuretic peptide; BP = blood pressure; C1D1 = Cycle 1 Day 1, etc.; CK = creatine kinase; CRP = C-reactive protein; EM = extramedullary; EOI = End of Infusion; FISH = fluorescence in situ hybridization; FLC = free light chain; HR= heart rate; Ig = immunoglobulin; PK = Pharmacokinetics; QID = 4 times a day; SOI = start of infusion; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; OSDI = Ocular Surface Disease Index

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 C1D1 unless otherwise specified.
2. 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.
3. Belantamab mafodotin will be administered intravenously on Day 1 (D1) of every 21-day cycle until disease progression, death, unacceptable toxicity, withdrawal of consent or end of study.
4. The End of treatment (EOT) follow-up visit is to assess any residual AEs or toxicities associated with Study treatment. The visit should occur -within 45 days after last dose or before the start any new anti-cancer therapy.
5. PD follow-up once every 21 days: Participants who discontinue IP for a reason other than PD, disease evaluations will continue to be performed once every 21 days (±7 days) until confirmed PD, death, start of a new anticancer treatment, withdrawal of consent, or end of the study whichever occurs first.
6. Screening examination will be performed by an ophthalmologist (or an optometrist if an ophthalmologist is not available) within 21 days prior to first dose. See Section 8.3.9 for the list of ophthalmic exam procedures.
7. On-study ophthalmic exams to be performed by an ophthalmologist (or an optometrist if an ophthalmologist is not available) pre-dose every 3 weeks (schedule of assessment window should be within 5 days prior to dosing, all efforts should be made to schedule as close to dosing as possible). After the 6th dose of belantamab mafodotin (no schedule of assessment window needed): If there are no significant (Grade 2 or above) ocular symptoms or vision changes the frequency of ophthalmologic exams may be decreased to every 3 months until end of treatment. In case of persistent ocular exam findings, newly developed ocular symptoms or vision changes, further ocular exams should be performed at least every cycle until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by the qualified eye care specialist (Appendix 9). See Section 8.3.9 for the list of ophthalmic exam procedures
8. Additional exams may be performed by the ophthalmologist (an optometrist if an ophthalmologist is not available), as clinically indicated.
9. 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: ECG, weight, vitals, pregnancy test. Please follow the visit schedule in the SOA above, and perform these activities prior to a belantamab mafodotin infusion
10. 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, end of infusion (EOI), and 1 hour post EOI. On subsequent dosing days, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), and at EOI. On days where vital sign time points align with PK sampling time points, vital signs must be assessed prior to PK samples being drawn. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

11. Refer to Table 9 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 Day 1 of Cycle 1. Creatinine only is required at PD visits (not a full chemistry).
12. Creatinine / albumin ratios (spot urine from first void) at screening and C1, C3, C5, C7 and every other cycle thereafter (local labs or central if local not available).
13. 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 negative-participant is eligible).
14. 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 must be measured.
15. 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 must be measured.
16. Perform only in women of childbearing 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, follicle stimulating hormone (FSH) and estradiol (as needed in women of non-child bearing potential only) should be performed at local lab. See Section 5.1, Section 8.3.5, and Appendix 4 for more details.
    a. Final pregnancy test (serum or urine) must be performed in women of childbearing potential at the EOT Visit, and 8 months after the last dose of study treatment may be via a urine pregnancy test kit mailed to the participant's home with results reported by telephone.
17. Echocardiography for LVEF performed within 3 months of screening are acceptable as screening value. For participants with an abnormal LVEF (per institutional standards), the participant is to follow-up with a cardiologist.
18. ECGs on dosing days: Triplicate ECGs to be performed at pre-dose (within 30 minutes prior to SOI) and EOI at cycle 1. Triplicate ECGs should be collected prior to PK sample on Cycle 1 Day 2, Day 4, Day 8 and Cycle 1 Day 15. Single ECG at screening, at all other cycles, and End of Study Treatment. On days where ECG time points align with PK sampling time points, ECGs must be performed within 30 minutes prior to PK samples being drawn (PK sample must be taken at the exact nominal time). ECGs will be collected and stored at site. See SRM for details on collection regarding ECGs.
19. PK samples to be taken in all participants for belantamab mafodotin ADC, total antibody and cys-mcMMAF measurements on:
    - C1D1 at pre-dose (within 30 minutes prior to SOI), at the end of infusion (EOI) (+5 min), 2 h post-SOI (±15 min), 4 h post-SOI (±15 min), 8 h post-SOI (±1 h), 24 h post-SOI (±2 h);
    - C1D4 anytime (±1 day);
    - C1D8 anytime (±1 day);
    - C1D15 anytime (±1 day);
    - C1D22 anytime (±1 day) (collect one PK sample only if the dose for the next cycle is delayed; this sample will combined)
    - For C2D1, C4D1, C6D1, C9D1, and C12D1, collect samples at pre-dose (within 30 min prior to SOI) and at the EOI (+5 min);
    - For every six cycles after C12 (e.g., C18, C24, etc.), collect one sample at pre-dose (within 30 min prior to SOI). However, one year after the first dose of last subject, PK samples will only be collected for the interpretation of ADA results in the following visits.
20. Collect 1 PK sample at each participant's final visit.
21. All ADA samples will be collected prior to each infusion at C1, C2, C4, C6, C9, C12, and every 6 cycles thereafter (C18, C24, etc.) until end of treatment (dosing days only) and at the last visit.
22. Disease Response Assessment: Response assessment must be conducted Q3W based on standard disease laboratory tests (serum and urine M protein test, FLC, IgD/E, if applicable), Ca corrected for albumin, bone marrow aspirate (in case of CR, or suspected PD if not evident otherwise). Assessment based on imaging has to be included in

participants with extramedullary disease at indicated time points. Response evaluation will be performed according to the IMWG Uniform Response Criteria for Multiple Myeloma 2016.

23. For participants who are discontinuing IP due to PD the confirmation must performed on a different date from a different blood collection within 14 days of the original disease progression. This may be performed at the at EOT follow-up visit.
24. Skeletal Survey: Imaging of bones for lytic lesions by a method aligned with the institutional guidance (X-ray, CT [Computed tomography], or MRI [Magnetic resonance imaging]). Skeletal survey results within 30 days prior to C1D1 are acceptable.
25. Only if clinically indicated or if worsening clinical symptoms suggest PD.
26. Imaging is only required for participants with extramedullary disease (CT, MRI, or PET [Positron Emission Tomography]/CT can be applied per local guidance). Screening assessment may be performed up to 30 days prior to C1D1. The same modality should be used throughout the study (i.e., if PET scan was used as baseline, participant needs to be followed by PET 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). Evaluations should be performed by the same method as at screening.
27. In participants with extramedullary MM, if the last radiographic assessment occurred ≥8 weeks prior to the participant's withdrawal from study treatment, and progressive disease has NOT been documented –then a new assessment (presence or absence extramedullary disease) should be obtained at the time the participants withdrew from study treatment.
28. Only required for participants with IgD/E myeloma, where serum m-component cannot be followed otherwise
29. FISH testing at least for: t (4;14), t (14;16), 17p13del, and +1q21. FISH results from samples taken within 60 days prior to first dose are acceptable. If this cannot be performed at a local lab the samples can be sent to the central lab
30. CCI [redacted]
31. Bone Marrow for disease assessment performed within 14 days prior to first dose is acceptable.
32. Bone marrow biopsy for IHC to confirm sCR after achieving a CR.
33. CCI [redacted]
34. Belantamab mafodotin administration: Study drug administration ±3-day window.
35. 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.
36. All related SAEs are to be collected from consent through PD follow-up.
37. Additional assessments may be conducted for those participants who experience a worsening in visual function. Participants who discontinue participation in the study will continue to be assessed during follow-up until resolution of visual symptoms. Continue to follow up with participants via telephone who are still experiencing visual symptoms even after discontinuation.

2. INTRODUCTION

2.1. Study Rationale

Multiple myeloma (MM) is a neoplastic plasma cell disorder that is characterized by osteolytic bone lesions, anaemia, hypercalcaemia and renal failure [Palumbo, 2011; Rajkumar, 2011a]. Worldwide, approximately 103,000 new MM cases and 80,000 deaths are diagnosed annually, MM accounts for 1% of all cancer and 10% of hematologic malignancies [Ferlay, 2010; Siegel, 2016]. Multiple myeloma is slightly more common in African-americans and Caucasians relative to Asians, the incidence rate is increasing in some Asian countries [Rajkumar, 2011b; Kim, 2014]. Based on GLOBOCAN report an estimated 20,066 new cases and 14,655 deaths will occur in China in 2018 [GLOBOCAN, 2018].

A variety of drugs and combination treatments have been evaluated and found effective in treating MM [NCCN, 2016; Moreau, 2017]. However, most, if not all, of these participants inevitably relapse [Richardson, 2003; Richardson, 2006; Jagannath, 2008]. Belantamab mafodotin is a humanised (IgG1) antibody-drug conjugate (ADC) which binds to B-cell maturation antigen(BCMA), a target widely expressed on malignant plasma cells in MM. The parent anti-BCMA antibody is conjugated to the microtubule inhibitor, Monomethyl auristatin-F (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 tumour necrosis factor (TNF) family (BAFF/BLyS), and a proliferation-inducing ligand (APRIL). Belantamab mafodotin induces immunogenic cell death (ICD) in a BCMA-expressing multiple myeloma cell line and leads to dendritic cell activation/maturation. Exposure of dendritic cells to tumour cells undergoing ICD induces an antigen-specific T cell response.

Study 208465 is designed to evaluate the safety, PK, immunogenicity and clinical activity of belantamab mafodotin in Chinese participants with RRMM who have received at least 2 prior lines of anti-myeloma therapy including an alkylator, a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD).

2.2. Background

Immunomodulatory drugs e.g. lenalidomide, thalidomide, pomalidomide) and proteasome inhibitors (PIs e.g. bortezomib, carfilzomib, ixazomib) are still the main pillars of MM treatment, and have been used in combination, often with dexamethasone, to deliver better efficacy [NCCN, 2016]. These highly active agents used in combination are providing tangible benefits for participants with MM [Rajkumar, 2011b]. Importantly, improvements in survival outcomes have been noted in participants with MM and current treatment strategies provide a very good chance for response in the first line. Unfortunately, duration of response and response rates decline dramatically in each subsequent line of treatment for this malignancy. Relapsed/ refractory multiple myeloma (RRMM) remains incurable and the need for new treatment modalities is well recognised. Three and four-drug combinations are now emerging for participants with RRMM. For example, a monoclonal antibody (mAb) such as daratumumab (targeting CD38) and

elotuzumab (targeting signalling lymphocyte activation molecule [SLAMF7]) represent treatments with novel mechanisms of action that are now used in combination with other standard regimens that include immunomodulatory imide drugs, proteasome inhibitors (PIs), and corticosteroids [Lonial, 2014; Lokhorst, 2015; NCCN, 2016]. Despite those new combinations, relapse rates remain high and high toxic effects may limit their application [NCCN, 2016].

In China, bortezomib and lenalidomide have been currently approved for 1st line use while daratumumab and pomalidomide have been newly approved as 2nd line plus MM treatment. RRMM participants double refractory to bortezomib and lenalidomide currently still have limited treatment options available while other new agents are under development in China. The China Center for Drug Evaluation, National Medical Products Administration (CDE, NMPA) has recommended Breakthrough Therapy Designation (BTD) for ciltacabtagene autoleucel. A B-cell maturation antigen (BCMA) targeted chimeric antigen receptor (CAR) T-cell therapy is under development for the treatment of adults with RRMM. Currently, a Phase 1 and Phase 2 studies are ongoing in China with ciltacabtagene autoleucel. Therefore, a high unmet medical need for MM exists in China.

Belantamab mafodotin is a first in class, afucosylated, humanised 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 tumour cells of all participants 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 internalised 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-tumour 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 tumour cells undergoing ICD induces an antigen-specific T-cell response, and if it acts similarly in humans could induce the participant's own immune response against the MM tumour.

BLENREP (belantamab mafodotin) monotherapy, for the treatment of adult patients with relapsed/refractory multiple myeloma is the first anti-BCMA (B-cell maturation antigen) therapy approved in the US and in the European Union. The efficacy and safety results from study BMA117159/DREAMM-1 and study 205678/DREAMM-2 indicate that belantamab mafodotin is an effective single-agent treatment option for patients with RRMM, with a novel MOA. In binding to BCMA on malignant plasma cells, belantamab mafodotin initiates cell killing via a multimodal-mechanism, including delivering MMAF to BCMA-expressing MM cells, inducing apoptosis, enhancing antibody-dependent

cellular cytotoxicity and antibody-dependent cellular phagocytosis, and inducing immunogenic cell death.

2.3. Human Experience with Belantamab Mafodotin

2.3.1. Clinical studies

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 Sep 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 [GlaxoSmithKline Document Number RPS-CLIN-004867; Trudel, 2019].

As of the efficacy cut-off date of 31 Aug 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 evaluable [NE]). For participants refractory to both immunomodulatory imide drugs 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 imide drug 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 Jan 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)].

2.3.2. 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 Sep 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 favourable safety profile (*i.e.* lower incidence of thrombocytopenia and neutropenia and less frequent dose delays or reductions) compared with the 3.4 mg/kg dose.

Adverse Events of Special Interest

Thrombocytopenia

In DREAMM-2 (data as of 31 Jan 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.

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 as of 31 Jan 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 2.5 mg/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 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.

Infusion-related reactions

Infusion-related reactions (IRRs) are expected for biologic agents. In DREAMM-2 (data as of 31 Jan 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).

2.3.3. Pharmacokinetics and Pharmacodynamics

The pharmacokinetics and pharmacodynamics of belantamab mafodotin (antibody-drug conjugate, including complex) with CCI), 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 11 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 CCI CCI and lower levels of albumin are associated with more advanced multiple myeloma or a higher multiple myeloma disease burden. Higher baseline IgG and CCI levels, and lower baseline albumin levels were associated with higher belantamab mafodotin clearance leading to lower average and trough concentrations (Ctau) of belantamab mafodotin. Higher baseline IgG and CCI levels were associated with higher cys-mcMMAF central volume of distribution leading to lower cys-mcMMAF Cmax.

In nonclinical studies, cys-mcMMAF had limited metabolic clearance. *In vitro* data suggested that 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 CCI levels were measured in Study BMA117159 and Study 205678. All participants exhibited reductions in free CCI concentration at end of infusion compared to baseline at Cycle 1, with a return to near-baseline level by 7 days after dosing, reflecting binding of belantamab mafodotin to CCI Maximum decreases ranged from 2% to 97%, which were qualitatively dose-dependent, with larger reductions in free CCI at higher doses.

Exposure-response analyses performed for Study 205678 and/or Study BMA117159 found that ocular safety endpoints were most strongly associated with 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.

Details of the characteristics of belantamab mafodotin, nonclinical, and clinical activity are provided in the Investigator's Brochure (IB) [Belantamab mafodotin GlaxoSmithKline Document Number RPS-CLIN-004867, 2021].

This is the first study for belantamab mafodotin in China to assess the safety, tolerability, pharmacokinetics (PK), immunogenicity and clinical activity of belantamab mafodotin in Chinese participants with MM.

2.4. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of belantamab mafodotin may be found in the IB [Belantamab mafodotin GlaxoSmithKline Document Number RPS-CLIN-004867].

2.4.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [Belantamab Mafodotin]		
Changes on Corneal Examination	Changes in corneal epithelium on ocular examination have been frequently observed with belantamab mafodotin such as superficial punctate keratopathy, microcyst-like changes, sub-epithelial haze, corneal erosions and corneal ulcers. These were most commonly associated with: blurred vision, dry eyes, photophobia, and changes in visual acuity. Participants with a history of dry eye were more prone to develop changes in the corneal epithelium. Based on available follow-up data, visual acuity returned to, or near baseline in most cases and no permanent loss of vision reported. Corneal ulcers or erosions are distinguished by the presence or absence of stromal involvement, respectively. The precise incidence has yet to be defined. The corneal defects (with or without stromal involvement) appeared as early as the second or third cycle but in most cases after 5 or more cycles of treatment	Active monitoring for corneal events according to the SoA (Table 1). In the event of new-onset eye-related symptoms (such as pain, significant loss of visual acuity, or bothersome foreign body sensation), participants are to urgently seek medical attention by a qualified eye care specialist (appropriate testing includes slit lap examination [includes fluorescein staining] and measurement of visual acuity). Appropriate management should be initiated immediately as defined in Section 6.6.1. Recommendations for dose delays/reductions and treatment stopping guidance are provided in Table 7 and Section 7.1.
Infusion related reaction (IRR)	IRRs were reported in participants treated with belantamab mafodotin. Most IRRs observed to date were Grade 1 to 2 and manageable with medical treatment.	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 IRR occurs during belantamab mafodotin administration, management will follow guidance in Section 6.6 and Section 7.1.4

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Thrombocytopenia	Thrombocytopenic events of all grades (1-4) are among the most common AEs associated with belantamab mafodotin. Belantamab mafodotin may cause transient thrombocytopenia in some participants, which for most cases recovered between doses. In the pooled safety population of study 205678 which included participants treated with belantamab mafodotin 2.5 and 3.4 mg/kg, thrombocytopenia was noted in 46% of participants and ranged between Grade 1 to 4 in severity.	Hematologic panels are monitored closely as outlined in Section 1.3. Supportive therapy (including transfusions) is provided according to standard medical practice, and dose reductions or treatment discontinuations are outlined in Section 6.6 and Section 7.1.
Other hematological effects	Neutropenic events, including febrile neutropenia have been observed with treatment with belantamab mafodotin. In a study of belantamab mafodotin in combination with lenalidomide/ dexamethasone, two fatal cases of severe infections associated with neutropenia were observed. Anemia is a common complication in the RRMM population and was frequently reported in the belantamab mafodotin clinical program.	Hematologic panels are monitored closely as outlined in Section 1.3. Consider prophylactic antibiotics, per physician discretion and local institutional guidance, in participants with Grade 3-4 neutropenia (ANC <1.0x109/L), even if afebrile. Immediately hospitalize participants with febrile neutropenia and initiate appropriate management, per local institutional guidance. Consider additional supportive treatment(s) per local practice (e.g., growth factors). Dose reductions or treatment discontinuations are outlined in Section 6.6 and Section 7.1.
Potential for cardiotoxicity related to an inflammatory response	Nonclinical studies, predominantly in monkey, increased activation of macrophages was noted in a number of organs at ≥3 mg/kg/week, reflective of a systemic inflammatory response. Minimal inflammatory changes (inflammatory cell infiltrate and/or haemorrhage) were also noted in hearts (atrial epicardium, ventricle endocardium) of single monkeys, which were nonadverse and reversible.	Participants with significant cardiac risk factors will be excluded from study participation. Electrocardiograms will be monitored as per Section 1.3. Treatment as medically indicated.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	No cardiac events were reported to date in MM participants receiving belantamab mafodotin in clinical trials.	Monitoring of other cardiac parameters as clinically indicated.
Hepatotoxicity	In nonclinical studies liver is a target organ for toxicity, with increased liver weights and/or raised hepatobiliary enzymes and transaminases observed I both rat and monkey. These changes in the liver were without clinical consequence in the shorter duration studies and in the rat 13-week study. In the monkey 13-week study, progression of liver toxicity to include minimal multifocal hepatocellular necrosis was observed at all doses administered (≥3 mg/kg/week). Mild elevations of liver enzymes have been reported in some participants treated with belantamab mafodotin.	Only participants with well-preserved liver function per the inclusion/exclusion criteria will be allowed on study. Participants with chronic Hepatitis B (HBV) and C will be excluded. Liver function tests will be regularly monitored (Section 1.3). In case of liver abnormalities management will be implemented according to clinical practice. Participants that meet liver stopping criteria (Section 7.1.1) will be withdrawn from the study.
Nephrotoxicity	Non-clinical safety studies have demonstrated dose dependent and reversible primary glomerular injury and tubular degeneration (in rat and monkey), accompanied by large molecular proteinuria (albuminuria) and enzymuria. Single cell necrosis of the kidney and bladder urothelium was also noted in the 13-week monkey study. Severe tubular degeneration/regeneration and marked glomerulonephritis exacerbated by immune complex disease, likely associated with ADA, led to the early euthanasia of one monkey following 5 weekly doses of 10 mg/kg. Increased albumin/creatinine ratio (albuminuria) not indicative of disease progression has been reported in clinical trials and named patient programs with belantamab mafodotin	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 Study treatment stopping criteria will be applied according to Section 6.6 and Section 7.1
Pulmonary toxicity (pneumonitis)	Nonclinical safety experiments have demonstrated the presence of microscopic changes in the lungs (prominent alveolar macrophages associated with eosinophilic material; mixed perivascular inflammation) in rats at all doses tested.	Monitoring for clinical signs and symptoms potentially related to pulmonary toxicity. If a participant experiences new or worsening pulmonary symptoms, (e.g., cough, dyspnea) without obvious etiology, appropriate diagnostic evaluation should be performed (see protocol Section 5.2)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Cases of pneumonitis, including fatal events, have been observed with belantamab mafodotin although a causal association has not been established. To date, no significant pulmonary toxicity has been reported in studies BMA117159 or 205678.	and further treatment with belantamab mafodotin delayed (refer to protocol Section 6.6). An overall benefit/risk assessment should be considered for the participant prior to continuing belantamab mafodotin treatment Further diagnostic tests and management will be implemented immediately according to recommendations provided in Section 6.6.
Immunosuppression	In nonclinical studies belantamab mafodotin has been associated with decrease in immunoglobulins in monkeys at all doses. An increase in immunoglobulins was seen in rats (rats are not an antigen specific species for belantamab mafodotin). Immunosuppression is frequently associated with an increased risk of infection. Serious and non-serious infections have been reported in belantamab mafodotin studies, including respiratory infections, pneumonia and sepsis.	Participants who have active infection will be excluded. Participants will be monitored for infections and those who develop infection will receive immediate treatment according to standard practice.
Potential for Other Laboratory abnormalities	An increased magnitude of AST relative to ALT consistent with increased skeletal troponin I was observed in the single dose monkey study. Increased skeletal troponin I and/or creatine kinase and aldolase was observed in the rat 3-week study. Cases of elevated aspartate aminotransferase (AST), lactic dehydrogenase (LDH) and creatine kinase (CK), and GGT alone or concomitant with no clear clinical correlate have been observed in clinical studies.	Laboratory parameters will be monitored as outlined in the SoA (Section 1.3). Participants with significant laboratory elevations (≥x3 ULN) should, where possible, have a sample tested for CK and LDH isoenzyme levels.
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]).	See Contraception requirements in Section 5.1 and Appendix 4. Pregnancy testing outlined in the SoA. 1.3

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Use of belantamab mafodotin in pregnant women may cause fetal harm.	
Impaired Male and Female 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. Ovarian toxicity (luteinized non-ovulatory follicles) was observed in a 3-week rat study (weekly dosing) and not observed following 12 weeks off dose. In a 13-week rat study where drug was administered once every 3 weeks, these changes were not observed.	Men who may wish to father children in the future will be advised to have sperm samples frozen and stored prior to belantamab mafodotin treatment. Women of child bearing potential who may desire offspring in the future will be counselled about the option of having eggs frozen before treatment. See Contraception requirements in Section 5.1 and Appendix 4.
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 data acquisition:	During the acquisition of imaging data (e.g MRI, CT, PET, ECG), non- disease or 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
Participants exposed to ionizing radiation	The ionizing radiation exposure arises due to the inclusion in the study of imaging scans. Participation in this study will involve various imaging procedures based on the needs of the participant, some of which are standard of care and some are additional requirements for the study. The risk arising from the additional radiation burden is considered justified by the benefit of the clinical information to be obtained, which is critical to the study and cannot readily be obtained another way. All participants will have skeletal survey imaging at screening, and depending on clinical condition, some participants may also require additional imaging exams at regular intervals. Some of these procedures use ionizing radiation to form images of your body. The imaging procedures and doses that may be used for	The study has been designed to keep the radiation dose as low as reasonably practicable whilst obtaining images of sufficient quality to meet the objectives.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	this study could include X-Ray skeletal survey (~2 mSv), CT (10-20 mSv), FDG PET/CT (14 mSv) and/or MRI (no radiation exposure). For comparison, the average global yearly background radiation dose is 2.4 mSv.	

TCR = T-cell receptor; mAb = Monoclonal antibody; AEs = Adverse Events, MRI = Magnetic resonance imaging; CT = Computed tomography; PET = Positron Emission Tomography.

2.4.2. Benefit Assessment

The study population enrolled in this study has a high-unmet medical need. Participants failing multiple lines of prior treatments do not have many therapeutic options left, and if response can be achieved with currently available drugs, it is usually of short duration. This study is being performed to study safety and pharmacokinetics data in participants who have been previously treated with multiple agents, including alkylator, PI and immunomodulatory imide drug.

Data from single-agent study BMA117159 support further evaluation of participants with MM failing currently available treatments.

Based on the available clinical data, and since 2.5 mg/kg has been selected as the recommended dose in the belantamab mafodotin clinical development program, (and as the dose approved in the U.S.A. and Europe), the 3.4 mg/kg dose may not be used in this study.

2.4.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants, the potential risks associated with belantamab mafodotin are justified by the anticipated benefits that may be afforded to participants with RRMM.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Objectives	
• To determine safety and tolerability of belantamab mafodotin in Chinese Participants with RRMM	• Adverse events (AE), i.e., number (%) of participants with DLTs, number (%) of participants with AEs
Secondary Objectives	
• To evaluate PK profile of belantamab mafodotin in Chinese Participants with RRMM	• ADC, total antibody and cys-mcMMAF PK parameters following IV single and repeat dose administration during dose escalation as data permit (e.g., AUC, Cmax, tmax)
• To evaluate safety and tolerability of belantamab mafodotin	• Changes in clinical signs and laboratory parameters, ocular findings on ophthalmic exam

Objectives	Endpoints
• To evaluate the clinical measures of efficacy of belantamab mafodotin	• ORR, defined as the percentage of participants with a confirmed partial response (PR) or better (i.e., VGPR, CR and stringent complete response [sCR]), according to the International Myeloma Working Group (IMWG) Response Criteria.
• To assess anti-drug antibody (ADA) formation after IV single and repeat dose administration of 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 OSDI
Exploratory Objectives	
CCI [redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a phase I, open-label dose-escalation study to explore safety, PK, tolerability, immunogenicity and clinical activity of belantamab mafodotin monotherapy in Chinese participants with RRMM. The study will enroll up to 12 evaluable participants (For study schematic refer Figure 1). This study will include two dose cohorts. Up to six evaluable participants are expected for each cohort and the actual numbers will depend on the safety observed. Each participant will be involved in the study until participant have progressed, died, withdrawn consent, discontinued treatment due to other reasons, or have been lost to follow-up.

4.1.1. Planned Dose Levels

Projected dose levels are 2.5 mg/kg and 3.4 mg/kg. De-escalation to 1.9 mg/kg will be allowed in case of ≥2 DLT at dose 2.5 mg/kg. No doses will be explored beyond 3.4 mg/kg, the dose that is considered to be the Maximum Feasible Dose (MFD).

Dose-escalation will follow a 3 + 3 dose-escalation procedure as shown in Table 2. Evaluation of available safety data from at least 3 participants that have completed a minimum of 21 days is required prior to defining a new dose level and to start the next dose cohort. There will be no intra-participant dose escalation. The first 3 participants in 2.5 mg/kg dose group will receive the study treatment sequentially with an observation window of 7 days, to observe acute toxicities. If the participating investigator and the coordinating investigator see no potential safety concerns from the first participant, the participating investigator and the coordinating investigator may recommend to enrol the next participant. Participants should not be enrolled at a higher dose level until at least 3-6 participants in the previous dose cohort complete 21 days of post-dose assessment.

Table 2 3 + 3 Dose-Escalation Guidelines

Number of Participants with DLT at a Given Dose Level	Action
0 out of 3 Participants	Escalate to next dose level and enter 3 Participants
1 out of 3 Participants	Accrue 3 additional evaluable Participants at current dose level for a total of 6 evaluable Participants • If 0 of the 3 Participants experience a dose-limiting toxicity (DLT), proceed to next dose level. • If 1 or more Participants experience a DLT, dose will be de-escalated to 1.9 mg/kg if the current dose cohort is 2.5 mg/kg, otherwise the dose-escalation is stopped and this dose is declared the maximum tolerated dose (MTD).
1 out of 6 Participants	Escalate to next dose level
2 or more Participants in a dosing cohort (up to 6 Participants)	Dose will be de-escalated to 1.9 mg/kg if the current dose cohort is 2.5 mg/kg, otherwise dose-escalation will be stopped. At this dose level, the MTD has been exceeded (highest dose administered).

Up to 6 participants will be enrolled into each of these dose levels with the above dose escalation rule followed.

As per current available safety and efficacy information of belantamab mafodotin studies, the 3.4 mg/kg dose cohort is converted to an optional cohort in the dose-escalation study design. Escalation may not proceed if not supported by emerging clinical data from other belantamab mafodotin studies.

4.1.2. Dose-Limiting Toxicity

The DLT observation window will be 21 days (1 cycle). Any participant that received at least 1 dose of belantamab mafodotin will be evaluated for DLTs using NCI-CTCAE Version 5.0 [NCI, 2017]. If participants prematurely discontinue for reasons other than toxicity but prior to completion of DLT observation period, additional participants may be enrolled as replacement participants at the discretion of the Sponsor in consultation with the investigator.

An event will be considered a DLT if its relationship to the investigational agent cannot be ruled out, occurs within the DLT reporting period and meets 1 of the following criteria:

a. Any Grade 3 or greater non-hematologic toxicity as described in NCI-CTCAE Version 5.0 [NCI, 2017], other than corneal events:

- Persists for >48 hours despite supportive treatment
- Leads to hospitalization

b. Haematologic toxicity:

- Grade 3 or greater febrile neutropenia lasting >48 hours despite adequate treatment:
  - Grade 3 CCI [redacted] CCI [redacted]
  - Grade 4 CCI [redacted]
    CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.
- Grade 4 thrombocytopenia CCI [redacted] CCI [redacted]

c. Grade 4 per the modified corneal grading scale provided in Table 7.

d. Liver toxicity meeting pre-specified GSK liver stopping criteria as outlined in Section 7.1.1.

A participant who develops a DLT will be allowed to continue study treatment if the toxicity did not meet pre-defined stopping criteria (Section 7.1)and recovered to Grade ≤1 within 14 days or after a longer recovery period if the investigator and medical monitor agree that for a given participant the potential benefits may outweigh the risks.

4.1.2.1. Completion of Dose Escalation

No doses will be explored beyond 3.4 mg/kg, the dose that is considered to be the Maximum Feasible Dose (MFD).

4.2. Scientific Rationale for Study Design

Participants with RRMM who have experienced relapse after previous treatment with alkylators, PI and immunomodulatory imide drug represent a population of unmet

medical need in China, for whom there is no approved treatment options. Given the clinical activity demonstrated in the BMA117159 study, the treatment with belantamab mafodotin might offer a benefit to this participant 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 RRMM population in China.

BMA117159 study has evaluated the safety and tolerability of belantamab mafodotin at doses ranging from 0.03 mg/kg IV up to 4.6 mg/kg IV. Belantamab mafodotin was well tolerated with no DLTs up to 4.6 mg/kg q3w; MTD was not reached, however, there was limited tolerability of the 4.6 mg/kg dose (prolonged fever, headache, severe fatigue). The maximum clinical benefit (ORR 60%) 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. Based on these data, GSK has initiated Study 205678, a global phase II study evaluating the safety and efficacy of belantamab mafodotin monotherapy (3.4 and 2.5 mg/kg administered once every 3 weeks) in participants with relapsed / refractory multiple myeloma.
As the safety profile of belantamab mafodotin is established in a predominantly Caucasian MM population, the primary objective of study 208465 is to evaluate safety and confirm appropriate dose for Chinese MM population. Given that there is no apparent evidence showing racial difference in MM and BCMA expression between Chinese and Western populations, global Phase II study selected dose (2.5 and 3.4 mg/kg) will be investigated in study 208465.

4.3. Justification for Dose

4.3.1. Belantamab Mafodotin Starting Dose Justification

The starting dose for belantamab mafodotin will be 2.5 mg/kg administered intravenously once every 3 weeks (Q3W) on Day 1 of each 21-day Cycle. The FTIH study tested doses up to 4.6 mg/kg, and global Phase II study selected 2.5 and 3.4 mg/kg for investigation in Study 205678. Currently there is no apparent evidence showing racial difference in MM and BCMA expression between Chinese and Western populations. However, PK difference may exist, as body weight usually affects clearance (CL) of monoclonal antibodies. Belantamab mafodotin dosing is adjusted by body weight. Thus, exposure difference is estimated low.

The starting dose is selected because of the following reasons.

- A starting dose lower than 2.5 mg/kg will have lower probability of getting clinical benefits based on the dose-response relationship in BMA117159. Also, the starting dose of 2.5 mg/kg had an acceptable safety profile in FTIH trial.
- De-escalation to 1.9 mg/kg will be allowed in case of ≥2 DLT at dose 2.5 mg/kg.

Although AEs leading to dose reduction started from 0.96 mg/kg in BMA117159, careful dose escalation and monitoring will be implemented to ensure participants' safety throughout the study.

4.4. End of Study Definition

The end of study is defined as when all participants have progressed, died, withdrawn consent, discontinued treatment due to other reasons, or have been lost to follow-up.

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

- The participant is lost to follow-up.
- The participant has withdrawn consent.
- The participant is no longer being followed at the investigator's discretion.
- The study is closed or terminated.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is 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 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. Histological or cytologically confirmed diagnosis of MM as defined according to IMWG, 2014 criteria [Rajkumar, 2014] and
    a. Has undergone autologous stem cell transplant or transplant is considered not feasible by local assessment.
    b. Has failed at least 2 prior lines of anti-myeloma treatments, containing ALL of the following classes of drugs: alkylating agent, immunomodulatory imide drug and PI.
    c. In addition, eligible participant needs to be refractory to an immunomodulatory imide drug (i.e., lenalidomide or pomalidomide), and to a proteasome inhibitor (i.e., bortezomib, ixazomib or carfizomib) as defined by IMWG criteria.
    d. Participants who failed with CD38 antibody (i.e., daratumumab) in previous clinical trials can also be considered to include if they meet the remainder of inclusion criteria in this protocol.
    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 functions as defined in Table 3

Table 3 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[1] Spot urine (albumin/creatinine ratios (spot urine)	≥30 mL/min/ 1.73 m^1 <500 mg/g (56 mg/mmoL)
Cardiac	
LVEF (Echo)	≥25%[2]

1. As calculated MDRD equation (Appendix 8)
2. It is acceptable to use an existing ECHO result, if performed within three months of screening. For participants with abnormal LVEF (per institutional standards), the participant is to follow-up with a cardiologist. For participants with low LVEF (per institutional standards), consider referring to cardiology per local standards of care.

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 4 months after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.

  A WOCBP must have a negative highly sensitive serum pregnancy test within 72 hours of dosing on C1D1 and agree to use effective contraception during the study and for 4 months after the last dose of study treatment.

  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 from the time of first dose of study until 6 months after the last dose of study treatment to allow for clearance of any altered sperm:
   - Refrain from donating sperm
     PLUS either:
   - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
     OR
   - Must agree to use contraception/barrier as detailed below:
     Agree to use a male condom, even if they have undergone a successful vasectomy and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year 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 5.0 must be ≤Grade 1 at the time of enrolment except for alopecia and Grade 2 peripheral neuropathy.

5.2. Exclusion Criteria

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

1. Systemic anti-myeloma therapy within <14 days, or plasmapheresis within 7 days prior to the first dose of study drug
2. Symptomatic amyloidosis, active POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes), active plasma cell leukemia at the time of screening.
3. Prior allogeneic stem cell transplant (SCT)
4. Current corneal epithelial disease except mild punctate keratopathy
5. 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.
6. Evidence of active mucosal or internal bleeding
7. Any major surgery within the last four weeks
8. 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.
9. 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.
10. 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.
11. 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).
12. Evidence of cardiovascular risk including any of the following:

a) QTcF interval >480 msecs (the QT interval values must be corrected for heart rate by Fridericia's formula [QTcF])
b) Evidence of current clinically significant untreated arrhythmias, including clinically significant ECG abnormalities such as 2nd degree (Mobitz 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 three 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 severe hypertension, e.g. 170/110

13. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to belantamab mafodotin, or any of the components of the study drug.

14. Pregnant or lactating female.

15. Active infection requiring antibiotic, antiviral, or antifungal treatment.

16. Known HIV infection.

17. 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)

18. 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 Considerations

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 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. STUDY TREATMENT

Study treatment is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study treatment(s) Administered

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 over 30-60 minutes.

Product name:	**Belantamab Mafodotin for Injection**
Dosage form:	**Belantamab mafodotin for Injection**: 100 mg/vial
Unit dose strength(s)/Dose Level(s):	**Belantamab mafodotin for Injection:** 100 mg/vial. Dosage(s): 2.5 mg/kg, or 3.4 mg/kg
Route/ Administration/ Duration:	Delivered as IV solution over 30-60 min (Section 6.1.1)
Dosing instructions:	**Belantamab mafodotin for Injection:** Reconstitute belantamab mafodotin lyophilized powder 100 mg/vial with water for injection (WFI) before use
Manufacturer/ Source of Procurement:	GSK

6.1.1. Belantamab Mafodotin Treatments Administered

Belantamab mafodotin will be administered to participants intravenously as mg/kg calculated dose at the study site. The dose to be administered will be calculated using actual body weight at baseline and may be reduced for toxicity according to protocol guidelines. It is recommended to prime the IV tubing with at least 15 mL prior to dosing. 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 over approximately 30- 60 minutes. Premedication is not required prior to infusion unless deemed medically necessary by the investigator, in which case it should be administered according to institutional recommendations.

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 4.

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 unacceptable toxicity (Section 7).

6.2. Preparation/Handling/Storage/Accountability

a. 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.

b. 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.

c. 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).

d. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.

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

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

6.3. Measures to Minimise Bias: Randomization and Blinding

This is an open-label, non-randomized study.

6.4. Study treatment Compliance

Belantamab mafodotin will be intravenously administered to participants at the study site. The dose to be administered is based on body weight calculation and may be reduced for toxicity according to protocol guidelines.

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

6.5. 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. 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.

6.5.1. 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 control or stability control.

6.5.2. 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.

Administration of live or live-attenuated vaccines are contraindicated 30 days prior to the first dose of study treatment and while on study treatment. Use of live or live-attenuated vaccines is further contraindicated for at least 70 days following the last dose of belantamab mafodotin. Killed or inactivated vaccines may be administered; however, the safety and response to such vaccines cannot be predicted.

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), OATP1B1, and OATP1B3 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.

6.5.3. Prohibited Device(s)

Contact lenses are prohibited while the participant is receiving belantamab mafodotin. Following discontinuation of belantamab mafodotin treatment, contact lens use may be restarted after a qualified eye care specialist (Appendix 9) confirms that there are no other contraindications.

6.6. Dose Modification

Table 4 details the permitted dose modifications of belantamab mafodotin. Table 5 and Table 6 contain dose modification guidance for drug-related AEs. See Table 7 for dose modification guidelines for belantamab mafodotin treatment-related changes in vision.

Table 4 Permitted Dose Reductions

Starting dose	Dose reduction
2.5 mg/kg	1.9 mg/kg
3.4 mg/kg	2.5 mg/kg, 1.9 mg/kg

If the participant cannot tolerate the drug after the allowed dose reduction of belantamab mafodotin to the lowest allowed dose of 1.9 mg/kg, he or she must discontinue treatment for lack of tolerability.

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

If a dose is delayed, the participant should wait for the next scheduled dose to resume treatment. In individual cases where in the judgment of the Investigator waiting a full cycle to resume treatment after delay (skipping dose) related to toxicity which has resolved would be detrimental to the participant's health, the PI should contact the Medical Monitor to discuss an earlier re-start. An earlier re-start may be considered only for participants who have recovered from toxicity to at least ≤Grade 1. The dosing with belantamab mafodotin cannot occur more frequently than every 21 days (±3-day

window). In such cases, efficacy and safety assessments must remain 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). Evaluations associated with a dose would be entered into the eCRF under the next scheduled cycle.

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

Table 5 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 or absolute increase by 3 mg/dL	>3.0 mg/dL from baseline or 3.0xULN	• 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 current dose • If confirmed on re-test and no clear evidence of disease progression o Interrupt treatment with belantamab mafodotin o Repeat testing within 4 weeks i. If spot urine <2000 mg/g (224 mg/mmol), may restart belantamab mafodotin with 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]
Urine Dipstick	2+	• May continue belantamab mafodotin dosing • Confirm by quantitative assessment using albumin/creatinine (spot urine from first void) • If albumin/creatinine >2000 mg/g, at the next cycle follow guidance above for Spot Urine.
	3+	• Interrupt treatment and follow up for recovery. Implement quantification of albumin/creatinine ratio
Thrombocytopenia (on days of dosing)	Grade 3	• No bleeding: continue treatment with 1 dose level reduction. Consider reverting to previous dose once thrombocytopenia recovered to Grade 2 or less • With bleeding: withhold the dose, continue treatment after recovery with 1 dose level reduction • Consider additional supportive treatment (e.g., transfusion), as clinically indicated and per local practice.
	Grade 4	• Withhold the dose. Consider restarting with 1 dose level reduction if recovered, or transfused to ≤Grade 3 only if there is no active bleeding at time of treatment restart • If thrombocytopenia is considered disease related, is not accompanied by bleeding, and recovers with transfusion to >25x10^9/L continuing treatment at 1 dose level reduction may be considered after discussion with the Medical Monitor

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 h AND ANC <1.0×10^9/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) on Day 1 of the subsequent cycle. • Prophylactic antibiotics, per physician discretion and local institutional guidance. Consider growth factors. • Local guidance must be followed for hematological monitoring, if more conservative than the protocol SoA specifications. • In cases of frequent recurrent neutropenia (ANC <1.0x10^9/L), consider dose reduction of belantamab mafodotin by 1 level
Infusion Reaction[b]	2	• Stop the infusion, provide medical treatment and continue at half the original infusion rate after resolution to Grade 0-1. Any future infusion needs to be pre-medicated.
	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 from study treatment
Pneumonitis	2	• Withhold treatment with belantamab mafodotin • Upon recovery, restart treatment with 1 dose level reduction. • If patient is already at the lowest dose level (1.9 mg/kg), then rechallenge with the same dose must be discussed with the Medical Monitor
	Grade 3-4	• Permanently discontinue from treatment

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 6 General Dose Modification and Management Guidelines for Drug-related Adverse Events Not Otherwise Specified

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, 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 study 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 study 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.

Table 7 Dose Modification Guidelines for Belantamab Mafodotin Treatment-Related Changes in Vision

Grade/description of toxicity (as described in NCI-CTCAE ver. 5.0)	Recommendations
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.	Continue treatment at current dose.
	Dose reduce by 25% (either to 2.5 or to 1.9 mg/kg) and continue treatment. • If already on 1.9 mg/kg, participant continues treatment at same dose. Upon resolution (e.g., Grade 1), re-escalation to previous dose may be considered.
	Hold treatment and allow to recover to Grade ≤2. Once recovered, dose reduce to 2.5 or to 1.9 mg/kg. • If already on 1.9 mg/kg, participant continues at same dose. If after event resolution eye symptoms are considered stable for at least 3 cycles and if vision is Grade ≤1, consider re-escalation (to 3.4 or 2.5 mg/kg).
	Hold treatment and allow to recover to Grade ≤2. Restart only after discussion with Medical Monitor for participants whose vision improves to Grade ≤2. If restart approved, once recovered to Grade ≤2, dose reduce to 2.5 or 1.9 mg/kg. If already on 1.9 mg/kg, participant continues at same dose.

CCI

6.6.1. Corneal Supportive Care Guidelines for Belantamab Mafodotin

Changes in visual acuity, which commonly manifests as changes in corneal epithelium observed on ocular examination, have been observed with antibody drug conjugates, including those conjugated to MMAF [Eaton, 2015].

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 corneal epithelium on ocular examination in close communication with GSK Medical Monitor.

Participants will be assessed by an ophthalmologist (or an optometrist if an ophthalmologist is not available) baseline and every three weeks. If there are no corneal examination findings (Grade 2 or above) at time of the Cycle 6 exam, participants may

have their ophthalmologic exams decreased to once every 3 months. In case of persistent ocular exam findings, newly developed ocular symptoms or vision changes, further ocular exams should be performed at least every cycle until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by the qualified eye care specialist (Appendix 9). See Section 8.3.9 for the list of ophthalmic exam procedures.

Participants who have ocular symptoms at end of study treatment will continue to be followed as indicated in the SoA (Section 1.3) for up to 12 months, or until full resolution of findings: defined as a return to participant's baseline, or until deemed clinically stable by an ophthalmologist (or an optometrist if an ophthalmologist is not available), whichever comes first. Clinically stable is defined as changes less than or equal to Grade 1 as per Table 7.

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 EOT. Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops (if administered). 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 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 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.

Prophylactic or therapeutic corticosteroid eye drops are not required but can be used if clinically indicated. An ophthalmology (or optometry, if ophthalmology is not available) consult is required for all participants who require steroid eye drops for more than 7 days.

Participants must avoid the use of contact lenses during the study. An ophthalmology/optometry consult is required for all participants who develop signs or symptoms of corneal toxicity.

A summary of prophylactic interventions for corneal toxicity associated with belantamab mafodotin is provided in Table 8.

Table 8 Prophylactic measures for corneal toxicity 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. Allow 5-10 minutes between administration of artificial tears and steroid eye drops (if administered)
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 6.6

6.7. Intervention after the End of the Study

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

Refer to Section 8 and the SOA (Table 1) for follow-up assessments of participants who are to be followed for disease progression after they permanently discontinue from study treatment.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

Participant will receive study treatment until disease progression, death or unacceptable toxicity (including but not restricted to meeting stopping criteria for significant toxicity as outlined in Section 6.6), loss to follow-up, or end of study (Section 4.4).

The study treatment must be permanently discontinued for any of the following reasons:

- disease progression or unacceptable toxicity (including protocol-defined safety stopping criteria)
- Pregnancy

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

- 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)
- participant is lost to follow-up

- study is closed or terminated.

The primary reason of 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 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 PD after study as specified in the SoA (Table 1).

PD 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:

- Progression is documented, or
- New anti-cancer therapy is initiated, or
- Lost to follow-up, or
- Withdrawal of consent, or
- Death occurs, or
- End of study (Section 4.4)

7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

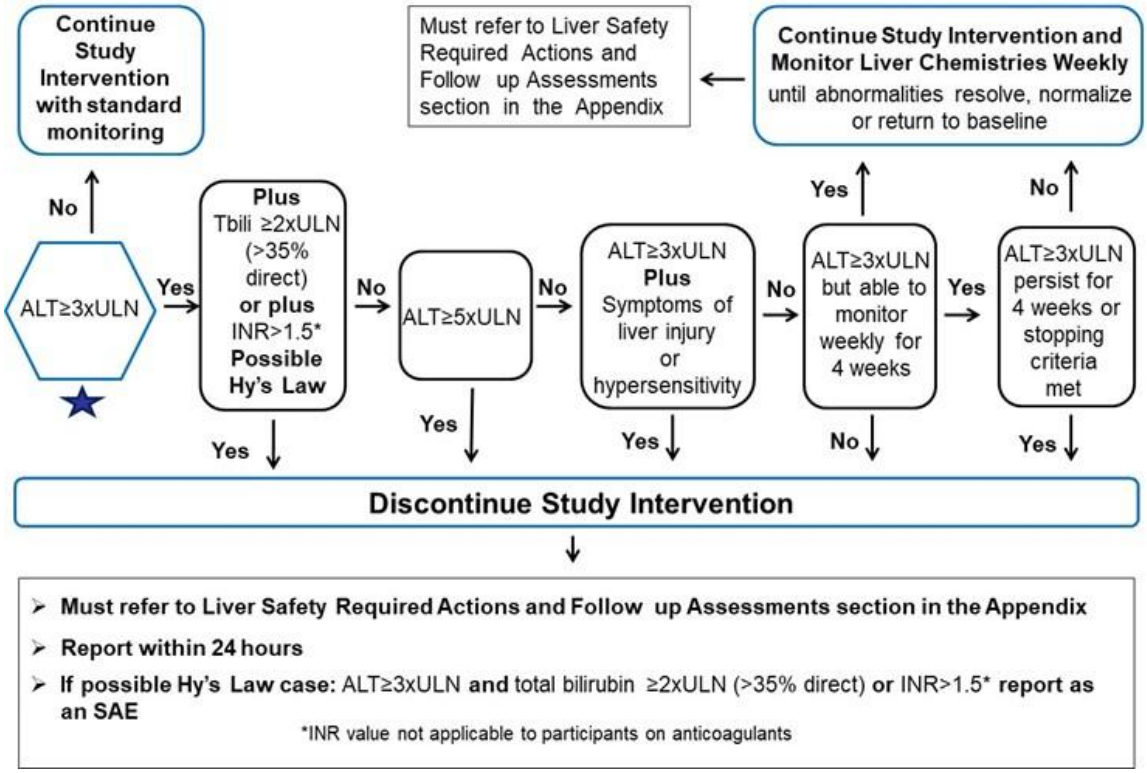
Discontinuation of study treatment for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the Figure 2

  OR

- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study treatment discontinuation is in the best interest of the participant.

Figure 2 Phase I Liver Chemistry Stopping and Increased Monitoring Algorithm for Participants WITH entry criteria ALT ≤2.5xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 5.

7.1.1.1. Study treatment Restart or Rechallenge after liver stopping criteria met

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

- GSK Medical Governance approval **is granted**
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for intervention restart/rechallenge is signed by the participant

Refer to Appendix 5 for details.

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.

7.1.2. 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 permanently discontinue study treatment but will continue in the study.

7.1.3. Stopping Criteria Based on Ocular Examination Findings

Belantamab mafodotin dose modifications and stopping criteria for treatment-related changes in visual acuity are detailed in Table 7, according to CTCAE criteria (Version 5.0, 2017). Participants who develop a Grade 4 event should be discussed with the GSK Medical Monitor to determine whether the participant can be allowed to continue 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 7).

7.1.4. Infusion-Related Reaction Stopping Criteria

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

Infusion related reactions should be managed by guidelines provided in Table 5. A participant that experiences a Grade 4 IRR must permanently discontinue study treatment but will continue in the study.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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.

Withdrawn participants will not be replaced.

7.3. Lost to Follow Up

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

A list of clinical laboratory tests is displayed in Appendix 2.

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

- Study procedures and their timing are summarised in the SoA.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilised for screening or

baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

- Visit Windows:
  - 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 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.
  - An ECHO completed within 3 months prior to screening can be used as a screening value.
  - Imaging applicable for participants with extramedullary disease must be completed within 30 days prior to first dose. .

    On study visits have a ±3-day window and PD follow-up visits have a ±7-day window.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

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
- IgD, IgE (only in participants with IgD or IgE myeloma)
- Serum Kappa, lambda free LC, FLC ratio
- Bone marrow aspirate at screening (in case of CR, CCI), or immunohistochemistry (IHC) to confirm sCR.
- Imaging of extramedullary disease (only in participants with extramedullary disease)
- Skeletal surveys at screening

Response evaluation will be performed according to the IMWG Uniform Response Criteria for Multiple Myeloma 2016 (Appendix 6).

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, and FLC) will be performed every 3 weeks (at the start of each cycle). The serum and urine immunofixation will be performed as clinical indicated at the time of first achieving CR or suspected PD after CR or sCR. 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 has to be performed as described in the SoA (Table 1).

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

The confirmation of PD must be performed within 14 days, but NOT on the same day, and NOT from the same blood draw as the initial test documenting PD. The assessments will be performed during End of Treatment (EOT) follow-up Visit (Table 1) for the Schedule of Activities of anti-cancer activity.

If the last disease assessment was greater than or equal to 6 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 PD follow-up visit following discontinuation from study treatment.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

At screening, on dosing days, and at 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.

8.2.2. Vital Signs

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

8.2.2.1. 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 1.3) In general, participants must also be monitored for at least 1 hour after the completion of the first infusion and may be discharged if considered clinically stable and all other study procedures have been completed.

8.2.2.2. 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 1.3) Participants may be discharged after the infusion has been completed if considered clinically stable and all other study procedures have been completed.

8.2.3. Electrocardiograms

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

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

8.2.4. 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.

8.2.5. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those, which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

8.2.6. ECOG Performance Status

Participant performance status will be assessed at Screening, using the Eastern Cooperative Oncology Group (ECOG) scale, provided in Appendix 7.

8.2.7. Visual Function Questionnaire

The impact of potential ocular toxicity on function and health-related quality-of-life will be assessed with the use of a visual function questionnaire, the OSDI. All participants will use the Self-Administered version of the questionnaire, 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 OSDI will be administered to participants in different regions based on the availability of translated versions.

8.2.7.1. 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.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (see Section 6).

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

- All SAEs will be collected from signing of the ICF until 70 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice at the time points specified in the SoA (Table 1). However, any SAEs assessed as related to study participation (e.g., study intervention, 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 follow up.
- All AEs will be collected from the start of treatment until 70 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice at the time points specified in the SoA.
- 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 3. 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.

8.3.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, non-serious AEs of special interest, will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, 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.

8.3.5. 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.

- Details of all pregnancies in female participants will be collected after the start of study treatment and for 8 months following last dose of belantamab mafodotin.

- Details of all pregnancies for female partners of male participants will be collected after the start of study treatment and 5 months following last dose of belantamab mafodotin.
- 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 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAE.

8.3.6. 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 3 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.

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

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to 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.

8.3.8. 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 scale provided in Table 7. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in Table 4. Dose modifications for belantamab mafodotin corneal events will be based on the GSK scale for corneal events in Table 7.

8.3.9. Ocular Examinations and Procedures

Participants will be assessed by ophthalmologist (or an optometrist if an ophthalmologist is not available) at screening/baseline.

A full *screening/baseline* ophthalmic examination for all participants must include for both eyes (OU):

a. Best corrected visual acuity
b. Documentation of manifest refraction and the method used to obtain best corrected visual acuity
c. Current glasses prescription (if applicable)
d. Intraocular pressure measurement
e. Full anterior segment (slit lamp) examination including fluorescein staining of the cornea. Anterior segment exam includes: conjunctiva, sclera, cornea, lens and anterior vitreous
f. Dilated funduscopic exam

The *on treatment* and *follow-up* ophthalmic exam should be performed for both eyes (OU) as described below and in the SoA (Section 1.3):

1. Best corrected visual acuity
2. Documentation of manifest refraction and the method used to obtain best corrected visual acuity.
3. Intraocular pressure measurement (if clinically indicated).
4. Anterior segment examination of the: conjunctiva, sclera, cornea (including fluorescein staining) and lens

The *end of study treatment and last follow-up* ophthalmic exam, if required, should match the *screening/baseline* exam.

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

8.4. 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 belantamab mafodotin can no longer be detected systemically (at least 3 months).

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 1.3). Each PK sample must be collected as close as possible to the planned time relative to the dose (which is 0 h) administered to the participant on PK days. The actual date and time of each blood sample collection will be recorded.

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

8.5.2. Pharmacokinetic Sample Analysis

Plasma analysis will be performed under the control of GSK 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 BIB protocol.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

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8.8.2. Immunogenicity Assessments

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

Serum samples for determination of anti-belantamab mafodotin antibodies will be taken from all participants in this study at the time-points specified in the SoA. Details of sample preparation, storage, and analysis will be provided in the SRM.

Samples will be analyzed for the presence of anti-belantamab mafodotin antibodies by a validated electrochemiluminescent immunoassay. First, all samples will be tested in a screening assay to identify potentially positive samples. Next, samples that screen positive will be further characterized for specificity in a confirmation assay, and, finally, for samples that test positive in the confirmation assay, the antibody titer values will be determined. For each participant, immunogenicity results, including the incidence and titers, will be reported. Raw data will be archived at the bioanalytical site (detailed in the SRM).

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

Due to limited sample size and the purpose of the study, no formal statistical hypotheses are being tested. Primary objective of the study is to determine safety and tolerability of belantamab mafodotin in Chinese Participants with RRMM. Analysis of the data will only utilise descriptive methods.

9.2. Sample Size Determination

The sample size planned arises from the predefined dose escalation criteria for dose selection and is not driven by statistical considerations. Based on the 3+3 dose escalation design the anticipated size will be up to 6 evaluable participants for each cohort and the actual numbers will depend on the safety observed.

9.3. Populations for Analyses

The '**All Treated Population'** is defined as all eligible participants who receive at least 1 dose of study treatment. An incorrect treatment schedule or drug administration or an early termination of treatment will not result in exclusion of participants from this population.

The '**DLT Evaluable Population'** is defined as all the eligible participants who have received the 1st dose as planned, and experienced a DLT during the cycle 1 or completed the cycle 1. Participants who have been replaced during cycle 1 will be excluded from the DLT evaluable population.

The '**PK Population'** is defined as those participants in the "All Treated" population from whom at least one PK sample was obtained, analyzed, and was measurable.

9.4. Statistical Analyses

9.4.1. Key Elements of Analysis Plan

Data will be listed and summarized according to the GSK reporting standards, where applicable. If data warrant, the response data will be summarized by dose level. Complete details will be documented in the Reporting and Analysis Plan (RAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and clinical study report.

Due to very small numbers per center, data from all participating centers will be pooled prior to analysis.

Demographic and baseline characteristics will be summarized.

9.4.2. Dose Limiting Toxicity

The DLT Evaluable Population will be used for evaluation of the number of participants experiencing any DLTs of each cohort.

For primary statistical analysis, the number and proportion of participants in the DLT population who experienced DLT during the Cycle 1 of study treatment will be presented by dose level.

9.4.3. Safety Analyses

The All Treated Population will be used for the analysis of safety data (except the DLT analysis). All serially collected safety endpoints will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a "worst-case" analysis. Complete details of the safety analyses will be provided in the Reporting and Analysis Plan (RAP).

9.4.4. Extent of Exposure

The number of participants in all treated population will be summarized according to the duration of therapy.

9.4.5. Adverse Events

Adverse events (AEs) will be coded using the standard MedDRA. Severity of corneal events will be graded using the scale provided in Table 7. The severity of other adverse events (AEs) will be graded by the investigator according to the National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE) (version 5.0).

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, serious adverse events (SAEs) and AEs leading to discontinuation of study treatment. Adverse events (AEs), if listed in the NCI-CTCAE (version 5.0) will be summarized by the maximum grade. Otherwise, the AEs will be summarized by maximum intensity.

The incidence of deaths and the primary cause of death will be summarized.

9.4.6. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) (version 5.0). Laboratory test results outside the reference ranges that do not have associated NCI-CTCAE criteria will be summarized using proportions.

9.4.7. Immunogenicity Analyses

For each participant, the results and titers of anti-belantamab mafodotin binding antibodies will be listed for each assessment time point 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.

9.4.8. Other Safety Measures

Data for vital signs, electrocardiograms (ECGs), and echocardiograms (ECHOs) will be summarized based on predetermined criteria identified to be of potential clinical importance (PCI) criteria.

9.4.9. Clinical Activity Analyses

Clinical activity will be assessed based on Objective Response, which is defined as the confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), CCI and partial response (PR) as assessed by IMWG Uniform Response Criteria for Multiple Myeloma 2016. The percentage of participants with objective response (Objective response rate [ORR]) will also be calculated. Clinical benefit rate with a confirmed minimal response (MR) or better, may be considered in addition to ORR.

Duration of response which is defined as the duration from the time measurement criteria are first met until the first date that progressive disease is objectively documented, will be presented descriptively among the participants who have achieved objective response.

9.4.10. Pharmacokinetic 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, total antibody and cys-mcMMAF). Concentrations will be listed for each participant and summarized (when appropriate) by planned time point and dose level.

Pharmacokinetic Parameters: PK analysis will be the responsibility of the CPMS department, GSK. Plasma belantamab mafodotin concentration-time data will be analysed by non-compartment methods using WinNonlin. Calculations will be based on the actual sampling times recorded during the study. For each dose and each participant, the following belantamab mafodotin (ADC, total antibody and cys-mcMMAF) PK parameters will be determined:

1) ADC and total antibody: after single dose: area under the plasma concentration-time curve (AUC(0-t), AUC(0-τ), and/or AUC(0-∞), maximum observed plasma concentration (Cmax), time to Cmax (tmax), last time point where the concentration is above the limit of quantification (tlast), systemic clearance (CL), volume of distribution at steady state (Vss), terminal phase elimination rate (λz), terminal phase half-life (t½). After repeat dose: Ctrough.
2) cys-mcMMAF: after single dose, Cmax, Tmax, t½, AUC(0-168), and AUC(0-t) will be derived, and after repeat dose Ctrough.

PK 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 and dose level. PK data and other related information (i.e. participant demographics, baseline clinical status, etc.) from this study will be pooled with overseas data for further population PK analysis. Full details of analysis approaches will be provided in the RAP.

9.4.11. Pharmacokinetic/Pharmacodynamic Analyses

If deemed appropriate and if data permit, dose/exposure-response relationships between belantamab mafodotin dose/exposure (e.g., dose, dose intensity, concentration, Cmax, or AUC) and clinical activity and/or toxicity (e.g., response, corneal event) may be explored based on pooled data from Study 208465 and overseas studies using population methods. If data permit, the effects of covariates (e.g., race, age, body weight) may be explored. Results of this analysis may be provided in a separate report.

9.4.12. Pharmacodynamic Biomarkers and Exploratory Response Prediction Biomarkers

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9.5. Interim Analyses

No interim analysis is planned in this study.

The final analysis will be carried out to provide updated safety and efficacy data of study treatment at the end of study, i.e., when all participants have progressed, died, withdrawn consent, discontinued treatment due to other reasons, or have been lost to follow-up.

9.5.1. Data Monitoring Committee (DMC)

No DMC is planned for this study.

9.5.2. Dose Escalation Committee (DEC)

The Dose Escalation Committee (DEC) will monitor intervention-emergent data on an ongoing basis throughout study conduct for the purpose of ensuring the continued safety

of participants enrolled in this study as described in the Dose Escalation Plan. The DEC will be chaired by the GSK medical monitor and membership will include a GSK clinical scientist, GSK safety physician, GSK statistician, GSK pharmacokineticist, along with additional GSK staff as appropriate and all participating investigators.

The DEC will review of relevant safety, PK, and PD data generated immediately after all participants treated in the same dose cohort have passed the DLT period.

Dose Escalation Meetings will be scheduled at the conclusion of the DLT assessment period for participants enrolled in each cohort to review safety data and determine the next dose level appropriate for study.

In addition, throughout the conduct of the study the DEC may decide to:

1) Modify the dose escalation of belantamab mafodotin proposed by the 3+3 model based on clinical judgement.
2) Investigate alternative dosing regimens
3) Modify the timing, frequency, and/or type of safety assessments performed during study conduct
4) Approve continuation of belantamab mafodotin study therapy in participants who have experienced DLT provided the toxicity did not meet study discontinuation criteria and has resolved at the time of re-start.
5) Request intervention of additional participants at previously completed dose levels for the purpose of obtaining additional safety, PK, PD, metabolite, or biomarker data (i.e. PK/PD/Metabolite).
6) Halt enrolment into any cohorts as deemed appropriate based on emerging clinical data at any time during the trial.

Dose escalation decisions will be made with DEC members after review of available safety data from at least one cycle of therapy with belantamab mafodotin. Available data will be provided to participants prior to each scheduled Dose Escalation Meeting. Attendees of Dose Escalation Meetings will include but not limited to DEC members. All dose escalation and safety decision will be documented in writing with copies maintained by GSK in the Trial Master File and submitted to each site for documentation. Decisions with potential impact on the safety of study participants (i.e., unfavorable change in risk/benefit assessment) will be promptly communicated to regulatory authorities and study sites as appropriate.

As per current available safety and efficacy information of belantamab mafodotin studies, the 3.4 mg/kg dose cohort is converted to an optional cohort in the dose-escalation study design. Escalation may not proceed if not supported by emerging clinical data from other belantamab mafodotin studies.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

11.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The 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, and all other applicable local regulations

11.1.2. Financial Disclosure

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

11.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorised 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 authorised 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 authorised representative.
- Participants who are rescreened are required to sign a new ICF.

11.1.4. Data Protection

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

11.1.5. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve participant care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

11.1.6. Data Quality Assurance

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

11.1.7. Source Documents

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

11.1.8. Study and Site Closure

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

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

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

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

11.1.9. Publication Policy

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

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

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

11.2. Appendix 2: Clinical Laboratory Tests

Table 9 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 carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
Magnesium	Phosphorous	Creatine kinase (CK)	LDH
eGFR	Spot urine (albumin / creatinine ratio)[5, 6]		
Urine[1]			
Routine Urine Dipstick (Urinalysis required if blood or protein is detected by dipstick)[6]			
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- according to 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.			

List of Clinical Laboratory Tests (cont.)

PK/ADA			
Pharmacokinetics (PK)[2]			
Anti Drug Antibodies (ADA)[2, 3]			
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			
CCI [redacted]			
Bone marrow for disease assessment[1]			
Bone marrow to confirm sCR by IHC[1]			
Bone marrow for FISH testing[7]			
Biomarker Measurements			
CCI [redacted]			

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. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥1+ (at Screening Visit), or ≥2+ (during study treatment), or with positive protein if urine dipstick protein quantification is not available.
7. FISH testing at least for: t(4;14), t(14;16), 17p13del, and +1q21. BM samples from within 60 days prior to first dose are acceptable for FISH analysis. If not available from local laboratory, it can be performed at central laboratory.

11.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.3.1. Definition of AE

AE Definition

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

Events Meeting the AE Definition

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

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

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

11.3.2. Definition of SAE

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

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

- Results in death
- Is life-threatening

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

Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

Results in persistent disability/incapacity

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

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

11.3.3. Definition of Cardiovascular Events

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

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

11.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

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

Assessment of Intensity

The investigator will assess intensity for each AE and SAE reported during the study according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 CCI

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

[1]Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[2] 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.

11.3.5. Reporting of SAE to GSK

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

11.4. Appendix 4: 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 treatment, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1 Premenarchal

2 Premenopausal female 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 female

- 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
• Vasectomised partner   • *Note: Vasectomised partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent**

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

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

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*
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 amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information of a female partner of a male study participant who becomes pregnant while participating in this study, and

for 6 months following last dose of belantamab mafodotin. This applies only to male participants who receive study treatment.

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

Female Participants who become pregnant

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

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

Phase I 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
Cannot Monitor	ALT ≥3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study intervention • 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, stabilise, 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	• 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]. • Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend • Blood sample for pharmacokinetic (PK) analysis, obtained within 45 days after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH), gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin. • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia

MONITORING:

If ALT≥3xULN AND total bilirubin ≥2xULN or INR >1.5:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs**
- Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline
- A specialist or hepatology consultation is recommended

For All other criteria (bilirubin <2xULN and INR ≤1.5):

- 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, stabilise or return to within baseline

- 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

If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5 obtain the following in addition to the assessments listed above:

- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week. (e.g., where the participant has been resident in the clinical unit throughout)
- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease: complete Liver Imaging and/or Liver Biopsy CRF forms.
- Liver biopsy may be considered and discussed with local specialist if available, for instance:
  - In patients when serology raises the possibility of autoimmune hepatitis (AIH)
  - In patients when suspected drug-induced liver injury (DILI) progresses or fails to resolve on withdrawal of study intervention
  - In patients with acute or chronic atypical presentation:
- If liver biopsy conducted complete liver biopsy form.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥3xULN **and** bilirubin ≥2xULN.

Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. All events of ALT ≥3xULN **and** 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 PK 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. Instructions for sample handling and shipping are in the SRM.

Phase I 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, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above If, after 4 weeks of monitoring, ALT <3xULN, bilirubin <2xULN and INR ≤1.5, monitor participants twice monthly until liver chemistries normalise or return to within baseline.

11.5.1. 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.

11.5.1.1. 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.[1] 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:

- Hypersensitivity [Andrade, 2009] 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 rechallenges [Hunt, 2010; Papay, 2009].
- 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 rechallenge- 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 8.3.4.

11.5.1.2. 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 11.5.1.1 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 8.3.4.

11.5.2. 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.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009; 54:84-90.

11.6. Appendix 6: International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma (2016)

Response	Standard IMWG Criteria[1]
sCR[2]	• CR as defined below plus normal FLC ratio and absence of clonal plasma cells in bone marrow by immunohistochemistry or 8-color, 2 tube multiparametric flow cytometry
CR[3]	• negative immunofixation of serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates[3]
VGPR[3]	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥90% reduction in serum M-protein plus urine M-component level <100 mg/24 h
PR	• ≥50% reduction of serum M-protein plus reduction in 24 hours urinary M-protein by ≥90% or to <200 mg/24 h • If the serum and urine M-protein are not measurable, a decrease ≥50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥50% reduction in plasma cells is required in place of M-protein criteria, provided baseline bone marrow plasma cell percentage was ≥30%. • In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas[4] is also required.
MR	• ≥25% but ≤49% reduction of serum M protein and reduction in 24-hour urine M protein by 50% to 89% • In addition to the above criteria, if present at baseline, 50% reduction in the size of soft tissue plasmacytomas[4] is also required. No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
SD	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for CR, VGPR, PR, MR or PD
PD[2]	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in 1 or more of the following: • Serum M-protein (absolute increase must be ≥0.5g/dL); • Serum M-protein increase ≥1g/dL, if the lowest M-component was ≥5g/dL; • Urine M-protein (absolute increase must be ≥200 mg/24 h; • In participants without measurable serum and urine M-protein levels, the difference; between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); • In participants without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow plasma cell absolute percentage of baseline status (absolute increase must be ≥10%). • Appearance of new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in longest diameter of a previous lesion >1 cm in short axis. • ≥50% increase in circulating plasma cells (minimum 200 cells per μL) if this is the only measure of disease.

CBR = clinical benefit rate; CR = complete response; FLC = free light chain; IMWG = International Myeloma Working Group; MR = minimal response; ORR = Objective response rate; PD = progressive disease; PR = partial response; sCR = stringent complete response; SD = stable disease; SPD=sum of the products of the maximal perpendicular diameters of measured lesions; VGPR = very good partial response.

Objective Response Rate: Participants achieving sCR, CR, VGPR, and PR.

Clinical Benefit Rate: Participants achieving sCR, CR, VGPR, PR, and MR.

1. All response categories require two consecutive assessments made any time before starting any new therapy
2. Clarifications to IMWG criteria for PD: Bone marrow criteria for PD are used only in participants without measurable disease by M protein and by FLC levels; "25% increase" refers to M protein, FLC, and bone marrow results but does not refer to bone lesions or soft tissue plasmacytomas; also, the "lowest response values" do not need to be a confirmed value.
3. Clarifications to IMWG criteria for coding CR and VGPR in participants in whom the only measurable disease is by serum FLC levels: CR in such participants is a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such participants requires a >90% decrease in the difference between involved and uninvolved FLC levels.
4. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For participants with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumour size will be determined by the SPD.

Notes:

- All category responses require no known evidence of progressive or new bone lesions if radiographic studies were performed.
- VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither.

CCI


CCI

11.7. Appendix 7: ECOG Performance Status1

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

Reference

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al,. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American journal of clinical oncology. 1982 Dec 1;5(6):649-56.

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

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

$$eGFR = 175 \times (Scr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

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

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

11.9. Appendix 9: Eye Care Specialist's Qualifications and Requirements

For examiners with a degree in optometry or ophthalmology, those involved in eye evaluations in the protocol must be able to provide comprehensive eye care to patients, ranging from routine check-ups to treatment and ongoing management of visual disease. This includes, as a minimum, the ability to perform the following activities:

- Comprehensive eye exams
- Visual acuity with manual refraction tests and analysis of results
- Slit lamp tests and analysis of results
- Intraocular pressure examination
- Dilated fundoscopic examination
- Diagnosis and treatment of ocular issues and diseases such as keratopathy or glaucoma
- Communication with patients on the effect of belantamab mafodotin on the eye

11.10. Appendix 10: 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
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase
AUC	Area under the curve
AV	Atrioventricular
BAFF	B-cell-activating factor belonging to the TNF family
BCMA	B-cell maturation antigen
BIB	Bioanalysis Immunogenicity and Biomarkers
BM	Bone marrow
BNP	B-type natriuretic peptide
BP	Blood Pressure
BUN	Blood urea nitrogen
C1D1	Cycle 1 Day 1
CBR	Clinical Benefit Rate
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council of International Organizations of Medical Sciences
CK	Creatine kinase
CL	Clearance
C_{max}	Maximum observed concentration
CO_2	Carbon dioxide
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatinine 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
DEC	Dose Escalation Committee

DICOM	Digital Imaging and Communications in Medicine
DILI	Drug-induced liver injury
DLT	Dose limiting toxicities
DMC	Data Monitoring Committee
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
EOT	End of treatment
FISH	Fluorescence in situ hybridization
FLC	Free light chain
FSH	Follicle stimulating hormone
FTIH	First Time in Human
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GSK	GlaxoSmithKline
HBV	Hepatitis B virus
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
IB	Investigator Brochure
ICD	Immunogenic cell death
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMWG	International Myeloma Working Group
IP	Investigational product
IRB	Institutional review board
IRR	Infusion related reaction
IUD	Intra-uterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
LC	Light chain
LDH	Lactate dehydrogenase
LLN	Lower limit of normal (range)
LVEF	Left ventricular ejection fraction

mAb	Monoclonal antibody
MDRD	Modified diet in renal disease
MM	Multiple myeloma
MMAF	Monomethyl auristatin-F
MOA	Mechanism of Action
MR	Minimal Response.
CCI [redacted]	
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
NCI	National Cancer Institute
NE	Not evaluable
CCI [redacted]	
NYHA	New York Heart Association
ORR	Objective Response Rate
OSDI	Ocular Surface Disease Index
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PR	Partial response
Q21D	Once every 21 days
Q3W	Once every 3 weeks
QID	Four times a day
QTc	Corrected QT interval (ECG)
QTcF	Corrected QT interval Fridericia
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RNA	Ribonucleic acid
RRMM	Relapsed / refractory multiple myeloma
SAE	Serious adverse event
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	Standardised uptake value
$t_{½}$	Terminal phase half-life
TCR	T-Cell receptor

TLS	Tumor Lysis syndrome
T_{max}	Time of maximum observed concentration
TNF	Tumor necrosis factor
UK	United Kingdom
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
US	United States
USP	United States Pharmacopeia
V	Volume of distribution
VGPR	Very good partial response
WBC	White blood cell
WFI	Sterile water for injection
WOCBP	Woman of Childbearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
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MedDRA
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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 2: 30-OCT-2020

Overall Rationale for the Amendment: Per current available safety and efficacy information of belantamab mafodotin studies, the 3.4 mg/kg dose cohort is converted to an optional cohort in the dose-escalation study design. It may be determined not to escalate to based on clinical data from other belantamab mafodotin studies.

Section # and Name	Description of Change	Brief Rationale
Section 2.1	As updated clinical experience language for studies BMA117159 and 205678 has been added to Section 2.2, the related information has been deleted from Section 2.1	Updated relevant clinical data available and included in Section 2.2.
Section 2.2	Updated clinical experience language for studies BMA117159 and 205678	Updated relevant clinical data available.
Section 2.3 Benefit/Risk Assessment	Risk assessment details have been updated based on the updated safety profile.	Program level update.
Section 1.1, Synopsis, Section 1.2 Schema, Section 2.3.2 Benefit Assessment, Section 4.1.1 Planned Dose Levels, Section 9.5.2 Dose Escalation Committee (DEC)	A sentence has been added to reflect that 3.4 mg/kg dose may not be used in the study.	Per current available safety and efficacy information of belantamab mafodotin studies, the 3.4 mg/kg dose cohort is converted to an optional cohort in the dose-escalation study design. It may be determined not to escalate to based on clinical data from other belantamab mafodotin studies.
Section 1.1 Synopsis, Section 9.2 Sample Size Determination	Up to six evaluable participants for each dose level.	To clarify the sample size by dose levels since 3.4 mg/kg dose level is an optional cohort in the study design.
Section 1.3 Schedule of activities (SoA) Section 6.6.1 Corneal Supportive Care Guideline for Belantamab Mafodotin	Modification for ophthalmic exam information	Program level update.

Section # and Name	Description of Change	Brief Rationale
Section 6.5.2 Prohibited Medication(s)	Information related to use of vaccine has been updated.	To enhance participants' safety, the period for prohibited medication use of live/live-attenuated vaccines has been extended
Section 6.5.3 Prohibited Device(s)	Information related to the use of contact lens has been updated.	Program level update.
Section 8	Information related to imaging has been updated.	For better clarity of the participants who need imaging .
Section 8.1 Efficacy Assessment	Sentence added that the serum and urine immunofixation will be performed at the time of first achieving CR or suspected PD after CR or sCR	For better clarity and consistency with SoA Table
Section 7.1.1 Liver Chemistry Stopping Criteria	Information of stopping criteria has been modified	Availability of updated standard language for protocols
Section 9.4.10 Pharmacokinetic Analysis	Additional AUC values added to parameter lists	To add parameters calculated in other studies to support comparisons
Appendix 5: Liver Safety: Required Actions and Follow-up Assessments and Study treatment Rechallenge Guidelines	Information of liver safety criteria has been modified	Availability of updated standard language for protocols
Appendix 9 Eye Care Specalist's Qualification and Requirements	Added Appendix 9: Eye Care Specialist's Qualifications and Requirements.	Program level update.
Section 10 References	New references were added and references were updated	Addition and update of references was done in parallel to changes in the main text.
Throughout the protocol	Changed the use of "subject", in the protocol to use "participant" only.	Clarification of wording
Whole document	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

Amendment 1: 02-Nov-2019

Overall Rationale for the Amendment: The Centre of Drug Evaluation (CDE) China has recommended that the study participants should be sequentially entered into the 2.5 mg/kg dose group to observe participants' tolerance completely and collect PK data, based on tolerability results, the subsequent dosing plan should be adjusted as appropriate. The safety monitoring and risk management were enhanced based on the available data about the product. Ocular examination details were updated as CDE suggested to pay attention to corneal examination and collection of patient-reported

symptoms during the clinical study based on the occurrence of corneal toxicity of this product. The pregnancy data collection and contraception period were revised as toxic effects on the fertility could be observed in repeat dose toxicity studies.

Section # and Name	Description of Change	Brief Rationale
Section 4.1.1. Planned Dose Levels	The first 3 participants in 2.5 mg/kg dose group will receive the study treatment sequentially with an observation window of 7 days, to observe acute toxicities. If the participating investigator and the coordinating investigator see no potential safety concerns from the first participant, the participating investigator and the coordinating investigator may recommend to enroll the next participant. If 1 or more participants experience a DLT, dose will be de-escalated to 1.9 mg/kg if the current dose cohort is 2.5 mg/kg.	To ensure adequate safety observation and data collection, prior to adding the next patient at the same dose level, based on tolerability results. Subsequent dosing plan can be adjusted as appropriate.
Section 1.1 Synopsis, Section 1.3. Schedule of Activities (SoA), Section 3 Objectives and Endpoints, 8.2.7. Visual Function Questionnaire	Collection of participant self-reported symptoms using the OSDI has been added.	Collection of participant self-reported symptoms during the clinical study based on the occurrence of corneal toxicity of this product
Section 2.3.1. Risk Assessment	Risk assessment details have been updated with two new risks (embryo-fetal toxicity and impaired male fertility) added and the risk of 'Potential for overdose specific to the preparation of study drug' removed. Changes on corneal examination, infusion related reaction, neutropenia, potential for cardiotoxicity related to an inflammatory response, hepatotoxicity, nephrotoxicity, and potential for other laboratory abnormalities were updated.	Based on the updated safety profile, use of belantamab mafodotin in pregnant women may cause fetal harm and in animal studies, belantamab mafodotin treatment has resulted in testicular toxicity and adverse effects on spermatogenesis. GSK does not recommend a specific treatment for an overdose as there is no specific antidote for the overdose of belantamab mafodotin. For the treatment of overdose can reach out to Section 8.4.

Section # and Name	Description of Change	Brief Rationale
Section 6.6. Dose Modification	Dose modification guidelines were updated for thrombocytopenia, febrile neutropenia and added for neutropenia	More details are added in this section based on the latest available information.
Section 7.	Update the wording in the section of discontinuation of study treatment and participant discontinuation/withdraw	Discontinuation section has been updated based on the information from the ongoing clinical programme.
Section 1.1 Synopsis, Section 5.1 Inclusion Criteria	Contraception period has been extended	The study drug has not been evaluated for reproductive toxicity in any of the clinical studies. To protect participants from fetal toxicity, pregnancy should be avoided for an extended period.
Section 1.3 Schedule of Activities (SoA), Section 8.3.5. Pregnancy, Section 11.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Pregnancy data collection periods have been extended and final pregnancy test time point has been changed,	To collect additional data to further define the safety profile of belantamab mafodotin in relation to fetal toxicity.
Section 8.3.9. Ocular Subset Examinations	Ocular exam details have been updated	Updated with latest procedure.
Section 1.3. Schedule of Activities (SoA), Section 2.3.1 Risk Assessment, Section 6.6 Dose Modification, Section 6.6.1 Corneal Supportive Care Guidelines for	Steroid eye drops administered as prophylaxis is no longer mandated but can be used if clinically indicated at the discretion of an eye-care specialist Update to the wording on frequency of ophthalmologic assessments New dose modification guidance (based on CTCAE 5.0)	Based on the data from the ongoing clinical programme: • Steroid eye drops were not found to provide benefit to participants. • It has been determined that participant symptoms should determine the need for ophthalmology exams The need for dose delay/reduction should be determined by participant

Section # and Name	Description of Change	Brief Rationale
belantamab mafodotin		symptoms (not asymptomatic corneal changes)
Section 9.5.2. Dose Escalation Committee	Dose Escalation Committee (DEC) details have been added	The DEC will monitor intervention-emergent data on an ongoing basis throughout study conduct for the purpose of ensuring the continued safety of participants enrolled in this study as described in the Dose Escalation Plan.
Previous Section 11.1.5. Committees Structure	Deleted this section which provided information on the Independent review committee (IRC)	IRC is not required for phase 1 studies, since efficacy is not a primary endpoint and can be adequately assessed by investigators.
Section 11.2. Appendix 2: Clinical Laboratory Tests	Removed the wording related to results to be stored by third party	Results will be stored at sites
Previous Section 11.8. Appendix 8: Corneal Event Severity Grading and Mitigation Strategy	Deleted the Appendix	Information on corneal event severity grading and mitigation strategy is already included under Section 6.6. Dose Modification and Section 6.6.1 Corneal Supportive Care Guidelines for Belantamab Mafodotin
Section 10 References	New references were added and references were updated	Addition and update of references were because of changes in the main text.
All Sections	Replaced “GSK2857916” with “Belantamab Mafodotin” throughout the document	Updated with generic name
Minor typographical errors were corrected in the document		