TITLE PAGE

Protocol Title: A Phase I Study to Evaluate the Pharmacokinetics and Safety of belantamab mafodotin Monotherapy in Participants with Relapsed and/or Refractory Multiple Myeloma (RRMM) Who Have Normal and Varying Degrees of Impaired Renal Function (DREAMM 12)

Protocol Number: 209626/Amendment 03

Compound Number: GSK2857916

Generic Name: belantamab mafodotin

Study Phase: Phase 1

Short Title: A Phase I Study of Belantamab Mafodotin in Multiple Myeloma Participants with Normal and Impaired Renal Function

Acronym: DREAMM 12

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Approval Date: 15 Jun 2022

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 3	*15 Jun 2022*	TMF-14740476
Amendment 2	*07-JAN-2022*	TMF-14365268
Amendment 1	*09-SEP-2020*	*2018N383427_01*
Original Document	*26-FEB-2020*	*2018N383427_00*

Amendment [3] 15 Jun 2022

Overall Rationale for the Amendment: Amendment 03 is a global amendment to remove the requirement for the collection and analysis of dialysate fluid and pre and post blood PK samples from End Stage Renal disease (ESRD) patients on hemodialysis. Additional changes were incorporated to clarify the management of participants post-final analysis to enable continued access to treatment. This includes removal of final/end of study analysis and data collection within the database beyond the primary analysis, which addresses the study objectives.

Section # and Name	**Description of Change**	**Brief Rationale**
Headers, cover page and Protocol Amendment Summary of Changes Table	Headers and cover page were updated with new document number; Protocol Amendment Summary of Changes Table section was created and populated to include details and rationale for this amendment. Text included/amended throughout document	Editorial changes to align with the GSK's new standard protocol template and language
Section 1.1 Synopsis, 1.3 Schedule of Activities (Table of Schedule of Activities), 3. Objectives and Endpoints, 8.5.1.1 Blood, 8.5.1.2 Dialysate fluid, 8.5.2. Belantamab Mafodotin PK sample analysis, 9.4.3 Pharmacokinetic Analyses,	Throughout text referring to dialysate fluid collection and analysis and pre and post blood PK collection for ESRD patients on hemodialysis removed. Section 8.5.1.2. Dialysate Fluid removed Table 15- Timing of blood and dialysate collection from dialysis participants removed	Removal of dialysate fluid collection is due to lack of a reliable bioanalytical assay. Removal of pre and post dialysis blood PK collection at dialysis sites as PK sampling outlined in table 14 is considered as sufficient to assess the cumulative effect of dialysis on cys-mcMMAF exposure, given the 3-weekly administration schedule and multiple PK samples over the dosing interval in all 4 patient groups.
Section 1.1 Synopsis, 4.3 End of Study Definition, 6.7 Intervention after the End of the Study and 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Text included/amended throughout document to allow for continued treatment in responding patients post final study analysis	Updated based on the recent program level wording

Section # and Name	Description of Change	Brief Rationale
Section 6.7 Intervention after the End of Study, Section1.1 Synopsis. Section, Table 18 Details of Analyses to be performed	Section 6.7 Intervention after the End of Study -Incorporation of Final analysis data cut-off date (approximately 6 months after LSFD) Section1.1 Synopsis Incorporation of text: Following the 6 months from last participant first dose (LPFD) Table 18 Details of Analyses to be performed- 'Primary Analysis' changed to 'Primary/Final analysis' and removal of 'Final Analysis/End of Study'	To align with the protocol study objectives which will be assessed at the time of Final analysis, approximately 6 months after LSFD/LPFD.
Throughout	Formatting and administrative edits and updates throughout the document	This was to ensure accuracy, clarity, conformity, flow, and typographical error corrections
Section 8.1.1: Response Evaluation	Removed use of GSK proprietary algorithm to derive response. Response will be assessed only according to the IMWG criteria by the investigator	Efficacy endpoints are exploratory only in this study and no Investigator independent efficacy assessments are planned and no longer deemed necessary in this study.
Section 4. Overall Design 4.1	Update inclusion criteria from: 'This is a Phase I study to assess the PK, safety, and tolerability of belantamab mafodotin monotherapy in participants with RRMM who have had at least 3 lines of prior treatment and have either normal or impaired renal functions' to 'This is a Phase I study to assess the PK, safety, and tolerability of belantamab mafodotin monotherapy in participants with RRMM who have had at least 3 lines of prior treatment (or at least 2 lines of prior treatment if ineligible for autologous stem cell transplantation) and have either normal or impaired renal functions'.	Updated and clarified protocol wording

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase I Study to Evaluate the Pharmacokinetics and Safety of belantamab mafodotin Monotherapy in Participants with Relapsed and/or Refractory Multiple Myeloma (RRMM) Who Have Normal and Varying Degrees of Impaired Renal Function (DREAMM 12)

Short Title: A Phase I Study of belantamab mafodotin in Multiple Myeloma Participants with Normal and Impaired Renal Function

Rationale: Renal impairment is a major complication of multiple myeloma (MM) and the majority of MM patients either are at risk or already have renal dysfunction at initial diagnosis. Patients with renally impaired MM require anti-tumor therapies adapted to reduced renal function, either by dose modifications or through selection of anti-myeloma drugs whose pharmacokinetics (PK) behavior is unaffected by the reduced renal function. Renal impairment can reduce the rate of elimination of drug primarily eliminated in urine but can also adversely affect the elimination of drugs that are primarily non-renally cleared by impacting some pathways of hepatic metabolism and transport mechanism. It is thus important to evaluate the potential impact of increased degrees of renal impairment on the PK and safety of MM drugs that are renally or non-renally cleared to provide adequate dosing guidance.

Belantamab mafodotin is an antibody-drug conjugate (ADC) consisting of an afucosylated humanized anti-BCMA monoclonal antibody (mAb) conjugated to the intracellular microtubule disruptor cysteine-monomethyl auristatin-F (cys-mcMMAF). In general, monoclonal antibody drugs are not renally excreted; however, following intravenous (IV) administration, belantamab mafodotin is catabolized leading to the release of cys-mcMMAF. After IV administration of radio-labelled cys-mcMMAF to rats, elimination was primarily in feces, with CCI in urine [GSK2857916 Investigator's Brochure (IB), GlaxoSmithKline Document Number RPS-CLIN-004867 09, 2021]. In study BMA117159 cys-mcMMAF was detected in human urine [GlaxoSmithKline Document Number 2018N357123_00 and GlaxoSmithKline Document Number 2020N435785_00]. While it is not anticipated that renal impairment would impact the PK of belantamab mafodotin, it is possible that cys-mcMMAF elimination may be affected.

To date, MM patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min) have been excluded in belantamab mafodotin clinical trials. Therefore, the efficacy, safety and PK of belantamab mafodotin (including that of cys-mcMMAF) have not been evaluated in patients with severe renal impairment Sufficient numbers of participants with moderate renal impairment were included in previous studies of belantamab mafodotin to conclude that mild/moderate renal impairment (eGFR 30-59 mL/min) was not a predictor of belantamab mafodotin or cys-mcMMAF clearance or did not increase toxicity. To date, patients with MM and severe renal impairment (eGFR <30 mL/min) have been excluded from belantamab mafodotin clinical trials. This study aims to determine whether the safety profile or PK of either belantamab mafodotin or cys-mcMMAF is altered in patients with severe renal impairment.

The current study aims to describe the relationship, if any, between renal function parameters and safety/PK parameters of belantamab mafodotin (ADC and total mAb) and cys-mcMMAF in participants with MM. If renal impairment is found to affect safety and/or PK, the results of this 2-part study are expected to provide guidance for appropriate labelling of belantamab mafodotin.

Also, as corneal findings have been observed after administration of belantamab mafodotin, tear fluid will be collected in Part 1 of this study in both treatment groups to evaluate the presence and, if technically feasible, the concentrations of belantamab mafodotin and free cys-mcMMAF in tears. This evaluation is planned to be limited to participants in Part 1 (participants with normal/mildly impaired [Group 1] and severely impaired [Group 2] renal function) only since this will provide a sufficient sample size (up to 20 participants). If tear collection is not possible from individual participants due to dry eyes disease or technical issues, additional participants may be asked to provide tear samples to allow for a sufficient sample size for analyses.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To describe the effects of renal impairment on the pharmacokinetics of belantamab mafodotin in participants with RRMM and with severe renal impairment, ESRD (not on dialysis) or ESRD (on dialysis) compared to participants with normal renal function	• Plasma belantamab mafodotin, total mAb, and cys-mcMMAF pharmacokinetic parameters, as data permits;
Secondary	
• To evaluate safety and tolerability using clinical parameters, including adverse events, vital signs, and clinical laboratory assessments in participants with RRMM who have normal or impaired renal functions	• Monitoring and incidence of adverse events, toxicity grading of clinical laboratory tests, and physical examinations, Change from baseline in vital signs (blood pressure and heart rate),
Exploratory	
• To explore any relationship between PK and renal function parameters	• Relationship between belantamab mafodotin and cys-mcMMAF PK parameters (e.g., Cmax, AUC) and baseline renal function parameters (e.g., eGFR)
• To evaluate the recovery of cys-mcMMAF in urine in Part 1 only	• Urine recovery over 24 hours at several time points following the first dose
• To assess anti-drug antibodies (ADAs) against belantamab mafodotin	• Incidence and titers of ADAs against belantamab mafodotin
• To evaluate the clinical measures of efficacy of belantamab mafodotin in participants with RRMM who have normal or impaired renal function	• ORR (Overall Response Rate) • CBR (Clinical Benefit Rate) • DoR (Duration of Response) • TTR (Time to Response) • TTP (Time to Progression)
• To explore the relationship between biological characteristics and clinical response	Tumor and blood-based analyses of DNA, RNA and protein changes including but not limited to baseline and on-treatment sBCMA and BCMA expression on myeloma cells

Objectives	Endpoints
• To evaluate the presence/concentrations of belantamab mafodotin and free cys-mcMMAF in tear fluid in participants with normal/mild or severely impaired renal function (Part 1 only) and explore relationship between tear fluid and plasma concentration	• Presence/concentrations of belantamab mafodotin and cys-mcMMAF in tear fluid at baseline and on treatment, as data permits • Relationship between tear fluid and plasma concentrations of belantamab mafodotin and of cys-mcMMAF, as data permits

Abbreviations: AUC = Area under the curve; BCMA = B-cell maturation antigen; Cmax = maximum observed concentration; DNA=deoxyribonucleic acid; ESRD = end stage renal disease RNA= ribonucleic acid

Overall Design: This is a Phase I study to access the PK, safety, and tolerability of belantamab mafodotin monotherapy in participants with RRMM who either have normal or impaired renal function. Renal impairment will be classified based on the Individual Glomerular Filtration Rate (iGFR) using the Modification of Diet in Renal Disease (MDRD) formula [Levey, 2006] based on body surface area calculation (based on actual body mass/weight) [Mosteller, 1987] and according to FDA-defined categories of severe, ESRD not on dialysis, or ESRD on dialysis [FDA DHHS, 2020].

Disclosure Statement: This is an open-label single-arm study in RRMM participants with various grades of impaired renal function.

Number of Participants: Approximately 100 participants will be screened in this study to ensure that a total of 32 (up to 36) participants will be enrolled.

Intervention Groups and Duration: This is a 2-part study in which participants with RRMM from 4 groups (stages of renal function) below will be enrolled. The 4 groups studied are participants with Stage 1 and 2 (normal or mild decrease in GFR) serving as control, and participants with stage 4 (severe decrease in GFR), and stage 5 renal impairment (ESRD, both types). For classification of renal function see below and see Table 6 and Figure 1 in Section 1.2 for more details.

Following the final analysis (data cut-off approximately 6 months from last participant first dose (LPFD)), study DREAMM-12 will move into the post analysis continued treatment (PACT) phase. At this time, the collection of new data for recruited participants who no longer receive study treatment will stop entirely and the clinical trial database will be closed. Those participants still benefiting from study drug in the opinion of their treating physician may continue to receive study drug and only SAEs, AEs leading to treatment discontinuation, overdose, pregnancy cases, and pre-specified ocular data will be reported via paper forms (see SRM for details).

Classification of Renal Function Based on Individual Glomerular Filtration Rate (iGFR)

Stage	Description	iGFR(mL/min)
1	Normal renal function	≥90
2	Mild impairment	60-89
3	Moderate impairment	30-59
4	Severe impairment	15-29
5	End Stage Renal Disease (ESRD), Kidney Failure	<15, not on dialysis
		<15, requiring dialysis

Reported individual Glomerular Filtration Rate (iGFR) = eGFR (by MDRD) x BSA (by Mosteller) / 1.73

MDRD Equation: eGFR) = **175** x $(S_{cr})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 *if female*) x (1.212 *if black or African American*).

Mosteller BSA: = $(height \times weight/3600)^{0.5}$

In the above formulas-S_{cr} (standardized serum creatinine) is expressed in mg/dL, height is expressed in cm, weight is expressed in kg and age is expressed in years. Source documents for the above formulas are FDA DHHS, 2020; Levey, 2006, and Mosteller, 1987. Calculators can be found in Appendix 12

Data Monitoring Committee: No

1.2. Schema

The study will include a Screening Phase, a Treatment Phase, and a Follow-up phase. Enrolled participants will be assigned to 1 of the 4 predefined groups based on renal function classification as defined in the Food and Drug Administration (FDA) draft guidance for industry [FDA DHHS, 2020].

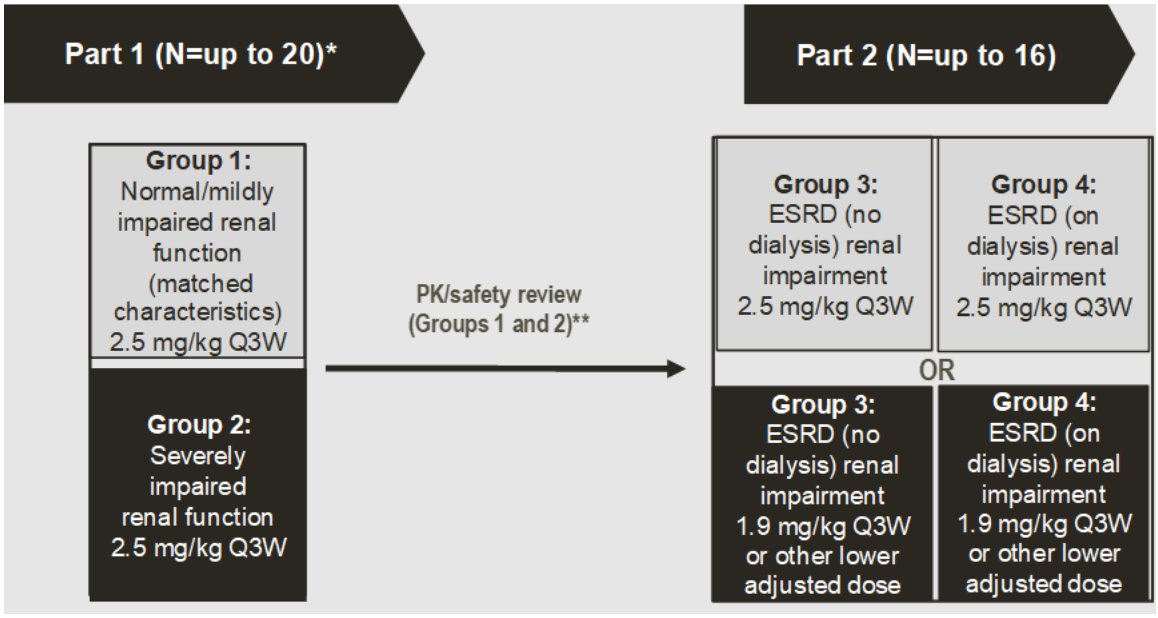
Parts and Groups of the study will be arranged as follows:

Part	Group	Renal Stage[i]	Description
1	1	1/2	Control (normal renal function/mild impairment)
1	2	4	Severe impairment
2	3	5	End Stage Renal Disease (ESRD) not on dialysis
2	4	5	End Stage Renal Disease (ESRD) on dialysis

(i) Based on FDA DHHS, 2020.

Enrollment sequence of the Parts and Groups are detailed in Figure 1.

Figure 1 Planned Enrollment Sequence



*Number of Participants in Group 1 enrolled can be 8 and up to 12, and 8 in Group 2.
** Modifications to study eligibility criteria may be made during the study by amendment pending the result(s) of regular in-stream safety review(s) and/or as a result of the Safety/Pharmacokinetic (PK) review between the completion of the enrolment of Part 1 and the opening of enrolment in Part 2. Dose may be adjusted for Part 2 to higher or lower than 1.9 mg/kg, or other adjusted dose.
ESRD = end stage renal disease (iGFR <15 mL/min) either not on hemodialysis or requiring hemodialysis

Part 1: will consist of 8 RRMM participants with severely impaired renal function (i.e., Group 2) and up to 12 RRMM participants with normal or mildly impaired renal function (i.e., Group 1), 8 of whom will be matched for baseline weight and baseline albumin levels with the Group 2 participants. Participants will be dosed with 2.5 mg/kg belantamab mafodotin IV Q3W (every 3 weeks) on Day 1 of every 21-day cycle.

Once 8 participants in Group 1 and 8 participants in Group 2 have completed their first cycle, all available PK, safety and tolerability data (including the renal function and drug related toxicities, if any) will be evaluated by the GlaxoSmithKline (GSK) study team (including members from clinical, clinical pharmacology modeling/simulation group, safety and statistics) and the study investigators to decide on the most appropriate dose to use in Part 2. Review of data will include (but will not be limited to) an evaluation of:

- Adverse events (AEs)/ Serious adverse events (SAEs)/ Adverse events of special interest (AESIs) (e.g., thrombocytopenia, infusion-related reactions [IRRs], corneal events) with grade and frequency of occurrence
- Number and reason for dose reductions and/or dose delays
- Number and grade of (S)AEs occurring upon rechallenge
- Number and grade of AEs leading to withdrawal from study treatment
- Laboratory data and assessments including renal and liver function data, including changes in toxicity grading
- Changes from baseline in vital signs

- Changes in physical examination findings (weight only)
- Plasma belantamab mafodotin, total mAb, and cys-mcMMAF pharmacokinetic data

Upon review of the data, the study team may decide on the following options:

- Initiate Part 2 with the 2.5 mg/kg Q3W dose
- Initiate Part 2 with a reduced dose of 1.9 mg/kg Q3W dose or other adjusted dose
- Stop the study if the benefit/risk is considered unfavorable regardless of any intervention.

Decisions will be made on an assessment of the comparative safety and PK profiles between Group 1 and Group 2. Consideration will be given to whether any differences in safety profile are due to the increased severity of renal disease in Group 2. The decision for Part 2 will be made considering results not only on their own, but with consideration of the background of further increased severity of disease in subsequent participants in Part 2.

Part 2: will consist of up to 16 participants with ESRD, targeting up to 8 ESRD participants not on dialysis (Group 3) and up to 8 ESRD participants on dialysis (Group 4). These 2 groups will be enrolled in parallel. Part 2 participants will be administered the selected dose of either 2.5 mg/kg or 1.9 mg/kg (or other adjusted dose) of belantamab mafodotin on Day 1 of every 21-day cycle. In Parts 1 and 2 of the study, safety data will be monitored in stream so that any potential safety concern is identified promptly, and appropriate actions taken as warranted. These in-stream safety reviews will be conducted by the GSK study team and also in meetings with the investigators.

A treatment cycle will consist of a single belantamab mafodotin administration on Day 1 of each 21-day cycle.

Additional participants may be enrolled at the Sponsor's discretion in consultation with the Investigators, e.g. in case of premature discontinuations that result in not having PK samples up to Day 21 of Cycle 1. Collection of AEs/SAEs will continue up to 70 days after the last dose of belantamab mafodotin has been administered. Participants experiencing AEs on-study which have not returned to Grade 1 and/or baseline (i.e., if the AE was present prior to starting treatment with belantamab mafodotin) prior to discontinuation, should be followed for safety until the AE has returned to Grade 1 or to baseline, or until new (experimental) treatment is commenced, whichever comes first.

Participants are estimated to be treated for up to 15-18 months. The total duration of the study is estimated to be up to 48 months. See Section 4.1.2 and Section 4.2 for more details.

1.3. Schedule of Activities (SoA)

For details on possible home healthcare and telemedicine approaches, please refer to Appendix 10

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

Table 1 Schedule of Activities

Procedures/Study Assessments	**Screening[2]**	**Treatment Period[3]**			**End of Treatment[4]**	**Follow-up[5]**
Cycle / Visit		**Treatment cycle C1**	**Treatment cycle C2 - CX**	**Q3W Assessments (irrespective of dosing)**		
Day		**D1 (predose unless otherwise specified)**				
Window	**-28**	**±3 days**				**±7 days**
Informed Consent[1]	X					
Baseline Demographics	X					
Medical History, Disease History and Characteristics	X					
Body Weight	X	X	X		X	
Height	X					
Safety						
ECOG Performance Status	X	X	X		X	
Physical Exam	X	X	X		X	
Ocular Exam[6]	X		X	X	X	X
Vital Signs (BP, Heart Rate, Body Temperature)[7]	X	X	X		X	
12-Lead ECG (single)	X					
Echocardiogram (ECHO) – Left ventricular ejection fraction (LVEF)	X (if not done within 3 months prior to screening)					
Laboratory Assessments						
Hematology[8]	X	X	X		X	
Clinical Chemistry[8]	X	X	X		X	X

Procedures/Study Assessments	**Screening[2]**	**Treatment Period[3]**			**End of Treatment[4]**	**Follow-up[5]**
Cycle / Visit		**Treatment cycle C1**	**Treatment cycle C2 - CX**	**Q3W Assessments (irrespective of dosing)**		
Day		**D1 (predose unless otherwise specified)**				
Window	**-28**	**±3 days**				**±7 days**
Estimated Glomerular Filtration Rate (eGFR) by MDRD formula (see 1.1 for individual GFR calculation)	X	X	X		X	
Urinalysis[9] tests: routine urine dipstick for protein OR Spot urine (creatinine/albumin ratio)	X	X	X	X	X	
HbsAg, HbcAb, and Hepatitis C Antibody, Hepatitis C RNA, Hepatitis B DNA[10]	X					
Pregnancy Test for WOCBP[11]	X	X	X		X	X
Disease Evaluations: Baseline disease assessments completed within 28 days (30 days for imaging) of C1D1 do not need to be repeated on C1D1. For participants who are discontinuing IP due to disease progression (PD), the confirmation based on laboratory parameters must be performed from a different blood collection either on the same day or preferably within 14 days of the original date of the disease progression before institution of any new anti-myeloma therapy.						
β2 Microglobulin	X			X		
SPEP (Serum Protein Electrophoresis)[12]	X	X		X	X	X
24-hr Urine Protein for UPEP (Urine Protein Electrophoresis)[13]	X			X	X	
Serum M Protein Calculation	X			X		
Serum Kappa Lambda Free LC, FLC Ratio	X			X	X	X
Serum Immunofixation[14]	X			only at the time of first achieving CR, then perform every 3 weeks until suspected PD after CR or sCR		
Urine Immunofixation[14]	X			only at the time of first achieving CR, then perform every 3 weeks until suspected PD after CR or sCR		
Ca^{2+} Corrected for Albumin (serum)	X			X	X	X
IgG, IgM, IgA	X			X	X	X
IgD/IgE[15]	X			X	X	X

Procedures/Study Assessments	**Screening[2]**	**Treatment Period[3]**			**End of Treatment[4]**	**Follow-up[5]**
Cycle / Visit		**Treatment cycle C1**	**Treatment cycle C2 - CX**	**Q3W Assessments (irrespective of dosing)**		
Day		**D1 (predose unless otherwise specified)**				
Window	**-28**	**±3 days**				**±7 days**
Imaging (only required for Extramedullary Disease Assessment)[16]	X		At the start of Cycle C4, and every 4 cycles thereafter		X	X
Skeletal Survey[17]	X			Only if clinically indicated		
Response Assessment by IMWG[18]		X		X	X	X
LDH and CK Isoenzyme Assays[19]	X	X		X	X	X
Treatments Administered						
Premedication if needed		X	X			
Belantamab mafodotin[20]		X	X			
Subsequent Treatment Information[21]						X
Ocular Supportive Care for Belantamab Mafodotin						
Preservative-free Artificial Tears[22]		X	X	X		
Cooling Eye Masks		Beginning with the start of each belantamab mafodotin infusion, participants may apply cooling eye masks to their eyes for as long as tolerated, up to 4 hours.				
Biomarkers and Genetics						
Pharmacokinetics[23]		X	X		X	
Urine PK[24]		X				
Tear Sampling[25]		X				
PGx Sample (optional, requires separate consent)		X				
Soluble BCMA (Serum)[26]		X	X		X	
Immunogenicity (ADA- Anti-drug Antibodies)[27]		X	X		X	
Ongoing Participant Review						
Adverse Events/SAEs		Adverse events and SAEs will be collected throughout the study up to 70-days after the last dose of study treatment, SAEs related to study participation or related to belantamab mafodotin are collected from time of consent until end of study.				
Concomitant Medications[28]	X	Ongoing				
Subsequent anticancer therapy						X

BM= Bone marrow; BCVA = best corrected visual acuity; C1D1 = Cycle 1 Day 1, etc.; CK = creatinine kinase; CTCAE = Common Term Criteria for Adverse Events; CR = Complete response; ECG = Electrocardiogram; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; eGFR = Estimated glomerular filtration rate; EOI = End of Infusion; EOT = End of Treatment; FISH = Fluorescence-in-situ hybridization; FLC = free light chain; FSH = Follicle-stimulating hormone; HbsAg = hepatitis B surface antigen; HbcAb = hepatitis B core antibody; IHC = Immunohistochemistry; IP = Investigational product; IMWG = International Myeloma Working Group; LVEF = Left ventricular ejection fraction; PD = progressive disease; PGx = pharmacogenomics; QID = 4 times a day; SAE = serious adverse event; SC = Subcutaneous; sCR = Stringent Complete Response; SOI = Start of Infusion; SPD = Sum of the Products of the maximal perpendicular Diameters; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis

1. Informed Consent must be signed before any study-specific assessments are performed.
2. All Screening assessments must be performed within 28 days prior to the first dose (i.e., Day 1). Screening Assessments do not need to be repeated on Cycle 1 Day 1 (C1D1) unless otherwise specified. Pre-first dose disease evaluation assessments and ocular exam completed within the 28-day screening period prior to C1D1 do not need to be repeated on C1D1, unless otherwise specified.
3. Belantamab mafodotin will be administered intravenously on Day 1 (D1) of every 21-day treatment cycle (C1-CX). Three-weekly (Q3W) assessments are to occur even if participants do not receive treatment. All safety assessments should be done prior to drug administration and Q3W (off treatment) assessments can be done ±3 days unless otherwise specified. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified.
4. The End of Treatment (EOT) visit will assess any residual AEs or toxicities associated with treatment; the participants must come in within 45 days after the last dose of study medication OR before the initiation of any other anti-myeloma treatment. AEs and SAEs will be collected until up to 70 days after the last dose. Participants who at the EOT visit have an AE that is >Grade 1, or an AE that has not yet returned to pre-first dose status, will be followed post treatment until the AE has returned to Grade 1 or to pre-first treatment.
5. Post treatment discontinuation, all participants will be followed for **AEs/SAEs and Ocular events** as per this table; and for **concomitant medication** if taken for an AE/SAE until withdrawal of consent, loss to follow-up, or the end of study, whichever occurs first. For participants who discontinue study treatment for reasons other than PD, **disease evaluations, clinical chemistry and LDC/CK isoenzyme assays** will continue to be performed at **every 3 weeks (Q3W) intervals (±7 days)** until confirmed PD, death, withdrawal of consent, or end of the study, whichever occurs first.
6. Screening ocular examination to be performed within 28 days prior to first dose (i.e., Day 1). On-treatment ocular exams to be performed Q3W prior to dosing up to the 6th dose of belantamab mafodotin. After the 6th dose of belantamab mafodotin, if there are no significant (KVA Grade 2 or above) treatment-related ocular exam finding, 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 or newly developed ocular symptoms or vision changes, more frequent ophthalmologic exams as clinically indicated by the eye care specialist may be performed. Ocular exam may be performed up to 5 days prior to second dose onwards (C2-CX). If not being dosed (i.e., on a dose-hold) where possible ocular exams should be coordinated with Q3W visits. Participants with treatment-related ocular exam findings, ocular symptoms, or change in vision at the EOT visit, will be followed at least every 3 months for up to 12 months, or until resolution (to Grade 1 or baseline) whichever comes first. See Section 8.2.7 for full details of ocular exam procedures.
7. On C1D1, vital signs should be assessed within 30 minutes prior to Start of Infusion (SOI), 15 mins after SOI (±10 min), within 15 min after End of Infusion (EOI), and at 1 hour (±10 min) after EOI. On subsequent dosing days (C2D1 onwards), vital signs must be assessed at pre-dose (within 30 minutes prior to SOI) and within 15 min after EOI, and as clinically indicated. On days when vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated. See Section 8.2.3 for details.
8. Refer to Table 22 for a comprehensive list of lab tests to be collected for all participants and analyzed locally. Results must be evaluated prior to treatment administration. If labs are completed within 72 hours prior to the first dose, these assessments do not need be repeated on C1D1. See Section 8.2.6 for details.
9. 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 and ≥2+ during study treatment and/or Q3W or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab. If local testing is not available, then central testing will be performed.
10. Hepatitis B virus (HBV)/Hepatitis C virus (HCV) testing to be performed at the local lab. Hepatitis C RNA testing will be done to determine a participant's eligibility. If HCV is positive. HBV DNA should be performed if positive for serology for Hepatitis B. Results must be received prior to dosing. For additional procedures during Screening and upon enrollment for participants who have positive serology for Hepatitis B and/or Hepatitis C, please refer to Table 2 and Table 3. See Section 5 Study Population for details.
11. For questionable cases, FSH and estradiol assessment should be performed at local lab. A negative serum pregnancy test must be obtained within 72 hours prior to C1D1. Other pregnancy tests may be either serum or urine based. Final pregnancy test (serum or urine) must be performed at the EOT Visit. Follow up pregnancy assessment by telephone for WOCBP only should be performed monthly for 4 months after the last dose of belantamab mafodotin and follow up for 6 months after start of treatment for pregnancies in female partners of male participants (Section 10.4).
12. Performed locally where possible otherwise centrally. SPEP to be performed every 3 weeks (Q3W).
13. Performed locally where possible otherwise centrally. 24-hour urine UPEP to be performed every 3 weeks (Q3W).

14. Performed locally where possible otherwise centrally. Post C1D1 Immunofixation (urine and serum) only to be performed at the time of suspected CR, then perform every 3 weeks until suspected PD after CR or sCR.
15. Only in participants with immunoglobulin D (IgD)/immunoglobulin E (IgE) myeloma (local lab, if not available can be performed centrally).
16. Imaging by either CT, MRI, or PET/CT per local guidance. Pretreatment imaging may be performed up to 30 days prior to C1D1. On treatment imaging to be performed at C4, and every 4 cycles within the first 12 months, thereafter only if clinically indicated. Needs to be performed by the same method throughout the study as was done pre-first treatment (i.e., if CT/PET scan was used as pre-first treatment, participant needs to be followed by CT/PET scans). Selected target lesion needs to be measured and followed over time. 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 tumor size will be determined by the sum of the products of the maximal perpendicular diameters of measured lesions (SPD). 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 participant withdrew from study treatment. A window of ±7 days is acceptable for imaging.
17. Imaging of bones for lytic lesions by method aligned with institutional guidance (X-ray, CT or MRI). Survey results within 30 days prior to C1D1 date are acceptable.
18. Disease response assessments: Response assessment must be conducted based on standard disease laboratory tests performed locally. Response evaluation will be performed according to the IMWG Uniform Response Criteria for Multiple Myeloma [Kumar, 2016].
    21. CK and LDH to be analyzed locally. If unexplained elevation in CK and LDH (≥3xULN) are observed on study, isoenzyme levels should be measured in local lab. If not possible locally, sample for isoenzyme levels should be sent for central testing. See Table 5 ("Potential for other laboratory abnormalities") for more details.20. Study drug administration ±3 day window only. Subsequent myeloma treatments should be recorded if available within the normal EOT follow-up.
22. Prophylactic preservative-free artificial tears to be administered in each eye at least 4 and up to 8 times PRN daily beginning on Cycle 1 Day 1 until End of Treatment.
23. Sampling times for PK are located in Table 14 8.5. An sBCMA sample must be obtained with each sample for PK. Collect 1 PK sample at EOT visit. Collect samples according to the schedule. If dosing is delayed at Cycle 2 or Cycle 4, the sample collected will be designated C1D22 or C3D22, as appropriate, and the C2D1/C4D1 samples will be collected prior to the dose when administered.
24. Urine PK samples for analysis of cys-mcMMAF will be collected in Part 1 only as in Table 15. Sampling times for urine are located in Section 8.5.
25. Tear collection will occur immediately before infusion, within 30 minutes after EOI, and at approximately 24 hours after EOI. The tear sample collection time points may be updated or discontinued based on emerging data. Tear samples will be analyzed centrally. Refer to Section 8.5.1.3 Tear Fluid.
26. Serum soluble BMCA (sBCMA) samples will be collected according to Table 14 in Section 8.5. A sBCMA sample must be obtained with each sample for PK. Samples collected according to the schedule. If dosing is delayed at Cycle 2 or Cycle 4, the sample collected will be designated C1D22 or C3D22, as appropriate, and the C2D1/C4D1 samples will be collected prior to the dose when administered. sBCMA sample to be collected at End of Treatment. sBCMA will be analyzed at central laboratory.
27. Serum samples for ADA to be collected (Predose: C1, C2, C4, C6, C9, C12, and every 6 cycles thereafter (C18, C24, etc.) until EOT and analyzed at a central laboratory. A serum sample for ADA should be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.
28. Once the participant has discontinued treatment, only concomitant medications related to AEs or SAEs will be collected.

Table 2 Additional procedures for Participants with positive serology for HBV

HBV Study Assessments	During Screening /Prior to starting treatment	During Treatment	EOT	Notes
HBV related Liver Imaging[3]	X[1]	X[1]	X[1]	1. Liver imaging (specific test per standard of care at local institution) in **HBsAg+ participants** to rule-out/identify cirrhosis, focal hepatic lesions, and/or biliary abnormalities at baseline. Repeat imaging at one year after starting treatment if still on treatment and twice yearly thereafter as long as participant remains on study treatment or as clinically indicated. 2. HBV-DNA testing prior to the start of belantamab mafodotin and subsequently every 3 months, or if LFT elevations requiring increased monitoring or stopping criteria occurs, or for any clinical suspicion of hepatitis reactivation. 3. For **HBsAg+ participants**, appropriate antiviral treatment per local guidance (e.g. tenofovir or entecavir) is started before starting belantamab mafodotin, continues through to completion of belantamab mafodotin therapy and should not be stopped unless advised by local hepatology or virology services.
HBV-DNA testing	X[2]	X[2]	X[2]	
Prevention of HBV reactivation	X[3]	X[3]	X[3]	

DNA = Deoxyribonucleic acid; HBsAg = Hepatitis B surface antigen; HBV = Hepatitis B Virus; LFT = liver function test
Note: The procedures listed in this table apply ONLY to participants in screening and who have been enrolled and who have positive serology for Hepatitis B; all procedures must be done as needed in addition to the required procedures for all participants detailed in Table 1. Samples to be analyzed by local laboratory, if not possible then central laboratory analysis may be conducted.
Please refer to Section 6.6.4 for management of participants with positive serology for HBV.

Table 3 Additional schedule of procedures: HCV+ Participants

HCV Study Assessments	During Screening /Prior to starting treatment	During Treatment	Post Treatment	Notes
HCV-RNA testing	X[1]	X[1]		1. HCV- RNA testing prior to the start of belantamab mafodotin and subsequently every 3 months, or if LFT elevations requiring increased monitoring or stopping criteria occurs, or for any clinical suspicion of hepatitis reactivation. 2. Antiviral treatment should be given to participants with HCV before enrolment using an 8 (to 12) week antiviral treatment course with curative intent per local guidance. Hep C RNA should be negative at 4 weeks washout period post anti-HCV therapy prior to enrolment.
Treatment of active HCV	X[2]			

HCV= Hepatitis C virus; LFT = liver function test

Note: The procedures listed in this table apply ONLY to participants in screening and who have been enrolled and who have a history of Hepatitis C; all procedures must be done as needed in addition to the required procedures for all participants detailed in Table 1. Samples to be analyzed by local laboratory, if not possible then central laboratory analysis may be conducted.

Table 4 Bone Marrow Aspirate/Biopsy Collection (for all participants)

Timepoint	BM aspirate or Biopsy for disease assessment[b]	BM aspirate for FISH testing[a,e]	BM biopsy for BCMA expression and biomarker research[b,f]	Optional BM and/or tissue sample at PD for BCMA expression and biomarker research[b,g]
Screening	X[c]	X	X	
Suspected CR/sCR	X[d]			
Suspected PD, only if PD is not otherwise evident	X[c]			
At PD				X

a. Performed at a local laboratory (FISH testing can be performed centrally if not possible locally).
b. Performed at a central laboratory.
c. For Disease assessment (%plasma cells) at Screening and at Suspected PD: BM aspirate and/or biopsy (preferred)
d. For participants achieving a CR, a bone marrow core biopsy is required to confirm sCR by IHC for absence of clonal cells. Only 1 bone marrow procedure required for CR and sCR assessment (testing can be performed centrally if not possible locally).
e. FISH testing to be performed locally at least for: t(4;14), t(14;16), amp(1q), del(1p) and del(17p13). If participant is known to have tested positive for t(4;14) or t(14;16) on previous tests, FISH for those translocations does not need to be repeated and results from previous tests are acceptable. For amp(1q), del(1p) and del(17p13), FISH results from samples taken within 60 days prior to first dose are acceptable. If testing cannot be performed at a local lab, the samples can be sent to the central lab. FISH results are required prior to enrollment.
f. BM biopsy or aspirate per institutional practice (biopsy is the preferred sample). Any remaining biopsy and/or aspirate sample may be used for biomarker research (which may include immune cell characterization and/or profiling and/or DNA/RNA analyses).
g. Optional BM core biopsy and/or aspirate and/or tissue sample (if from extramedullary tumor) for BCMA expression and biomarker research may be collected at PD to evaluate mechanisms of response/resistance. Separate consent required for this optional sample at PD.

2. INTRODUCTION

2.1. Study Rationale

Renal impairment is a major complication of multiple myeloma (MM) and the majority of MM patients either are at risk or already have renal dysfunction at initial diagnosis [Rajkumar, 2016]. Patients with renally impaired MM require anti-tumor therapies adapted to reduced renal function, either by dose modifications or through selection of anti-myeloma drugs whose pharmacokinetic (PK) behavior is unaffected by the reduced renal function. Renal impairment can reduce the rate of elimination of drugs primarily eliminated in urine but can also adversely affect the elimination of drugs that are primarily non-renally cleared by impacting some pathways of hepatic metabolism and transport mechanism [Miners, 2017]. It is thus important to evaluate the potential impact of increased level of renal impairment on the PK and safety of MM drugs that are renally or non-renally cleared to provide adequate dosing guidance.

Belantamab mafodotin is an antibody-drug conjugate (ADC) consisting of an afucosylated humanized anti-BCMA mAb conjugated to the intracellular microtubule disruptor monomethyl auristatin-F (MMAF). In general, monoclonal antibody drugs are not renally excreted; however, following intravenous (IV) administration, belantamab mafodotin is catabolized leading to the release of cys-mcMMAF, the small molecule component of belantamab mafodotin is 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). While it is not anticipated that renal impairment would impact the PK of belantamab mafodotin, it is possible that cys-mcMMAF elimination may be affected.

To date, MM patients with severe renal impairment (eGFR/creatinine clearance [CrCl] <30 mL/min/1.73 m^2) have been excluded in belantamab mafodotin clinical trials. Therefore, the efficacy, safety and PK of belantamab mafodotin (including that of cys-mcMMAF) have not been evaluated in participants with severe renal impairment. In the Phase I/II study BMA117159 [NCT02064387], the CrCl screening requirement was ≥60 mL/min in Part 1 and ≥50 mL/min in Part 2. In the ongoing pivotal Phase II Study 205678 (with belantamab mafodotin monotherapy in relapsed MM participants; [NCT03525678]) and subsequent belantamab mafodotin combination studies, the eGFR cut-off is ≥30 and ≥40 mL/min/1.73 m^2, respectively. In addition, results from a population PK analysis using data from BMA117159 and Study 205678 indicated that mild/moderate renal impairment was not a significant predictor of belantamab mafodotin or cys-mcMMAF clearance (see Section 2.2.1.3). Therefore, these groups of renal impairment are not included in the present study.

The current study aims to determine the relationship, if any, between renal function parameters and safety/PK parameters of belantamab mafodotin (ADC and total mAb) and cys-mcMMAF in participants with MM.

To assess the effects of renal impairment on the pharmacokinetics of belantamab mafodotin, PK parameters will be assessed in relapsed/refractory multiple myeloma

(RRMM) participants with normal or mild impairment renal functions (Group 1) and various levels of impaired renal function (Groups 2-4). In a population PK analysis, data did not identify mild renal impairment as a significant covariate affecting the pharmacokinetics of belantamab mafodotin when compared to normal participants. This population was also the largest subgroup with renal function status to be treated with belantamab mafodotin in previous studies. These 2 factors justify the use of normal /mild renal impairment grouping as the appropriate comparator group for the other levels of impaired renal function. The population PK data demonstrate that belantamab mafodotin pharmacokinetics are influenced by participant characteristics, including sBCMA, immunoglobulin G (IgG), albumin, and body weight. Therefore, Group 1 participant albumin and body weight values should closely match those in Group 2.

To evaluate safety and tolerability of belantamab mafodotin and cys-mcMMAF, adverse events, including all observed corneal events on-study, will be documented in all 4 Groups.

To better comprehend the mechanism behind the corneal findings that have been previously observed following administration of belantamab mafodotin, tears will be collected in Part 1 only of this study to evaluate the presence and, if technically feasible, the concentrations, of belantamab mafodotin and free cys-mcMMAF in tears. Concurrently, urine samples will be collected in these participants to measure cys-mcMMAF.

The overall design of this renal impairment study is in accordance with FDA guidance [FDA DHHS, 2020] and the results of this 2-part study are expected to provide guidance for appropriate labelling of belantamab mafodotin in RRMM participants with various degrees of renal impairment

2.2. Background

MM is an incurable disease that accounts for 1% of all cancers and for 10% of all hematologic malignancies. Worldwide, approximately 176,000 new cases are diagnosed annually [Levey, 2021], and an estimated 35,000 new cases and over 12,000 deaths will occur in the U.S. in 2021 [Siegal, 2018].

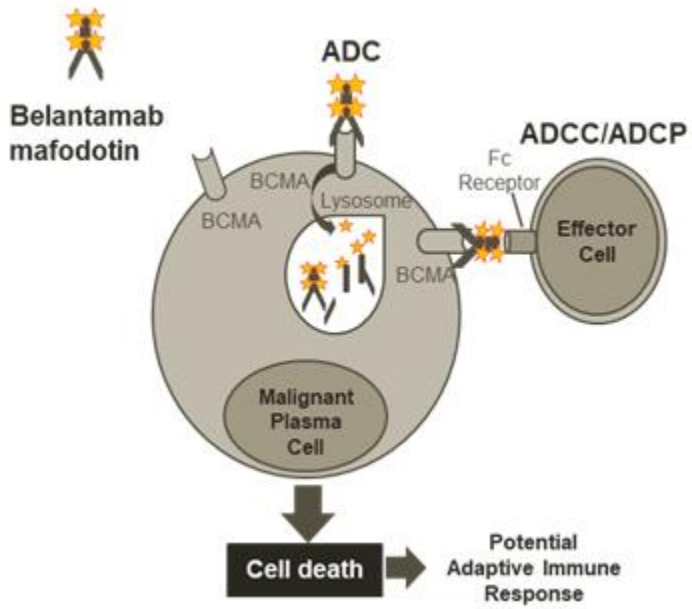
Belantamab mafodotin is approved as monotherapy (in United States [US] and European Union [EU]) for treatment of RRMM [Lonial, 2020; for exact labelling indication see belantamab mafodotin USPI, 2020; belantamab mafodotin SmPC, 2020]. Data from clinical trials supported language in the approved prescribing information indicating that no dose reductions are recommended for participants with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73m^2. However, currently there is no data to support or guide dosing in participants with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m^2 not on dialysis or requiring dialysis. With severe renal impairment being a frequent complication in participants with RRMM, characterizing the PK profile and establishing a safe dosing regimen for participants with RRMM and severe renal impairment is important. The present study is designed to answer this clinically relevant question.

Belantamab mafodotin is an IgG molecule conjugated with a small molecule cys-mcMMAF with a high molecular weight (approximately 152 kDa). Molecules of this size are essentially excluded from glomerular filtration; thus, changes to renal function are unlikely to affect the elimination of belantamab mafodotin. Cys-mcMMAF is the small molecule that is released from belantamab mafodotin during deconjugation or intracellular proteolysis. Pre-clinical and clinical data indicate limited renal elimination of cys-mcMMAF. Following IV dosing of ^{3}H-cys-mcMMAF to rats, radioactivity was excreted in feces CCI and urine CCI [GSK2857916 Investigator's Brochure (IB), GlaxoSmithKline Document NumberRPS-CLIN-004867 09, 2021]. In the phase I, dose escalation Study BMA117159, urine was collected for a 24 h time period during cycle 2 and cys-mcMMAF was detected.

While no clinically significant differences in the pharmacokinetics of belantamab mafodotin were observed based on normal to mild or moderate renal impairment (eGFR $\geq$ 30 mL/min/1.73m^2) and no clinically meaningful increase in exposure or toxicity is expected for participants with more severe renal impairment, this study is being conducted to confirm these results in this population.

Belantamab mafodotin binds to BCMA and kills MM cells via a multi-modal mechanism including delivery of cytotoxic MMAF (cysteine maleimidocaproyl MMAF [cys-mcMMAF]) to BCMA-expressing MM cells, thereby inducing apoptosis, enhancing antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, and inducing immunogenic cell death (Figure 2) [Tai, 2014; Montes, 2019]. Exposure of dendritic cells to tumor cells undergoing immunogenic cell death is expected to result in an antigen-specific T-cell response, enhancing the immunogenic response against MM.

Figure 2 Belantamab Mafodotin MoA



ADCC/ADCP=antibody-dependent cell-mediated cytotoxicity/antibody-dependent cellular phagocytosis
Abbreviations: ADC=antibody drug conjugate; ADCC/ADCP=antibody-dependent cellular cytotoxicity/antibody-dependent cellular phagocytosis; BCMA=B-cell maturation antigen.

2.2.1. Clinical Experience

Study BMA117159/DREAMM-1, the first time in human study of belantamab mafodotin as monotherapy [Trudel, 2019], has been completed. The study established that a dose of belantamab mafodotin 3.4 mg/kg administered IV on Day 1 of each 21-day Q3W treatment cycle was an appropriate maximum dose to be continued in Phase II of the study. DREAMM-1 has been completed and the final study report has been published [GSK Document Number 2020N435785_00, 2020].

Study 205678/DREAMM-2 is the pivotal Phase II monotherapy study, evaluating the safety and efficacy of two dose levels of belantamab mafodotin in participants with 4L+RRMM [Lonial, 2020]. The efficacy and safety of two doses of belantamab mafodotin monotherapy in participants with RRMM refractory to proteasome inhibitors and, immunomodulatory drugs and in those who failed anti-CD38 antibody treatment. Based on the results of this study, the 2.5 mg/kg Q3W dose of belantamab mafodotin in the control arm is the approved monotherapy dose (in US and EU) for treatment of RRMM [Lonial, 2020; belantamab mafodotin USPI, 2020; belantamab mafodotin SmPC, 2020]. The primary analysis has been reported; however, the study is considered ongoing.

2.2.1.1. 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 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. Two additional analyses were conducted and were consistent with the primary analysis data. Both dose levels, 2.5 and 3.4 mg/kg, were shown to have a positive benefit/risk profile [Li, 2017; Lonial, 2020].

As of the cut-off date of 31 January 2020, the study met its primary endpoint for ORR in both the 2.5 mg/kg [ORR 32% (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)]

2.2.1.2. Safety

The safety of belantamab mafodotin as a single agent was evaluated in DREAMM-2. Participants received belantamab mafodotin at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Among these participants, 22% were exposed for 6 months or longer.

Serious adverse events (SAEs) occurred in 40% of participants who received belantamab mafodotin. SAEs in >3% of participants included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal AEs occurred in 3.2% of participants, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

Permanent discontinuation due to an AE occurred in 8% of participants who received belantamab mafodotin; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation.

Dosage interruptions due to an AE occurred in 54% of participants who received belantamab mafodotin. AEs which required a dosage interruption in >3% of participants included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%).

Dose reductions due to an AE occurred in 29% of participants. AEs which required a dose reduction in >3% of participants included keratopathy (23%) and thrombocytopenia (5%).

The most common AEs (≥20%) were keratopathy, decreased visual acuity, nausea, blurred vision, pyrexia, infusion-related reactions, and fatigue. The most common Grade 3 or 4 (≥5%) laboratory abnormalities were lymphocytes decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyl transferase increased.

Adverse Events of Special Interest

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

Corneal Events

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

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 Grades 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.

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).

2.2.1.3. Pharmacokinetics and Pharmacodynamics in Humans

The pharmacokinetics and pharmacodynamics of belantamab mafodotin (antibody-drug conjugate, including complex with soluble BCMA (sBCMA), 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 [GSK2857916 IB, GlaxoSmithKline Document Number RPS-CLIN-004867 09, 2021]. There was limited accumulation (less than 2-fold) of belantamab mafodotin or cys-mcMMAF during subsequent cycles.

Belantamab mafodotin pharmacokinetics were well described by a linear, two-compartment population model, with a time-varying decrease in clearance in a population

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

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

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

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

Exposure-response analyses performed for Study 205678 and/or Study BMA117159 found that ocular safety endpoints were most strongly associated with belantamab mafodotin exposure, while efficacy endpoints had a weaker association with belantamab mafodotin exposure. Both safety and efficacy endpoints were associated with participant 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) analysis demonstrated that belantamab mafodotin or cys-mcMMAF did not have a significant effect on cardiac repolarization.

Additional information related to belantamab clinical PK, PD, and exposure-response relationships can be found in the IB [GSK2857916 IB, GlaxoSmithKline Document Number RPS-CLIN-004867 09, 2021].

2.3. Benefit/Risk Assessment

In accordance with the International Conference on Harmonisation (ICH), this study has been designed to minimize risk and maximize benefit to study participants. Table 5 lists the benefit/risk assessment for this study.

Additional information about the known and expected benefits and risks, detailed information of nonclinical and clinical findings information regarding warnings, precautions, contraindications, adverse events, and other pertinent information that may impact participant eligibility is provided in the belantamab mafodotin IB [GlaxoSmithKline Document Number RPS-CLIN-004867 09, 2021].

2.3.1. Risk Assessment

The following section outlines the risk assessment and mitigation strategy for belantamab mafodotin in this protocol.

Table 5 Summary of Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Thrombocytopenia	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.	Routine hematologic monitoring as outlined in the SoA. Supportive therapy per local medical practice (*e.g.* platelet transfusion). Recommendations for dose reduction and treatment discontinuation criteria are detailed in Section 6.6 and Section 7.1.
Other Hematological Effects	Neutropenic events, including febrile neutropenia have been observed 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.	Routine hematologic monitoring as outlined in the SoA. Supportive therapy per local medical practice (*e.g.* growth factors). Prophylactic antibiotics, per local institutional guidance, in participants with Grade 3-4 neutropenia. Immediate hospitalization of participants with febrile neutropenia. Recommendations for dose reduction and treatment discontinuation criteria are detailed in Section 6.6 and Section 7.1.
Pulmonary **– Pneumonitis**	Nonclinical safety experiments have demonstrated the presence of progressive microscopic changes in the lungs (prominent alveolar macrophages associated with eosinophilic material; mixed perivascular inflammation) in rats, at all doses tested. Cases of pneumonitis, including fatal events, have been observed with belantamab mafodotin although a causal association has not been established.	Monitoring for clinical signs and symptoms related to pulmonary toxicity. If a participant experiences new or worsening pulmonary symptoms, (e.g., cough, dyspnea) without obvious etiology, appropriate diagnostic evaluation should be performed (see protocol Section 8.3) 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 in cases of suspected pneumonitis as described in Section 7.1.
Immunosuppression	In nonclinical studies, belantamab mafodotin has been associated with decrease in immunoglobulins in monkeys, at all doses. An increase in	Participants with an active infection excluded.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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.	Monitoring for infections and immediate treatment according to standard practice.
Keratopathy (changes to the corneal epithelium, potentially resulting in vision changes)	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 keratopathy (changes in the corneal epithelium upon examination), dry eyes, blurred vision 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 of the corneal epithelium and visual acuity as outlined in the SoA. 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. Recommendations for dose delays / reductions and treatment stopping guidance are provided in Section 6.6 and Section 7.1.
Embryo-Fetal Toxicity	Nonclinical reproductive studies with belantamab mafodotin have not been conducted. Embryo-foetal toxicity is expected due to the cytotoxic component, cys-mcMMAF via nonspecific uptake and/or BCMA-mediated toxicity (due to reports of BCMA expression in human placental cells [Langat, 2008]). Use of belantamab mafodotin in pregnant women may cause fetal harm.	Pregnancy testing outlined in the SoA Contraception requirements detailed in Section 5.1 and Section 10.4.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Infusion-related Reactions (IRRs)	IRRs were reported in participants treated with belantamab mafodotin. Most IRRs were Grade 1 to 2 and were manageable with treatment.	Close monitoring for signs of IRR. Consider premedication for IRR in participants at risk. If an IRR occurs, follow the guidance in Section 7.1.3.
Impaired Male and Female Fertility	In animal studies, belantamab mafodotin treatment has resulted in testicular toxicity and adverse effects on spermatogenesis. Reversibility of testicular and ovarian toxicity is unknown at this time. Ovarian toxicity (luteinized non-ovulatory follicles) was observed in a 3-week rat study (weekly dosing) and was not observed following 12 weeks off dose. In a 13-week rat study where drug was administered once every 3 weeks, these changes were not observed.	Men who may wish to father children in the future will be advised to have sperm samples frozen and stored prior to belantamab mafodotin treatment. WOCBP 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 Section 10.4.
Nephrotoxicity	Nonclinical safety experiments have demonstrated primary glomerular injury and tubular degeneration/regeneration (in rat and monkey). The morphologic changes were accompanied by large molecular weight proteinuria (albuminuria) and enzymuria. Single cell necrosis of the kidney and bladder urothelium was also noted in the chronic study. The renal changes were dose-dependent and reversible. Severe tubular degeneration/regeneration and marked glomerulonephritis as a result of immune complex disease associated with 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 studies and named participant programs with belantamab mafodotin.	Kidney function monitoring including albumin/creatinine ratio. Education of participants on the need of maintaining adequate urinary output. Dose modification guidelines for increased serum creatinine and urinary albumin/creatinine ratio are outlined in Section 6.6 and Section 7.1.
Potential for Other Laboratory Abnormalities	Increased magnitude of aspartate aminotransferase (AST) relative to alanine aminotransferase (ALT) consistent with increased skeletal troponin I was observed in the single dose monkey study. Increased skeletal troponin I and/or creatine kinase and	Monitoring of laboratory parameters as outlined in the SoA. Participants with significant laboratory elevations (≥ x3 ULN) should, where possible, have a sample sent for central testing of CK and LDH isoenzyme levels.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	aldolase was observed in the rat 3-week study. Cases of elevated AST, lactic dehydrogenase (LDH) and creatine kinase (CK) alone or concomitant with no clear clinical correlate have been observed in clinical studies.	
Risks from Study Procedures		
Bone Marrow Aspiration/biopsy	Pain, infection, bleeding may occur after the procedure.	Participants will be treated according to institutional practice.
Incidental Findings During Image Acquisition	During the acquisition of imaging data (e.g., MRI, PET-CT), non-MM disease or clinically relevant abnormalities could be found by the radiographer performing the exams.	Copies of all medical images that include non-disease, clinically relevant abnormalities will be shared with the site for storage

Refer to the belantamab mafodotin IB for further information.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To describe the effects of renal impairment on the pharmacokinetics of belantamab mafodotin in participants with RRMM and with severe renal impairment, ESRD (not on dialysis) or ESRD (on dialysis) compared to participants with normal and mildly impaired renal function	• Plasma belantamab mafodotin, total mAb, and cys-mcMMAF pharmacokinetic parameters, as data permits;
Secondary	
• To evaluate safety and tolerability using parameters, including adverse events, vital signs, and clinical laboratory assessments in participants with RRMM who have normal or impaired renal functions	• Monitoring and incidence of adverse events, toxicity grading of clinical laboratory tests, and physical examinations, change from baseline in vital signs (blood pressure and heart rate),
Exploratory	
• To explore any relationship between PK and renal function parameters	• Relationship between belantamab mafodotin and cys-mcMMAF PK parameters (e.g., maximum observed concentration [Cmax], area under the curve [AUC]) and baseline renal function parameters (e.g., eGFR)
• To evaluate the recovery of cys-mcMMAF in urine in Part 1 only	• Urine recovery over 24 hours at several time points following the first dose
• To assess ADAs against belantamab mafodotin	• Incidence and titers of ADAs against belantamab mafodotin
• To evaluate the clinical measures of efficacy of belantamab mafodotin in participants with RRMM who have normal or impaired renal function	• ORR (Overall Response Rate) • CBR (Clinical Benefit Rate) • DoR (Duration of Response) • TTR (Time to Response) • TTP (Time to Progression)
• To explore the relationship between biological characteristics and clinical response	• Tumor and blood based analyses of DNA, RNA and protein changes including but not limited to baseline and on-treatment sBCMA and BCMA expression on myeloma cells
• To evaluate the presence/concentrations of belantamab mafodotin and free cys-mcMMAF in tear fluid in participants with normal/mild or severely impaired renal function (Part 1 only) and explore relationship between tear fluid and plasma concentration	• Presence/concentrations of belantamab mafodotin and cys-mcMMAF in tear fluid at baseline and on treatment, as data permits • Relationship between tear fluid and plasma concentrations of belantamab mafodotin and cys-mcMMAF, as data permits

Note: ESRD is an end-stage renal disease where participants are either not undergoing or require hemodialysis.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase I study to assess the PK, safety, and tolerability of belantamab mafodotin monotherapy in participants with RRMM who have had at least 3 lines of prior treatment (or at least 2 lines of prior treatment if ineligible for autologous stem cell transplantation) and have either normal or impaired renal functions. Renal impairment will be classified based on the iGFR using the MDRD formula and individual's body surface area according to FDA-defined categories of severe, ESRD (not on dialysis), or ESRD (on dialysis) [FDA DHHS, 2020] (Section 1.1).

4.1.1. Number of Participants

Approximately 100 participants are expected to be screened in this study to ensure a total of 32 (up to 36) participants will be enrolled.

4.1.2. Participant Recruitment and Groups

All participants will undergo screening assessments within 28 days of the initial dosing to determine their eligibility for enrollment into the study.

The study is composed of 2 parts and will enroll up to 36 participants into 4 groups as summarized in Table 6 Participants will be enrolled into each group according to their iGFR levels (as defined by MDRD formula and BSA).

- Part 1 will enroll participants with normal or mildly impaired renal function (Group 1; n=up to 12) 8 of whom will be matched for baseline weight and baseline albumin levels to the participants with severe renal impairment (Group 2; n=8).
- Part 2 will enroll up to 16 participants with ESRD in 2 groups, targeting up to 8 in each group: those who are not on hemodialysis (Group 3; n= up to 8), and those who are on hemodialysis (Group 4; n= up to 8).
- As shown in the Study Schema (Section 1.2), the study will proceed from Part 1 to Part 2 based on the review of all available PK, safety and tolerability data from all participants enrolled in Part 1, Cycle 1 (Groups 1 and 2).

  For a more detailed description of the enrolment process, please refer to Section 1.2 Schema.

Table 6 Description of Study Groups

Part	Group	Renal function group	iGFR* (mL/min)	Number of participants
1	1	Normal/mildly impaired renal function	≥60	8 (up to 12)
	2	Severe renal impairment	15-29	8
2	3	ESRD	<15 (not on dialysis)	Up to 8 (not on dialysis)
	4	ESRD	<15 (on hemodialysis)	Up to 8 (on dialysis)

Note: ESRD = end-stage renal disease (iGFR <15 mL/min) where participants are neither undergoing or require hemodialysis; iGFR: individual glomerular filtration rate [FDA DHHS, 2020].
*See Section 1.1 and Appendix 12 for iGFR formula.

In accordance with the 2020 FDA draft Guidance for Industry [FDA DHHS, 2020], the renal function groups should be comparable with respect to factors known to affect the drug's PK. The population PK analysis performed based on data from the monotherapy studies DREAMM-1 and DREAMM-2 identified four main covariates influencing the PK of belantamab mafodotin and cys-mcMMAF. These were disease-related covariates (i.e., baseline sBCMA, baseline IgG, and baseline albumin) in addition to baseline body weight. Typical participant simulations performed with the population PK model to understand the impact of covariate on exposure variables over the observed covariate range showed that body weight and baseline albumin were the most impactful for cys-mcMMAF exposure (Cmax and Cavg), with a reduced impact of baseline sBCMA and baseline IgG. Therefore, the control group with normal or mildly impaired renal function (Group 1) will be matched to the severe renal impairment group (Group 2) with respect to baseline body weight (±20%) and baseline albumin levels (±10%).

The study (in both parts) will include a Screening Phase, a Treatment Phase, and a safety Follow-up Phase. The safety Follow-up phase will be at least 70 days after the last dose of belantamab mafodotin. The overall study duration is expected to be up to 48 months. Participants are estimated to be treated for up to 15-18 months.

Following their screening assessments, enrolled participants will be allocated to 1 of the 4 predefined groups based on their renal function classification (Table 6) as defined in the FDA draft guidance for industry [FDA DHHS, 2020].

In addition, if participants prematurely discontinue the study prior to the end of Cycle 1, additional participants may be enrolled at Sponsor's discretion.

4.1.3. Study Intervention and Duration

4.1.3.1. Study Intervention

Belantamab mafodotin will be administered IV over approximately 30 minutes at the study-recommended monotherapy dose of 2.5 mg/kg in Part 1 on Day 1 (D1) of every 21-day cycle until confirmed disease progression, death, unacceptable toxicity, withdrawal of consent, or end of study, whichever occurs first. The belantamab mafodotin dose in Part 2 will depend on the outcome of Part 1. Any dose level below 1.9 mg/kg a priori is not planned to be studied; yet, if belantamab mafodotin exposure similar to that seen at a

1.9 mg/kg dose can be achieved with a lower dose, this lower dose may be recommended for Part 2, as appropriate.

The starting dose to be administered will be based on actual body weight calculated at baseline (2.5 mg/kg). However, if the change in body weight is greater than 10%, the dose will be re-calculated based on the actual body weight at the time of dosing. The dose may be reduced to address toxicity as described in Section 6.6.2.

4.1.3.2. Study Treatment Discontinuation

Participants will be treated until PD, unacceptable toxicity, withdrawal of consent, withdrawal due to adverse event (AE), lost to follow-up, death, end of study whichever occurs first. Further details can be found in Section 7.1

4.2. Justification for Dose

A dose of 2.5 mg/kg is the dose proposed for Part 1 of the study. This is also the regulatory agency approved dose for belantamab mafodotin monotherapy in RRMM when administered on a Q3W schedule for participants with normal to moderately impaired renal function [USPI, 2020].

While participants with moderate renal impairment have also received 3.4 mg/kg in Study 205678 with manageable toxicities, the starting dose of 2.5 mg/kg is considered adequate for Part 1 of the current study.

As shown on the study design Schema 1 (Section 1.2), the dose in Part 2 will be decided by PK, safety and tolerability data generated in Part 1 of the study. Dose levels other than 2.5 mg/kg or 1.9 mg/kg Q3W dose a priori are not planned; however, if belantamab mafodotin exposure similar to that seen at these doses can be achieved with another dose, this other dose may be recommended for Part 2, as appropriate.

4.3. End of Study Definition

Following the final analysis (see Table 18) the study will move into the PACT phase and the clinical study database will be closed to new data. Participants who are receiving belantamab mafodotin may continue to receive belantamab mafodotin if they are gaining clinical benefit as assessed by the investigator, or can choose to discontinue belantamab mafodotin.

The end of study is defined when the last patient had their last visit (last subject last dose plus 70 day SAE reporting period). GSK retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) including those that lead to study discontinuation and pre-specified ocular events that are ongoing at the time of at the end of the study. All participants will be monitored and receive follow-up care in accordance with standard local clinical practice.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment 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. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in the study protocol.
2. Male and/or female must be 18 years of age or older, at the time of signing the informed consent.

   In Republic of Korea, participants must be 19 years of age or older at the time of signing informed consent.

3. ECOG performance status 0-2. (Section 10.7).
4. Histologically or cytologically confirmed diagnosis of MM, as defined in IMWG criteria [Kumar, 2016], ***and***
   - Has undergone autologous stem cell transplant (SCT) or is considered transplant-ineligible, ***and***
   - Has failed at least 2 prior lines of anti-myeloma treatments, including an immunomodulatory drug (e.g., lenalidomide or pomalidomide) and a proteasome inhibitor (e.g., bortezomib, ixazomib or carfilzomib).

     In Republic of Korea, patients should also have relapsed or refractory disease after treatment with an anti-CD38 antibody, if accessible to patients, or other suitable local standard of care

5. Has measurable disease with at least one of the following:
   - Serum M-protein ≥0.5 g/dL (≥5 g/L)
   - Urine M-protein ≥200 mg/24 h
   - 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:
   - Transplant was >100 days prior to study enrollment
   - No active infection(s)
   - Participant meets the remainder of the eligibility criteria outlined in this protocol

7. Adequate organ system functions as defined by the laboratory assessments listed below.

Table 7 Organ System Function

Organ System and Laboratory Tests	Laboratory Values
Hematologic	
Absolute neutrophil count[1]	≥1.0 × 10^9/L
Hemoglobin	≥7.0 g/dL (or 4.9 mmol/L)
Platelets	≥50 × 10^9/L
Hepatic	
Total bilirubin	≤1.5 × ULN; (Isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
Alanine aminotransferase	≤2.5 × ULN
Renal	
iGFR[2] Group 1: Normal/mildly impaired Group 2: Severe Group 3: ESRD (not on dialysis) Group 4: ESRD (on dialysis)	≥60 mL/min 15-29 mL/min <15 mL/min <15 mL/min
Cardiac	
LVEF by ECHO[3]	≥40%

NOTE: Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may re-test the participant and the subsequent within range screening result may be used to confirm eligibility.

1. Without growth factor support for the past 14 days, excluding erythropoietin.
2. As calculated by MDRD formula and individual BSA (Section 1.1). Participants must have stable renal disease without evidence of renal progressive disease (stable renal disease is defined as no significant change, such as a stable eGFR, for 12 weeks prior to study entry) [FDA DHHS, 2020].
3. It is acceptable to use an existing ECHO result if performed within three months of screening. For participants with 40% or lower LVEF (per institutional standards), consider referring to cardiology per local standards of care.

8. Main additional inclusion criteria in Group 1 (matched control participants): Matched to at least one severely renal impaired participant by baseline body weight (±20%) and baseline albumin levels (±10%).

9. Female Participants:

   Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

   - Is not a 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 (Section

10.4) during the intervention period and for 4 months after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period.

The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

Additional requirements for pregnancy testing during and after study intervention are provided in Section 10.4 and the SoA (Section 1.3).

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.

10. Male Participants:

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

Male participants are eligible to participate if they agree to the following from the time of first dose of study until 6 months after the last dose of study treatment to allow for clearance of any altered sperm:

Refrain from donating sperm and either:

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

  OR

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

Agree to use a male condom even if they have undergone a successful vasectomy and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Section 10.4 when having sexual intercourse with a WOCBP (including pregnant females).

5.2. Exclusion Criteria

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

1. Active plasma cell leukemia at the time of screening. Symptomatic amyloidosis, active POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes), Waldenstroem Macroglobulinemia.
2. Participants had a prior allogeneic SCT.

NOTE: Participants who have undergone a syngeneic bone marrow transplant will be allowed only if there is no history of, or no currently active graft-versus-host-diseases (GvHD).

3. Participant has received an investigational drug within 14 days or 5 half-lives, whichever is shorter, preceding the first dose of study drug. This includes prior treatment with a monoclonal antibody. The only exception is emergency use of a short course of systemic corticosteroids (equivalent to, or less than: dexamethasone 40 mg/day for a maximum of 4 days) before treatment.
4. Prior belantamab mafodotin therapy.
5. Participant has received a strong OATP inhibitor within 14 days or 5 half-lives, whichever is shorter, preceding the first dose of study drug (see SRM for more details).
6. Systemic active infection requiring treatment.
7. Any unresolved toxicity ≥ Grade 2 from previous treatment except for alopecia, or peripheral neuropathy up to Grade 2.
8. Plasmapheresis within 7 days prior to the first dose of study drug. Screening laboratory values must be performed after last plasmapheresis.
9. Any major surgery within the last 4 weeks prior to Day 1 of Screening.
10. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions (including lab abnormalities except renal impairment) that could interfere with participant's safety, obtaining informed consent or compliance to the study procedures.
11. Evidence of active mucosal or internal bleeding.
12. 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.
13. Participants with previous or concurrent malignancies other than multiple myeloma are excluded, unless the prior malignancy has been considered medically stable for at least 2 years. The participant must not be receiving active therapy, other than hormonal therapy for this disease. NOTE: Participants with curatively treated non-melanoma skin cancer are allowed without a 2-year restriction.
14. Evidence of cardiovascular risk, including any of the following:
    - Evidence of current clinically significant untreated arrhythmias, including clinically significant ECG abnormalities including 2nd degree (Mobitz Type II) or 3rd degree atrioventricular (AV) block.
    - History of myocardial infarction acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within 3 months of Screening.
    - Class III or IV heart failure as defined by the New York Heart Association functional classification system [NYHA, 1994].
    - Uncontrolled hypertension.

15. Known immediate or delayed hypersensitivity reaction or idiosyncratic reaction to drugs chemically related to belantamab mafodotin, or any of the components of the study treatment.
16. Known human immunodeficiency virus (HIV) infection, unless the participant can meet all of the following criteria:
    - Established anti-retroviral therapy (ART) for at least 4 weeks and HIV viral load <400 copies/mL prior to first dose.
    - CD4+ T-cell (CD4+) counts ≥350 cells/ L
    - No history of AIDS-defining opportunistic infections within the last 12 months

    Note: consideration must be given to ART and prophylactic antimicrobials that may have a drug:drug interaction and/or overlapping toxicities with belantamab mafodotin (See Section 6.5.2).
17. Participants with hepatitis B will be excluded unless the following criteria can be met Table 8

Table 8 Hepatitis B criteria

Serology	Screening	During Study Treatment
HbcAb+, HbsAg-	• HBV DNA undetectable	• Monitoring and management per protocol (Section 6.6.4) • Antiviral treatment instituted if HBV DNA becomes detectable
HBsAg+ at screen or within 3 months prior to first dose	• HBV DNA undetectable • Highly effective antiviral treatment started at least 4 weeks prior to first dose of study treatment • Baseline imaging per protocol • Participants with cirrhosis are excluded	• Antiviral treatment maintained throughout study treatment • Monitoring and management per protocol (Section 6.6.4)

Note: Presence of isolated Hepatitis B surface antibody (HBsAb), indicating previous vaccination, will not exclude a participant

18. Positive hepatitis C antibody (Hep C Ab) test result or positive hepatitis C RNA test result at Screening or within 3 months prior to first dose of study treatment unless the participant can meet the following criteria:
    - RNA test negative
    - Successful anti-viral treatment (usually 8 weeks duration) is required, followed by a negative HCV RNA test after a washout period of at least 4 weeks prior to first dose.
19. Participants with renal impairment due to hepatic disease (hepatorenal syndrome).

20. Current corneal epithelial disease except for mild punctuate keratopathy (Section 2.2.1.2).
21. Participant is a woman who is pregnant or breastfeeding.

5.3. Lifestyle Considerations

Contact lenses are prohibited for participants while they are receiving belantamab mafodotin treatment. Contact lens use may be restarted after a qualified eye care specialist (Appendix 9) confirm there are no other contraindications. Use of bandage contact lenses is allowed for the treatment of corneal epithelial disease as prescribed by an ophthalmologist/eye care professional.

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

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently 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 [Schulz, 2010; Moher, 2010]. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

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

6. STUDY INTERVENTION

6.1. Study Intervention(s) Administered

Belantamab mafodotin will be administered to participants intravenously over approximately 30 minutes as 2.5 mg/kg in Part 1 (Groups 1 and 2) and potentially using an adjusted dose in Part 2 (Group 3 and Group 4) with actual doses calculated at the study site based on body weight.

Product Name	belantamab mafodotin
Dosage Form	Lyophilized powder, 100 mg/vial in single-use vial for reconstitution
Unit Dose Strength(s)/Dose Level(s)	100 mg/vial / 2.5 mg/kg
Route/Administration/Duration	IV infusion (see SRM for details) over approximately 30 minutes[a]
Dosing Instructions	Reconstitute belantamab mafodotin lyophilized powder 100 mg/vial with water for injection (WFI) before use. Dilute belantamab mafodotin in normal 0.9% saline to the appropriate concentration for the dose. Doses of belantamab mafodotin are to be administered as an IV infusion via an infusion pump. See Investigator' Brochure for compatible administration materials.
Manufacturer/Source of Procurement	GSK

a. 30-minute infusion will be the starting rate for Part 1 participants. Following completion of Part 1, infusions may be prolonged in the event of an infusion reaction as needed. If multiple participants experience clinically significant infusion reactions, the infusion rate may be slowed for all future administrations of study treatment(s) for all participants. Should this global change in infusion rate be required, it will be communicated to the sites in writing.

6.2. Preparation/Handling/Storage/Accountability

Instructions for the preparation, storage, and accountability of the study intervention include:

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
- Only participants enrolled in the study may receive study drug and only authorized site staff may supply or administer it. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Under normal conditions of handling and administration, study intervention 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.

- Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual.
- Precaution will be taken to avoid direct contact with the study drug. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the Medical Monitor and/or GSK study contact.

6.3. Measures to Minimize Bias: Randomization and Blinding

This study is not blinded or randomized.

6.4. Study Intervention Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- When participants are dosed at the site, they will receive study drug directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study drug and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug.
- Belantamab mafodotin will be intravenously administered to participants at the site. Administration will be documented in the source documents and reported in the case report form (CRF).

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.

Once the participant has discontinued treatment, only concomitant medication related to AEs or SAEs will be collected.

Participants will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until the end of the study (Final Study Visit). Any concomitant medication(s), including non-prescription medication(s)

and herbal product(s), taken during the study will be recorded in the electronic case report form (eCRF). Additionally, a complete list of all prior anti-cancer therapies will be recorded in the eCRF.

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

6.5.1. 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 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 chronic obstructive pulmonary disease (COPD) exacerbations. Chronic low dose replacement therapy (less than or equal to 10 mg prednisolone) is allowed in participants with adrenal insufficiency.
- Elimination pathways for belantamab mafodotin and cys-mcMMAF have not been characterized in humans. Cys-mcMMAF was not an inhibitor, an inducer, or a good substrate of cytochrome P450 enzymes in vitro. Cys-mcMMAF was shown to be a substrate of P-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; however, strong OATP inhibitors are also prohibited during the first 3 cycles unless considered medically necessary. See the SRM for more information.
- Administration of live or live-attenuated vaccines are contraindicated 30 days prior to the first dose of 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 response to such vaccines cannot be predicted.
- Plasmapheresis is 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, is prohibited.

6.6. Dose Modification

6.6.1. Adjustments Due to Body Weight

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

6.6.2. Dose Reductions for Toxicity

After Cycle 1 participants may have their dose modified (delayed or reduced) for toxicities as recommended in this section. Permitted dose reductions for belantamab mafodotin are shown in Table 9. See Table 10 for dose modification guidelines for AEs associated with belantamab mafodotin.

Dose modification guidelines for cornea-related AEs associated with belantamab mafodotin are summarized in Table 12. Determination of the recommended dose modification of belantamab mafodotin should be based on the most severe corneal toxicity per the Keratopathy and Visual Acuity (KVA) scale in Table 11.

Table 9 Permitted Dose Reductions for Belantamab Mafodotin

Starting Dose	1st Reduction
2.5 mg/kg	1.9 mg/kg

- Only 1 dose reduction (to 1.9 mg/kg) is permitted for the starting dose of 2.5 mg/kg.
- If the participant cannot tolerate the drug after the allowed dose reduction of belantamab mafodotin, the participant will permanently discontinue treatment for lack of tolerability.
- Starting dose below 1.9 mg/kg a priori is not planned; yet if belantamab mafodotin exposure similar to that seen at a 1.9 mg/kg dose can be achieved with a lower dose, this lower dose may be recommended for Part 2, as appropriate.
- 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, upon consultation with the GSK Medical Monitor.

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

Resuming treatment with belantamab mafodotin will be possible with or without dose reduction after the toxicity has resolved to Grade 1 or less. Refer to Table 11, Table 13 and Table 14 for dose modification details.

Table 10 Dose Modification Guidelines for Belantamab Mafodotin-Related AEs

Toxicity[a]	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[d]	If absolute serum creatinine increases from baseline by >0. 5 mg/dL	• Repeat serum creatinine or iGFR 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[b]
Serum creatinine >Grade 3 (compared to baseline) [d]	>3.0 mg/dL from baseline	• Provide appropriate medical treatment. • Hold treatment with belantamab mafodotin • Discuss with Medical Monitor[b] to determine appropriateness of further dosing
Spot urine (creatinine / albumin ratios) [d]	>2000 mg/g (or 224 mg/mmol)	• Re-test (at least 7 days apart) • If not confirmed, continue belantamab mafodotin at pre-held 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 o If spot urine ≤2000 mg/g (224 mg/mmol) may restart belantamab mafodotin with 1 dose level reduction[b]. o 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.
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

Toxicity[a]	Grade/description of toxicity	Recommendations for belantamab mafodotin
Thrombocytopenia (on days of dosing) Graded according to NCI-CTCAE criteria	Grade 3	• No bleeding: continue treatment with 1 dose level reduction. Consider reverting to previous dose once thrombocytopenia recovered to Grade 2, or less. • With bleeding: withhold the dose, continue treatment after recovery with 1 dose level reduction. • Consider additional supportive treatment (e.g., transfusion), as clinically indicated and per local practice.
	Grade 4	• Withhold the belantamab mafodotin dose. Consider restarting with 1 dose level reduction if recovered 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 >25 x10^9/L, continuing treatment with dose reduction may be considered after discussion with the Medical Monitor.
Febrile neutropenia Graded according to NCI-CTCAE criteria	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 25% dose reduction of belantamab mafodotin, if neutropenia was drug-related.
Afebrile Neutropenia Graded according to NCI-CTCAE criteria	Grade 3-4 (Defined as ANC <1.0x10^9/L)	• If noted on Day 1 of any cycle, withhold belantamab mafodotin dose. • Resume belantamab mafodotin at pre-held dose once neutropenia recovers to Grade ≤2 (ANC ≥1.0x109/L) on Day 1 of a subsequent cycle. • Prophylactic antibiotics, per physician discretion and local institutional guidance. Consider growth factors. • Local guidance must be followed for hematological monitoring if more conservative than the protocol SoA specifications. • In cases of frequent recurrent neutropenia (ANC <1.0x109/L), consider dose reduction of belantamab mafodotin.
Infusion reaction[c]	Grade 2	Stop the infusion, provide medical treatment and continue at slower rate after resolution to Grade 0-1
	Grade 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.
	Grade 4	Permanently discontinue

Toxicity[a]	Grade/description of toxicity	Recommendations for belantamab mafodotin
Pneumonitis	Grade 2	• Withhold treatment with belantamab mafodotin • Upon recovery, restart treatment with 1 dose level reduction. • If participant is already at the lowest dose level (1.9 mg/kg), then rechallenge with the same dose must be discussed with the Medical Monitor.
	Grade 3-4	Permanently discontinue treatment with belantamab mafodotin

a. The treatment-related decisions can be made based on local laboratory results if central results are not available or delayed.
b. Medical Monitor may consult GSK's nephrotoxicity panel about plans to continue therapy.
c. If symptoms resolve within 1 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 should be pre-medicated for the next scheduled dose.
d. These criteria do not apply to participants on dialysis.

Table 11 Keratopathy Visual Acuity (KVA) Scale for Treatment-related Corneal Events

Grade per KVA Scale	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Corneal Toxicities				
Corneal examination finding(s)	Mild superficial keratopathy[1]	Moderate superficial keratopathy[2]	Severe superficial keratopathy[3]	Corneal epithelial defect[4]
***Change in Snellen equivalent BCVA*[5]**	Decline from baseline of 1 line on Snellen Visual Acuity	Decline from baseline of 2 or 3 lines (and Snellen Visual Acuity not worse than 20/200)	Decline from baseline by more than 3 lines (and Snellen Visual Acuity not worse than 20/200)	Snellen Visual Acuity worse than 20/200

Abbreviations: BCVA=Best Corrected Visual Acuity; KVA=Keratopathy Visual Acuity.
1. Mild superficial keratopathy: mild superficial punctate keratopathy (documented worsening from baseline), with or without symptoms.
2. Moderate superficial keratopathy: any/or a combination of: moderate superficial punctate keratopathy, patchy microcyst-like deposits, subepithelial haze (peripheral), or a new peripheral stromal opacity.
3. Severe superficial keratopathy; any/or a combination of: severe superficial punctate keratopathy, diffuse microcyst like deposits involving the central cornea, subepithelial haze (central), or a new central stromal opacity.
4. Corneal epithelial defect such as corneal ulcers. Corneal ulcer by definition means an epithelial defect with underlying stromal infiltration.
5. Changes in visual acuity due to treatment-related corneal findings.
   - For participants who have BCVA worse than 20/20 in either eye at baseline, dose modification for that eye will be determined by the worsening of vision from baseline only (not by absolute BCVA at the visits).
   - If a participant has a baseline BCVA of 20/200 or worse in an eye, then belantamab mafodotin-related changes in vision in the other eye will drive the dose modification. If a participant has baseline BCVA of 20/200 or worse in both the eyes, then the decision to delay or reduce belantamab mafodotin dose will be based on PI's assessment of benefit vs. risk based on corneal exam findings following a discussion with the qualified eye care specialist

- Snellen equivalent BCVA is recommended to be tested on a visual acuity chart which has an approximately equal number of letters per line and equal spacing between lines.
- If a participant has cataract surgery the BCVA should be re-baselined and visual acuity assessed from the new baseline value.

Table 12 Dose Modifications for Belantamab Mafodotin Treatment-related Corneal Events Based on the KVA Scale:

Grade per KVA scale	Grade 1	Grade 2	Grade 3	Grade 4
***Recommended** **Dosage Modifications**	Continue treatment at current dose.	Withhold belantamab mafodotin until improvement in **both** corneal examination findings and changes in BCVA to Grade 1 or better and resume at current dose.	Withhold belantamab mafodotin until improvement in **both** corneal examination findings and changes in BCVA to Grade 1 or better and resume at reduced dose. If already on lowest dose, participant should continue treatment after recovery to Grade 1 or better with the same dose	Consider permanent discontinuation of belantamab mafodotin. If based on benefit risk assessment, treatment of belantamab mafodotin is being considered, withhold treatment until improvement in **both** corneal examination findings and change in BCVA to Grade 1 or better and resume at reduced dose. If already on lowest dose, participant should continue treatment after recovery to Grade 1 or better with the same dose

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

6.6.2.1. Corneal Supportive Care Guidelines for Belantamab Mafodotin

Corneal events and changes in vision which are commonly manifested as a superficial microcystic keratopathy, have been observed with antibody drug conjugates, including those conjugated to MMAF [Eaton, 2015].

Sites are required to establish a close collaboration with a qualified eye care specialist who will be responsible for assessing participants in close communication with GSK Medical Monitor and possibly a GSK ophthalmologist, and managing those who develop corneal toxicity.

Participants will be assessed by a qualified eye care specialist (Appendix 9) at screening/ baseline, and then Q3W prior to dosing up to the sixth dose of belantamab mafodotin (assessment window of up to 5 days prior to dosing, but all effort should be made to schedule as close to belantamab mafodotin dosing as possible), as detailed in the SoA. If there are no significant ocular (Grade 2 or above) examinations findings, participant's symptoms or vision changes at the time of the sixth dose exam, participants may have their ophthalmologic exams decreased to once every 3 months. If a participant subsequently develops vision changes or other ocular symptoms, the participant should be promptly evaluated by a qualified eye care specialist. In case of persistent ophthalmic exam findings, newly developed ocular symptoms or vision changes at the sixth dose exam, the participants will have further ophthalmologic exams, at least every cycle until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by the qualified eye care specialist.

Participants who have corneal signs per the KVA scale for eye disorders present at End of Treatment will continue to be followed at least every 3 months for up to 12 months, or until resolution (Grade 1 or baseline), whichever comes first.

Corticosteroid eye drops are not required as prophylaxis but can be used therapeutically if clinically indicated per discretion of an eye-care specialist. Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops (if administered together).

If steroid eye drops are deemed medically necessary and prescribed, intraocular pressure must be monitored if used for >7 days.

6.6.2.1.1. Ocular Prophylaxis

Ocular prophylaxis should be instituted for all participants as detailed in the SoA. Ocular prophylaxis includes:

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

- Beginning with the start of each belantamab mafodotin infusion, participants may apply cooling eye masks to their eyes for as long as tolerated, up to 4 hours.

Table 13 General Dose Modification and Management Guidelines for Drug-Related AEs Not Otherwise Specified

Severity	Management	Follow-up
Grade 1	• Administer symptomatic treatment as appropriate • Continue study drug(s)[1,2]	• 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 one dose level reduction. If recovery takes >3 weeks- consult GSK MM • If symptoms continue or worsen to Grade 3-4, see below
Grade 3	• Provide appropriate medical treatment • Consider Consulting subspecialist	Delay treatment till recovery to Grade 1 or baseline. Consider dose reduction. Consider consultation with GSK MM. Exceptions: Participants who develop Grade 3 toxicities which respond to standard treatment and resolve to Grade 1 within 48 hours may continue treatment at scheduled or reduced dose
Grade 4	• Provide appropriate medical treatment • Consider Consulting subspecialist • Discuss with Sponsor/Medical Monitor	Interrupt treatment. Further treatment with 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

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

6.6.3. Guidance on Dose Delays for Treatment

The precise timings of the treatment cycles may vary due to treatment delays, but disease evaluation assessments regardless of when participants receive treatment are calculated Q3W from C1D1.

Some assessments are linked specifically to belantamab mafodotin dosing (C1-CX visits in the SoA). These assessments will only be necessary if belantamab mafodotin is given. If belantamab mafodotin is held or delayed, these assessments do not need to be done.

Often the two types of assessments described above will occur at the same visit; however, in the event of a dose delay, the timing of assessments related to *dosing* will be adjusted based on the new dosing schedule whilst the Q3W assessments for *efficacy* should continue on the same schedule regardless of dosing as outlined in the SOA (Section 1.3).

Where dosing has been delayed or halted for a period of time, cycle visits and disease assessment visits (Q3W) can occur as two separate visits. These visits may be brought back on track using visit windows.

Where possible ocular visits should be coordinated with Q3W visits.

6.6.4. Management of Hepatitis B+ Participants

Management or consultation by local hepatology or infectious disease services is required. If no subspecialist support is available, consultation with GSK Medical Director is required prior to enrolment into the study for participants with positive titres to Hepatitis B.

Participants should be monitored according to the schedule in SoA Table 1 and Table 2.

Participants who experience clinically significant elevations in liver chemistry should follow liver event monitoring and stopping criteria (Section 7.1.1 and Appendix 6), and careful evaluation should be immediately initiated for evaluation of etiology including HBV DNA testing.

Participants who develop detectable HBV DNA levels during study treatment should be reviewed by local specialist(s) immediately (within 1 week) and appropriate therapy and monitoring instituted. In addition, study treatment should be withheld, and GSK Medical Director should be notified. Agreement with Medical Director must be obtained prior to further dosing of study treatment.

6.7. Intervention after the End of the Study

There is no planned intervention following the EOS. However, participants receiving belantamab mafodotin at the time of the final analysis data cut-off date (approximately 6 months after LSFD), may continue to receive belantamab mafodotin if in the opinion of their treating physician, they are continuing to derive clinical benefit from continued treatment. Study treatment will continue until a study discontinuation (see Section 4.1.3.2) as assessed by the investigator has been met.

Investigators will report all SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases until 70 days after receipt of their last dose of study treatment in accordance with Section 8.3.4 (Reporting of Serious Adverse Events). Pre-specified ocular data (see SRM) will be reported for up to 12 months from the end of PACT treatment or until resolution (to Grade 1 or baseline), whichever comes first. Post final analysis data cut-off, reporting and follow-up of SAEs, AEs leading to treatment discontinuation, overdose, pregnancy cases and pre-specified ocular data will be done via paper forms (see SRM for details). For dispensing of study treatment and drug accountability in the PACT phase please refer to the SRM. All other assessments will revert to standard of care at their site.

Refer to the SoA (Section 1.3) for follow-up assessments of participants after they permanently discontinue from study treatment.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Drug

Participants will receive study treatment according to the SoA (Section 1.3). Study drug must be permanently discontinued in the case of:

- Disease progression, as defined by IMWG criteria [Kumar, 2016], or unacceptable toxicity
- Participant has met any of the protocol defined safety stopping criteria
- Pregnancy

In addition, study treatment may be permanently discontinued for any of the following reasons:

- Important deviation(s) from the protocol
- Request of the participant or proxy (withdrawal of consent by participant or proxy)
- Investigator's discretion, after discussion with the medical monitor and mutual agreement
- Concurrent illness that prevents further administration of study treatment(s)
- Participant is lost to follow-up
- The study is closed or terminated

If the participant voluntarily discontinues from treatment due to toxicity, the AE will be recorded as the primary reason for permanent discontinuation on the eCRF.

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

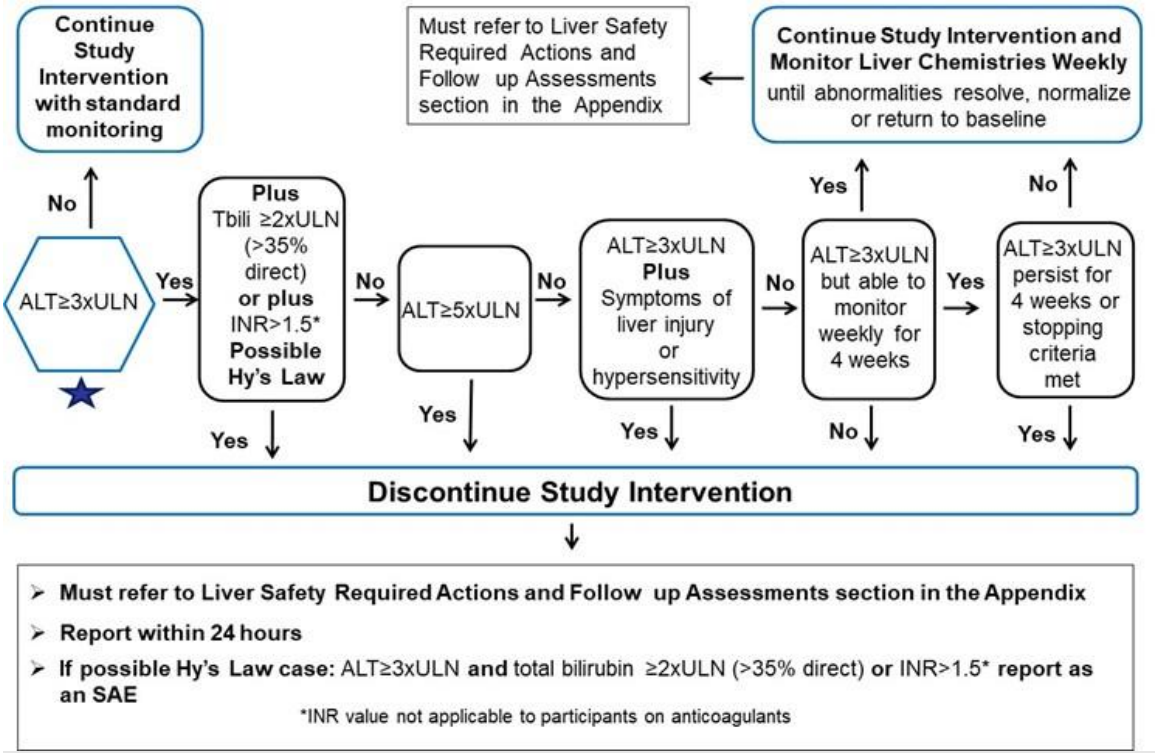
All participants who permanently discontinue study treatment will have safety assessments at the time of discontinuation and during EOT follow-up as specified in the SoA (Section 1.3).

Participants who permanently discontinue study treatment are to be followed until documented disease progression (confirmed PD according to IMWG), death, withdrawal of consent, loss to follow-up, or the end of study (as described in Section 4.3), whichever occurs first, regardless of reason for treatment discontinuation.

7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry-related 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 the participant satisfies any of the stopping rules as shown in Figure 3.

Figure 3 Liver Chemistry Stopping and Monitoring Event Algorithm



Refer to Section 10.6 for liver safety actions and follow-up assessments.

7.1.1.1. Study Intervention Restart or Rechallenge after Liver Stopping Criteria Met

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

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

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

Refer to Appendix 6 and the Study Reference Manual for full guidance.

7.1.2. Corneal Event Stopping Criteria

Dose modifications and stopping criteria of belantamab mafodotin for treatment-related corneal events should be based on grading of corneal events according to the guidelines of KVA Scale Table 11.

Participants who develop a Grade 4 corneal event according to the KVA scale must be discussed in detail between the treating eye care specialist (Appendix 9), the Medical Monitor and possibly a GSK ophthalmologist, in order to determine whether the participant should be allowed to continue treatment with belantamab mafodotin, or permanently discontinue treatment (Table 12). The decision will be documented in study files, together with individual benefit-risk assessment.

7.1.3. Infusion-Related Reaction Management and Stopping Criteria

Premedication is not required prior to infusion unless deemed medically appropriate by the investigator following evaluation of IRRs in prior anti-myeloma treatments. Premedication should be administered in any participant who experienced a Grade 2 or higher IRR at first or any subsequent infusion with belantamab mafodotin.

For infusion reactions of any grade/severity, immediately interrupt the belantamab mafodotin infusion and manage symptoms. Once reaction symptoms resolve, resume the infusion at a reduced rate. Premedication may be required with subsequent infusions (see Table 10 for management details). A participant that experiences a Grade 4 IRR should be permanently withdrawn from the study.

7.1.4. Allergic and Anaphylactic Reaction Stopping Criteria

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

7.2. Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA (Section 1.3) for data to be collected at the time of study treatment discontinuation follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-up

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

- The site must attempt to contact the participant and re-schedule the missed visit as soon as possible.
- The site must counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to continue or if the investigator believes that the participant should continue in the study.
- In cases where the participant is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record. Should the participant continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up."

8. STUDY ASSESSMENTS AND PROCEDURES

A list of clinical laboratory tests is displayed in Table 22 (Section 10.2). The timing of each assessment is listed in the Schedule of Activities (Section 1.3).

The timing of the assessments must allow the blood draw to occur at the exact nominal time. Detailed procedures for obtaining each assessment are provided in the SRM.

- Study procedures and their timing are summarized in the SOA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Demographic and baseline assessments will include year of birth, sex, race, and ethnicity.
- Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.1 and Section 5.2.
- Immediate safety concerns must be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SOA (Section 1.3).
- Baseline disease assessments must be completed with 28 days prior to dosing start unless otherwise specified. Refer to the SoA (Section 1.3).
- Screening assessments performed within the permitted time do not need to be repeated on C1D1 unless otherwise specified.
- Safety labs completed within 72 hours of first dose do not need to be repeated on C1D1.
- Pregnancy testing must be completed within 72 hours prior to first dose.
- ECHO must be completed within 3 months prior to first dose.
- Imaging must be completed within 30 days prior to first dose.
- On-study visits have a ±3-day window.
- Follow-up visits have a ±7-day window.

8.1. Efficacy Assessments

Standard disease assessments for RRMM will include the following assessments:

- UPEP, Urine Immunofixation, 24-hour collection for urine M-protein
- SPEP, Serum M-protein, serum immunofixation
- Calcium corrected for albumin
- IgG, IgM, IgA
- IgD, IgE (only in participants with IgD or IgE myeloma)
- Serum kappa, lambda free LC, FLC ratio
- BM (aspirate preferred) at Screening and to confirm CR. BM biopsy for IHC to confirm sCR
- Positron emission tomography/computed tomography (PET/CT) imaging (in participants with extramedullary disease)
- PET/CT is required upon achieving CR or sCR
- Skeletal surveys at Screening

Baseline serum/urine disease assessment will be completed during screening period (within 28 days prior to the first dose of study treatment) and baseline imaging within 30 days prior to the first dose of study treatment. On study serum and urine-based assessments (M-protein, FLC, immunofixation) will be performed every 3 weeks. Details for the preparation and shipment of samples for central laboratory assessments will be provided in the SRM.

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

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

For post-first dose assessments, a window of ±3 days is permitted to allow for flexible scheduling refer to Section 6.6.3.

For participants who are discontinuing study intervention due to PD, the confirmation of PD must be performed from a different sample collection performed either on the same day, or preferably within 14 days of the original disease progression, before institution of any new anti-myeloma therapy. The assessments to be performed during the EOT Visit are described in the SoA (Section 1.3). If the last imaging assessment was greater than or equal to 8 weeks prior to the participant's discontinuation from study treatment and progressive disease has not been documented, a new disease assessment must be obtained at the time of discontinuation from study treatment.

8.1.1. Response Evaluation

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

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 physical examination including height (once at Screening only) and weight is to be performed.

8.2.2. ECOG Performance Status

Participant performance status will be assessed at Screening and then as specified in the SoA, using the ECOG scale provided in Section 10.7

8.2.3. Vital Signs

Vital sign measurements must include systolic and diastolic blood pressure, temperature, and pulse rate. On days when vital sign assessment align with blood sampling assessments, vital signs should be assessed prior to blood samples being drawn at their nominal time, where possible. On days when vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

8.2.3.1. First Infusion

Belantamab mafodotin is administered IV over a period of approximately 30 minutes.

Monitoring intervals: vital signs are to be measured at the following time points at the time of first belantamab mafodotin infusion:

- Within 30 minutes prior to Start of Infusion (SOI)
- 15 mins after SOI (± 10 min)
- Within 15 min after End of Infusion (EOI)
- At 1 hour (± 10 min) after EOI.

8.2.3.2. Subsequent Infusions

On subsequent dosing days, vital signs must be assessed pre-dose (within 30 minutes prior to SOI) and within 15 min after EOI, and as clinically indicated. Participants may be discharged after the infusion has been completed if considered clinically stable and all other study procedures have been completed.

8.2.4. Electrocardiograms

A 12-lead ECG is obtained at screening as specified in the Schedule of Activities. No further ECGs are required, but if obtained as part of medical care, a 12-lead ECG should be performed by qualified personnel at the site after the participant has at least a 5-minute rest.

8.2.5. Echocardiogram

Echocardiograms must be performed at screening (or have been performed within 3 months of the screening visit) to assess cardiac ejection fraction for the purpose of study eligibility, and then as clinically indicated. The evaluation of the echocardiographer must include an evaluation for LVEF. For ECHOs performed on study, the results must be documented in the eCRF.

8.2.6. Clinical Safety Laboratory Assessments

Clinical laboratory tests to be performed are listed in Table 22 (Section 10.2). Refer to the SoA for the timing and frequency (Section 1.3). Details for the preparation and shipment of samples for central laboratory assessments will be provided in the Central laboratory manual.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values that are significantly abnormal during participation in the study or within 70 days after the last dose of study treatment must be repeated until the values return to normal or baseline.

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

8.2.7. Ophthalmic Assessments

Study sites must establish a close collaboration with a qualified eye care specialist (Appendix 9) who will be responsible for assessing participants while they are on study and managing participants who develop corneal changes associated with belantamab mafodotin. Management of participants with corneal findings must be performed in close communication with the GSK Medical Monitor and the coordinating eye care specialist.

Participants will be assessed by a qualified eye care specialist (Appendix 9) at Screening/Baseline.

A full screening/baseline ophthalmic examination for all participants must include for both eyes:

1. Best corrected visual acuity
2. Documentation of manifest refraction used to obtain best corrected visual acuity
3. Current glasses prescription (if applicable)
4. Intraocular pressure measurement and time checked
5. Anterior segment (slit lamp) examination with focus on the cornea and lens, including fluorescein staining of the cornea
6. Dilated funduscopic exam

The on-treatment and follow-up ophthalmic exams should be performed as described below and in the SoA.

This should include:

1. Best corrected visual acuity
2. Documentation of manifest refraction and the method used to obtain best corrected visual acuity
3. Anterior segment (slit lamp) examination with focus on the cornea and lens, including fluorescein staining of the cornea
4. Intraocular pressure measurement (if clinically indicated)
5. Dilated funduscopic exam (if clinically indicated)

The EOT and last follow-up ophthalmic exam should match the screening/baseline exam.

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

Participants will be assessed by a qualified eye care specialist (Appendix 9) at screening/pre-first dose and then Q3W prior to dosing up to the sixth dose of belantamab mafodotin (assessment window of up to 5 days prior to dosing from the second dose onwards).

- If there are no significant (Grade 2 or above) ocular examinations findings, participant's symptoms or vision changes at the time of the sixth dose exam, participants may have their ophthalmologic exams decreased to once every 3 months until End of Treatment.
- If a participant subsequently develops vision changes or other ocular symptoms, the participant should be promptly evaluated by a qualified eye care specialist.
- In case of persistent ocular exam findings, newly developed ocular symptoms or vision changes, the participants will have further ophthalmologic exams, at least

every cycle until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by the qualified eye care specialist.

Participants with treatment-related change in vision or ocular AEs at the End of Treatment will be followed at least every 3 months or more frequently as clinically indicated for up to 12 months until resolution (to Grade 1 or baseline) by qualified eye care specialist, whichever comes first.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3.

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 intervention or the study, or that caused the participant to discontinue the study intervention (see Section 7).

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

- All SAEs will be collected from the start of study intervention up to 70 days after discontinuing all study interventions, at the time points specified in the SoA (Section 1.3). 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 any follow-up.
- All AEs will be collected from the start of treatment up to 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 intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF 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 Section 10.3. 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 after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.
- For participants in the PACT phase of the study, GSK will continue to collect safety information including SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases and pre-specified ocular data via paper forms which will be reported directly to GSK (see SRM for details).

SAEs, overdose and pregnancy cases will be reported during the PACT treatment period and for up to 70 days after last dose. Additionally, any SAE that are ongoing at the time of the final analysis data cut-off must be followed up to resolution unless the event is considered by the investigator unlikely to resolve, or the patient is lost to follow-up. Pre-specified ocular data will continue to be collected for participants receiving belantamab mafodotin after the start of PACT as follows: Participants without significant ocular examinations findings, symptoms or vision changes when entering the PACT phase will be required to have an ocular assessment at least every 3 months until the end of treatment. Participants who at the time of entering PACT have ocular symptoms or vision changes, or develop these during PACT treatment, the ocular assessment will occur every cycle until resolution (KVA Grade 1 or baseline). After the end of PACT treatment, participants with treatment-related ocular examination findings, ocular symptoms, or vision changes will be followed at least every 3 months for up to 12 months from the end of treatment or until resolution (to KVA Grade 1 or baseline), whichever comes first. For participants without ocular examination findings, ocular symptoms, or vision changes at the end of PACT treatment, no further ocular exams are required. In addition, participants who stopped belantamab mafodotin prior to PACT but have ongoing ocular events at the time of final analysis data cutoff/start of PACT, will be followed at least every 3 months for up to 12 months from the end of treatment or until resolution (KVA Grade 1 or baseline), whichever comes first. GSK retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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 and non-serious AEs of special interest (Section 8.3.7) will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor or designee has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention 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 an SAE or other specific safety information (e.g., summary or listing of SAEs) 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

Information for female participants known to be pregnant during the screening part or before exposure to study will not be collected.

Details of all pregnancies in female participants will be collected after the start of study treatment and for 4 months following the last dose of belantamab mafodotin.

Details of pregnancies from female partners of male participants will be collected after the start of study treatment and for 6 months following the 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 Section 10.4.

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

8.3.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.3.3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRF page must be completed in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion. The Death CRF page must be completed immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within1 week of when the death is reported.

Death due to the disease under study is to be recorded in the Death eCRF. For death due to reasons other than disease under study, record death in the standard Death Details eCRF form.

8.3.7. Adverse Events of Special Interest

Adverse events of special interest (AESI) for belantamab mafodotin are corneal events, thrombocytopenia, and IRRs. Corneal events associated with belantamab mafodotin will be graded according to the KVA scale. Other treatment-related ocular AEs are to be

reported based on NCI-CTCAE v5.0 criteria for eye disorders. Severity of all other AESIs will be graded using NCI- CTCAE (v5.0).

Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in Section 6.6. Dose modifications for belantamab mafodotin corneal events will be based on the guidelines (KVA scale) presented in Table 12.

8.4. Treatment of Overdose

GSK does not recommend a specific treatment for an overdose of belantamab mafodotin.

An overdose of belantamab mafodotin is considered if more than 10% above the calculated dose is administered.

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

- Contact the GSK Medical Monitor immediately.
- Monitor the participant closely for AEs, SAEs, and laboratory abnormalities until they have resolved, and belantamab mafodotin concentrations are predicted to be within the anticipated range in absence of the overdose.
- Obtain a plasma sample for PK analysis and a blood sBCMA sample as soon as the overdose situation is recognized, and contact the GSK Medical Monitor for further guidance with regards to additional sample collection (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.
- Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

8.5.1. Belantamab Mafodotin Sample Collection for Pharmacokinetics

8.5.1.1. Blood

Blood samples for PK analysis of belantamab mafodotin (ADC and total antibody) and cys-mcMMAF will be collected at the time points indicated in Table 14. Full PK profiles will be obtained in all participants in Cycles 1 and 3 with limited sampling obtained in some other cycles. Each PK sample should be collected as close as possible to the planned time. 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 relevant sample processing document (e.g., SRM, Central Laboratory Worksheet [CLW])

Pharmacokinetic and accompanying sBCMA sample collection may be terminated when sufficient data have been collected.

All PK, sBCMA and ADA samples once collected can be analyzed if the sample date and time have been recorded in the eCRF.

For participants undergoing hemodialysis, the first hemodialysis session should occur on Cycle 1 Day 3 and subsequent dialysis sessions should occur on days when PK and sBCMA blood sample collections do not occur (as outlined in Table 14).

Table 14 Timing of Blood Sample Collection for Belantamab Mafodotin PK and sBCMA

Cycle 1	Cycle 2	Cycle 3	Cycles 4 and 6, 9 and 12	>Cycle 12 Q6 cycle (C18, C24, etc)[1]	Comments
Predose	Predose	Predose	Predose	Predose	Within 30 min prior to SOI
EOI	EOI	EOI	EOI		To be collected from 0 to up to 15 min following EOI (tear collection up to 30 min)
2 h after SOI		2 h after SOI			Within±15 min of collection timepoint
4 h after SOI		4 h after SOI			Within±15 min of collection timepoint
8 h after SOI		8 h after SOI			Within±1 h of collection timepoint
24 h after SOI	24 h after SOI	24 h after SOI			Within ±2 h of collection timepoint
C1D4 - anytime[2]		C3D4 - anytime[2]			±1 day
C1D8 – anytime[2]		C3D8 - anytime[2]			±1 day
C1D15 - anytime[2]		C3D15 - anytime[2]			±1 day
C1D22 – anytime[3]		C3D22 – anytime[4]			Predose if dosed. At visit if not dosed.

EOI = end of infusion; SOI = start of infusion

[1]Pharmacokinetic samples will be collected until either 15 to 18 months or End of Treatment.

[3] C1D22 is not a planned sample. If dosing is delayed at Cycle 2, the sample collected on the original planned Cycle 2 dosing day will be designated C1D22. The predose C2D1 sample will be collected prior to the Cycle 2 dose when administered.

[4] C3D22 is not a planned sample. If dosing is delayed at Cycle 4, the sample collected on the original planned Cycle 4 dosing day will be designated C3D22. The predose C4D1 sample will be collected prior to the Cycle 4 dose when administered.

8.5.1.2. Urine

Urine PK samples for analysis of cys-mcMMAF will be collected in Part 1 only. A baseline predose urine sample will be collected on C1D1. In addition, twenty-four-hour (± 2 hours) urine samples will then be collected on C1D1 (to start just prior to start of

infusion), as well as C1D4, C1D8, C1D15, and C1D21 (C1D21 to finish prior to start of infusion in Cycle 2). The actual start and stop date and time of each urine sample collection will be recorded in addition to the volume of urine recovered and if all urine was collected within the specified interval.

Table 15 Timing of Urine Collection in Part 1

Timepoint	Cycle 1 Day 1	Cycle 1 Day 4	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 1 Day 21
Predose	X				
0-24 hours (± 2 hours)	X	X	X	X	X

8.5.1.3. Tear Fluid

All participants with normal/mild or severely impaired renal function (Part 1) will also undergo collection of tear fluid for analysis of belantamab mafodotin and cys-mcMMAF at baseline and on-treatment. Tear collection will occur immediately before infusion, within 30 minutes after EOI, and at approximately 24 hours after EOI. The tear sample collection time points may be updated or discontinued based on emerging data. Additional tear samples may be collected from participants during Part 1 and Part 2 in case insufficient tear fluid was collected from previous participants due to collection challenges, participant suffering from dry eyes, or analytical technical issues.

Refer to the SRM for further details, which also details appropriate use of the eye numbing drops (Proparacaine).

8.5.2. Belantamab Mafodotin PK Sample Analysis

PK Samples will be analyzed using an appropriately validated assay method by or under the supervision of the sponsor.

Plasma, urine and tear fluid collection process will be detailed in the relevant sample processing documents (e.g., SRM, Lab Manual). The presence/concentrations of belantamab mafodotin (ADC and total antibody) and/or cys-mcMMAF will be determined in plasma and urine samples using an approved bioanalytical methodology, where technically feasible. Raw data will be archived at the bioanalytical site.

Once the plasma and urine has been analyzed for belantamab mafodotin (ADC and total antibody) and cys-mcMMAF, any remaining plasma or urine may be analyzed for other compound-related metabolites or to evaluate safety or efficacy aspects related to concerns arising during or after the study and the results may be reported under a separate GSK protocol.

8.6. Belantamab Mafodotin Immunogenicity

Immunogenicity samples will be analyzed using an appropriately validated assay method by or under the supervision of the sponsor.

Serum samples for the analysis of anti-belantamab mafodotin antibodies (ADA) will be collected from all participants according to the SoA (predose Cycles 1, 2, 4, 6, 9, 12, and every 6 cycles thereafter (Cycle 18, Cycle 24, etc.) until EOT. Additionally, serum samples should be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. Raw data will be archived at the bioanalytical site documented in the relevant sample processing documents (e.g., SRM, CLW). Analysis will be conducted using an approved analytical methodology.

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

The detection and characterization of antibodies to belantamab mafodotin will be performed using validated assays. The anti-belantamab mafodotin antibody assay was designed to detect antibodies to belantamab mafodotin, the unconjugated monoclonal antibody and the linker-payload. Additionally, plasma samples will be collected at the same time points (see SoA) as the immunogenicity samples and analyzed to determine the belantamab mafodotin plasma concentration.

8.7. Pharmacodynamics

See Section 8.9 for details of biomarkers to be collected.

8.8. Genetics

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

Information regarding genetic research is included in Appendix 5. In approving the clinical protocol, the IEC/IRB and, where required, the applicable regulatory agency, are also approving the genetic research described in Appendix 5 unless otherwise indicated.

Where required by regulatory authorities, approval of the genetic assessments can occur after approval is obtained for the rest of the study. In that case, written approval will indicate that approval of the genetic assessments is being deferred and the study, except

for genetic assessments, can be initiated. If genetic assessments are not approved, they will not be conducted.

Genetic analyses will not be performed on these serum samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained. At visits during which serum samples for the determination of multiple aspects of study intervention will be taken, one sample of sufficient volume can be used.

8.9. Biomarkers

Biomarker research is part of this study and will involve peripheral blood (serum), bone marrow, and tumor biopsies, refer to Table 4. Soluble BCMA (sBCMA), BCMA tumor expression will be assessed with their relationship to response to belantamab mafodotin. Any samples collected during this study may be used to measure novel biomarkers (including DNA, RNA, and protein-based measurements) to identify factors associated with the biological and clinical responses to belantamab mafodotin and future research. If relevant, this approach may be extended to include the identification of biomarkers associated with AEs. Unless stated otherwise, these investigations may be performed irrespective of whether a response to belantamab mafodotin is observed.

Samples will be collected at the time points indicated in the SoA (Section 1.3). The sample collection strategy may be adjusted on the basis of emerging data from this study or other studies involving belantamab mafodotin in order to ensure optimal evaluation of any potential biomarkers. If biomarkers are potentially predictive of response or associations with AEs are identified, samples may be used for the development of validated assays and/or diagnostic tests. Additionally, novel biomarkers involving RNA analysis, DNA analysis, or protein analysis may also be incorporated, as data warrants. These analyses may include but not be limited to:

- Bone marrow BCMA expression by IHC and RNA analysis performed on bone marrow biopsy/aspirate
- Bone marrow aspirate or tumor tissue may be evaluated by DNA/RNA sequencing.
- Measurement of the serum levels of sBCMA

All biomarker and BM samples (biopsy and aspirate), once collected, can be analyzed if the sample date and time have been recorded.

The analysis of the biomarkers identified in this section will be performed using analytical method(s) appropriate to the study endpoint(s) being assessed by or under the supervision of the sponsor.

Genetic analyses will not be performed on these samples (unless consent for this was included in the informed consent). Participant confidentiality will be maintained. At visits during which samples for the determination of multiple aspects of study intervention will be taken, one sample of sufficient volume can be used.

8.9.1. BCMA Myeloma Expression

BCMA expression is expected to be present in all multiple myeloma cells, and there is likely variability between cells and differences in membranous and cytosolic localization expression patterns. It is important to determine if there is any association between the expression levels of BCMA on multiple myeloma cells and clinical responses. Bone marrow samples will be collected during this study at the time points indicated in the SoA.

An optional tissue sample (BM biopsy and/or aspirate, or fresh tissue/tissue block from extramedullary tumor) may be collected upon disease progression from participants who have signed a separate consent for this sample. Participation in this part of the study is optional and all enrolled participants will be given the opportunity to contribute samples. Participation may be declined without effect on medical care during the clinical study.

8.9.2. sBCMA Sample Collection and Analysis

The BCMA receptor undergoes gamma-secretase mediated cleavage, leading to release of the BCMA extracellular domain as sBCMA into the circulation [Laurent, 2015]. In an exploratory setting, examinations into the potential prognostic value of sBCMA, through examinations of baseline and on treatment levels of sBCMA relative to response, will be conducted.

Samples will be collected to measure concentrations of sBCMA at the time points specified in Table 14 Section 8.5.

Serum analysis for sBCMA will be performed under control of GSK. Raw data will be archived at the bioanalytical site as documented in the relevant sample processing documents (e.g., SRM, CLW, SOW). Analysis will be conducted using the currently approved analytical methodology.

The actual date and time of each blood sample collection will be recorded in the eCRF. Details on sBCMA blood sample collection including blood volumes, processing, storage, and shipping procedures are provided in the SRM.

8.9.3. RNA Transcriptome Research

Transcriptome studies may be conducted using microarray, RNAseq and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of ribonucleic acid (RNA) species resulting in a transcriptome profile for bone marrow samples. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to response to belantamab mafodotin or the pathogenesis of multiple myeloma.

8.10. Medical Resource Utilization and Health Economics

Health Economics/medical resource utilization parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan will be finalized prior to data base lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Statistical Hypotheses

No formal hypothesis will be tested in this study; however, an estimation approach will be taken to characterize the PK of belantamab mafodotin (including ADC and the total antibody) and cys-mcMMAF in participants with severe renal impairment, ESRD (not on dialysis), and ESRD (on dialysis), compared with matched participants with normal or mild renal function.

9.2. Sample Size

Thirty-two to 36 participants will be targeted for PK analysis for this study. It is estimated that approximately 100 participants need to be screened, and up to 36 participants to be enrolled. The study is composed of 2 Parts that include up to 12 participants with normal or mildly impaired renal function and 8 with severe renal impairment for Part 1, up to 8 participants with ESRD (not on dialysis) and up to 8 participants with ESRD (on dialysis) for Part 2.

The above targeted sample size was chosen based on feasibility, to address the objectives of the study. This sample size is considered sufficient to determine whether the pharmacokinetics in participants with renal impairment is meaningfully different from participants with normal renal function.

For Cmax and AUC[0-168h] of cys-mcMMAF, the variance of the natural log-transformed data is 0.224 and 0.245 respectively (estimated from Study BMA117159). Assuming variance of 0.245 and 8 participants with normal renal function and 8 participants with severe renal impairment will be evaluable for PK analysis in Part 1, the estimated distribution of observed ratio between sample mean ([R_obs]: severe vs. normal) of Cmax or AUC0-168h are shown in Table 16.

Table 16 Estimated Distribution of Observed Ratio

True Ratio	Observed Ratio Severe Renal Impairment vs. Normal Renal Function)		
Severe vs. Normal	Probability (%)		
	(R_obs≤1.25)	(1.25<R_obs≤1.5)	(R_obs>1.5)
1.00	81.6	13.3	5.1
1.05	75.9	16.6	7.5
1.10	69.7	19.8	10.5
1.15	63.2	22.7	14.2
1.20	56.6	25.1	18.4
1.25	50.0	26.9	23.1
1.30	43.7	28.1	28.2
1.35	37.8	28.7	33.5
1.40	32.4	28.6	39.0
1.45	27.4	28.0	44.6
1.50	23.1	26.9	50.0
1.60	15.9	23.8	60.3
1.70	10.7	19.9	69.3
1.80	7.0	16.0	76.9
1.90	4.5	12.4	83.0
2.00	2.9	9.4	87.7

Note: Probabilities were calculated assuming natural log of Cmax or AUC0-168h follows normal distribution. As shown in the above table, if the true ratio (severe vs normal) is 1.0 (i.e., no difference), there is more than 80% (81.6%) chance that the observed ratio from Part 1 of the study will be less than 1.25; if the true ratio (severe vs normal) is 1.5 (i.e., significant difference), there is <25% (23.1%) chance observed Cmax ratio from Part 1 study will be <1.25.

9.3. Populations for Analyses

Four specific analysis populations have been defined for this study, as shown in Table 17.

Table 17 Analysis Populations Defined for the Study

Population	Description
Screened	All participants who sign the ICF to participate in the clinical study. Participants in this population will be used for screen failure summary
Enrolled	All participants who sign the ICF, pass the screening, and enter the study
Safety	All enrolled participants receiving at least 1 dose of belantamab mafodotin
PK	All participants in the safety analysis set who had at least one post first dose PK assessment

9.4. Statistical Analyses

The planned PK/safety, interim and primary/final analyses are listed in detail in Table 18.

Table 18 Details of Analyses to Be Performed

Analysis	Timing	Endpoints included	Data to be used
Safety/PK Analysis	When all Part 1 participants have completed[1] Cycle 1	All primary (PK) and secondary (safety) endpoints	All data available at the time of the data cut
Interim Analysis	6 months after the last participant in Part 1 has received first dose	All endpoints	All data available for Part 1 participants only
Primary/Final Analysis	6 months after the last participant in Part 2 has received first dose	All endpoints	All data

1. Completed or withdrawn from the study prior to the relevant time point.
2. See section 4.3.

All summaries and analyses will be produced by enrollment group (Groups 1-2 or Groups 1-4 as applicable). If appropriate, the ESRD participants data may also be combined into an 'All ESRD' group. Group 1 (participants with normal and mildly impaired renal function) will be considered the control group for all comparisons, however, as these groups will not be matched, results of any comparisons between normal and ESRD participants will be interpreted with caution.

9.4.1. Efficacy Analyses

All efficacy analyses will be performed on the Safety Population as defined in Table 19. All efficacy endpoints are considered as exploratory endpoints.

Table 19 Statistical Analysis Methods for Efficacy Endpoints

Endpoint	Statistical Analysis Methods
Exploratory	Exploratory efficacy endpoints of this study include ORR, CBR, DoR, TTR and TTP. No hypothesis testing will be performed on these endpoints. ORR is defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR and sCR), according to the IMWG Response Criteria [Kumar, 2016], A participant with best confirmed response of PR or better (sCR+CR+VGPR+PR) will be considered as a responder for ORR. The corresponding 95% exact CI for ORR will also be provided. Participants with unknown or missing response will be treated as non-responders; i.e., these participants will be included in the denominator when calculating percentages of response. Clinical benefit rate is defined as the percentage of participants with a confirmed minimal response (MR) or better (i.e., MR, PR, VGPR, CR, and sCR), according to the IMWG Response Criteria [Kumar, 2016]. CBR will be summarized in the same way as ORR. Duration of response is defined as the time from first documented evidence of PR or better until the earliest date of disease progression (PD) or death due to PD per IMWG among participants

Endpoint	Statistical Analysis Methods
	who achieve a response (i.e., confirmed PR or better). Descriptive statistics (mean, standard deviation, median, range) will be provided for participants who achieve PR or better, by censoring status. Time to progression is defined as the time from randomization until the earliest date of PD or death due to PD per IMWG. Determination of dates of TTP event will be described in the SAP. Descriptive statistics will be provided for participants with PD or who die due to PD and descriptive statistics of time on follow-up will be provided for participants who do not have PD. Time to response is defined as the time between the date of randomization and the first documented evidence of response (PR or better), among participants who achieve a response (i.e., confirmed PR or better). Descriptive statistics will be provided for participants who achieve PR or better

CBR: Clinical Benefit Rate; CI: confidence interval; CR: Complete Response; DoR: Duration of Response; MR: Minimal Response MR; SD: Stable Disease; NE: non-evaluable; ORR: Overall Response Rate; PD: Progressive Disease; PR: Partial Response; SAP: Statistical Analysis Plan; sCR: stringent Complete Response; TTE: time-to-event; TTP: Time-to-Progression; TTR: Time-to-Response; VGPR: Very Good Partial Response.

9.4.2. Safety Analyses

All safety analyses (Table 20) will be performed on the Safety Population.

Table 20 Statistical Analysis Methods for Safety Endpoints

Endpoint	Statistical Analysis Methods
Secondary	Adverse Events: All AEs, serious or non-serious, will be reported from the start of treatment up to 70 days after the last dose of study treatment, until the participant withdraws consent for study participation, or until the participant starts subsequent anticancer therapy, whichever occurs first. AEs will be recorded using standard medical terminology and graded according to the NCI-CTCAE, version 5.0. For AE reporting, the verbatim term used in the CRF by investigators to identify adverse events will be coded using the latest version of MedDRA coding dictionary [NCI, 2017]. Adverse events will be summarized by frequency and proportion of total participants, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs, and AEs leading to discontinuation of study treatment. Adverse events, if listed in the NCI-CTCAE (version 5.0) or the KVA scale, will be summarized by the maximum grade. Characteristics (e.g., number of occurrences, action taken, grade, etc.) of the following AEs of clinical interest will be summarized separately: • The incidence of deaths and the primary cause of death will be summarized. • Clinical Laboratory Evaluation: The evaluation of clinical laboratory tests will focus on selected laboratory analytes from the hematology and blood chemistry panel. • Descriptive statistics (mean, standard deviation, median, range) will be used to summarize observed laboratory values and change from baseline in observed value at each scheduled visit or worst-case post-baseline, as appropriate. • The worst-case- toxicity grade in hematology and chemistry result during the treatment will be summarized. Other Safety Measures: Data for laboratory evaluations, vital signs and ocular assessments will be summarized. For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries

Endpoint	Statistical Analysis Methods
	will include frequencies and corresponding percentages. Further details will be provided in the Statistical Analysis Plan (SAP).
Exploratory	Will be described in the SAP.

9.4.3. Pharmacokinetic Analyses

Concentration-Time Data: Linear and semi-logarithmic individual concentration-time profiles and mean and median profiles (by group, when appropriate) will be plotted for belantamab mafodotin (ADC and total mAb) and cys-mcMMAF. Concentrations of belantamab mafodotin (ADC and total mAb) and cys-mcMMAF will be listed for each participant and summarized (when appropriate) by planned time point and group and matrix (e.g., plasma, urine, dialysate, or tear fluid, as data permits).

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

Plasma belantamab mafodotin (ADC, total mAb) and cys-mcMMAF concentration-time data will be analyzed by non-compartmental methods using WinNonlin. Calculations will be based on the actual sampling times recorded during the study.

From the plasma concentration-time data, the following PK parameters will be determined for belantamab mafodotin (ADC and total mAb) as data permit, for each participant after each dose of belantamab mafodotin:

- Maximum observed plasma concentration (Cmax), time to Cmax (tmax), concentration at the end of infusion (C-EOI), and predose plasma concentration (Ctrough)
- For Cycle 1 and Cycle 3: area under the plasma concentration-time curve from 0 to the end of the dosing interval, tau, AUC(0-tau) and last time point where the concentration is above the limit of quantification (tlast).

For cys-mcMMAF, Cmax, tmax, C-EOI and AUC(0-168h), and tlast will be computed at Cycle 1 and Cycle 3, as data permit.

Plasma concentration-time data from this study may be combined with data from other studies and may be analyzed using a population pharmacokinetic approach. These analyses may be described in a separate SAP and results provided in a separate report.

From urine collection in Part 1 participants, the amount recovered in each 24-hour urine collection [Ae(0-t1), Ae(t2-t3), etc.] will be computed from urine cys-mcMMAF concentration and urine volume and the overall amount excreted over a dosing interval will be estimated from these data. The fraction of cys-mcMMAF dose excreted in urine [Fe(0-t)] will also be computed. The renal clearance of cys-mcMMAF (CLr) may also be estimated.

9.4.3.1. Statistical Methods for PK Analysis

Statistical analyses of the PK parameters data (Table 21) will be the responsibility of Clinical Statistics, GSK.

Table 21 Statistical Analysis Methods for Pharmacokinetic Endpoints

Endpoint	Statistical Analysis Methods
Primary	Primary Plasma PK parameter [Cmax, AUC(0-tau)] and urine PK parameter (CLr) will be analyzed separately on the log scale by means of an ANOVA model including renal function group (normal, severe, ESRD (not on dialysis) and ESRD (on dialysis)) as a fixed effect. The intent is to analyze PK profiles at both Cycle 1 and Cycle 3 separately. The model may also include baseline covariates (such as gender, age, body weight, BMI, race, albumin, IgG and sBCMA) if appropriate. The geometric mean of each PK parameter will be derived from the model for each renal function group. The ratio of the PK parameter geometric means between the control group and each one of the other renal function groups and their 90% CI will also be derived from the model. If a lower dose is used for ESRD participants, analysis will be performed on dose-normalized PK exposure parameters (AUC(0-tau), Cmax). Plasma concentrations of belantamab mafodotin and the associated PK parameters will be listed, and summary statistics (n, mean, median, standard deviation, minimum, maximum, and coefficient of variation) will be presented by day and group. Mean and individual plasma concentration versus time profiles will be presented graphically on linear and semilogarithmic scales.
Exploratory	Graphical evaluation and mathematical model describing the relationship between PK parameters (Cmax, AUC(0-tau)) and baseline renal function parameters (iGFR) will be explored. Graphical visualization of the relationship between tear fluid and plasma concentration may be performed. Tear fluid concentration will be listed and summarized, if feasible. If data permit, urine recovery of cys-mcMMAF in Part 1 will be listed and summarized.

9.4.4. Other Analyses

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

9.5. Interim Analysis

Details of the interim analyses are provided in Table 18. Full details of the endpoints and outputs generated for each planned analysis will be described in the SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. 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, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. 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.

10.1.3. Informed Consent Process

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

10.1.4. Data Protection

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

10.1.5. 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 study 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 study participants are used to maximum effect in the creation of knowledge and understanding
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

  The sponsor or designee is responsible for the data management of this study including quality checking of the data
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary 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.

10.1.7. 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 the SRM.

10.1.8. 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 intervention development

10.1.9. 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.

10.2. Appendix 2: Clinical Laboratory Tests

Table 22 Protocol-required Clinical Laboratory Tests

Hematology			
Platelet count	Red Blood Cell (RBC) Indices:	Automated WBC Differential:	
RBC count	Mean corpuscular volume (MCV)	Neutrophils	
White blood cell (WBC) count (absolute)	Mean corpuscular hemoglobin (MCH)	Lymphocytes	
Reticulocyte count	Mean corpuscular hemoglobin concentration (MCHC)	Monocytes	
Hemoglobin		Eosinophils	
Hematocrit		Basophils	
Clinical Chemistry			
Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin
Creatinine	Chloride	Alanine aminotransferase (ALT)	Uric acid
Glucose (non-fasting)	Total bicarbonate	Gamma glutamyl transferase (GGT)	Albumin
Sodium	Calcium	Alkaline phosphatase	Total protein
Magnesium	Phosphorous	Creatine kinase (CK)	Lactate dehydrogenase (LDH)
eGFR			
Urine			
Spot urine (from first void) for albumin/creatinine ratio OR urine dipstick for protein Note: 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			
Other Laboratory Tests (as indicated in Section 1.3)			
Pregnancy Test (urine or blood) FSH and estradiol (as needed in women of childbearing potential only); HBsAg, HBcAb, Hepatitis C RNA test (optional), HBV-DNA if applicable Note: Hepatitis C RNA testing will be done to determine participant eligibility if hepatitis C antibody positive.			
PK and ADA			
belantamab mafodotin pharmacokinetics (PK) Anti-drug antibodies (ADA) to belantamab mafodotin			
Disease Evaluation Laboratory Tests			
UPEP	Serum immunofixation	Ca corrected for albumin (serum)	
SPEP	Urine immunofixation	IgG, IgM, IgA, IgD/IgE	
FLC ratio	24-hour urine collection for M protein	Beta-2 microglobulin	
Bone Marrow Aspiration / Biopsy			
Bone marrow for disease assessment, BM for FISH analysis; BM aspirate for BCMA expression; BM biopsy to confirm sCR (by IHC)			
Biomarker Measurements			
sBCMA (serum)			
Optional Testing (Informed consent for optional sub-studies [e.g., genetic research] must be obtained before collecting a sample)			
Pharmacogenomics sample; Optional tissue sample at PD for BCMA (BM aspirate, or fresh tissue/tissue block from extramedullary tumor)			

Investigators must document their review of each laboratory safety report.

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

10.3.1. 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 intervention, whether or not considered related to the study intervention. • 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 intervention.

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 condition detected or diagnosed after study intervention 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 intervention 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. • 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. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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.

10.3.2. 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, that meets one or more of the criterial listed:
• 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 (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. 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

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

Assessment of Intensity

The investigator will assess intensity for each AE and SAE reported during the study according to NCI-CTCAE Version 5.0 and assign it to 1 of the following categories:

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

Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

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

Grade 5: Death related to AE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention 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 intervention 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.

10.3.5. 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 the SRM.

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

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of childbearing potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high 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.

10.4.2. Contraception Guidance

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

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

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

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

10.4.3. Collection of Pregnancy Information

Male participants with partners who become pregnant:

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

Female participants who become pregnant:

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study and for 4 months following the 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 intervention by the investigator, will be reported to GSK as described in Section 10.3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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

10.5. Appendix 5: Use/Analysis of DNA

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

10.6. Appendix 6: Liver Safety: Required Actions, Follow-up Assessments, and Study Intervention Re-challenge Guidelines

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

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥5xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥3xULN and INR >1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>Follow-up Assessments</th></tr>
<tr><td>• 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 as described in the Follow Up Assessment column
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)
<u>MONITORING:</u>
If ALT ≥3xULN AND total bilirubin ≥ 2xULN or INR >1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver</td><td>• Viral hepatitis serology[4]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend
• Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5].
• Blood sample for pharmacokinetic (PK) analysis and a blood sample for sBCMA, obtained within 70 days after last belantamab mafodotin dose.
• 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</td></tr>
</table>

event follow up assessments within **24 hours** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria (total bilirubin <2xULN and INR ≤1.5):** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline **RESTART/RECHALLENGE** • **Restart/rechallenge is allowed per protocol but do not resume study intervention unless GSK approval is granted;** • If restart/rechallenge is **not granted**, permanently discontinue study intervention and continue participant in the study for any protocol specified follow up assessments. • Refer to Restart/Rechallenge guidelines in Section 10.6.1	• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter medications • Record alcohol use on the liver event alcohol intake 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) to evaluate liver disease; complete Liver Imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance: ○ In participants when serology raises the possibility of autoimmune hepatitis (AIH) ○ In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention ○ In participants with acute or chronic atypical presentation: • If liver biopsy conducted complete liver biopsy form.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN **and** 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. 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. 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/sBCMA blood sample draw and the date/time of the last dose of study intervention prior to PK/sBCMA blood sample draw on the CRF. If the date/time of the last dose cannot be approximated OR a PK/sBCMA sample cannot be collected in the time period indicated above, do not obtain a PK/sBCMA sample. Instructions for sample handling and shipping are in the SRM.

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

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN **but** <5xULN **and** total bilirubin <2xULN, or INR ≤1.5, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • For HBV participants, obtain HBV-DNA testing • For HCV participants, obtain HCV-RNA testing • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin and INR) until they resolve, stabilize or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

10.6.1. 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, if required, is obtained
- 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.

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

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

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

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

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

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

- The Principal Investigator (PI) requests consideration of rechallenge with study intervention for a participant who is receiving compelling benefit with study intervention that exceeds risk, and no effective alternative therapy is available.
- IRB/IEC approval for rechallenge with study intervention has been obtained, if required.

If the rechallenge is approved by GSK in writing:

- The participant must be provided with a clear description of the possible benefits and risks of study treatment administration including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the re-challenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for re-challenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment re-challenge, participant meets protocol-defined liver chemistry stopping criteria, study treatment must be permanently discontinued.
- GSK medical monitor, and the IRB/IEC as required, must be informed of the participant's outcome following study treatment re-challenge.
- GSK must be notified of any AEs as per Section 8.3.

10.6.1.2. 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 10.6 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 10.3.

10.7. Appendix 7: ECOG Performance Status

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

Oken, 1982

10.8. Appendix 8: Abbreviations and Trademarks

Abbreviations

ADA	Anti-drug antibodies
ADC	Antibody-drug conjugate
ADCC	Antibody-dependent cellular cytotoxicity
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
Anti-CD38	Anti-CD38 antibody
APRIL	A proliferation-inducing ligand
AST	Aspartate aminotransferase
AUC	Area under the curve
AV	Atrioventricular
BAFF	B-cell-activating factor belonging to the TNF family
BCL	Bandage contact lenses
BCMA	B-cell maturation antigen
BCVA	Best corrected visual acuity
BSA	Body surface area
β-HCG	Beta human chorionic gonadotropin
BIB	Bioanalysis Immunogenicity and Biomarkers
BiTe	Bispecific antibodies
BLRM	Bayesian logistic regression model
BM	Bone marrow
BUN	Blood urea nitrogen
C1D1	Cycle 1 Day 1
C2D1	Cycle 2 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
CLD	Dialysis clearance
CLW	Central Laboratory Worksheet
Cmax	Maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CPK	Creatine phosphokinase
CR	Complete Response
CRF	Case report form
CRcl	Creatinine clearance

CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Predose plasma concentration
CV	Cardiovascular
D1	Day 1
DAMP	Danger-associated molecular pattern
DILI	Drug-induced liver injury
dL	Deciliters
DNA	Deoxyribonucleic acid
DoR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOI	End of Infusion
EOT	End of Treatment
ESRD	End stage renal disease
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
FLC	Free light chain
FSH	Follicle-stimulating hormone
FTIH	First-time-in-human trial
g	Grams
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GSK	GlaxoSmithKline
GvHD	Graft-versus-host disease
HBcAb	Hepatitis B core antibody
HBsAB	Hepatitis B surface antibody
HBV	Hepatitis B virus
HbsAg	hepatitis B surface antigen
HCV	Hepatitis C virus
HepCAb	Hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRT	Hormone replacement therapy
IB	Investigator’s Brochure
ICD	Immunogenic cell death
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee

IgA	Immunoglobulin A
IgD	Immunoglobulin D
IgE	Immunoglobulin E
iGFR	Individual Glomerular Filtration Rate
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IMWG	International Myeloma Working Group
INR	International normalization ratio
IP	Investigational product
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRT	Interactive response technology
IUD	Intra-uterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
L	Liters
LC	Light chain
LDH	Lactate dehydrogenase
LFT	Liver function test
LPFD	Last Patient First Dose
LSFD	Last Subject First Dose
LVEF	Left ventricular ejection fraction
m^2	Meter square
mAb	Monoclonal antibody
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mg/kg	Milligrams per kilogram
min	Minutes
mL	Milliliters
MM	Multiple myeloma
mmol	Millimole
mmol/L	Millimoles per liter
MMAF	Monomethyl auristatin-F
MoA	Mechanism of action
mPFS	Median Progression-free Survival
MR	Minimal Response
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
NCI	National Cancer Institute
NE	Not evaluable
nm/s	Nano meters per second

NYHA	New York Heart Association
OATP	Organic-anion transporting polypeptide
ORR	Overall Response Rate
OS	Overall Survival
PACT	Post Analysis Continued Treatment
PCR	Polymerase chain reaction
PD	Progressive Disease
PET	Positron emission tomography
P-gp	P-glycoprotein
PFS	Progression-free Survival
PGx	Pharmacogenomics
PI	Proteasome inhibitor
PK	Pharmacokinetics
PR	Partial Response
Q3W	Once every 3 weeks
QID	Four times a day
QTc	Corrected QT interval (ECG)
QTcF	Corrected QT interval Fridericia
RBC	Red blood cell
RNA	Ribonucleic acid
RRMM	Relapsed / refractory multiple myeloma
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sBCMA	Soluble B-cell maturation antigen
sCR	Stringent Complete Response
SCT	Stem cell transplant
SD	Stable Disease
SDV/SDR	Source Data Verification/Source Document Review
SoA	Schedule of Activities
SOI	Start of Infusion
SPD	Sum of the products of the maximal perpendicular diameters of measured lesions
SPEP	Serum protein electrophoresis
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reaction
t½	Terminal phase half-life
TLS	Tumor lysis syndrome
tlast	Last time point where the concentration is above the limit of quantification
tmax	Time of maximum observed concentration
TNF	Tumor necrosis factor
TTP	Time to Progression
TTR	Time to (best) Response
TTR	Time to Response
UK	United Kingdom
ULN	Upper limit of normal

UPEP	Urine protein electrophoresis
VGPR	Very Good Partial Response
Vss	Volume of distribution at steady-state
WBC	White blood cell
WFI	Sterile water for injection
WOCBP	Woman of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies	Trademarks not owned by GlaxoSmithKline group of companies
NONE	None

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

For examiners with a degree in ophthalmology or optometry, those involved in eye evaluations in the protocol will, at a minimum be able to provide comprehensive eye care to participants, which includes routine check-ups, treatment and ongoing management of visual disease. Qualified eye care specialists, including optometrist, will also be able to communicate with participants on the effect of belantamab mafodotin on eye.

Specifically, qualified eye care specialists must be able to:

- Perform comprehensive eye exams
- Perform visual Acuity with manual refraction tests and analyse results
- Perform slit lamp tests and analyse results
- Perform intraocular pressure examination
- Dilated fundoscopic examination
- Diagnose and treat ocular issues and diseases such as keratopathy or glaucoma.

10.10. Appendix 10: Home Healthcare and Telemedicine Approaches

Home Healthcare (General Visit)

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

Activities that may be done as part of a home healthcare visit must follow the schedule provided in the SoA (Section 1.3) and include:

- Collection of blood and urine samples including:
  - Safety assessments which may include routine blood and urine sampling
  - PK and ADA specimen collection
  - Efficacy assessments to be sent to central lab
  - Biomarker, immunogenicity and genetic assessments
  - Pregnancy tests

  Note: Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until their intended use. Please refer to the SRM/lab manual for sample collection and storage requirements.
- Measurement of vital signs (BP, heart rate, body temperature) and weight.
- Physical examination
- Administration of study drug (subcutaneous delivery only, no infusions).
- Administration of pre/post-medication
- Identification and reporting of concomitant medications.
- Dosing diary review for medication compliance.
- Identification and reporting of AEs/SAEs.
  Note: The investigator or other qualified medical professional must ensure reporting of AEs and SAEs is completed in accordance with the protocol and applicable regulations and that the appropriate medical intervention, therapeutic intervention, and/or support measures are instituted, as necessary.

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

Home Healthcare (Ophthalmologic Exam)

Where applicable country and local regulations and infrastructure allow, protocol-required eye exams may be done in the participant's home or specified alternative eye care specialist clinic. Activities that may be done as part of in-home eye exams must follow the schedule provided in the SoA (Section 1.3) and include:

- Visual Acuity (VA) by near-chart VA or pinhole.
- Slit lamp exam
- Tonometry
- Ophthalmoscopy

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

Telemedicine

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

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

- Medical evaluation of the participant
- Identification and reporting of concomitant medications.
- Dosing diary review for medication compliance.
- Identification, management, and reporting of AEs and SAEs.

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

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

10.11. Appendix 11: Data Management/Monitoring

Source Data Verification/Source Document Review (SDV/SDR)

During periods in which on-site monitoring is not permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution and in accordance to with local law and regulatory guidance documents.

Remote SDV/SDR will be proposed to study sites to meet a participant and/or critical data quality need, e.g., to assess participant safety or to ensure data integrity. The study specific monitoring plan will be updated in accordance with remote monitoring practices adopted for the country/study. The participant informed consent will be updated in line with local regulations to permit remote monitoring practices. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.

eCRF/CRF Final or Interim Sign off Process:

The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 and 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing the electronic data capture (eDC) platform using his/her unique eCRF login credentials.

Essential Document Sign Off Process:

If an investigator is unable to print and sign essential documents such as Protocol/Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK.

10.12. Appendix 12: Glomerular Filtration Rate Calculations

Background: In 2020 the FDA updated their guidance for determining renal function in pharmacokinetic studies. CCI [redacted] This requires use of the standardized MDRD* equation for estimation of GFR, and subsequent individualization of GFR by BSA for drug dosing. For comparison, the individual GFR of each participant will be normalized to 1.73.

Patient data required for calculations: serum creatinine (mg/dL), height (cm), weight (kg), gender and race.

Calculation 1:

eGFR by MDRD = 175 x Serum Cr $^{-1.154}$ x Age $^{-0.203}$ x 1.212 (if patient is black) x 0.742 (if female)

Link to Online Calculator: https://www.mdcalc.com/mdrd-gfr-equation

Answer 1: _____

Calculation 2:

BSA by Mosteller = (height (cm) x weight (kg) / 3600)$^{0.5}$

Link to Online Calculator: http://www.medcalc.com/body.html

Answer 2: _____

Calculation 3:

Patient's individual GFR for study: (eGFR by MDRD x Mosteller BSA)/1.73

OR (Answer 1 x Answer 2)/1.73

Answer 3: _____

If Answer 3 is:

a. ≥60, they would be eligible by iGFR for Part 1 Group 1
b. 15-29, they would be eligible by iGFR for Part 1 Group 2
c. <15, they would be eligible by iGFR for Part 2

Sources: FDA DHHS, 2020; Levey, 2006, and Mosteller, 1987.

*Modification of Diet in Renal Disease

10.13. Appendix 13: Protocol Amendment History

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

10.13.1. Amendment [2] 07-Jan-2022

Overall Rationale for the Amendment: Amendment 02 is a global amendment to include program-wide updated Keratopathy Visual Acuity (KVA) scale/footnotes; to update eligibility criteria for glomerular filtration rate calculations, human immunodeficiency virus positive (HIV+), hepatitis B positive (Hep B+), and hepatitis C positive (Hep C+) participants, all in order to align with the latest regulatory (United States Food and Drug administration [US FDA]) guidance; include modified inclusion criteria to meet the enrolment requirements from the regulatory agency of South Korea; and to allow additional tear sample collections in more participants should the tear sampling in the earlier enrolled participants yield insufficient tear amounts for assay analysis. Additional changes were incorporated which align with the new GlaxoSmithKline (GSK) protocol template and updated program level safety and pharmacokinetic (PK) language in line with the Investigator's Brochure (IB) update and/or updates as listed in table below.

Section # and Name	Description of Change	Brief Rationale
Headers, cover page and Protocol Amendment Summary of Changes Table	Headers and cover page were updated with new document number; Protocol Amendment Summary of Changes Table section was created and populated to include details and rationale for this amendment. Text included/amended throughout document	Editorial changes to align with the GSK's new standard protocol template and language
Throughout	Administrative updates to add clarification and/or remove discrepancies	Editorial changes were made for accuracy, clarity, conformity, flow, and typographical error corrections
Throughout	'Up to' has been used when referring to participant numbers in Part 2 (groups 3 and 4).	This was to ensure consistency in the document
Throughout	Updated Reference for trials in patients with impaired renal function	To align with the latest regulatory guidance for Pharmacokinetics Assessment in Patients with Impaired Renal Function
Section 1.1 Synopsis	Classification of Renal Function Stage 2 updated/clarified	To align with the latest regulatory guidance
Section 1.2 Study Schema	Study schema error was corrected Group 1 amended and group description updated in line with guidance	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities/ Table 1	Treatment cycle and Q3W and treatment visits clarified	To align with GSK program wide guidance. allowing flexibility in the timelines;
	Disease evaluation intervals defined	Clarification
	Serum and urine immunofixation only required at screening visit & complete response (CR)	Clarification
	Clarified that imaging is only required for extramedullary disease assessment	Clarification
	Bone marrow assessment section has been removed and is now represented in a separate table.	Simplification
	Redundant footnotes removed, editorial changes made	Removal of redundant text
	Hepatitis B virus (HBV)/Hepatitis C virus (HCV) testing footnote references to other tables made	In line with new eligibility criteria
	SPEP and UPEP negative result confirmation at central laboratory no longer required.	Simplification
	Clarified that standard disease laboratory tests to be performed locally.	Clarification
	Row for collection of subsequent therapy data added	Corrected omission. To reflect what is collected in the electronic data capture
	Updated wording on ocular event follow-up	In alignment with program level language
	Timing of assessments simplified to allow more flexibility.	Simplification
Section 1.3. Schedule of Activities	Added Table 2 for additional procedures for participants with a history of Hepatitis B	To align with the updated eligibility criteria and latest regulatory guidance
	Added Table 3 for additional procedures for participants with a history of Hepatitis C	To align with the updated eligibility criteria and latest regulatory guidance
	Added Table 4 for bone marrow (BM) Aspirate and Biopsy collection	To clarify BM sample collection

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis and Section 2. Introduction	Inclusion of new data from the recent belantamab mafodotin Investigator's Brochure (Version 09) including risk language update.	Updated based on the recent investigator brochure including safety and PK program level wording and other program language
Section 3 Objective and Endpoint	Replaced VGPR/CR/sCR with Clinical benefit rate	Correction; aligned with Objectives and Endpoint in Section 1.1
Section 4.1.3.2 Study Treatment Discontinuation	Text deleted as this was a repetition of Section 7.1	To avoid duplication of content
Section 4.1.4 Data Monitoring Committee	Section deleted as no longer relevant	Ensure only relevant text is present
Section 4.2 Justification for Dose	Redundant text deleted following release of latest version of IB (Version 9)	To avoid duplication of content
Section 5.1. Inclusion Criteria	Criteria 2 and 4 modified to meet the enrolment requirements from the regulatory agency of South Korea Criterion 2 following text included: In Republic of Korea, participants must be 19 years of age or older, at the time of signing informed consent. Criterion 4 following text included: In Republic of Korea, patients should also have relapsed or refractory disease after treatment with an anti-CD38 antibody, if accessible to patients, or other suitable local standard of care	South Korea regulatory authority required text
Section 5.2 Exclusion Criteria	Exclusion criteria for HIV+, Hep B+, and Hep C+ participants updated Criterion 14 cardiovascular risk amended	To align with the latest regulatory guidance Clarification and program level change
Section 6.2 Preparation/Handling/ Storage/Accountability	Safety precaution for handing of study drug added	To align with program level language
Section 6.6.2 Dose Reductions for Toxicity	Dose Modification Guidelines for Belantamab Mafodotin-Related AEs table amended Updated KVA scale footnotes	Clarification and program level change
Section 6.6.3 Guidance on Dose Delays for Treatment	Addition of Section	Clarification
Section 6.6.4 Management of Hepatitis B+ Participants	Addition of Section	To align with the latest regulatory guidance

Section # and Name	Description of Change	Brief Rationale
Section 7.1 Discontinuation of Study Drug	Addition of "current illness that prevents further administration of study drug" as reason for discontinuation	Clarification
Section 7.1.2 Left ventricular Ejection Fraction (LVEF) Stopping Criteria	The section was removed.	Discharged risk
Section 8. Study Assessments and Procedures	Allowed flexible language regarding order of assessments. Physical examinations no longer specified in detail Triplicate ECG text deleted Update to biomarker text to include that if biomarkers may be potentially predictive of response or associations with AEs are identified, samples may be used for the development of validated assays and/or diagnostic tests. Clarification of when echocardiogram can be performed detailed	Clarification and program level change
Section 8.5.1. Belantamab Mafodotin Sample Collection for Pharmacokinetics; Section 1.1 Synopsis; and Section 3 Objectives and Endpoints	Clarification of blood, dialysate fluid, urine and tear fluid sampling included Tears sample analysis wording changed to qualitative analysis only Flexible wording regarding tears exploratory endpoint included	Clarification Due to analytical methodology limitations, ADC and cys-mcMMAF concentrations can only be measured qualitatively in tear fluid Clarification
Section 9 Statistical Considerations	Introduction Section added Definition of the PK population and PK analysis updated Data monitoring committee section deleted as not applicable	Clarification Clarification To align with other changes in protocol and only keep sub-sections which are relevant
Section 10.2 Appendix 2: Clinical Laboratory Tests	Redundant text removed	Reduce repetition and clarification

Section # and Name	Description of Change	Brief Rationale
Section 10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Time frame for collection of pregnancy information post study drug added	In line with program level guidance
Section 10.6 Appendix 6: Liver Safety: Required Actions, Follow-up Assessments, and Study Intervention Re-challenge Guidelines	Language updated according to program language and HBV & HCV participants	To align with the updated eligibility criteria
Previous section 10.8 Appendix 8: Modified Diet in Renal Disease (MDRD) Formula	Deleted and text incorporated in Section 1.1 of protocol	Reduce repetition
Section 10.11 Appendix 11: Data Management/Monitoring	Added a new appendix	To accommodate program level change
Section 10.12 Appendix 12: Calculations	New appendix	To provide guidance on the updated GFR calculations
Section 10.13 Appendix 13: Protocol Amendment History	Included to show previous changes	In keeping with new protocol template
Section 11 References	References updated as necessary	Updated in line with changes in this protocol amendment

10.13.2. Amendment [1] 09-SEP-2020

Overall Rationale for the Amendment: The protocol has been amended in line with the new protocol template and updated program level safety and PK languages, which include the following:

- Combination of three separate tables in Schedule of Activities (SoA) into one table to reduce redundancy, included revision of some footnotes in the SoA.
- More clinical data were provided to update the Clinical Experiences section.
- Changed inclusion criteria of eGFR ≥90 mL/min/1.73 m^2 for group 1 (normal group) to be eGFR ≥60 mL/min/1.73 m^2 (normal/mildly renal impaired group)
- Removed the NCI-CTCAE ver. 5.0. and adopted Keratopathy Visual Acuity (KVA) Scale as corneal toxicity scale.
- Updated Benefit/Risk Assessment summary
- Updated definition of end of the study.
- Updated data scopes for analysis after Cycle 1 and part 1 of the study in Statistical Analysis section.
- Updated planned analyses for the study

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Removed "ECGs" from secondary objectives; and removed "ECG findings" from secondary endpoints	Incidence of cardiac events reported to date with belantamab mafodotin was relatively low and mostly Grade 1-2. ECG findings should be exploratory endpoint instead of secondary endpoint.
1.1 Synopsis	Changed “VGPR/CR/sCR” in exploratory end points to “CBR (Clinical Benefit Rate)”	Clarification of wording
1.1 Synopsis	Changed biomarker exploratory objective to “• To explore the relationship between biological characteristics and clinical response”. And changed biomarker exploratory endpoint to “Tumor and blood based analyses of DNA, RNA and protein changes including but not limited to baseline and on-treatment sBCMA and BCMA expression on myeloma cells.”	Program level update
1.2 Schema	Changed to a new schema to reflect dose schedules and possible dose adjustment.	Clarification of wording
1.3 Schedule of Activities	Combined Table 1, Table 2 and Table 3 into Table 1.	Make the SoA section consistent with the most up to date template.
1.3 Schedule of Activities	Added “X (QID)” to the row Preservative-free Artificial Tears at Q3W assessment	Preservative-free artificial tears need to be applied to participants daily during treatment.
1.3 Schedule of activities	Added footnote "CK- and LDH-isoenzymes will be analyzed if unexplained elevations in CK and LDH are observed on study. Can be performed at central laboratory. See Table 2 (“Potential for other laboratory abnormalities”) for more details." to LDH and CK isoenzyme Assays	Add more details to the assays
1.3 schedule of Activities	Removed “regardless of dosing” from "study assessment" footnote	Clarification of wording
1.3 Schedule of Activities	For "Imaging extramed disease", remove "X" from Q3W	Reduce frequency of examinations
1.3 Schedule of Activities	Removed "will have further ophthalmologic exams" from "Ocular exam"	Clarification of wording
1.3 Schedule of Activities	Footnote for Pharmacokinetic, added "All PK, sBCMA, and ADA samples once collected (regardless of dosing) will be analyzed if the sample date and time have been recorded."	Clarification of wording
1.3 Schedule of Activities	Changed "Urinalysis (dipstick) OR Spot Urine (albumin/creatine ratio) tests" to Urinalysis[15] tests: routine urine dipstick for protein”.	Clarification of wording
1.3 Schedule of Activities	Removed tear sample collection from "treatment period D1 of C2-Cx"	Minimize the time points for tear collection to reduce patient burden.
2.1 Study Rational	Added “multidrug resistance associated proteins (MRP)1, MRP2, and MRP3, a borderline substrate of bile salt export pump (BSEP)”.	Program level update

Section # and Name	Description of Change	Brief Rationale
2.1 Study Rational	Added "In a population PK analysis, data did not identify mild renal impairment as a significant covariate affecting the pharmacokinetics of belantamab mafodotin when compared to normal participants. This population was also the largest subgroup with renal function status to be treated with belantamab mafodotin in previous studies. These 2 factors justify the use of normal/mild renal impairment grouping as the appropriate comparator group for the other levels of impaired renal function."	Clarify the need to include mildly impaired renal function participants to the control group.
2.2.2 Clinical Experience	Added "Based on the efficacy and safety findings (summarized below), belantamab mafodotin was approved in Aug 2020 by the US FDA and European authorities for the treatment of certain groups of patients with RRMM."	Program level change
2.2.2 Clinical Experience	Removed all original contents and added subsection 2.2.2.1. Phase I FTIH Study BMA117159/DREAMM-1BMA117159 "; 2.2.2.2 Phase II Study 205678/DREAMM-2; 2.2.2.3 Safety; 2.2.2.4 Pharmacokinetics and Pharmacodynamics in Humans	Program level safety and clinical experiences update
2.3 Benefit/Risk Assessment	Added "In accordance with the International Conference on Harmonisation (ICH), this study has been designed to minimize risk and maximize benefit to study participants. Table 2 lists the benefit/risk assessment for this study."	Program level update
2.3 Benefit/Risk Assessment Table 2	Replaced Table 2 with the most up to date summary	Program level update
3. OBJECTIVES AND ENDPOINTS	Changed exploratory objective for biomarker to "To explore the relationship between biological characteristics and clinical response". And changed exploratory endpoint for biomarker to "Tumor and blood based analyses of DNA, RNA and protein changes including but not limited to baseline and on-treatment sBCMA and BCMA expression on myeloma cells".	Program level update
4.1.2. Participant Recruitment and Groups. Table 3	Changed inclusion criteria of eGFR ≥90 mL/min/1.73 m2 for group 1 (normal group) to be eGFR ≥60 mL/min/1.73 m2 (normal/mildly renal impaired group)	Modified the eGFR to include participants with mild renal impairment
4.2 Justification for Dose	Changed "This is the recommended dose" to "This is also the regulatory agency approved dose".	Clarification of wording
4.2 Justification for Dose	Changed "Any dose level below 1.9 mg/kg a priori is not planned; yet, if belantamab mafodotin exposure similar to that seen at a 1.9 mg/kg dose can be achieved with a lower dose, this lower dose may be recommended for Part 2, as appropriate." to "Dose levels other than 2.5 mg/kg or 1.9 mg/kg Q3W dose a priori are not planned; however, if belantamab mafodotin exposure similar to that seen at these doses can be achieved with another dose, this other dose may be recommended for Part 2, as appropriate."	Add flexible language for dose adjustment

Section # and Name	Description of Change	Brief Rationale
4.3 End of Study Definition	Removed "End of study is defined as when all participants have completed the study, have died, were lost to follow-up, have withdrawn consent, or moved to a roll-over study." Added: "Participants are considered to have completed the study if they are followed until end of study. End of study is defined as when all participants have either died, progressed, withdrawn consent or have been followed for a minimum of 12 months from last participant first dose (LPFD). Participants who have not died, progressed or withdrawn consent at the time the study is closed will continue to have access to belantamab mafodotin if considered to be beneficial by the investigator. In the event a rollover study is available, such study might be used for continued access.	Clarification of wording
5.1. Inclusion Criteria Table 4	Changed eGFR ≥90 mL/min/1.73 m^2 to eGFR≥60 mL/min/1.73 m^2	Study data supported and regulatory agency agreed that the "normal" matching group can include participants that have normal or mildly impaired renal function.
5.2 Exclusion Criteria #1	Added "Waldenstroem Macroglobulinemia" to exclusion criteria # 1	Clarification of wording
5.2 Exclusion Criteria #3	Changed to "Participant has received an investigational drug within 14 days or 5 half-lives, whichever is shorter, preceding the first dose of study drug. This includes prior treatment with a monoclonal antibody. The only exception is emergency use of a short course of systemic corticosteroids (equivalent to, or less than: dexamethasone 40 mg/day for a maximum of 4 days) before treatment."	Clarification of wording
5.3 Lifestyle Considerations	Added conditions when contact lenses can be used. Moved the vaccine language to 6.5.: Concomitant Therapy.	Clarification of wording
6.6.2 Dose reductions for toxicity Table 6	Added Urine Dipstick use	Clarification of wording
6.6.2.1 Corneal Supportive Care Guidelines for Belantamab Mafodotin	Removed the NCI-CTCAE ver. 5.0. as corneal toxicity scales. Added Table 7: Keratopathy Visual Acuity (KVA) Scale for Treatment-related Corneal Toxicities and Table 8: Dose Modifications for belantamab mafodotin based on the KVA scale:	Program level update
6.6.2.1 Corneal Supportive Care Guidelines for Belantamab Mafodotin	Changed "Treatment-related ocular AEs are to be reported based on NCI-CTCAE v5.0 criteria for eye disorders" to "KVA scale"	Program level update
6.6.2 Dose Reductions for Toxicity	Added "Corneal ulcer by definition means an epithelial defect with underlying stromal infiltration."	Program level update
6.6.2.1 Corneal Supportive Care Guidelines	Added "Corticosteroid eye drops are not required as prophylaxis but can be used therapeutically if clinically indicated per discretion of an eye-care specialist. Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops (if administered together)."	Program level update

Section # and Name	Description of Change	Brief Rationale
6.6.2.1 Corneal Supportive Care Guidelines for Belantamab Mafodotin	Added Table 9: General Dose Modification and Management Guidelines for Drug-Related AEs Not Otherwise Specified	Program update
6.6.2.1.1. Ocular Prophylaxis	Added a sub-section under 6.6.2.1 for details on ocular prophylaxis.	Program level update
6.7. Intervention after the End of the Study	Changed "To provide continued access to study drug, participants who benefit from this study may be rolled over to another continuation study when Study 209626 is completed or closed." To "All participants who have not progressed at the time of the final analysis will be offered belantamab mafodotin for further treatment until progression or unacceptable toxicity."	Clarification of wording
7.1 Discontinuation of Study Intervention	Deleted "In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and time to progression, as appropriate. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention."	Clarification of wording
7.1.1 Liver Chemistry Stopping Criteria	Updated Figure 2: Liver Chemistry Stopping and Monitoring Event Algorithm – Normal Hepatic Function	Program level update
7.1.2 QTC stopping Criteria	Deleted Section 7.1.2, and renumber the contents under Section 7.1.	QTC risk is low, and the study is not collecting ECG during treatment period
7.1.3 Corneal Event Stopping Criteria	Updated the whole section	Program level update
8.2.3.1 First Infusion	Added "On subsequent dosing days, vital signs must be assessed pre-dose (within 30 minutes prior to SOI) and within 15 min after EOI, and as clinically indicated."	Clarification of wording
8.2.7. ophthalmic Assessments	Added details of how the participants will be assessed by a qualified eye care specialist at screening/baseline and then Q3W prior to dosing up to the sixth dose of belantamab mafodotin.	Program level update
8.2.7. ophthalmic Assessments	Deleted "Participants who have treatment-related ocular AEs per the NCI-CTCAE v5.0 criteria for eye disorders present at end of study treatment will continue to be followed every 3 months for up to 12 months, or until resolution (to Grade 1 or baseline) by qualified eye care specialist, whichever comes first."	Reduce redundency
8.3. Adverse Events and Serious Adverse Events	Deleted "Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary and grouped by system organ class according to NCI-CTCAE (version 5.0). Dose modifications as a result of corneal events will be based on guidelines presented in Table 8."	Reduce redundency
8.3.5 Pregnancy	Changed follow up of pregnant females after the last dose from 9 months to 4 months.	Program level update

Section # and Name	Description of Change	Brief Rationale
8.2.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs	Deleted the section, added "Death due to the disease under study is to be recorded on the Death eCRF" to 8.3.6.	Reduce redundancy
8.2.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs	Deleted "	
8.3.7. Adverse Events of Special Interest	Changed "Adverse events of special interest (AESI) for belantamab mafodotin are corneal events, thrombocytopenia and infusion-related reactions and graded (CTCAE, v5.0). Severity of corneal events will also be graded using CTCAE v5.0. Dose modifications for belantamab mafodotin corneal events will be based on guidelines presented in Table 9." To "Adverse events of special interest (AESI) for belantamab mafodotin are corneal events, thrombocytopenia, and IRRs. Corneal events associated with belantamab mafodotin will also be graded according to the KVA scale. Other treatment-related ocular AEs are to be reported based on NCI-CTCAE v5.0 criteria for eye disorders. Severity of all other AESIs will be graded using NCI- CTCAE (v5.0)."	Program level change
8.4 Treatment of Overdose	Changed bullet point "Obtain an additional plasma sample for PK analysis if requested by the GSK Medical Monitor (determined on a case-by-case basis)." to "Monitor the participant closely for AEs, SAEs, and laboratory abnormalities until they have resolved, and belantamab mafodotin concentrations are predicted to be within the anticipated range in absence of the overdose. Obtain a plasma sample for PK analysis and a blood sBCMA sample if requested by the GSK Medical Monitor (determined on a case-by-case basis)."	Clarification of wording
8.5.1.1. Blood	Combined columns titled "Cycle 4, 6" and "Cycle 9 and 12 and q6 cycles" to one column titled "Cycle 4, 6, 9 and 12"	Both columns collected samples at the same time points.
8.5.1.2. Dialysate Fluid	Added sample collection window "the dialysate fluid for analysis of cys-mcMMAF will be collected over each 1-hour (± 5 min) collection interval of that session. On other PK days, the PK sample will be collected prior to a hemodialysis session if one were to occur that day."	Clarification of wording
8.5.1.3 Urine	Added sample collection window "A baseline predose urine sample will be collected on C1D1. Twenty-four-hour (± 2 hours)"	Clarification of wording
8.5.2 Belantamab Mafodotin PK Sample Analysis	Added "All PK, sBCMA, and ADA samples once collected (regardless of dosing) will be analyzed if the sample date and time have been recorded."	Clarification of wording
8.5.2 Belantamab Mafodotin PK Sample Analysis	Deleted "detailed in the relevant sample processing documents (e.g., SRM, CLW, SOW)."	Clarification of wording

Section # and Name	Description of Change	Brief Rationale
8.9 Biomarkers	Biomarkers section updated to better reflect biomarker strategy for this study	In line with program level requirements
9.2 Sample Size	Changed “up to 40 participants” to “up to 36 participants”.	Clarification of wording
9.4 Statistical Analyses	Added data analysis and data scopes after the completion of Cycle 1 and part 1 of the study, added Table 14 to summarize all planned analysis throughout the study.	Clarification of wording
9.4.3. Pharmacokinetic Analyses	Deleted AUC0-t ,CL, Vss, λz, C-EOIand t½ from belantamab mafodotin PK parameters, and changed PK parameter for cys-mcMMAF from “Cmax, tmax, Ctrough, AUC [AUC(0-168h), AUC(0-tlast), AUC(0-tau) and/or AUC(0-∞), %AUCext if AUC(0-∞) computed], tlast, λz, and t½” to “Cmax, tmax, AUC(0-168h), and tlast will be computed at Cycle 1 and Cycle 3, as data permit.”	Removed PK parameters that recent program data suggest will not be determinable because of lack of measurable concentrations or computation of CL, Vss, t1/2 may be deterimined using POPPK analysis in separate report
Table 15 Statistical Analysis Methods for Efficacy Endpoints	Added "or death due to PD" and "Descriptive statistics (mean, standard deviation, median, range) will be provided for participants who achieve PR or better, by censoring status." to DoR definition. Add "or death due to PD" and "Descriptive statistics will be provided for subjects with PD or who die due to PD and descriptive statistics of time on follow-up will be provided for subjects who do not have PD." to TTP definition. Add "Descriptive statistics will be provided for participants who achieve PR Sor better" to TTR definition. Delete "For DoR, TTP and TTR, descriptive statistics (mean, standard deviation, median, range) will be provided. For duration of response and time to progression, the number and percentage of censored participants will also be shown."	Clarification of wording
Table 16 Statistical Analysis Methods for Safety Endpoints	Changed “CTCAE (version 5.0)” to “KVA scales” Added laboratory evaluations, ocular assessments. Deleted ECG and ECHOs from secondary endpoints	Incidence of cardiac events reported to date with belantamab mafodotin was relatively low and mostly Grade 1-2. ECG findings will be exploratory endpoint instead of secondary endpoint.
Table 17 Statistical Analysis Methods for Pharmacokinetic Endpoints	Deleted AUC0-t, AUC0-tau CL, t1/2 from primary end points	Removed PK parameters that recent program data suggest will not be determinable because of lack of measurable concentrations or computation of CL, t1/2 may be determined using POPPK analysis in separate report
9.4.5. Data Monitoring Committee	Added 9.4.5. Data Monitoring Committee section	Protocol template compliance
9.5 Interim Analysis	Deleted the original text and changed it to “Details of the interim analyses are provided in Table 14. Full details of the endpoints and outputs generated for each planned analysis will be described in the SAP.”	Clarification of wording
10.2 Appendix 2: Clinical Laboratory Tests: Table 18	Rearranged the footnotes to a new numeric order.	Clarification of wording

Section # and Name	Description of Change	Brief Rationale
10.2 Appendix 2: Clinical Laboratory Tests: Table 18	"BM biopsy to confirm sCR (by IHC)[3] ", changed to "BM biopsy to confirm sCR (by IHC)[2] "	Clarification of wording
10.2 Appendix 2: Clinical Laboratory Tests: Table 18	"PK and ADA[1]" and "Biomarker Measurements[2]" change to "PK and ADA[3]" and "Biomarker Measurements[3]"	Clarification of wording
10.2 Appendix 2: Clinical Laboratory Tests: Table 18	Changed Urine test to "Spot urine (from first void) for albumin/creatinine ratio[2] OR urine dipstick for protein[4]", and added footnote" 4. 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."	Clarification of wording
10.2 Appendix 2: Clinical Laboratory Tests: Table 18	In section Optional testing, removed "clot" from "BM aspirate clot".	Change in sample type; high assay failure due to hemodilution in bone marrow aspirate clot.
10.2 Appendix 2: Clinical Laboratory Tests: Table 18	Added footnote "By central lab if UPEP is negative, at the time of first achieving CR, then perform every 3 weeks until suspected PD after CR or sCR." Added this footnote to Serum immunofixation and Urine immunofixation.	Clarification of wording
10.6 Appendix 6	Deleted "Blood sample for pharmacokinetic (PK) analysis, obtained 45 days after last belantamab mafodotin dose", and replaced with "Blood sample for pharmacokinetic (PK) analysis and a blood sample for sBCMA, obtained within 70 days after last belantamab mafodotin dose"	Add sBCMA sample collection, also extend the safety follow up to 70 days.
10.6 Appendix 6	Replaced footnote 6 with ". Record the date/time of the PK/sBCMA blood sample draw and the date/time of the last dose of study intervention prior to PK/sBCMA 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/sBCMA sample cannot be collected in the time period indicated above, do not obtain a PK/sBCMA sample. Instructions for sample handling and shipping are in the SRM"	Clarification of wording
10.10. Appendix 10	Added Appendix 10: Eye Care Specialist's Qualifications and Requirements.	Program level update
10.11 Appendix 11	Added Appendix 11: Home Health Care and Telemedicine Approaches	Program level update
Throughout the protocol	Remove INR data collection	INR data are not relevant in a renal impairment study
Throughout the protocol	Changed screening window from 21 days to 28 days	Program level updates
Throughout the protocol	Changed the follow up period with Women of Child Bearing Potential from 9 months to 4 months	Program level updates
Throughout the protocol	Changed the use of "subject", "participant" or "patient" in the protocol to use "participant" only	Clarification of wording
Throughout the protocol	Changed the use of "Report Analysis Plan" (RAP) in the protocol to use "Statistical Analysis Plan" (SAP)	Clarification of wording

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Changed the safety follow up after the last dose from 45 days to 70 days.	Program level update
Throughout the protocol	Removed roll-over to another study language	Program does not allow participants to roll over to another study
Throughout the protocol	Changed “normal renal function” to “normal/mildly impaired renal function”.	Suggested by regulatory agency to include mildly impaired renal function participants in the control group (grouop 1).
Throughout the protocol	Changed reference of IB to GlaxoSmithKline Document Number 2013N175128_08; GSK2857916, Belantamab Mafodotin IB, 2020	Program IB update

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