Protocol Amendment 5

Study ID: 207495

Official Title of Study: A Phase III, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of Single Agent Belantamab Mafodotin Compared to Pomalidomide Plus Lowdose Dexamethasone (Pom/Dex) in Participants With Relapsed/Refractory Multiple Myeloma (RRMM) (DREAMM 3)

NCTID: NCT04162210

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TITLE PAGE

Protocol Title: A Phase III, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of Single Agent Belantamab Mafodotin Compared to Pomalidomide plus Low-dose Dexamethasone (pom/dex) in Participants with Relapsed/Refractory Multiple Myeloma (RRMM) (DREAMM 3)

Protocol Number: 207495/Amendment 5

Compound Number: GSK2857916

Study Phase: Phase 3

Short Title: Phase III Study of Single Agent Belantamab Mafodotin versus Pomalidomide plus Low-dose Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma

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Approval Date: 07 Sep 2022

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	*Date of Issue*	*DNG/TMF Number*
Amendment 5	07 Sep 2022	TMF-14920746
Amendment 4	07 Sep 202220-Apr-2022	TMF-14577505
Amendment 3	21-Oct-2021	TMF-14062052
Amendment 2	20-Sept-2021	TMF-13954921
Amendment 1	23-Oct-2020	2017N336101_01
Original Protocol	30-Sep-2019	2017N336101_00

Amendment 5: 07 Sep 2022
This amendment is considered to be non-substantial based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union because it neither significantly impacts the safety of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

This protocol amendment changes the method for the primary analysis of efficacy endpoints from being based on algorithm-derived confirmed response and dates per IMWG [Kumar, 2016] criteria, to being based on investigator-assessed responses and dates per IMWG. The primary efficacy analysis will be supported by a pre-specified Independent Review Committee (IRC) audit for the analysis of the efficacy endpoints.

In addition, the definition for duration of response was updated, the countries included in the North East Asia subgroup defined, the required number of events for the primary PFS analysis aligned, the language for anti-myeloma therapy updated, and the PACT language including ocular follow up update.

Section # and Name	**Description of Change**	**Brief Rationale**
Throughout the protocol	Change from anti-cancer therapy wording to anti-myeloma therapy	To define the allowance of local therapy for unrelated malignancies, to define the scope of permitted myeloma therapy, to clarify confirmation of disease progression as per IMWG criteria prior to initiating a new anti-myeloma therapy, to define prior lines of therapy appropriately
Section 1.1 Synopsis Section 5.1 Overall Design Section 5.4 EOS Definition Section 10.5: Planned analysis	Clarification to when final analysis will occur	Clarification
Section 1.1 Synopsis Section 5.1 Overall Design Section 5.4 EOS Definition Section 9.3.1 Time period and Frequency for	Update to PACT language to clarify End of Study vs Final analysis langauge; to clarify ocular assessment during the PACT phase	Clarification

Section # and Name	Description of Change	Brief Rationale
Collecting AE and SAEs		
Section 1.1 Synopsis Section 4: Objectives and endpoints Section 10.4.1 Efficacy Analyses	Change to duration of response (DoR) definition to include death due to any cause.	Health authority request to update DoR definition
Section 4: Objectives and endpoints Section 9.1 Efficacy Assessments Section 10.4.1 Efficacy Analyses. Section 11.1.5 Committee Structures	Removal of algorithm-derived assessment of response and instead, efficacy analysis will be based on Investigator-assessed response, supported by the results of an IRC audit	Health authority request for PFS to be determined by Investigator-assessed response, supported by the results of an IRC audit
Section 7.5.1 Permitted Medications	Clarify treatment for an unrelated malignancy	To allow optimal patient treatment
Section 7.5.2 Prohibited Mediications	Clarify prohibited treatments	To ensure appropriate treatment in the study
Section 7.6.2.1 Belantamab mafodotin – Arm 1 (Table 11)	Dose modification for creatinine and ACR updated	To align with CTCAE
Section 7.7: Continued Access to Study Intervention after the End of the Study	Title updated to distinguish between Continued access after EOS and after Final analysis	To align with PACT process
Section 7.7.1: Continued Access to Study Intervention after Final DCO prior to EOS	New section to distinguish between Continued access after EOS and after Final analysis	To align with PACT process
Section 9.1.1 Independent review Committee	New section to explain the purpose and scope of the IRC	To align with the implementation of an IRC audit
Section 10.4.1 Efficacy Analyses	NE Asia region definition clarified to be a region consisting of Japan, China, and Republic of Korea	Health authority request to clarify definition of NEA pooled analysis based on ICH E17 guidelines
Section 10.2: Sample Size Determination	Change in PFS events required from ‘at least’ 151 to ‘approximately’ 151	To align language throughout the statistical consideration section
Section 10.5: Planned analysis	Correction of footnote for OS IA	Correction

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Protocol Summary

1.1. Synopsis

Protocol Title: A Phase III, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of Single Agent Belantamab Mafodotin Compared to Pomalidomide plus Low-dose Dexamethasone (pom/dex) in Participants with Relapsed/Refractory Multiple Myeloma (RRMM) (DREAMM 3)

Short Title: Phase III Study of Single Agent Belantamab Mafodotin versus Pomalidomide plus Low-dose Dexamethasone in Participants with Relapsed/Refractory Multiple Myeloma

Rationale: Multiple myeloma (MM) is an incurable malignancy which accounts for 1% of all cancers and for 10% of all hematologic malignancies. A variety of drugs and combination treatments have been evaluated and found effective in treating MM. However, despite those treatment options, most, if not all, MM patients will ultimately develop resistance to existing therapies supporting the urgent need for new treatments.

Immunomodulatory agents, such as lenalidomide and pomalidomide, are an important cornerstone of treatment for relapsed/refractory MM (RRMM). Pomalidomide administered with low-dose dexamethasone (pom/dex) is approved in the US, European Union (EU) and a number of other countries worldwide for patients with RRMM who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on, or within 60 days of completion of, the last therapy. In the Phase III trial MM-003, which compared pom/dex with high-dose dexamethasone (HD) in this patient population, the median overall survival (OS, 12.7 [95% confidence interval (CI): 10.4, 15.5] vs. 8.1 [95% CI: 6.9,10.8] months; hazard ratio (HR): 0.74 [95% CI: 0.56, 0.97]; p=0.0285) and progression-free survival (PFS, 4.0 [95% CI: 3.6, 4.7] vs. 1.9 [95% CI: 1.9, 2.2] months; HR: 0.48 [95% CI: 0.39, 0.60]; p<0.0001) were significantly longer with pom/dex than with HD alone. An overall response rate (ORR) of 31% was achieved with pom/dex. Pom/dex has been widely adopted globally as a treatment regimen for patients with advanced RRMM and is recommended in treatment guidelines.

Belantamab mafodotin (GSK2857916) is a humanized (IgG1) immuno-conjugate which binds to BCMA, a target widely expressed on malignant plasma cells in MM. The parent anti-BCMA antibody is conjugated to the small molecule microtubule inhibitor monomethyl auristatin-F (MMAF), which is released inside the malignant cell after binding and internalization of the antibody.

Single agent belantamab mafodotin has demonstrated to have a strong single-agent activity with a well-defined manageable safety profile in heavily pre-treated participants with RRMM (Q3W schedule via intravenous (IV) administration), based on final data from the First-Time-in-Human (FTIH) study BMA117159 (DREAMM-1) in participants who were refractory to at least one line of therapy and primary analysis data from the ongoing Phase II study 205678 (DREAMM 2) in participants who have failed at least 3

prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and who are refractory to an immunomodulatory agent and a proteasome inhibitor.

In the FTIH DREAMM-1 study, as of the efficacy cut-off date of 31 August 2018, in the 32 out of 35 participants in the Part 2 expansion cohort who were refractory to both immunomodulatory agents and proteasome inhibitors (PIs) and were treated with belantamab mafodotin (3.4 mg/kg IV), the ORR was 56% (95% CI: 37.7, 73.6) and median progression free survival (mPFS) was 7.9 months (95% CI: 2.3, Not estimable [NE]). In BMA117159, belantamab mafodotin demonstrated an acceptable safety profile. The most commonly reported adverse events (AEs) were cough, increased aspartate aminotransferase, and nausea, all of which were mostly mild or moderate (Grade 1 or 2), in addition to corneal events and thrombocytopenia, which are consistent with the known toxic effects of other MMAF-linked antibody-drug conjugates (ADCs) and were found to be manageable.

The ongoing Phase II study 205678/DREAMM-2 is evaluating these two IV single agent doses (2.5 and 3.4 mg/kg) in participants who have failed at least 3 prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and who are refractory to an immunomodulatory agent and a proteasome inhibitor. A total of 194 participants received frozen drug product in the main cohort. The study met its primary endpoint for ORR. As of the cut-off date of 31 January 2020, ORRs were 31% (97.5% CI 21.7,43.6) in the 2.5 mg/kg arm and [35% (97.5% CI 24.8,47.0) in the 3.4 mg/kg arm. The median duration of response (DoR) was 11.0 months (95% CI: 4.2, not reported [NR]) at 2.5 mg/kg and 6.2 months (95% CI: 4.8, NR) at 3.4 mg/kg. The mPFS was 2.8 months (95% CI: 1.6, 3.6) and 3.9 months (95% CI: 2.0, 5.8), respectively and the median OS was 13.7 months (95% CI: 9.9, NR) at 2.5 mg/kg and 13.8 months (95% CI: 10.0, NR) at 3.4 mg/kg. 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.

Further information on the effects of belantamab mafodotin are available in the Investigator's Brochure.

The efficacy and safety results from BMA117159 and primary analysis data from study 205678 indicate that belantamab mafodotin is an effective single agent treatment option for patients with RRMM, with a novel mechanism of action (MOA). In binding to BCMA on malignant plasma cells, belantamab mafodotin initiates cell killing via a multimodal-mechanism, including delivering MMAF to BCMA-expressing MM cells, inducing apoptosis, enhancing antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, and inducing immunogenic cell death. Further evaluation of single agent belantamab mafodotin is warranted in a randomized Phase III study against pom/dex, an established standard of care in RRMM.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the efficacy with belantamab mafodotin vs pomalidomide plus low dose dexamethasone (pom/dex) in participants with relapsed/refractory multiple myeloma (RRMM)	• PFS, defined as the time from the date of randomization until the earliest date of documented disease progression (according to IMWG Response Criteria) or death due to any cause
Key Secondary	
• To compare the overall survival with belantamab mafodotin vs pom/dex in participants with RRMM	• OS, defined as the time from randomization until death due to any cause
Secondary	
• To compare other markers of efficacy of belantamab mafodotin vs pom/dex in participants with RRMM	• ORR, defined as the percentage of participants with a confirmed PR or better per IMWG • Clinical benefit rate (CBR), defined as the percentage of participants with a confirmed minimal response (MR) or better per IMWG • DoR, defined as the time from first documented evidence of PR or better until PD per IMWG or death due to any cause among participants who achieve confirmed PR or better • TTR, defined as the time between the date of randomization and the first documented evidence of response (PR or better) among participants who achieve confirmed PR or better. • TTP, defined as the time from the date of randomization until the earliest date of documented PD (per IMWG Response Criteria) or death due to PD
• To evaluate the safety and tolerability of belantamab mafodotin vs pom/dex in participants with RRMM	• Incidence of adverse events (AEs) and changes in laboratory parameters • Ocular findings on ophthalmic exam
• To evaluate the pharmacokinetic profile of belantamab mafodotin	• Plasma concentrations of belantamab mafodotin, total monoclonal antibody (mAb), and cys-mcMMAF
• To assess anti-drug antibodies (ADAs) against belantamab mafodotin	• Incidence and titers of ADAs against belantamab mafodotin
• To evaluate the tolerability of belantamab mafodotin vs pom/dex based on self-reported symptomatic adverse effects	• Symptomatic adverse effects as measured by the PRO-CTCAE and OSDI
• To evaluate and compare changes in symptoms and health-related quality of life (HRQOL) of belantamab mafodotin to pom/dex.	• Health-related QOL as measured by EORTC QLQ-C30, EORTC QLQ-MY20* and EORTC IL52*.
• To assess Minimal Residual Disease (MRD) in participants who achieve ≥VGPR or better for belantamab mafodotin vs pom/dex	• MRD negativity rate, defined as; the percentage of participants who are MRD negative by NGS method

ADA= anti-drug antibodies; AE = adverse event; BCMA = B cell maturation antigen; cys-mcMMAF= cysteine maleimidocaproyl monomethyl auristatin-F; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; EORTC IL52 = Disease Symptoms domain of EORTC QLQMY20; EORTC QLQC30 = EORTC Quality of Life Questionnaire 30 item Core module; EORTC QLQMY20 EORTC Quality of Life Questionnaire 20 item Multiple Myeloma module; HCRU = health care resource utilization; HRQoL = health related quality of life; IMWG = International Myeloma Working Group; MRD = minimal residual disease; NGS = Next Generation Sequencing; ORR = overall response rate; OS = overall survival; OSDI = Ocular Surface Disease Index; PD = progressive disease; PFS = progression-free survival; pom/dex = pomalidomide/ dexamethasone; PR = partial response; PROCTCAE = Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QOL = quality of life; RRMM = relapsed/refractory MM; SAE = serious adverse event; TTP = time to progression;

Objectives	Endpoints
TTR -= time to response; VGPR= very good partial response *EORTC IL52 applies to participants enrolled under the original protocol; EORTC QLQ-MY20 applies to participants enrolled under protocol amendment 1	

Overall Design:

This study is a Phase III, open-label, randomized, multicenter study evaluating the efficacy and safety of single agent belantamab mafodotin compared to pom/dex in participants with RRMM.

The study will include a screening period, study treatment period, and follow-up (see Figure 1).

During screening participants will be evaluated for study eligibility per protocol as defined in the Inclusion and Exclusion criteria. Eligible participants must have been previously treated with at least two prior lines of therapy, including at least 2 consecutive cycles of both lenalidomide and a proteasome inhibitor (PI), (given separately or in combination) and must have documented progression (a) on, or within 60 days of completion of the last therapy or (b) must be non-responsive while on last treatment, where non-responsive is defined as not achieving at least Minimal Response (MR) after 2 complete treatment cycles. In such cases lack of achieving of MR must be determined no earlier than at least 4 weeks after the last treatment.

Following screening, participants will be centrally randomized in a 2:1 ratio to either Arm 1 (single agent belantamab mafodotin) or Arm 2 (pom/dex), as described in Intervention Groups and Duration. No cross-over will be allowed during the study until the final OS analysis.

The study assessments will be performed during Screening, prior to the first dose of Cycle 1, and during each cycle of treatment.

Upon permanent discontinuation of study treatment, participants will enter the follow-up phase: PFS follow-up for participants who discontinue study treatment but have not yet progressed and OS follow-up for participants with progressive disease (including those who were previously in PFS follow-up and have subsequently progressed). Participants are to follow the assessments as specified in the SoA.

Number of Participants:

Approximately 320 participants will be randomized in a 2:1 ratio, in favor of Arm 1. Arm 1 (single agent belantamab mafodotin) will enroll approximately 214 participants and Arm 2 (pom/dex) will enroll approximately 106 participants. The randomization will be based on stage (International Staging System [ISS]), prior treatment with an anti-CD38 agent (with a 40% global enrollment cap for participants with prior anti-CD38 treatment),

and number of prior lines of therapy (with a 55% global enrollment cap for participants with ≤3 prior lines) using a central Interactive Response Technology (IRT) system.

If the number of participants required by local regulatory agencies are not recruited within the planned recruitment target, enrollment may continue in separate cohorts until the country enrollment requirements are met. Additional participants that are enrolled in separate cohorts will not be included in the analysis portion of the study planned for the marketing authorization application, which is based on approximately 151 events. However, these additional participants will be included in country-specific supplemental analyses, as detailed in the country-specific Statistical Analysis Plan (SAP).

Intervention Groups and Duration:

In this open-label randomized study comparing belantamab mafodotin vs pom/dex (see Figure 2 for a treatment and assessment schedule in both arms):

Arm 1: Single agent Belantamab mafodotin

Belantamab mafodotin will be administered intravenously at 2.5 mg/kg on Day 1 (D1) of a Q3W schedule (e.g., 21-day cycle). The dose to be administered is based on actual body weight calculated at baseline. If the change of body weight is greater than 10%, the dose should be re-calculated based on the actual body weight at the time of dosing. The dose may be reduced to address toxicity according to protocol guidelines.

Premedication (e.g., systemic corticosteroids) is not required unless deemed medically necessary by the investigator, in which case it should be administered according to institutional recommendations. If an infusion-related reaction (IRR) occurs during administration, the infusion rate may be reduced or halted at the discretion of the investigator depending on the severity of the symptoms.

Arm 2: Pomalidomide and low-dose dexamethasone (Pom/Dex)

Pomalidomide will be administered orally at the approved starting dose of 4 mg daily on Days 1 to 21 of each 28-day cycle, with dexamethasone administered orally at a dose of 40 mg once weekly (Days 1, 8, 15, and 22) as outlined in Section 5.3.2. For participants over 75 years old, dexamethasone should be administered at the lower dose of 20 mg once weekly (Days 1, 8, 15, and 22).

End of Treatment and End of Study Definitions:

Participants in both arms will be treated until disease progression, death, unacceptable toxicity, withdrawal of consent, lost to follow-up, or end of study, whichever comes first.

The final analysis will occur when the planned 250 deaths for final OS analysis have occurred. If 250 OS events cannot be achieved, the final analysis will occur when all participants have died, are lost to follow up or have withdrawn consent. If OS is significant at 70% IF, no formal statistical testing will be conducted after 250 death events and OS data will continue to be collected until all participants have died, are lost

to follow up, or withdrawn consent, or for 2 years after the OS analysis at 70% IF, whichever occurs first.

Following the final analysis, including any country-specific (expansion cohort) analysis, DREAMM-3 will move into the post analysis continued treatment (PACT) phase where the study remains open to provide continued access to treatment for study participants who are continuing to derive clinical benefit. At that time, the collection of new data for participants who no longer receive study treatment will stop entirely and the clinical trial database will be closed. Participants in survival follow-up will be considered to have completed the study. Those participants still benefiting from study treatment in the opinion of their treating physician may continue to receive study treatment and only SAEs, AEs leading to treatment discontinuation, overdose, and pregnancy cases, and pre-specified ocular data (Arm 1 only), will be reported directly to GlaxoSmithKline (GSK).

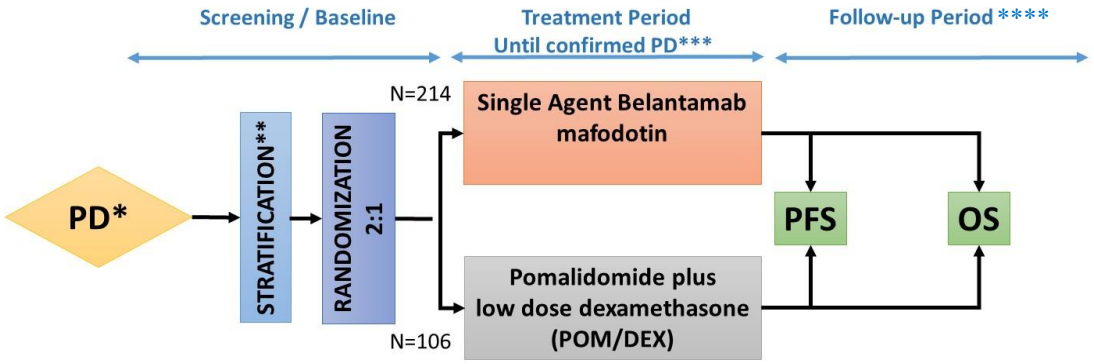
The end of study (EOS) is defined as the date when the last participant had their last visit (last subject last dose plus 70 days SAE reporting period).

Independent Data Monitoring Committee:

An Independent Data Monitoring Committee (IDMC) will be employed for this study to review data at defined time points as outlined in the IDMC charter. The IDMC will be comprised of at least two physicians and one statistician external to GSK.

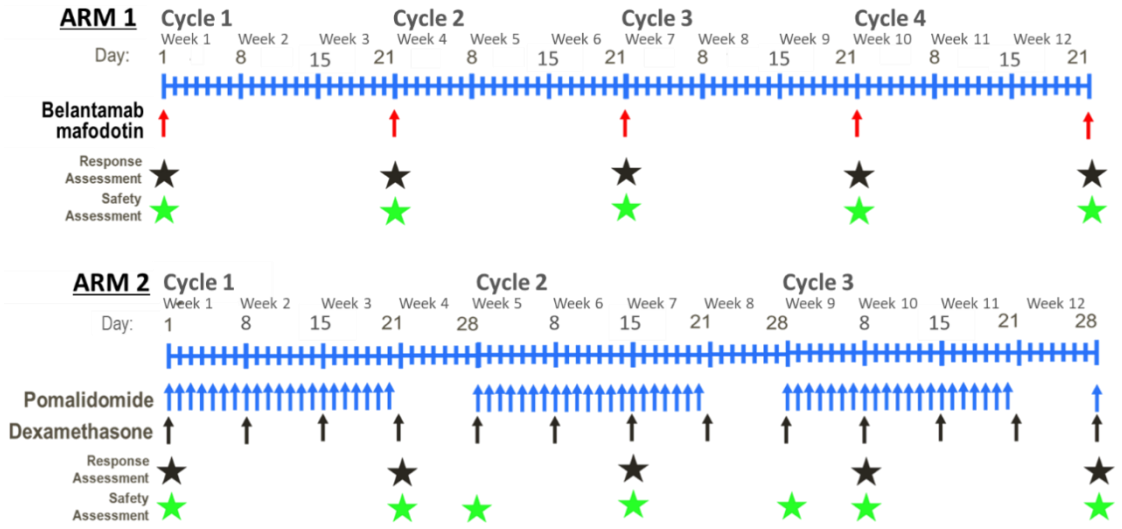
1.2. Schema

Figure 1 Study Design Schema



* Progression on or within 60 days of last treatment, or non-responsive while on last treatment (See IC. 4b)
** Stratification based on International Staging System (ISS), number of prior lines of therapy and prior usage of anti-CD38 antibody treatment
*** Until progressive disease (PD), death, unacceptable toxicity, withdrawal of consent, lost to follow-up or end of study, whichever comes first. If at the end of OS follow-up, patients are still on treatment, PACT will be implemented and only safety data will be collected (See Section 9.3.1).
**** includes follow-up for progression-free survival on subsequent line of therapy (PFS2)

Figure 2 Treatment and Assessment Schema



This chart represents an example of the planned treatment and assessment timepoints, but do not take into account any dose delays dose. Please refer to the Schedule of activities (SoA) (Section 2) for details on how visits are scheduled.

2. SCHEDULE OF ACTIVITIES (SOA)

All assessments planned for participants in Study 207495 are shown in the Time and Events Tables.

Table 1: Screening Assessments – Both Arms

Table 2: On-Treatment Assessments – Arm 1 – Belantamab mafodotin

Table 3: On-Treatment Assessments – Arm 2 – Pom/Dex

Table 4: End of Treatment and Follow Up Assessments – Both Arms

Table 5: [redacted]

Table 6: Hepatitis B(HBV) SoA – additional procedures

Table 7: Hepatitis C (HCV) SoA- additional procedures

The details of these assessments are provided in footnotes to the tables, with more details provided in Section 9. Additional information on resuming study treatments after dose interruption/delay is provided in Section 7.4.

For details on possible home healthcare and telemedicine approaches, please refer to Appendix 13

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 participant's particular study site and only SAEs, AEs leading to discontinuation of study treatment,

overdoses, prespecified ocular data (Arm 1 only), and pregnancies will be reported directly to the Sponsor via paper forms (see Section 5.4, Section 7.7 and Section 9.3.1). For participant discontinuing treatment in the PACT phase, no end of treatment visit is required.

Table 1 Schedule of Activities: Screening Assessments – Arm 1 - belantamab mafodotin and Arm 2 - Pom/Dex

Screening Assessments – Arm 1 - belantamab mafodotin and Arm 2 - pom/dex		
Screening Study Assessments[1,5]	**Screen**	**Notes**
Informed Consent	X	1. All Screening assessments must be performed within 28 days prior to first dose. Informed Consent must be signed before any study-specific assessments are performed. Screening Assessment do not need to be repeated on Cycle 1 Day 1 (C1D1) unless otherwise specified. 2. Informed consent for optional genetics research must be obtained before collecting the sample. The sample will be collected at the first opportunity after a participant has met all eligibility requirements. 3. Screening ocular examination will be performed by a qualified eye care specialist such as ophthalmologist/optometrist (Appendix 12, see Section 9.2.6 for list of ocular exam procedures). 4. Perform only in women of child-bearing potential. Two serum pregnancy tests should be performed at screening. The first test should be performed within 10 to 14 days prior to first dose and the second test within 24 hours prior to administration of first dose. For questionable cases (child-bearing status), follicle-stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential only) should be performed at local lab (see Section 9.2.7 for more details). 5. Refer to Appendix 2 for a comprehensive list of laboratory tests that must be collected for all participants and if analysed locally or centrally. 6. If completed within 72 hours prior to the first dose, this assessment does not need to be repeated on C1D1 7. eGFR as calculated by Modified Diet in Renal Disease (MDRD) formula (Appendix 10) 8. Albumin/ creatinine ratio (spot urine preferably from first void). 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, 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. 9. Refer to Table 6 for participants with positive serology for Hepatitis B and Table 7 for participants with positive serology for Hepatitis C. 10. Single ECG on Screening, unless QTcF is prolonged, in which case triplicate ECGs are required. To be performed after at least 5 min rest. 11. Imaging of bones for lytic lesions by a method aligned with the institutional guidance (e.g. X-ray, CT, or MRI). Same modality used at Screening must be used throughout study. 12. Imaging (i.e., CT, MRI, or PET-CT) is only required for participants with extramedullary disease (EMD) per local guidance. The same modality used at screening must be used throughout the study. 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
Demography	X	
Medical History, Disease History and Characteristics (includes substance abuse)	X	
Prior anti-myeloma therapy (including radiation and transplants)	X	
Physical Exam	X	
Inclusion/Exclusion criteria	X	
Past and current medical conditions	X	
Concomitant Medication	X	
Optional Genetics Consent[2]	X	
Screening Safety Assessments[1,5]		
Ocular Exam[3]	X	
ECOG Performance Status	X	
Vital Signs (BP, HR, Body Temperature)	X	
Weight and Height	X	
Serum Pregnancy Test (WOCBP only)[4]	X	
Hematology[5]	X[6]	
Clinical chemistry[5]	X[6]	
Estimated Glomerular Filtration (eGFR)[7]	X[6]	
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)[8]	X[6]	
HBsAg, HBcAb, HCV tests[9]	X	
12-lead ECG[10]	X	
Screening Disease Evaluation[1,5]		
Skeletal Survey[11]	X	
Beta2 microglobulin	X	
UPEP 24 hr urine collection	X[6]	
Urine immunofixation	X[6]	
SPEP	X[6]	

Screening Assessments – Arm 1 - belantamab mafodotin and Arm 2 - pom/dex		
Screening Study Assessments[1,5]	**Screen**	**Notes**
Serum Immunofixation	X[6]	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 perpendicular diameters of measured lesions (SPD). See also Section 9.1. and SRM for additional information. 13. Only required for participant with IgD/E myeloma. 14. 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, regardless of when the previous tests were performed. 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. 15. Portion of the sample collected for disease assessment will be used for FISH testing, and MRD testing. Any remaining biopsy and aspirate sample will be used for biomarker research. 16. BM biopsy is the preferred sample for these exploratory analyses. If for any reason BM biopsy is not obtainable, BM aspirate may be collected for BCMA expression and biomarker research 17. Minimal residual disease (MRD) testing by NGS method.
Extramedullary Disease (EMD) Assessment[12]	X	
Serum Kappa, Lambda free Light chain, FLC ratio	X[6]	
Calcium corrected for albumin (serum)	X	
IgG, IgM, IgA	X	
IgD/E, if applicable[13]	X	
Bone Marrow (BM) Aspiration/Biopsy[1,5]		
BM (biopsy or aspirate) for disease assessment (percent plasma cells)[15]	X	
BM aspirate for FISH testing[14,15]	X	
BM biopsy for BCMA expression and biomarker research[15,16]	X	
BM aspirate for baseline MRD testing[15,17]	X	

Abbreviations:

BCMA = B cell maturation antigen; BM = bone marrow; BP = Blood pressure; cfDNA = Circulating free DNA; CT = Computed tomography; DNA = deoxyribonucleic acid; eGFR = Estimated glomerular filtration rate; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EMD = extramedullary disease; CCI [redacted]; FISH = Florescent in situ hybridization; FLC = Free light chain; HBcAb = Hepatitis B core antibody; HBsAG = Surface antigen of Hepatitis B virus; HCV = Hepatitis C virus; HIV = Human Immunodeficiency Virus; Ig = Immunoglobulin; IHC = Immunohistochemistry; HR = Heart rate; MRD = Minimal residual disease; MRI = Magnetic resonance imaging; PET = Positron emission tomography; RNA = ribonucleic acid; SOI = start of infusion; SPEP = Serum protein electrophoresis; SRM = Study Reference Manual; UPEP = Urine protein electrophoresis; WOCBP = Women of child-bearing potential

Table 2 Schedule of Activities: On-Treatment Assessments – Arm 1 - belantamab mafodotin

On-Treatment Assessments – Arm 1 – belantamab mafodotin				
Study Assessments[1,7]	**C1D1[2]**	**Q3W (From Week 4, regardless of dosing)**	**D1 of Each 21-day Cycle (from C2-CX), if dosing[3]**	**Notes**
ECOG Performance Status	X	X		1. Assessments scheduled on days of dosing must be done prior to drug administration, unless otherwise specified. All other assessments can be done ±3 days unless otherwise specified. The Q3W assessments must be carried out even if participant is not dosed, unless otherwise specified. All Q3W assessment days must be calculated from C1D1 irrespective of any changes in dosing cycle. 2. Baseline 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. If no treatment is administered at Cycle visit, the following assessments do not need to be performed, unless clinically indicated: physical exam, vital signs, weight, pregnancy test, PK sample, ADA sample and soluble BCMA sample (except if collected with MRD assessment) 4. AEs/SAEs will be collected from start of study treatment until at least 70 days after the last dose of study treatment. All SAEs related to study participation (e.g., protocol mandated procedures, tests, or change in existing therapy) are to be collected from consent through OS follow-up. All AEs/SAEs will be followed until the event is resolved, stabilized, otherwise explained or the participant is lost to follow up (see Section 9.3). CCI [redacted] 5. On C1D1 (first infusion) dosing day, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI), within 15 mins after EOI, and 1-hour post EOI. On subsequent dosing days, vital signs must be assessed at pre-dose (within 30 minutes prior to SOI) and within 15 mins after EOI. On days where vital sign time points align with blood sampling time points, vital signs should be assessed prior to blood samples being drawn. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated. 6. On-treatment ocular exams to be performed up to 5 days prior to dosing from second cycle onwards. On-treatment ocular exams to be performed Q3W prior to dosing, up to the 6th dose of belantamab mafodotin. At the time of the 6th dose of belantamab mafodotin, if there are no significant (KVA Grade 2 or above) treatment-related ocular examinations findings, ocular symptoms, or vision changes, the frequency of ocular exams may decrease to once every 3 months until the end of treatment. If a participant subsequently develops vision
Adverse Events[4]	Ongoing			
Concomitant Medications	Ongoing			
Safety Assessments				
Physical Examination	X		X[3]	
Vital Signs (BP, HR, Body Temperature)[5]	X		X[3]	
Ocular Exam		X[6]		

On-Treatment Assessments – Arm 1 – belantamab mafodotin				
Study Assessments[1,7]	**C1D1[2]**	**Q3W (From Week 4, regardless of dosing)**	**D1 of Each 21-day Cycle (from C2-CX), if dosing[3]**	**Notes**
Weight	X		X[3]	changes or other ocular symptoms, the participant should be promptly evaluated by a qualified eye care specialist such as ophthalmologist/optometrist. In case of persistent ocular exam findings, newly developed ocular symptoms or vision changes, the participants will have further exams, at least every cycle until resolution or baseline, or more frequently as clinically indicated by the qualified eye care specialist such as ophthalmologist/optometrist (Appendix 12). See Section 9.2.6 for full details of ocular exam procedures. 7. Refer to Appendix 2 for a comprehensive list of laboratory tests that must be collected and whether analysed locally or centrally for all participants. 8. If completed within 72 hours prior to the first dose, this assessment does not need to be repeated on C1D1 9. eGFR as calculated by Modified Diet in Renal Disease (MDRD) formula (see Appendix 10). 10. Albumin/creatinine ratio (spot urine, preferably from first void) to be performed every 6 weeks from C1D1 OR 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 ≥2+, 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 11. Perform only in women of child-bearing potential. The C1D1 pregnancy test is a serum test and should be within 24 hours prior to administration of first dose. Subsequent CXD1 pregnancy tests may be either serum or urine and each pregnancy test must be performed within 72 hours prior to dosing. 12. To be assessed based on disease laboratory tests and imaging (if applicable) as outlined in this table. Response assessment is based on International Myeloma Working Group (IMWG) [Kumar, 2016]. 13. Disease evaluation (except imaging and skeletal survey) will be performed every 3 weeks (± 3 days) even if treatment is not administered. For participants who are discontinuing study intervention due to PD, the confirmation of PD based on laboratory parameters must be performed from a different sample collection performed 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. This may be performed at the EOT visit. 14. Only if clinically indicated or if worsening clinical symptoms suggest skeletal PD. Imaging is not required if the PD is evident otherwise. Same modality used at Screening must be used throughout study. Imaging of bones for lytic lesions by a method aligned with the institutional guidance (e.g., X-ray, CT, or MRI). 15. At time of first achieving unmeasurable M protein on SPEP/UPEP and at Q3W visit from week 4 until
Hematology[7]	X[8]	X		
Clinical Chemistry[7]	X[8]	X		
eGFR[9]	X[8]	X		
Urinalysis (dipstick) or Spot Urine (albumin/creatinine ratio)[10]	X[8]	X[Q6W]		
Pregnancy Test (WOCBP only)[11]	X		X[3]	
Disease Evaluation Assessments[13]				
Response Assessment[12]		X		
Skeletal Survey		X[14]		
UPEP 24 hr urine collection	X[8]	X		
Urine Immunofixation		X[15]		
SPEP	X[8]	X		
Serum immunofixation		X[15]		

On-Treatment Assessments – Arm 1 – belantamab mafodotin				
Study Assessments[1,7]	**C1D1[2]**	**Q3W (From Week 4, regardless of dosing)**	**D1 of Each 21-day Cycle (from C2-CX), if dosing[3]**	**Notes**
Extramedullary disease assessment (by CT or MRI or PET/CT)		X[16]		suspected PD. 16. Imaging (i.e., CT, MRI or PET-CT) is only required for participants with extramedullary disease Q12 weeks (e.g., Week 13, W25, W37, etc.) through 1 year and then as clinically indicated. The same modality used at screening must be used throughout the study. See Section 9.1 for more information on imaging, EMD measurement and follow-up, PD due to EMD. Refer also to the SRM for additional information. 17. Only required for participants with IgD/E myeloma. 18. For BCMA expression analysis by IHC and biomarker research at PD: BM biopsy is the preferred sample for these exploratory analyses, but if not obtainable, aspirate may also be used. Informed consent for the optional tissue sample must be obtained before collecting a sample. 19. MRD testing to be performed at the time of first achieving response of VGPR or better, and repeated every 6 months for 2 years, and then yearly until PD. In case of deepening of response from VGPR to CR, MRD sample should be collected at the time of CR assessment and repeated every 6 months for 2 years and then yearly until PD. 20. At the time of suspected CR for confirmation of PC% <5% (always) or at time of suspected PD (only if not evident otherwise). Bone marrow core biopsy is preferred. 21. In participants achieving a CR, bone marrow biopsy to confirm sCR by IHC (κ/λ ratio). 22. PET/CT required after first achieving MRD negativity by NGS, preferably within 42 days of testing negative 23. Belantamab mafodotin administration on D1 of Cycle C2-CX ±3-days. All scheduled cycle visits must be calculated from C1D1. Please refer to Section 7.6 in case a dose is delayed. 24. See Section 7.1.1 for more detail on supportive Care information 25. For pharmacokinetic sampling schedule, refer to Section 9.5. Pharmacokinetic samples are required according to the schedules for Standard and Enhanced PK collection for all participants receiving belantamab mafodotin (Table 18 and Table 19). 26. Blood samples for ADA measurement in serum will be collected prior to the start of the infusion on dosing days at Cycles 1, 2, 6, 9, 12, and every 6 cycles thereafter (e.g., Cycle 18, Cycle 24, etc.). 27. cfDNA samples to be collected pre-infusion on C1D1, and all MRD assessment timepoints. 28. Soluble BCMA (serum): Collect sBCMA samples at the same PK timepoints as specified in Table 18 (enhanced schedule) and Table 19 (standard schedule). Additionally, sBCMA samples should be taken at
Serum Kappa, Lambda free light chain, FLC ratio	X[8]	X		
IgG, IgM, IgA		X		
IgD/E, if applicable[17]		X		
Calcium corrected for albumin (serum)		X		
Bone Marrow (BM) Aspiration/Biopsy				
Optional Tissue sample at PD: BM biopsy or aspirate for BCMA expression and biomarker research		X[18]		
BM aspirate for MRD testing		X[19]		
BM biopsy or aspirate for disease assessment (percent plasma cells)		X[20]		
BM biopsy to assess sCR by IHC		X[21]		
PET/CT upon achieving MRD negativity by NGS		X[22]		

On-Treatment Assessments – Arm 1 – belantamab mafodotin				
Study Assessments[1,7]	**C1D1[2]**	**Q3W (From Week 4, regardless of dosing)**	**D1 of Each 21-day Cycle (from C2-CX), if dosing[3]**	**Notes**
Treatment				every MRD assessment timepoint. 29. Informed consent for optional genetic research must be obtained before collecting a sample. The sample will be collected at the first opportunity after a participant has met all eligibility requirements preferably on C1D1 30. Only applicable for participants enrolled under the original protocol 31. Only applicable for participants enrolled under protocol amendment 1 C [redacted]
Premedication (as needed)	X		X	
Belantamab mafodotin	X		X[23]	
Supportive Care				
Cooling eye masks[24]	X		X	
Preservative-free artificial tears[24]	X		X	
PK and ADA				
Pharmacokinetics[25]	X		X[3]	
Immunogenicity (ADA)[26]	X		X[3]	
Biomarkers and Genetics				
cfDNA (plasma)[27]	X	X MRD only		
Soluble BCMA[28]	X	X MRD only	X[3]	
Optional Genetic Sample[29]	X			
Health Outcomes				
PRO-CTCAE	X	X		
OSDI	X	X		
CCI [redacted]	X	X		
EORTC QLQ-C30	X	X		
EORTC IL52[30]	X	X		
EORTC QLQ-MY20[31]	X	X		
CCI [redacted]	X	X(Q6W)		
[redacted]	X	X(Q6W)		

On-Treatment Assessments – Arm 1 – belantamab mafodotin				
Study Assessments[1,7]	**C1D1[2]**	**Q3W (From Week 4, regardless of dosing)**	**D1 of Each 21-day Cycle (from C2-CX), if dosing[3]**	**Notes**
CCI [redacted]		X(Q6W)		
[redacted]	X	X		

Abbreviations:

ADA = Anti-Drug Antibody; BP = Blood pressure; BM = bone marrow; cfDNA – circulating free DNA; CR = Complete response; CT = Computed tomography; eGFR = Estimated glomerular filtration rate; ECOG PS= Eastern Cooperative Oncology Group Performance Status; EMD = extramedullary disease; EOI = End of Infusion; EORTC IL52 = Disease Symptoms domain of EORTC QLQ-MY20; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module; EORTC-QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma Module;CCI [redacted] ;CCI [redacted]; FLC = Free light chain;CCI [redacted] HR = Heart rate; Ig = Immunoglobulin; IHC = Immunohistochemistry; MRD = Minimal residual disease; MRI = Magnetic resonance imaging; NGS = Next generation sequencing OS = Overall survival; OSDI = Ocular Surface Disease Index; PC = plasma cells; PD = Progressive disease; PET = Positron emission tomography; PFS = progression-free survival CCI [redacted]; PK = Pharmacokinetics; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events; QID = 4 times a day; sCR = Stringent complete response; SAE = Serious adverse event; SOI = start of infusion; SPEP = Serum protein electrophoresis; SRM = Study Reference Manual; UPEP = Urine protein electrophoresis; VGPR = Very good partial response; WOCBP = Women of child-bearing potential

Table 3 Schedule of Activities: On-Treatment Assessments – Arm 2 – Pom/Dex

On-Treatment Assessments: Treatment Arm 2 (Pomalidomide/Dexamethasone)				
Study Assessments[1,7]	**C1D1[2]**	**Q3W (From Week 4, regardless of dosing)**	**D1 of Each 28-day Cycle (C2-CX) if dosing[3,4]**	**Notes**
ECOG Performance Status	X	X		1. Assessments scheduled on days of dosing must be done prior to drug administration, unless otherwise specified. All other assessments can be done ±3 days unless otherwise specified. All Q3W assessments must be carried out even if participant is not dosed, unless otherwise specified. All Q3W assessment days must be calculated from C1D1 irrespective of any changes in dosing cycle. 2. Baseline 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. For Arm 2, treatment cycles are 28 days (see Figure 2). 4. If no treatment is administered on a given visit, the following assessments do not need to be performed, unless clinically indicated: physical exam, vital signs, weight, hematology 5. AEs/SAEs will be collected from the start of study treatment until at least 70 days after the last dose of study treatment. All SAEs related to study participation (e.g., protocol mandated procedures, tests, or change in existing therapy) are to be collected from consent through OS follow-up. All AEs/SAEs will be followed until the event is resolved, stabilized, otherwise explained or the participant is lost to follow up (see Section 9.3). 6. On-treatment ocular exams to be performed by a qualified eye care specialist such as ophthalmologist/optometrist every 6 months (±14 days) after C1D1 or as clinically indicated. See Section 9.2.6 for a list of ocular exam procedures. 7. Refer to Appendix 2 for a comprehensive list of lab tests that must be collected and whether analysed locally or centrally for all participants. 8. If completed within 72 hours prior to the first dose, this assessment need not be repeated on Day 1 of Cycle 1. 9. Monitor hematology weekly for the first 8 weeks of treatment and every cycle thereafter. 10. eGFR as calculated by Modified Diet in Renal Disease (MDRD) formula (see Appendix 10). 11. Albumin/creatinine ratio (spot urine, preferably from first void) to be performed every 6 weeks from C1D1 OR 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 ≥2+, 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.
Adverse Events[5]	Ongoing			
Concomitant Medications	Ongoing			
Safety Assessments				
Physical Examination	X		X^{4}	
Vital Signs (BP, HR, Body Temperature)	X		X^{4}	
Ocular Exam[6]		X^{Q6M}		
Weight	X		X^{4}	
Hematology[7]	X^{8}	X	$X^{4,9}$	
Clinical Chemistry[7]	X^{8}	X		
eGFR[10]	X^{8}	X		
Urinalysis or Spot Urine for albumin/ creatinine ratio[11]	X^{8}	X^{Q6W}		
Pregnancy Test[12]	X		X	
REMS/Pregnancy prevention program registration[13]	X	X		

On-Treatment Assessments: Treatment Arm 2 (Pomalidomide/Dexamethasone)				
Study Assessments[1,7]	**C1D1[2]**	**Q3W (From Week 4, regardless of dosing)**	**D1 of Each 28-day Cycle (C2-CX) if dosing[3,4]**	**Notes**
Disease Evaluation Assessments[15]				12. Perform only in women of child-bearing potential. Pregnancy tests should be performed weekly during the first 4 weeks (first cycle) and then every 4 weeks thereafter in women with regular menstrual cycles, or every 2 weeks in women with irregular menstrual cycles. The C1D1 pregnancy test is a serum test and should be within 24 hours prior to administration of first dose. Subsequent D1CX pregnancy tests should be performed within 72 hours prior to dosing and pregnancy tests may be either serum or urine. See Section 9.2.7 and Appendix 4 for more details. 13. Applicable as required by local guidelines. Ensure counselling is completed and documented as required by applicable pregnancy prevention program. See Section 9.2.8 and SRM for full details. 14. To be assessed based on disease laboratory tests and imaging (if applicable) as outlined in this table. Response assessment is based on International Myeloma Working Group (IMWG) [Kumar, 2016]. 15. Disease evaluation (except imaging and skeletal survey) will be performed every 3 weeks (± 3 days) even if treatment is not administered. For participants who are discontinuing study intervention due to PD, the confirmation of PD based on laboratory parameters must be performed from a different sample collection performed 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. This may be performed at the EOT visit. 16. Only if clinically indicated or if worsening clinical symptoms suggest skeletal PD. Imaging is not required if the PD is evident otherwise. Same modality used at Screening must be used throughout study. Imaging of bones for lytic lesions by a method aligned with the institutional guidance (e.g., X-ray, CT, or MRI). 17. At time of first achieving unmeasurable M protein on SPEP/UPEP and at Q3W visits from Week 4 until suspected PD. 18. Imaging (i.e., CT, MRI or PET-CT) is only required for participants with extramedullary disease (EMD) Q12 weeks (e.g., Week 13, W25, W37, etc.) through 1 year and then as clinically indicated. The same modality used at screening must be used throughout the study. See Section 9.1 for more information on imaging, EMD measurement and follow-up, PD due to EMD. Refer also to the SRM for additional information. 19. Only required for participants with IgD/E myeloma. 20. For BCMA expression analysis by IHC and biomarker research at PD: BM biopsy is the preferred sample for these exploratory analyses, but if not obtainable, aspirate may also be used. Informed consent for the optional
Response Assessment[14]		X		
Skeletal Survey		X[16]		
UPEP 24 hr urine collection	X[8]	X		
Urine Immunofixation		X[17]		
SPEP	X[8]	X		
Serum immunofixation		X[17]		
EMD assessment (by CT or MRI or PET/CT)		X[18]		
Serum Kappa, Lambda free light chain, FLC ratio	X[8]	X		
IgG, IgM, IgA		X		
IgD/E, if applicable[19]		X		
Calcium corrected for albumin (serum)		X		

On-Treatment Assessments: Treatment Arm 2 (Pomalidomide/Dexamethasone)				
Study Assessments[1,7]	**C1D1[2]**	**Q3W (From Week 4, regardless of dosing)**	**D1 of Each 28-day Cycle (C2-CX) if dosing[3,4]**	**Notes**
Bone Marrow (BM) Aspiration/Biopsy				
Optional Tissue sample at PD: BM biopsy or aspirate for BCMA expression and biomarker research		X[20]		
BM aspirate for MRD testing		X[21]		
BM biopsy or aspirate for disease assessment (percent plasma cells)		X[22]		
BM biopsy to assess sCR by IHC		X[23]		
PET/CT upon achieving MRD negativity by NGS		X[24]		
Treatment				
Thromboprophylaxis	Ongoing[25]			
Pomalidomide[26]	X		X	
Dexamethasone[26]	X		X	
Dispense/Return Medication Diary[27]	X		X	
Biomarkers and Genetics				
cfDNA (plasma)[28]	X	X MRD only		
Soluble BCMA[29]	X	X MRD only		
Optional Genetic	X			

On-Treatment Assessments: Treatment Arm 2 (Pomalidomide/Dexamethasone)				
Study Assessments[1,7]	**C1D1[2]**	**Q3W (From Week 4, regardless of dosing)**	**D1 of Each 28-day Cycle (C2-CX) if dosing[3,4]**	**Notes**
Sample[30]				
Health Outcomes				
PRO-CTCAE	X	X		
OSDI	X	X		
CCI	X	X		
EORTC QLQ-C30	X	X		
EORTC IL52[31]	X	X		
EORTC QLQ-MY20[32]	X	X		
CCI	X	X(Q6W)		
	X	X(Q6W)		
		X(Q6W)		
	X	X		

Abbreviations:

BP = Blood pressure; BM = bone marrow; cfDNA = Circulating free DNA; CR = Complete response; CT = Computed tomography; eGFR = Estimated glomerular filtration rate; ECOG PS= Eastern Cooperative Oncology Group Performance Status; EOI = End of Infusion; EMD = Extramedullary disease; EORTC IL52 = Disease Symptoms domain of EORTC QLQ-MY20; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module; EORTC-QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma Module; CCI FLC = Free light chain; CCI HR = Heart rate; Ig = Immunoglobulin; IHC = Immunohistochemistry; MRD = Minimal residual disease; MRI = Magnetic resonance imaging; NGS = Next generation sequencing; OS = Overall survival; OSDI = Ocular Surface Disease Index; PC = plasma cells; PD = Progressive disease; PET = Positron emission tomography; PFS = progression-free survival; CCI PRO-CTCAE = Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events; REMS = Risk Evaluation and Mitigation Strategy; sCR = Stringent complete response; SAE = Serious adverse event; SOI = start of infusion; SPEP = Serum protein electrophoresis; SRM = Study Reference Manual; VGPR = Very good partial response; UPEP = Urine protein electrophoresis; WOCBP = Women of child-bearing potential

Table 4 Schedule of Activities: End of Treatment and Follow-Up Assessments – Arm 1 – belantamab mafodotin and Arm 2 – Pom/Dex

Schedule of Activities: End of Treatment and Follow-Up Assessments – Arm 1 – belantamab mafodotin and Arm 2 – pom/dex				
Study Assessments[9]	**End of Treatment Visit[1]**	**PFS Follow-up[2]**	**OS Follow-up[3]**	**Notes**
Physical Exam	X	X		1. The End of Treatment (EOT) visit will occur within 30 days after last dose or before the start of any new anti-myeloma therapy (whichever occurs first). 2. PFS follow-up: Participants who discontinue study treatment for a reason other than PD, disease evaluations will continue to be performed at every 3 weeks (±3 days) from the last Q3W assessment visit until confirmed PD, death, start of a new anti-myeloma treatment, withdrawal of consent, lost to follow-up or end of the study whichever occurs first. Once participant progresses, move to OS follow-up. 3. OS follow-up: After PD is documented, participants will be followed for survival and progression after subsequent anti-myeloma therapy (PFS2) by chart review, phone call, or any form of communication every 12 weeks (±14-day window) from the last Q3W assessment as referenced in 5.4. Participant does not need to come in for visit unless they are being followed for treatment-related ocular examination findings, ocular symptoms, or vision changes that are present at the end of study treatment. Record the participant's survival status and whether subsequent treatment for disease was given. If the final OS analysis occurs at the OS IA for efficacy (Section 10.5), OS data will continue to be collected for all participants every 24 weeks until all have died, are lost to follow up or withdrawn consent, or for 2 years after the final OS analysis, whichever occurs first. 4. AEs/SAEs will be collected up to at least 70 days after the last dose of study treatment. All SAEs related to study participation (e.g., protocol mandated procedures, tests, or change in existing therapy) are to be collected from consent through OS follow-up. All AEs/SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up. 5. Concomitant medications administered after the End of treatment (EoT) should only be recorded for SAEs/AESIs as defined in Section 9.3.3. 6. See Section 9.2.6 for list of ophthalmic exam procedures. 7. **ARM 1 ONLY:** Participants with treatment-related ocular examination findings, ocular symptoms, or vision changes at the end of treatment will be followed at least every 3 months for up to 12 months, or until resolution to KVA Grade 1 or baseline, whichever comes first. 8. Final pregnancy test (serum or urine) must be performed in women of childbearing potential at least 70 days of the last dose of belantamab mafodotin and at least 4 weeks after the last dose of pomalidomide/dexamethasone study treatment. Follow-up pregnancy assessment by telephone (for WOCBP only) should be performed 4 months after the last dose of belantamab mafodotin study treatment. 9. Refer to Appendix 2 for a comprehensive list of lab tests that must be collected for all participants and whether
Safety				
Adverse Events[4]	X	X	X	
Concomitant Medications[5]	X	X		
Ocular Exam[6]	X	X[7]	X[7]	
ECOG Performance Status	X	X		
Vital Signs (BP, HR, Body Temperature)	X			
Weight	X			
Pregnancy Test[8]	X			
Hematology[9]	X	X		
Clinical chemistry[9]	X			
eGFR[10]	X			
Urinalysis or Spot Urine (albumin/ creatinine ratio)[11]	X			
ARM 2 ONLY				
Return Medication Diary[12]	X			
PK/ADA – ARM 1 ONLY				
Pharmacokinetics (blood) for belantamab mafodotin[13]	X			
Immunogenicity (ADA) [13]	X			
Biomarker				
Soluble BCMA (serum) [13]	X			
cfDNA (plasma)	X			

Schedule of Activities: End of Treatment and Follow-Up Assessments – Arm 1 – belantamab mafodotin and Arm 2 – pom/dex				
Study Assessments[9]	**End of Treatment Visit[1]**	**PFS Follow-up[2]**	**OS Follow-up[3]**	**Notes**
Disease Evaluation				
Skeletal Survey[14]	X	X		
Imaging for EMD[15]	X	X		
UPEP 24 hr urine collection	X	X		
Urine immunofixation[16]	X	X		
SPEP	X	X		
Serum Immunofixation[16]	X	X		
Serum Kappa, lambda free LC, FLC ratio	X	X		
Calcium corrected for albumin (serum)	X	X		
IgG, IgM, IgA	X	X		
IgD/E[17]	X	X		
Response Assessment[18]	X	X		
Bone Marrow (BM) Aspiration/Biopsy				
BM aspirate for MRD testing	X[19]	X[19]		
BM biopsy or aspirate for disease assessment (percent plasma cells)	X[20]	X[20]		
BM biopsy to assess sCR by IHC	X[21]	X[21]		
Optional Tissue Sample at PD: BM biopsy or aspirate for BCMA expression and biomarker research	X[22]	X[22]		

analysed locally or centrally.
10. eGFR as calculated by the Modified Diet Renal Disease (MDRD) formula (see Appendix 10).
11. Albumin/creatinine ratio (spot urine, preferably from first void) OR 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 ≥2+, 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 (first void).
12. Participant diary will be used to keep a record of self-administered dexamethasone and pomalidomide
13. Collect one PK sample (Arm 1 only), one ADA sample (Arm 1 only), and one sBCMA sample (Arm 1 and Arm 2) at end of treatment visit. Between 6 and 12 weeks after last dose of study treatment, and assuming no initiation of new anti-myeloma therapy, collect one PK (Arm 1 only), one ADA sample (Arm 1 only), and one sBCMA sample (Arm 1 and Arm 2). Sample may be collected at any planned follow-up visit.
14. Imaging of bones for lytic lesions by a method aligned with the institutional guidance (e.g., X-ray, CT, or MRI). Only if clinically indicated, or if worsening clinical symptoms suggest skeletal PD. Imaging is not required if the PD is evident otherwise. Same modality used at Screening must be used throughout study. As clinical indicated, imaging is only required for participants with known extramedullary disease (EMD) either by CT, MRI, or PET/CT per local guidance. Same modality used at Screening must be used throughout study. See Section 9.1 for more information on imaging, EMD measurement and follow-up, PD due to EMD. Refer also to the SRM for additional information.
15. As clinically indicated, imaging is only required for participants with known extramedullary disease (EMD) either by CT, MRI, or PET/CT per local guidance. Same modality used at Screening must be used throughout study. See Section 9.1 for more information on imaging, EMD measurement and follow-up, PD due to EMD. Refer also to the SRM for additional information.
16. At time of first achieving unmeasurable M Protein in SPEP/UPEP and until suspected PD
17. Only required for participants with IgD/E myeloma.
18. To be assessed based on disease laboratory tests and imaging (if applicable) as outlined in this table. Response assessment is based on IMWG 2016 criteria.
19. MRD testing to be performed by a central lab at the time of first achieving response of VGPR or better, and repeated every 6 months for 2 years and then yearly until PD. In case of deepening response from VGPR to CR, MRD sample should be collected at the time of CR assessment and repeated every 6 months for 2 years and then yearly until PD.
20. Bone marrow core biopsy and/or aspirate for flow cytometry or immunohistochemistry (IHC); at the time of

Schedule of Activities: End of Treatment and Follow-Up Assessments – Arm 1 – belantamab mafodotin and Arm 2 – pom/dex				
Study Assessments[9]	**End of Treatment Visit[1]**	**PFS Follow-up[2]**	**OS Follow-up[3]**	**Notes**
Health Outcomes				
PRO-CTCAE	X			
OSDI[23]	X	X	X	
CCI	X			
EORTC-QLQ-C30	X	X[24]	X[25]	
EORTC IL52[26]	X	X[24]	X[25]	
EORTC QLQ-MY20[27]	X	X[24]	X[25]	
CCI	X	X[24]	X[25]	
	X	X[24]		
	X	X[24]		
	X			
Post-PD status				
Subsequent Anti–MM Treatment[28]		X	X	
Survival Status[29]			X	

Abbreviations:

ADA = Anti-Drug Antibody; BP = Blood pressure; BM = bone marrow; cfDNA = Circulating free DNA; CR = Complete response; CT = Computed tomography; eGFR = Estimated glomerular filtration rate; ECOG PS= Eastern Cooperative Oncology Group Performance Status; EMD = Extramedullary disease; EORTC IL52 = Disease Symptoms domain of EORTC-QLQ-MY20; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module; EORTC-QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma Module; CCI ; CCI ; FLC = Free light chain; CCI HR = Heart rate; Ig = Immunoglobulin; IHC = Immunohistochemistry; MRD = Minimal residual disease; MRI = Magnetic resonance imaging; NGS = Next generation sequencing; OS = Overall survival; OSDI = Ocular Surface Disease Index; PC = plasma cells; PD = Progressive disease; PET = Positron emission tomography; PFS = Progression Free Survival; CCI ; PK = Pharmacokinetics; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events; sCR = Stringent complete response; SAE = Serious adverse event; SOI = start of infusion;; SPEP = Serum protein electrophoresis; SRM = Study Reference Manual; VGPR = Very good partial response; UPEP = Urine protein electrophoresis

CCI

[redacted]

Table 6 Hepatitis B (HBV) SoA – additional procedures

Note: the procedures listed in this table apply ONLY to participants in screening and who have been enrolled and who have a 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

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.
HBV-DNA testing	X[2]	X[2]	X[2]	2. HBV-DNA testing prior to the start of study treatment and subsequently every 3 months, or if LFT elevations requiring increased monitoring or stopping criteria occurs, or for any clinical suspicion of hepatitis reactivation. HBV-DNA testing will be performed at a local lab. If local testing is not available, then central testing will be performed
Prevention of HBV reactivation	X[3]	X[3]	X[3]	3. For **HBsAg+ participants**, appropriate antiviral treatment per local guidance (e.g. tenofovir or entecavir) is started before starting study treatment, continues through to completion of study treatment and should not be stopped unless advised by local hepatology or virology services.
HBeAg and HBeAb testing	X[4]			4. Only for Japan: HBsAg+ participants only

Table 7 Hepatitis C (HCV) SoA – additional procedures

Note: the procedures listed in this table apply ONLY to participants in screening and who have been enrolled and who have a positive serology for Hepatitis C; all procedures must be done as needed **in addition** to the required procedures for all participants detailed in Table 1

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 study treatment and subsequently every 3 months, or if LFT elevations requiring increased monitoring or stopping criteria occurs, or for any clinical suspicion of hepatitis reactivation. HCV-RNA testing will be performed at a local lab. If local testing is not available, then central testing will be performed 2. Antiviral treatment should be given to participants with HCV before enrollment 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 enrollment.
Treatment of active HCV	X[2]			

3. INTRODUCTION

Multiple myeloma (MM) is an incurable malignancy and accounts for 1% of all cancers and for 10% of all hematologic malignancies [Moreau, 2017]. Worldwide, approximately 103,000 new cases are diagnosed annually, and an estimated 32,110 new cases and 12,960 deaths will occur in the United States in 2019 [Cowan, 2018; Siegel, 2019]. There have been significant advances in treatment for MM, including novel therapies like second and third -generation proteasome inhibitors (PIs), immunomodulatory drugs, and recent addition of monoclonal antibodies (mAbs) [National Comprehensive Cancer Network (NCCN), 2018; Moreau, 2017]. Those advances have contributed to incremental gains in PFS and OS, but most MM patients still relapse and ultimately develop resistance to existing therapies. Therefore, there is an urgent need to develop treatments with novel MOA which could potentially prevent the cross resistance to existing therapies [Kumar, 2004; Richardson, 2003; Richardson, 2006; Jagannath, 2008]. Details of the characteristics of belantamab mafodotin, nonclinical, and clinical activity are provided in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2013N175128_08].

3.1. Study Rationale

Immunomodulatory drugs are an important cornerstone of treatment for patients with relapsed/refractory MM (RRMM). These include lenalidomide and more recently pomalidomide. Pomalidomide administered with low-dose dexamethasone (pom/dex) is approved in the US, European Union (EU) and a number of other countries worldwide for patients with RRMM who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on, or within 60 days of completion of, the last therapy [e.g., POMALYST PI and Imnovid SmPC].

Pom/dex has been previously studied in patients with relapsed MM refractory to lenalidomide and bortezomib in the Phase III trial MM-003, which compared pom/dex with high-dose dexamethasone (HD) [San Miguel, 2013]. The median overall survival (OS) (12.7 [95% CI: 10.4, 15.5] vs. 8.1 [95% CI: 6.9, 10.8] months; HR: 0.74 [95% CI: 0.56, 0.97]; p=0.0285) and progression-free survival (PFS, 4.0 [95% CI: 3.6, 4.7] vs. 1.9 [95% CI: 1.9, 2.2] months; HR: 0.48 [95% CI: 0.39, 0.60]; p<0.0001) were significantly longer with pom/dex than with HD alone. An overall response rate (ORR) of 31% was achieved with pom/dex (complete response [CR]: 1%; very good partial response [VGPR]: 5%; partial response [PR]: 26%). The most common Grade 3 to 4 hematological adverse events (AEs) were neutropenia (48% vs. 16%), anemia (33% vs. 37%), and thrombocytopenia (22% vs. 26%). Serious adverse events (SAEs; defined as Grade 5 events requiring hospitalisation or resulting in disability or incapacity) occurred in 61% and 53% of participants in the pom/dex and HD groups, respectively. The most common cause of death in both groups was progression of disease (68% vs. 64%), with the second most common cause being infection (10% vs. 19%). Treatment-related AEs leading to death were seen in 4% and 5% participants, respectively.

Belantamab mafodotin (GSK2857916) is a first in class, antibody-dependent cellular cytotoxicity (ADCC) enhanced, humanized immunoglobulin G1 (IgG1) antibody-drug conjugate (ADC) that binds specifically to B-cell maturation antigen (BCMA), a target

present on mature B cells and on tumor cells in patients with MM [Tai, 2015; Tai, 2006]. The antibody is conjugated to the microtubule inhibitor maleimidocaproyl monomethyl auristatin-F (mcMMAF) and is produced as an afucosylated form that generates an enhanced ADCC response. As demonstrated in the FTIH study this novel mechanism of action can be reasonably expected to overcome cross resistance to existing therapies.

Single agent belantamab mafodotin has demonstrated meaningful clinical benefit in two clinical studies conducted in heavily pre-treated participants with RRMM (Q3W schedule via IV administration); the first time in human (FTIH) study BMA117159 and the ongoing 205678/DREAMM 2 study evaluating single agent doses of 2.5 mg/kg and 3.4 mg/kg. See Section 3.4, Human Experience with Belantamab Mafodotin, for details on efficacy and safety results from studies BMA117159/DREAMM-1 and 205678/DREAMM-2.

The efficacy and safety results from study BMA117159/DREAMM-1 and study 205678/DREAMM-2 indicate that belantamab mafodotin is an effective single-agent treatment option for patients with RRMM, with a novel MOA. In binding to BCMA on malignant plasma cells, belantamab mafodotin initiates cell killing via a multimodal-mechanism, including delivering MMAF to BCMA-expressing MM cells, inducing apoptosis, enhancing antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, and inducing immunogenic cell death. These data support further evaluation of single agent belantamab mafodotin in a randomized Phase III study against pom/dex, an established standard of care in RRMM participants.

3.2. Background on BCMA and Multiple Myeloma

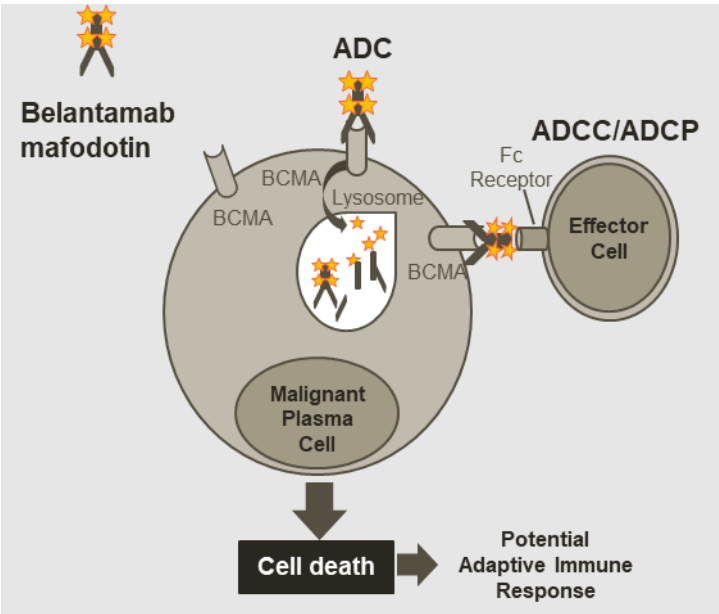
B-cell maturation antigen (BCMA), also designated as tumor necrosis factor receptor superfamily member 17 (TNFRSF17), is expressed on the surface of normal and malignant B lymphocytes at later stages of differentiation [Novak, 2004]. Ligands targeting BCMA such as B cell-activating factor (BAFF, TNFSF13B), along with a proliferation-inducing ligand (APRIL, TNFSF13) activate cell proliferation pathways and upregulate anti-apoptotic proteins in MM cell lines [Bellucci, 2005; Moreaux, 2004]. Mice deficient for BCMA are viable, have normal B-cell development, and exhibit normal humoral responses [Belnoue, 2008; Varfolomeev, 2004; Jiang, 2011]. BCMA is widely expressed on malignant plasma cells in all MM patients [Tai, 2015; Tai, 2006]. The restricted expression profile of BCMA makes it a very good target for a therapeutic antibody with direct cell killing activity and is expected to have limited off target effects [Tai, 2015]. Soluble BCMA (sBCMA) is present in the serum of MM patients, and its levels have been postulated to correlate with response to therapy and OS [Sanchez, 2012].

BCMA has been validated as a therapeutic target in MM [Tai, 2015]. Study BMA117159 demonstrated single-agent activity of belantamab mafodotin in heavily pre-treated MM participants. Chimeric Antigen Receptor T-Cells (CAR-T) based therapies targeting BCMA have also demonstrated significant activity in MM [Cohen, 2016]. Other approaches utilizing bispecific antibodies (BiTe) have also entered development and have shown clinical activity [Topp, 2018].

3.3. Antibody-Drug Conjugate Belantamab Mafodotin

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 3) [Tai, 2014; Montes De Oca, 2019]. Exposure of dendritic cells to tumor cells undergoing immunogenic cell death is expected to result in an antigen-specific T-cell response, enhancing the immunogenic response against MM.

Figure 3 Belantamab Mafodotin Mechanism of Action (MoA)



ADCC/ADCP=antibody-dependent cell-mediated cytotoxicity/antibody-dependent cellular phagocytosis, ADC=antibody drug conjugate, BCMA = B-cell maturation antigen

3.4. Human Experience with Belantamab Mafodotin

3.4.1. Clinical studies

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

FTIH study BMA117159/DREAMM-1

In the FTIH DREAMM-1 study, which consisted of a dose escalation phase (Part 1, n=38) and a dose expansion phase (Part 2, n=35), as of the primary analysis cut-off date of 31 August 2018, a total of 73 participants with RRMM received at least 1 dose of belantamab mafodotin [GlaxoSmithKline Document Number 2013N175128_08; Trudel, 2019].

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

Phase II study 205678/DREAMM-2

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

As of the cut-off date of 31 January 2020, the ORR was 31% (97.5% CI 21.7,43.6) in the 2.5 mg/kg and 35% (97.5% CI 24.8,47.0) in the 3.4 mg/kg frozen treatment. 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)].

3.4.2. Safety

Single-agent belantamab mafodotin was demonstrated to have a manageable safety profile in heavily pre-treated participants with RRMM. Safety data for single-agent belantamab mafodotin were pooled (data as of 20Sep2019) for DREAMM-2 study and supportive FTIH study DREAMM-1 by treatment cohorts of 2.5 mg/kg and 3.4 mg/kg.

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

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

Adverse Events of Special Interest

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

The median time to onset of Grade 2 or above corneal findings (best corrected visual acuity 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 [redacted] 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 Grade 1 and 4. The incidence of Grade 3 bleeding events was low (2%), with no Grade 4 or 5 events reported in participants treated with belantamab mafodotin 2.5 mg/kg.

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

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).

Additional information can be found in Section 5.3.1.

3.4.3. Pharmacokinetics and Pharmacodynamics in Humans

The pharmacokinetics of and pharmacodynamics belantamab mafodotin (antibody-drug conjugate, including the 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. 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 (National Cancer Institute - Organ Dysfunction Working Group [NCI-ODWG] classification). Higher serum levels of β_2-microglobulin, IgG, and soluble BCMA (sBCMA) and lower levels of albumin are associated with more advanced multiple myeloma or a higher multiple myeloma disease burden. Higher baseline IgG and sBCMA levels were associated with higher cys-mcMMAF central volume of distribution leading to lower cys-mcMMAF Cmax.

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

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

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

Additional information related to belantamab clinical PK, PD, and exposure-response relationships can be found in the Investigator's Brochure [GlaxoSmithKline Document Number 2013N175128_08]

3.5. Benefit/Risk Assessment

Additional information about the known and expected benefits and risks, detailed information of nonclinical and clinical findings information regarding warnings, precautions, contraindications, adverse events, and other pertinent information that may impact participant eligibility is provided in the belantamab mafodotin Investigator's Brochure [GlaxoSmithKline Document Number 2013N175128_08] and pomalidomide and dexamethasone product labels, respectively.

The following section outlines the risk assessment and mitigation strategy primarily for belantamab mafodotin in this protocol. For pomalidomide and dexamethasone, the approved product labels should be referenced (see the Study Reference Manual [SRM] for details).

3.5.1. Risk Assessment

The following table outlines the risk assessment and mitigation strategy for this protocol. Details on risks for pomalidomide and dexamethasone can be found in respective prescribing information; see Study Reference Manual (SRM).

Table 8 Risk Assessment and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Treatment belantamab mafodotin		
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 according to the SoA (Section 2). 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 7.1.1. Recommendations for dose delays/reductions and treatment stopping guidance are provided in Section 7.6.2.
Infusion related reaction (IRR)	IRRs were reported in participants treated with belantamab mafodotin. Most IRRs observed were Grade 1 to 2 and manageable with treatment.	Close monitoring for signs of IRR. Consider premedication for IRR in patients at risk. If an IRR occurs, follow guidance in Section 7.6.2.
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	Routine hematologic monitoring as outlined in Section 2. Supportive therapy (including transfusions) is provided according to local medical practice Recommendations for dose reductions or treatment discontinuations are

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	severity	outlined in Section 7.6.2. and Section 8.1.
Other hematological effects	Neutropenic events, including febrile neutropenia have been observed with treatment with belantamab mafodotin, In a study of belantamab mafodotin in combination with lenalidomide/ dexamethasone, two fatal cases of severe infections associated with neutropenia have been 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 Section 2. Consider prophylactic antibiotics, per physician discretion and local institutional guidance, in participants with Grade 3-4 neutropenia Immediately hospitalize participants with febrile neutropenia Consider additional supportive treatment(s) per local practice (e.g., transfusion, growth factors). Recommendations for dose reductions or treatment discontinuations are outlined in Section 7.6.2. and Section 8.1.
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 trials and named patient programs with belantamab mafodotin.	Participants will be monitored for kidney function, including albumin/creatinine ratio. Participants will be educated about the need of maintaining adequate urinary output. Dose modification guidelines for increased serum creatinine and urinary albumin/creatinine ratio are outlined in Section 7.6.2. and Section 8.1.
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 potentially related to pulmonary toxicity. If a participant experiences new or worsening pulmonary symptoms, (e.g., cough, dyspnea) without obvious etiology, appropriate diagnostic evaluation should be performed (see protocol Section 11.3.3) and further treatment with belantamab mafodotin delayed (refer to protocol Section 7.6). 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 7.6.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Immunosuppression	In nonclinical studies, belantamab mafodotin has been associated with decrease in immunoglobulins in monkeys, at all doses. An increase in immunoglobulins was seen in rats (rats are not an antigen specific species for belantamab mafodotin). Immunosuppression is frequently associated with an increased risk of infection. Serious and non-serious infections have been reported in belantamab mafodotin studies, including respiratory infections, pneumonia and sepsis.	Participants who have active infection are excluded. Participants will be monitored for infections and those who develop infection will receive immediate treatment according to standard practice.
Potential for Other Laboratory abnormalities	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 aldolase was observed in the rat 3-week study. Cases of elevated AST, lactate dehydrogenase (LDH) and creatine kinase (CK) alone or concomitant with no clear clinical correlate have been observed in clinical studies.	Laboratory parameters will be monitored as outlined in the SoA (Section 2). Participants with significant laboratory elevations (≥x3 ULN) should, where possible, have a sample sent for central testing of CK and LDH isoenzyme levels.
Embryo-Fetal Toxicity	Nonclinical reproductive studies with belantamab mafodotin have not been conducted. Embryo-fetal toxicity is expected due to the cytotoxic component, cys-mcMMAF via nonspecific uptake and/or BCMA-mediated toxicity (due to reports of BCMA expression in human placental cells [Langat, 2008]. Use of belantamab mafodotin in pregnant women may cause fetal harm.	Pregnancy testing outlined in the SoA. (Section 2) See Contraception requirements in Section 6.1 and Appendix 4.
Impaired Male and Female Fertility	In animal studies, belantamab mafodotin treatment has resulted in testicular toxicity and adverse effects on spermatogenesis. Reversibility of testicular toxicity is unknown at this time. Ovarian toxicity (luteinized non-ovulatory follicles) was observed in a 3-week rat study (weekly dosing) and 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 before treatment. Women of childbearing potential who may desire offspring in the future will be counseled about the option of having eggs frozen before treatment. See Contraception requirements in Section 6.1 and Appendix 4.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risks from Study Procedures		
Bone marrow aspiration/biopsy	Pain, infection, bleeding may occur after the procedure	Participants will be treated according to institution's practice
Incidental findings during image acquisition	During the acquisition of imaging data (e.g., MRI, CT, PET), non-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 Investigator's Brochure for further information.

3.5.2. Benefit Assessment

This study is being performed to study the efficacy and safety of single agent belantamab mafodotin compared to pom/dex, a global standard of care (SoC) for patients with RRMM who have been previously treated with at least two prior therapies, including lenalidomide and a proteasome inhibitor. This study population has a high unmet medical need as patients failing multiple lines of prior treatments do not have many therapeutic options left, and if response can be achieved with currently available drugs, it is usually of short duration. For pom/dex, based on available data, approximately a third of patients responded and the median PFS was 4.0 months [San Miguel, 2013].

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

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

3.5.3. Overall Benefit: Risk Conclusion

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

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To compare the efficacy with belantamab mafodotin vs pomalidomide plus low dose dexamethasone (pom/dex) in participants with relapsed/refractory multiple myeloma (RRMM)	• PFS, defined as the time from the date of randomization until the earliest date of documented disease progression (according to IMWG Response Criteria) or death due to any cause
Key Secondary	
• To compare the overall survival with belantamab mafodotin vs Pom/Dex in participants with RRMM	• OS, defined as the time from randomization until death due to any cause
Secondary	
• To compare other markers of efficacy of belantamab mafodotin vs pom/dex in participants with RRMM	• ORR, defined as the percentage of participants with a confirmed PR or better per IMWG • Clinical benefit rate (CBR), defined as the percentage of participants with a confirmed minimal response (MR) or better per IMWG • DoR, defined as the time from first documented evidence of PR or better until PD per IMWG or death due to any cause among participants who achieve confirmed PR or better • TTR, defined as the time between the date of randomization and the first documented evidence of response (PR or better) among participants who achieve confirmed PR or better. • TTP, defined as the time from the date of randomization until the earliest date of documented PD (per IMWG Response Criteria) or death due to PD
• To evaluate the safety and tolerability of belantamab mafodotin vs pom/dex in participants with RRMM	• Incidence of adverse events (AEs) and changes in laboratory parameters • Ocular findings on ophthalmic exam
• To evaluate the pharmacokinetic profile of belantamab mafodotin	• Plasma concentrations of belantamab mafodotin, total mAb, and cys-mcMMAF
• To assess anti-drug antibodies (ADAs) against belantamab mafodotin	• Incidence and titers of ADAs against belantamab mafodotin
• To evaluate the tolerability of belantamab mafodotin vs pom/dex based on self-reported symptomatic adverse effects	• Symptomatic adverse effects as measured by the PRO-CTCAE and OSDI
• To evaluate and compare changes in symptoms and health-related quality of life (HRQOL) of belantamab mafodotin to pom/dex.	• Health-related QOL as measured by EORTC QLQ-C30, EORTC IL52* and EORTC QLQ-MY20*
• To assess Minimal Residual Disease (MRD) in participants who achieve ≥VGPR or better for belantamab mafodotin vs pom/dex	• MRD negativity rate, defined as; the percentage of participants who are MRD negative by NGS method
Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	[redacted]

ADA= anti-drug antibodies; AE = adverse event; AUC = Area under the curve; [redacted]; BCMA = B cell maturation antigen; DOR = duration of response; [redacted]; EORTC-IL52 = Disease Symptoms domain of EORTC QLQMY20; EORTC QLQC30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30 item Core module; EORTC QLQMY20 = European

Objectives	Endpoints
Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20 item Multiple Myeloma module; CCI HRQoL = health related quality of life; IMWG = International Myeloma Working Group; KVA = Keratopathy Visual Acuity; MRD = minimal residual disease; NGS = Next Generation Sequencing; ORR = overall response rate; OS = overall survival; OSDI = Ocular Surface Disease Index; PD = progressive disease; PFS = progression-free survival; CCI ; pom/dex = pomalidomide/dexamethasone; PR = partial response; PROCTCAE = Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QOL = quality of life; RRMM = relapsed/refractory MM; SAE = serious adverse event; CCI ; TTP = time to progression; TTR -= time to response; VGPR= very good partial response * = EORTC IL52 applies to participants enrolled under the original protocol; EORTC QLQ-MY20 applies to participant enrolled under protocol amendment 1; CCI	

5. STUDY DESIGN

5.1. Overall Design

This is a Phase III, open-label, randomized, multicentre study evaluating the efficacy and safety of single agent belantamab mafodotin compared to pom/dex in participants with RRMM.

The study will include a Screening Period, a Study Treatment Period, and Follow-up (Section 1.2).

During Screening, participants will be evaluated for study eligibility per protocol as defined in the Inclusion/Exclusion criteria (see Section 6). Eligible participants must have been previously treated with at least two prior lines of therapy, including at least 2 consecutive cycles of lenalidomide and a proteasome inhibitor (PI), (given separately or in combination) and must have documented progression (a) on, or within 60 days of completion of the last therapy or (b) Must be non-responsive while on last treatment, where non-responsive is defined as not achieving at least Minimal Response (MR) after 2 complete treatment cycles. In such cases lack of achieving of at least MR must be determined no earlier than at least 4 weeks after the last treatment.

Following Screening, approximately 320 participants will be centrally randomized in a 2:1 ratio to either Arm 1 (single agent belantamab mafodotin) or Arm 2 (pom/dex), as described in Section 1.1. Participants will be stratified based on the following: previous treatment with anti-CD38 (Y/N), with a 40% global enrollment cap for participants with prior anti-CD38 treatment, stage (International Staging System [ISS]) (I/II or III), and number of prior lines of therapy (≤3 vs >3), with a 55% global enrollment cap for participants with ≤3 prior lines. Crossover to belantamab mafodotin arm will not be allowed until significant survival benefit is demonstrated on OS analysis.

If the number of participants required by local regulatory agencies are not recruited within the planned recruitment target, enrollment may continue in separate cohorts until the country enrollment requirements are met. Additional participants that are enrolled in separate cohorts will not be included in the analysis portion of the study planned for the

marketing authorization application, which is based on approximately 151 events. However, these additional participants will be included in country-specific supplemental analyses, as detailed in the country-specific Statistical Analysis Plan (SAP).
During the Study Treatment Period, safety and disease assessments will be performed regularly according to the schedule of activities (Section 2) for each arm. Participants in both arms will be treated until PD, death, unacceptable toxicity, withdrawal of consent, loss to follow-up or end of OS follow-up, whichever comes first. End of OS follow-up is defined in Section 5.4. Dose interruptions or reductions may be required following potential drug-associated toxicities.

CCI

For participants who discontinue study treatment for reasons other than PD, disease evaluations will continue to be performed every 3 weeks (±3 days) until confirmed (documented) PD, death, start of a new anti-myeloma treatment, withdrawal of consent, or end of the study, whichever occurs first. In case of PD, participants will be followed to ascertain survival status and subsequent anti-myeloma therapy (PFS2), every 12 weeks (±14 days) until withdrawal of consent, lost to follow-up, death or the end of the study.

Following the final analysis, includingany country-specific (expansion cohort) analysis, DREAMM-3 will move into the post analysis continued treatment (PACT) phase. At that time the collection of new data for participants who no longer receive study treatment will stop entirely and the clinical trial database will be closed. Participants in survival follow-up will be considered to have completed the study. Those participants still benefiting from study treatment in the opinion of their treating physician may continue to receive study treatment and only SAEs, AEs leading to treatment discontinuation, overdose, and pregnancy cases, and pre-specified ocular data (Arm 1 only) will be reported directly to GSK.

The EOS is defined as the date when the last participant had their last visit (last subject last dose plus 70 days SAE reporting period).

5.2. Scientific Rationale for Study Design

The combination regimen of pom/dex has been previously studied in patients with relapsed MM refractory to lenalidomide and bortezomib in the Phase III trial MM-003, which compared pom/dex with high-dose dexamethasone (HD). The median overall survival (OS, 12.7 [95% CI: 10.4, 15.5] vs. 8.1 [95% CI: 6.9, 10.8] months; HR: 0.74 [95% CI: 0.56, 0.97]; p=0.0285) and progression-free survival (PFS, 4.0 [95% CI: 3.6, 4.7] vs. 1.9 [95% CI: 1.9, 2.2] months; HR: 0.48 [95% CI: 0.3; p<0.0001) were significantly longer with pom/dex than with HD alone. An overall response rate (ORR) of 31% was achieved [San Miguel, 2013].

Belantamab mafodotin has demonstrated strong single-agent activity in two clinical studies conducted in heavily pre-treated participants with RRMM (Q3W schedule via IV administration, see Section 3.4.1) and the results compare favourably with those of pom/dex above.

In light of the efficacy data and acceptable safety/tolerability profile demonstrated to date, it is hypothesized that treatment with belantamab mafodotin will lead to greater patient benefit, as measured by progression-free survival (PFS) and overall survival (OS), compared to the SoC combination of pom/dex. The randomized two-arm design of this study will provide a comparison of the efficacy as measured by PFS and OS between the two treatment groups: Arm 1 receiving belantamab mafodotin and Arm 2 receiving the combination of pomalidomide with low dose dexamethasone.

5.3. Justification for Dose

5.3.1. Belantamab mafodotin – Arm 1

The proposed belantamab mafodotin RRMM single agent dose of 2.5 mg/kg administered on a Q3W schedule was selected based on data from the FTIH BMA117159 study [Trudel, 2019; Trudel, 2018] and the primary analysis of the ongoing Phase II Study 205678 (see Section 3.4).

In the Phase I study BMA117159, as of the efficacy clinical cut-off date of 31 August 2018, a total of 73 participants with RRMM have received at least 1 dose of belantamab mafodotin. In Part 1, 38 participants were enrolled at dose levels ranging from 0.03 mg/kg to 4.6 mg/kg. In Part 2, a total of 35 participants with MM and 6 participants with NHL received at least 1 dose of 3.4 mg/kg belantamab mafodotin (RP2D). In general, belantamab mafodotin has been well tolerated, with manageable toxicities. The most commonly reported individual treatment-related AEs were vision blurred (40%), dry eye (29%), fatigue (27%), AST increased, thrombocytopenia and nausea (19, 26% each), and chills (23%). The most common SAEs reported were lung-associated infections and infusion-related reaction (IRR).

A Bayesian logistic regression model (BLRM) was used to determine the dose-response relationship for both ORR and ≥Grade 2 corneal event rate (as determined by NCI-CTCAE grading) based on data from all 73 participants with RRMM in BMA117159. The model showed that the posterior probability of observing an ORR ≥30% is 100% in the 3.4 mg/kg dose group and 83% in the 2.5 mg/kg dose group. Similarly, the posterior probability of observing ≥Grade 2 corneal event rate is also higher in the 3.4 mg/kg dose group. Based on this analysis, these two doses (2.5 and 3.4 mg/kg) were selected for further evaluation.

In the ongoing DREAMM-2 study, the two single agent doses (2.5 mg/kg and 3.4 mg/kg) are being studied via a two-arm, randomized design in participants who have failed at least 3 prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and who are refractory to an immunomodulatory agent and a PI. Both dose levels, 2.5 and 3.4 mg/kg, had a positive benefit/risk profile based on the primary efficacy and safety analysis (cut-off date of 21 June 2019) and updated analysis (cut-off 31 January 2020) [GlaxoSmithKline Document Number 2013N175128_08; Li, 2017; Lonial, 2020].

Overall, there were no new safety signals identified in the 205678 study, and the profile of adverse events was similar to the experience in DREAMM-1 for both arms. The dose of 2.5 mg/kg appeared to have a lower incidence of adverse events and less frequent dose delays and reductions, and it resulted in similar efficacy with 3.4 mg/kg dose as measured by ORR.

In summary, the selection of the dose of 2.5 mg/kg Q3W for future single agent studies with belantamab mafodotin is based on the available data with single agent belantamab mafodotin in heavily pretreated patients with relapsed/refractory MM from 2 studies, DREAMM-1 (BMA117159) and DREAMM-2 (205678), which showed clinically meaningful efficacy with a manageable safety profile in a heavily pre-treated patient population.

5.3.2. Starting dose of SOC (Pom/Dex) – Arm 2

Pomalidomide will be administered orally at the approved starting dose of 4 mg daily on Days 1 to 21 of each 28-day cycle, with dexamethasone administered at a dose of 40 mg once weekly (Days 1, 8, 15, and 22), or at the lower dose of 20 mg once weekly (Days 1, 8, 15, and 22).

5.4. End of Study Definition

A final analysis data cut-off (DCO) representing the end of data collection, prior to the EOS, is defined as the DCO date for the final analysis (see Section 10.5). Following the final DCO date the study may move into the PACT phase and the clinical study database will be closed to new data. Participants who are receiving belantamab mafodotin [and/or study drug(s)] may continue to receive belantamab mafodotin [and/or study drug(s)] if they are gaining clinical benefit as assessed by the investigator until they meet any protocol-defined treatment discontinuation criteria. Participants in survival follow-up at the time of the final DCO date will be considered to have completed the study. Although the clinical study database will be closed at the time of the final DCO date, the study remains open until all participants discontinue study treatment [and complete the 70-day safety follow-up] and the EOS definition is reached.

The final analysis will occur when the planned 250 deaths for final OS analysis have occurred. If 250 OS events cannot be achieved, the final analysis will occur when all participants have died, are lost to follow up or have withdrawn consent. If OS is significant at 70% IF, no formal statistical testing will be conducted after 250 death events and OS data will continue to be collected until all participants have died, are lost to follow up, or withdrawn consent, or for 2 years after the OS analysis at 70% IF, whichever occurs first.

The end of study is defined when the last patient had their last visit (last subject last dose plus 70 days SAE reporting period).

Cross-over to belantamab mafodotin will not be permitted.

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

1. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. Participants must be 18 or older, at the time of signing the informed consent.
   NOTE: In Republic of Korea, participants must be over 19 years of age inclusive, at the time of signing informed consent.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (Appendix 9).
4. Histologically or cytologically confirmed diagnosis of MM as defined according to International Myeloma Working Group (IMWG), [Rajkumar, 2014], and:
   a. Has undergone autologous stem cell transplant (SCT), or is considered transplant ineligible, and
   b. Has received at least 2 prior lines of anti-myeloma treatments, including at least 2 consecutive cycles of both lenalidomide and a proteasome inhibitor (given separately or in combination), AND
      i. Must have documented disease progression on, or within 60 days of, completion of the last treatment OR
      ii. Must be non-responsive while on last treatment, where non-responsive is defined as not achieving at least Minimal Response (MR) after 2 complete treatment cycles. In such cases lack of achieving of at least MR must be determined no earlier than at least 4 weeks after the last treatment
5. Has measurable disease with at least one of the following:
   a. Serum M-protein ≥0.5 g/dL (≥5 g/L)
   b. Urine M-protein ≥200 mg/24 hours
   c. Serum free light chain (FLC) assay: Involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65)
6. Participants with a history of autologous SCT are eligible for study participation provided the following eligibility criteria are met:
   a. Transplant was >100 days prior to initiating study treatment
   b. No active infection(s)
   c. Participant meets the remainder of the eligibility criteria outlined in this protocol
7. Adequate organ system functions as defined in Table 9

Table 9 Adequate Organ System Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.0x10^9/L
Hemoglobin	≥8.0 g/dL
Platelets	≥50x10^9/L
Hepatic	
Total bilirubin	≤1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
ALT	≤ 2.5xULN
Renal	
Estimated glomerular filtration rate (eGFR)[1] Spot urine (albumin/creatinine ratios)	≥30 mL/min/1.73 m^2 ≤500 mg/g (56 mg/mmol)

1. As calculated by Modified Diet in Renal Disease (MDRD) formula (Appendix 10).

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 retest the participant, and the subsequent within range screening result may be used to confirm eligibility.

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

   a. Male Participants:

   Male participants are eligible to participate if they agree to the following during the intervention period and until 6 months* after the last dose of study intervention to allow for clearance of any altered sperm:

   - Refrain from donating sperm

   PLUS, either:

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

   OR

   - Must agree to use contraception/barrier as detailed below depending on whether they are randomised to Arm 1 (belantamab mafodotin) or Arm 2 (pom/dex), even if they have undergone a successful vasectomy:

     Agree to use a male condom throughout study treatment including the 6 month* follow-up period even if they have undergone a successful vasectomy and a female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 4 when having sexual intercourse with a pregnant woman or a woman of childbearing potential who is not currently pregnant.

     **Four weeks for male participants on Treatment Arm 2 (pom/dex).*

b. Female Participants:

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

- Is not a woman of childbearing potential (WOCBP) [Appendix 4]

OR

- Is a WOCBP and agrees to abide by the following:
- **Arm 1 (belantamab mafodotin):** Use a contraceptive method that is highly effective (with a failure rate of <1% per year) which includes abstinence, preferably with low user dependency during the intervention period and for 4 months after the last dose of study treatment.
- **Arm 2 (pom/dex):** Due to pomalidomide being a thalidomide analogue with risk for embryo-fetal toxicity and prescribed under a pregnancy prevention/controlled distribution program, WOCBP participants will be eligible if they commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control (one method that is highly effective), beginning 4 weeks prior to initiating treatment with pomalidomide, during therapy, during dose interruptions and continuing for at least 4 weeks following discontinuation of pomalidomide treatment.
- Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing pomalidomide therapy.
- And agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period.
- The investigator should confirm the effectiveness of the contraceptive method(s) ahead of the first dose of study intervention.

Additional requirements for pregnancy testing during and after study intervention are located in Appendix 4.

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

9. All prior treatment-related toxicities (defined by National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 5.0, 2017) must be ≤Grade 1 at the time of enrollment, except for alopecia and Grade 2 peripheral neuropathy.

6.2. Exclusion Criteria

Participants will not be eligible for inclusion in this study if any of the following criteria apply:

1. Symptomatic amyloidosis, active POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes); active plasma cell leukemia at the time of screening.
2. Systemic anti-myeloma therapy or use of an investigational drug within <14 days or 5 half-lives, whichever is shorter, before the first dose of study intervention.
3. Prior treatment with an anti-MM monoclonal antibody within 30 days prior to receiving the first dose of study intervention.
4. Prior BCMA-targeted therapy or prior pomalidomide treatment.
5. Plasmapheresis within 7 days prior to the first dose of study intervention.
6. Prior allogeneic stem cell transplant.
   NOTE – Participants who have undergone syngeneic transplant will be allowed only if no history of, or currently active, GvHD.
7. Any major surgery within the last 4 weeks.
8. Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect participant's safety). Participants with isolated proteinuria resulting from MM are eligible, provided they fulfil criteria included in Table 9
9. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other conditions (including lab abnormalities) that could interfere with participant's safety, obtaining informed consent, or compliance with study procedures.
10. History of (non-infectious) pneumonitis that required steroids, or current pneumonitis.
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, oesophageal 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 second 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:

a. Evidence of current clinically significant uncontrolled arrhythmias, including clinically significant electrocardiogram (ECG) abnormalities including 2nd degree (Mobitz Type II) or 3rd degree atrioventricular block.

b. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within 3 months of Screening.

c. Class III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system (Appendix 11)

d. Uncontrolled hypertension.

15. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to belantamab mafodotin, pomalidomide, dexamethasone or any of the components of the study intervention.
16. Pregnant or lactating female.
17. Active infection requiring treatment.
18. Known human immunodeficiency virus (HIV), 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
    - CD4+ T-cell (CD4+) counts ≥350 cells/uL
    - 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 or other combination products as relevant (See Section 7.5.3, Drug Interactions)
19. Patients with Hepatitis B will be excluded unless the following criteria can be met

Serology	**Screening**	**During Study Treatment**
HbcAb+, HbsAg-	• HBV DNA undetectable	• Monitoring per protocol (Section 2) • Antiviral treatment instituted if HBV DNA becomes detectable
HBsAg+ at screen or ≤3 months prior to first dose of study treatment	• HBV DNA undetectable • Highly effective antiviral treatment started ≥4 weeks prior to first dose of study treatment • Baseline imaging per protocol (Section 2) • Participants with cirrhosis are excluded • Japan only: Must test HBeAg and HBeAb	• Table of Antiviral treatment maintained throughout study treatment • Monitoring and management per protocol (Section 2)

Note: Presence of HBsAb indicating previous vaccination will not exclude a participant

Abbreviations: DNA=deoxyribonucleic acid; HBcAb=hepatitis B core antibody; HBsAb= hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HBeAg=hepatitis B e antigen; HBeAb=hepatitis B e antibody.

20. Positive hepatitis C antibody test result or positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment unless the participant can meet the following criteria:
    - Hepatitis C RNA test negative at Screening
    - 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.

    Hepatitis RNA is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.
21. Participants unable to tolerate thromboembolic prophylaxis
22. Current corneal epithelial disease except for mild punctate keratopathy

6.3. Lifestyle Considerations

6.3.1. Contact Lenses

Contact lenses are prohibited in participants randomized to Arm 1 (belantamab mafodotin) while the participant is receiving belantamab mafodotin. Following discontinuation of belantamab mafodotin treatment, contact lens use may be restarted after the qualified eye care specialist such as ophthalmologist/optometrist (Appendix 12) confirms there are no other contraindications.

6.3.2. Tobacco

Pomalidomide/dexamethasone arm only: Cigarette smoking reduced pomalidomide AUC by 32% to 50% due to CYP1A2 induction. Participants who use tobacco products should be advised that smoking may reduce the efficacy of pomalidomide. [POMALYST PI] and [Imnovid SmPC].

6.3.3. Other Lifestyle Considerations

In Arm 2, participants must not donate blood during treatment with pomalidomide and for 4 weeks following discontinuation of study treatment, as transfused blood might be given to a pregnant female whose fetus must not be exposed to pomalidomide.

6.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened. Rescreened participants must be assigned a new unique participant number that is different from the initial number. Rescreening of a participant more than once requires discussion with the Medical Director. Refer to the SRM for further details.

7. STUDY INTERVENTION

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

7.1. Study Intervention(s) Administered

ARM Name	**Arm 1**	**Arm 2**
Intervention Name	belantamab mafodotin (GSK2857916)	pom/dex (Pomalidomide plus low dose Dexamethasone)
Type	Experimental treatment	Active comparator
Dose Formulation	Powder for solution for infusion	Pomalidomide: capsule Dexamethasone: tablet
Dosage Level(s)	2.5 mg/kg on day 1 of every 21-day cycle	Pomalidomide – 4 mg daily on Days 1 - 21 of each 28-day cycle Dexamethasone – 40 mg or at lower 20 mg dose[b] once weekly (Days 1, 8, 15, and 22)
Route of Administration	Intravenous solution over at least 30 minutes[a]	Oral
Dosing instructions	Reconstitute belantamab mafodotin for injection 100 mg/vial with 2.0 mL of water for injection (WFI), sterile Dilute belantamab mafodotin in normal 0.9% saline to the appropriate concentration, per the investigator's brochure, for the dose. Doses of belantamab mafodotin are to be administrated as an IV infusion via an infusion pump. See Investigator's Brochure for compatible administration materials.	Refer to labels for dosing instructions [e.g. POMALYST PI; Imnovid SmPC]

a. Infusions may be prolonged in the event of an infusion reaction. If multiple participants experience clinically significant infusion reactions, the infusion rate may be slowed for all future administrations of study treatment(s) for all participants. Should this global change in infusion rate be required, it will be communicated to the sites in writing.
b. For participants >75 years old

7.1.1. Supportive Care Guidelines for Belantamab Mafodotin – Arm 1

Corneal events, which commonly manifest as superficial 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 such as ophthalmologist/optometrist (Appendix 12) who will be responsible for assessing participants and managing those who develop corneal examination findings in close communication with GSK Medical Director.

Please refer to Section 9.2.6.1 for ocular examinations, procedures and assessment schedule for participants in arm 1.

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

Corticosteroid eye drops are not required as prophylaxis but can be used therapeutically if clinically indicated as per discretion of an eye-care specialist. If steroid eye drops are deemed medically necessary and prescribed, intraocular pressure must be monitored if used for >7 days. Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops (if administered). While not yet clinically demonstrated, it is theoretically possible that the application of a cooling eye mask during belantamab mafodotin administration, and in the first few hours after infusion may subsequently decrease ocular side effects.

On the day of infusion, at the discretion of the participant and the investigator, the following may be considered:

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

In treatment arm 1, participants must avoid the use of contact lenses during the study. See Section 6.3 for further details.

7.1.2. Supportive Care Guidelines for Pom/Dex – Arm 2

Thromboembolic monitoring and prophylaxis are recommended as per institutional guidelines in participants in Arm 2 (pom/dex) based on assessment of risk factors [POMALYST PI; Imnovid SmPC]. Please refer to Section 7.6.2.2 for dose modification guidelines for pomalidomide- and dexamethasone-related adverse events.

7.2. Preparation/Handling/Storage/Accountability

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

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions 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).

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

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 Director and/or GSK study contact.

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

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

7.3. Measures to Minimize Bias: Randomization and Blinding

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

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

Each participant will be assigned a unique number that will not be reassigned to another participant if a participant assigned a number is found to be a Screen Failure. The unique participant number will remain for the duration of the study.

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

This is an open-label study; therefore, no blinding of treatment identity is needed for either belantamab mafodotin or pom/dex arm. However, to ensure trial integrity steps will be taken to restrict access to key information while the study is ongoing and prevent data aggregation except for where specified in the protocol.

Upon completion of all the required screening assessments, eligible participants will be registered via an Interactive Response Technology (IRT), by the investigator or authorized site staff. The IRT system allows study sites to register and randomize participants, and also records stratification information.

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

- previous treatment with anti-CD38 therapy (Y/N)
- ISS I/II or III
- number of prior lines of therapy (≤3 vs >3)

Randomization will be done centrally using a randomization schedule, which will assign participants in a 2:1 ratio to:

- Arm 1: 2.5 mg/kg IV Q3W
- Arm 2: pomalidomide 4 mg orally daily on Days 1 to 21 Q4W (28-day cycle)/ dexamethasone 40 mg once weekly (Days 1, 8, 15, and 22) Q4W (28-day cycle)

For participants >75 years old, dexamethasone 20 mg once weekly (Days 1, 8, 15, and 22) Q4W (28-day cycle)

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

Every attempt should be made for Dosing (C1D1) to occur on the same day as randomisation call, or as early as possible after the call where for logistical reason same day dosing is not possible.

Returned study intervention should not be re-dispensed to the participants.

Study Specific User Guide for IRT system will be provided to the study site in the SRM. For each country specific expansion cohort, a separate randomization schema will be utilized.

7.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and reported in the electronic case report form (eCRF). The dose of study intervention 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 intervention. Study intervention start and stop dates, including dates for study intervention delays and/or dose reductions will also be recorded in the eCRF.

Belantamab mafodotin is to be administered as an IV infusion, via an infusion pump. Premedication is not required prior to infusion unless deemed medically necessary by the investigator, in which case it should be administered according to institutional recommendations.

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

7.5. 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 enrollment or receives during the study must be recorded in the eCRF along with:

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

- dosage information including dose and frequency

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

Participants will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until the End of Treatment (EoT) visit. Concomitant medications administered after the EoT visit should be recorded for SAEs/AESIs as defined in Section 9.3. Any concomitant medication(s), including non-prescription medication(s) and herbal product(s), taken during the study will be recorded in the source records and eCRF. Additionally, a complete list of all prior anti-myeloma therapies will be recorded in the eCRF.

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

7.5.1. 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. Thromboembolic monitoring and prophylaxis is recommended as per institutional guidelines in participants in Arm 2 (pom/dex) based on assessment of risk factors [POMALYST PI; Imnovid SmPC].

While on study, a participant who is diagnosed with an unrelated malignancy that can be addressed by local therapy can remain on study, study treatment may be resumed after discussion with the GSK Medical Director. The participant should continue to be followed for disease progression of multiple myeloma as per the SoA.

7.5.2. Prohibited Medication(s)

Chronic treatment with oral steroids other than study medication is prohibited while the participant is on study, unless for treatment of acute complications related to study treatment, including prophylaxis and/or management of IRR, or exacerbations of chronic conditions (no longer than 7 days). Inhaled steroids are allowed for management of asthma or COPD exacerbations. Chronic low dose replacement therapy (less ≤10 mg/day prednisolone) is allowed in participants with adrenal insufficiency.

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

For guidance on prohibited concomitant medications with pomalidomide and dexamethasone usage see the relevant package insert in the SRM.

Other prohibited therapies for all participants include:

- Plasmapheresis: prohibited from 7 days prior to first dose through the end of study.
- Any other approved or investigational anti-myeloma therapy not specified in this protocol (including but not limited to immunomodulatory and antineoplastic drugs or proteasome inhibitors). This is inclusive of all medications with activity against multiple myeloma and medications used for other indications that have anti-myeloma properties.
- Investigational agents other than belantamab mafodotin

7.5.3. Drug Interactions

For participants enrolled in Arm 1: Elimination pathways for belantamab mafodotin and cys-mcMMAF have not been characterized in humans. However, cys-mcMMAF was shown to be a substrate of P-gp and OATP transporters, and to be a poor substrate of CYP enzymes in vitro. Caution should be exercised when belantamab mafodotin is combined with strong inhibitors of P-gp, and strong inhibitors of OATP should be avoided unless considered medically necessary. Additional information is provided in the SRM. Anti-HIV and anti-microbials that are OATP inhibitors (list provided below; list covering other classes of drugs) are thus prohibited unless considered medically necessary. Preferably alternative antimicrobials and anti-HIV drugs would need to be prescribed to these patients.

For guidance on drug interactions with pomalidomide and dexamethasone usage see the relevant package insert in the SRM.

- OATP inhibitors: Prohibited unless considered medically necessary
- Anti-HIV drugs: atazanavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
- Anti-HCV drugs: simeprevir, telaprevir
- Antibiotics drugs: clarithromycin, erythromycin, rifampin/rifampicin
- Antifungals drugs: itraconazole
- Others: cyclosporine, eltrombopag, gemfibrozil

7.6. Dose Modification and Delay

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

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

Dosing delays to the next cycle are permitted in the case of medical/surgical events or for logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, participant vacation, and/or holidays, but not for participants' decision to delay treatment).

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

7.6.1. Dose Adjustments Due to Body Weight

7.6.1.1. Belantamab mafodotin – Arm 1

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

7.6.1.2. Pom/Dex – Arm 2

Pomalidomide is administered at a fixed dose level, with no adjustments for body weight as indicated in pomalidomide product labels [e.g. POMALYST PI; Imnovid SmPC].

Dexamethasone is administered at a fixed dose level, with no adjustments for body weight.

7.6.2. Dose Modifications

7.6.2.1. Belantamab mafodotin – Arm 1

Table 10 details the permitted dose modifications of belantamab mafodotin. Table 11 and Table 12 contain dose modification guidance for drug-related AEs.

See Table 13 for grading of corneal events (Keratopathy Visual Acuity [KVA] scale) and Table 14 for dose modification guidelines for belantamab mafodotin treatment based on the KVA scale.

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[redacted]

Table 10 Permitted Dose Reductions

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

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

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

If a dose is delayed, the participant should wait for the next scheduled dose to resume treatment. In individual cases where in the judgment of the Investigator waiting a full cycle to resume treatment after delay (skipping dose) related to toxicity which has resolved would be detrimental to the participant's health, the PI should contact the

Medical Director to discuss an earlier re-start. An earlier re-start may be considered only for participants who have recovered from toxicity to at least ≤Grade 1. The dosing with belantamab mafodotin cannot occur more frequently than every 21 days (±3-day window). In such cases, efficacy and safety assessments must remain every 3 weeks in line with initial efficacy and safety assessments on study, which may result in 2 separate visits (1 for dosing, 1 for disease assessments). Evaluations associated with a dose would be entered into the eCRF under the next scheduled cycle.

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

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

Toxicity	Grade/description of toxicity	Recommendations
Serum creatinine Graded according to NCI-CTCAE criteria	Grade 2 >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	• Repeat within 48 hours if elevation cannot be explained by concomitant sepsis, TLS, other severe condition with fever or dehydration. • If confirmed: withhold belantamab mafodotin, initiate treatment and monitoring as clinically indicated, and follow for resolution. • Discuss any further dosing with Medical Director
	Grade 3 >3.0 x baseline; >3.0 - 6.0 x ULN Or Grade 4 >6.0 x ULN	• Provide appropriate medical treatment • If drug related, permanently discontinue treatment with belantamab mafodotin • If due to another cause (e.g. sepsis, dehydration), withhold treatment with Belantamab Mafodotin. Upon recovery to Grade 1, restart treatment at the same dose level.
Spot urine (albumin/creatinine ratios)	>2000 mg/g (or 224 mg/mmol)	• Re-test (at least 7 days apart). • If not confirmed, continue belantamab mafodotin at current dose • If confirmed on re-test and no clear evidence of disease progression o Interrupt treatment with belantamab mafodotin o Repeat testing within 4 weeks o If spot urine <2000 mg/g (224 mg/mmol), may restart belantamab mafodotin with a dose reduction o If spot urine remains >2000 mg/g (224 mg/mmol) after 4 weeks, consider permanently discontinuing belantamab mafodotin provide treatment as clinically indicated and follow for resolution[a]

Toxicity	Grade/description of toxicity	Recommendations
Urine Dipstick	2+	• May continue belantamab mafodotin dosing • Confirm by quantitative assessment using albumin/creatinine (spot urine from first void) • If albumin/creatinine >2000 mg/g, at the next cycle follow guidance above for Spot Urine.
	3+	• Interrupt treatment and follow up for recovery. Implement quantification of albumin/creatinine ratio
Thrombocytopenia (on days of dosing)	Grade 3	• **No bleeding**: continue treatment with 1 dose level reduction. Consider reverting to previous dose once thrombocytopenia recovered to Grade 2 or less • **With bleeding**: withhold the dose, continue treatment after recovery with 1 dose level reduction • Consider additional supportive treatment (e.g., transfusion), as clinically indicated and per local practice.
	Grade 4	• Withhold the dose. Consider restarting with 1 dose level reduction if recovered, or transfused to ≤Grade 3 only if there is no active bleeding at time of treatment restart • If thrombocytopenia is considered disease related, is not accompanied by bleeding, and recovers with transfusion to >25x10^9/L continuing treatment at 1 dose level reduction may be considered after discussion with the Medical Director
Febrile neutropenia Graded according to NCI CTCAE criteria	Grade 3-4 (Defined as: single temp of 38.3°C, or sustained 38°C for >1 hr AND ANC <1.0x10^9/L)	• Withhold the dose and immediately hospitalize participant with appropriate management, per local institutional guidance. • Consider additional supportive treatment per local practice (e.g. growth factors). • Upon recovery, consider a dose reduction of belantamab mafodotin, if neutropenia was drug related
Neutropenia without fever Graded according to NCI CTCAE criteria	Grade ≥3 (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 ≥ 1.0x10^9/L) on Day 1 of the subsequent cycle. • Prophylactic antibiotics, per physician discretion and local institutional guidance. Consider growth factors. • Local guidance must be followed for hematological monitoring, if more conservative than the protocol SoA specifications. • In cases of frequent recurrent neutropenia (ANC

Toxicity	Grade/description of toxicity	Recommendations
		<1.0x10^9/L), consider dose reduction of belantamab mafodotin by 1 level
Infusion Reaction[b]	Grade 2	• Stop the infusion, provide medical treatment and continue at half the original infusion rate after resolution to Grade 0-1
	Grade 3	• Further treatment with belantamab mafodotin needs to be discussed with Medical Director. 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 from treatment
Pneumonitis	Grade 2	• Withhold treatment with belantamab mafodotin • Upon recovery, restart treatment with 1 dose level reduction. • If patient is already at the lowest dose level (1.9 mg/kg), then rechallenge with the same dose must be discussed with the Medical Director
	Grade 3-4	• Permanently discontinue from treatment

a. Further treatment may be allowed on case by case basis after discussion with Medical Director who may consult GSK's nephrotoxicity panel.

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

Table 12 General Dose Modification and Management Guidelines for Belantamab Mafodotin-Related Adverse Events Not Otherwise Specified[a]

Severity	Management	Follow-up
Grade 1	• Administer symptomatic treatment as appropriate • Continue study drug(s)[a]	• Provide close follow-up to evaluate for increased severity, no dose modification necessary
Grade 2	• Administer symptomatic treatment • Investigate etiology • Consider consulting subspecialist, and/or diagnostic procedure	*Symptoms resolved in ≤7 days:* • Continue after resolution at the current dose *Symptoms ongoing >7 days or worsening*: • Delay study drug[b], or consider dose reduction • If recovery takes >3 weeks- consult GSK medical director (MD) • If symptoms continue or worsen to Grade 3-4, see below
Grade 3	• Provide appropriate medical treatment • Consider Consulting subspecialist	• Delay treatment till recovery to Grade 1 or less. • Consider dose reduction. • Consider consultation with GSK MD. **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 Director	• Interrupt treatment. • Further treatment with belantamab mafodotin only allowed on individual basis if in the discussion with GSK MD it is agreed that benefits outweigh the risks for a given participant

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

Table 13 Keratopathy Visual Acuity (KVA) Scale for Treatment-related Corneal Events

Grade per KVA scale		Grade 1	Grade 2	Grade 3	Grade 4
Corneal Events	***Corneal examination finding(s)***	Mild superficial keratopathy[a]	Moderate superficial keratopathy[b]	Severe superficial keratopathy[c]	Corneal epithelial defect[d]
	Change in Snellen-equivalent BCVA[e,f,g]	Decline from baseline of 1 line on Snellen-equivalent BCVA	Decline from baseline of 2 or 3 lines (and Snellen-equivalent BCVA not worse than 20/200)	Decline from baseline by more than 3 lines (and Snellen-equivalent BCVA not worse than 20/200)	Snellen-equivalent BCVA worse than 20/200

a. Mild superficial keratopathy: Mild superficial punctate keratopathy (documented worsening from baseline), with or without symptoms.
b. Moderate superficial keratopathy: Any/ or a combination of: moderate superficial punctate keratopathy, patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity.
c. Severe superficial keratopathy: any/ or a combination of: severe superficial punctate keratopathy, diffuse microcyst-like deposits, sub-epithelial haze (central), or a new central stromal opacity.
d. Corneal epithelial defect such as corneal ulcers (with underlying stromal infiltration).
e. 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 such as ophthalmologist/optometrist.
f. 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.
g. If a participant has cataract surgery the BCVA should be re-baselined and visual acuity assessed from the new baseline value.

BCVA- best corrected visual acuity

Table 14 Dose Modification for Belantamab Mafodotin Treatment based on the KVA scale (Table 13)

Grade per KVA scale	Grade 1	Grade 2	Grade 3	Grade 4
Recommended Dosage Modifications[a]	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[b].	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[b].

a. 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.
b. If already on 1.9 mg/kg, participant continues treatment at same dose.

7.6.2.2. Pom/Dex – Arm 2

Dose interruptions and reductions are permitted per pomalidomide and dexamethasone labels [e.g. POMALYST PI; Imnovid SmPC]. Guidance from the most recent applicable labels, together with any additional institutional guidance that may apply, should be followed.

Pom/dex may be resumed upon recovery during the ongoing cycle. A cycle will be defined as 28 days, with pomalidomide dosed on Days 1-21 followed by 7 days off treatment and dexamethasone once weekly (Days 1, 8, 15, and 22). This cycle length and dosing durations are irrespective of start or duration of pom/dex use. Missed doses will not be made up. For example:

- Scenario 1: Delayed pom/dex start: Pom/dex is not started on D1 of a new cycle due to an AE. If recovery occurred on any day between D1-21 of this cycle. Pom/dex can be resumed and continued until D21.

- Scenario 2: Pom/dex interrupted due to AE midcycle: If the AE recovers before D21, the treatment with pom/dex may be resumed for the remaining days of the 21 days of that cycle. The D1 for this given cycle remains the same date (from before interruption).
- Scenario 3: Pom/dex use interrupted due to AE which did not recover during D1-D21: In this case a participant would not receive pom/dex for remaining (or all) days of this cycle. Pom/dex would be skipped for the entire cycle (D1-D28) and would be resumed on D1 of the following cycle, assuming the participant has recovered and can be dosed.

The maximum number of doses of dexamethasone per Cycle is four; on Day 1, Day 8, Day 15 and Day 22. Missed doses will not be made up. In case of an AE that in the judgment of investigator is related to dexamethasone, the cycle may continue only with pomalidomide administration until the participant has recovered and can receive dexamethasone at full or reduced dose.

Efficacy and safety assessments must remain every 3 weeks after the previous efficacy and safety assessments which may result in 2 separate visits (1 for dosing and 1 for disease assessments).

Treatment with pom/dex will continue until disease progression or unacceptable toxicity.

- To initiate a new cycle of pomalidomide, the neutrophil count must be $\geq 1 \times 10^9$/L, and the platelet count must be $\geq 50{,}000$ per mcL ($\geq 50 \times 10^9$/L).
- In case of neutropenia, the physician should consider the use of growth factors.
- For other Grade 3 or 4 adverse reactions judged to be related to pomalidomide, hold treatment and restart treatment at 1 mg less than the previous dose when adverse reaction has resolved to ≤ Grade 2 at the physician's discretion.
- If adverse reactions occur after dose reductions to 1 mg, then the medicinal product should be discontinued.
- Pomalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Pomalidomide must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, and should not be resumed following discontinuation for these reactions (see local label for further details).
- If strong inhibitors of CYP1A2 (e.g. ciprofloxacin, enoxacin and fluvoxamine) are co-administered with pomalidomide, reduce the dose of pomalidomide by 50%.

See Table 15 for dose modifications guidelines for pomalidomide-related AEs. Table 16 details recommended dose modifications for dexamethasone-related AEs. The relevant local prescribing information should be reviewed for further details and adhered to if more conservative than protocol guidance.

Table 15 Dose Modifications Guidelines for Pomalidomide – Related to Hematologic Adverse Events

Toxicity	Dose Modification
Neutropenia	
ANC < 500 per mcL (< 0.5 x 10^9/L) or Febrile neutropenia (fever ≥ 38.5°C and ANC < 1,000 per mcL [<1 x 10^9/L])	Interrupt pomalidomide treatment, follow CBC weekly
ANC return to ≥1 x 10^9/L	Resume pomalidomide treatment at 3 mg daily
For each subsequent drop < 500 per mcL (< 0.5 x 10^9/L)	Interrupt pomalidomide treatment
Return to ≥ 500 per mcL or to ≥1 x 10^9/L	Resume pomalidomide treatment at 1 mg less than the previous dose
Thrombocytopenia	
Platelet count < 25,000 per mcL (<25 x 10^9/L)	Interrupt pomalidomide treatment, follow CBC weekly
Platelet count returns to > 50,000 per mcL (≥50 x 10^9/L)	Resume pomalidomide treatment at 3 mg daily
For each subsequent drop < 25,000 per mcL (< 25 x 10^9/L)	Interrupt pomalidomide treatment
Return to ≥ 50,000 per mcL (≥50 x 10^9/L)	Resume pomalidomide treatment at 1 mg less than the previous dose

ANC – Absolute Neutrophil Count; CBC – Complete Blood Count. mcL = microliter

Table 16 Dose Modifications for Dexamethasone

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

Dexamethasone dose reduction levels:

- ≤ 75 years of age.
    - Starting dose 40 mg, dose level -1 20 mg, dose level -2 10 mg, on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
    - At investigator discretion, if a participant ≤ 75 years of age has comorbidities that may result in excessive toxicity with a 40 mg starting dose of dexamethasone, a starting dexamethasone dose of 20 mg may be used, as described below.
- > 75 years of age.
    - Starting dose 20 mg, dose level -1 12 mg, dose level -2 8 mg, on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

If recovery from toxicities is prolonged beyond 14 days, then the dose of dexamethasone will be decreased by one dose level.

7.7. Continued Access to Study Intervention after the End of the study

Study participants that continue to benefit from study intervention beyond the DCO date will continue to have access to study intervention until the EOS as defined in Section 5.4. There is no planned intervention following the EOS.

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

Refer to the SoA (Section 2) for follow-up assessments of participants who are to be followed for disease progression and survival after they permanently discontinue from study drugs until the DCO date and to Section 9.3.1 for follow-up assessments from the DCO date to the EOS.

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

Participants receiving belantamab mafodotin or pomalidomide/dexamethasone at the time of the final analysis may continue to receive belantamab mafodotin or pomalidomide/dexamethasone, if in the opinion of their treatment physician, they are continuing to derive clinical benefit from continued treatment, and they do not meet a protocol-defined treatment discontinuation criteria (Section 8.1). Study treatment will continue until a study discontinuation (see Protocol Section 8.1) as assessed by the investigator has been met.

Participants who continue study treatment in the PACT phase will be cared for in accordance with local standard clinical practice. Participants will continue to be monitored for all SAEs, AEs leading to treatment discontinuation, prespecified ocular data, overdoses and pregnancy while receiving belantamab mafodotin or pomalidomide/dexamethasone. Information relating to participant care will be recorded on participant medical records but, with the exception of SAEs, AEs leading to treatment discontinuation, prespecified ocular data, overdoses and pregnancy outcomes that must continue to be reported to GSK, but will not otherwise be reported for the purposes of this study.

Investigators must report all SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases until 70 days after receipt of their last dose of study treatmen t in accordance with Section 9.3.1. Pre-specified ocular data (Arm 1 only) (see SRM) will be reported as outline in Section 9.3.1.

During the PACT phase, recording and follow up of SAEs, AEs leading to treatment discontinuation, overdose, pregnancy and pre-specified ocular data (Arm 1 only) will be done via paper forms (see SRM for details). For dispensing of study treatment and maintaining drug accountability in the PACT phase please refer to the SRM. All other assessments will revert to standard of care at their site.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Intervention

Participants will receive study treatment until disease progression, withdrawal of consent, death, unacceptable toxicity (including but not restricted to meeting stopping criteria for significant toxicity as outlined in Section 8.2), loss to follow-up, or end of study (Section 5.4).

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

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

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

- deviation(s) from the protocol
- request of the participant or proxy (withdrawal of consent by participant or proxy)
- investigator's discretion
- concurrent illness that prevents further administration of study treatment(s)
- participant is lost to follow-up
- study is closed or terminated

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

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

Once a participant has permanently discontinued from study treatment, the participant will continue to be followed until the end of study.

All participants who discontinue from study treatment for any reason other than confirmed progression or death will be followed up for PFS, OS, and progression after subsequent anti-myeloma therapy (PFS2) as specified in the SoA (see Section 2).

PFS Follow-up:

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

- Progression is documented, or
- New anti-myeloma therapy is initiated, or
- Lost to follow-up, or
- Withdrawal of consent, or
- Death occurs, or
- End of OS follow-up (Section 5.4)

OS Follow-up:

All participants who permanently discontinue study treatment and have experienced disease progression or have started new anti-myeloma therapy will be followed for survival and progression after new anti-myeloma therapy until the end of OS follow-up as described in Section 5.4

8.2. Safety Stopping Criteria

8.2.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology. Discontinuation of study treatment for abnormal liver tests is required when the participant satisfies any of the stopping rules as shown in Figure 4 and Figure 5.

Figure 4 Liver Chemistry Stopping and Increased Monitoring Algorithm

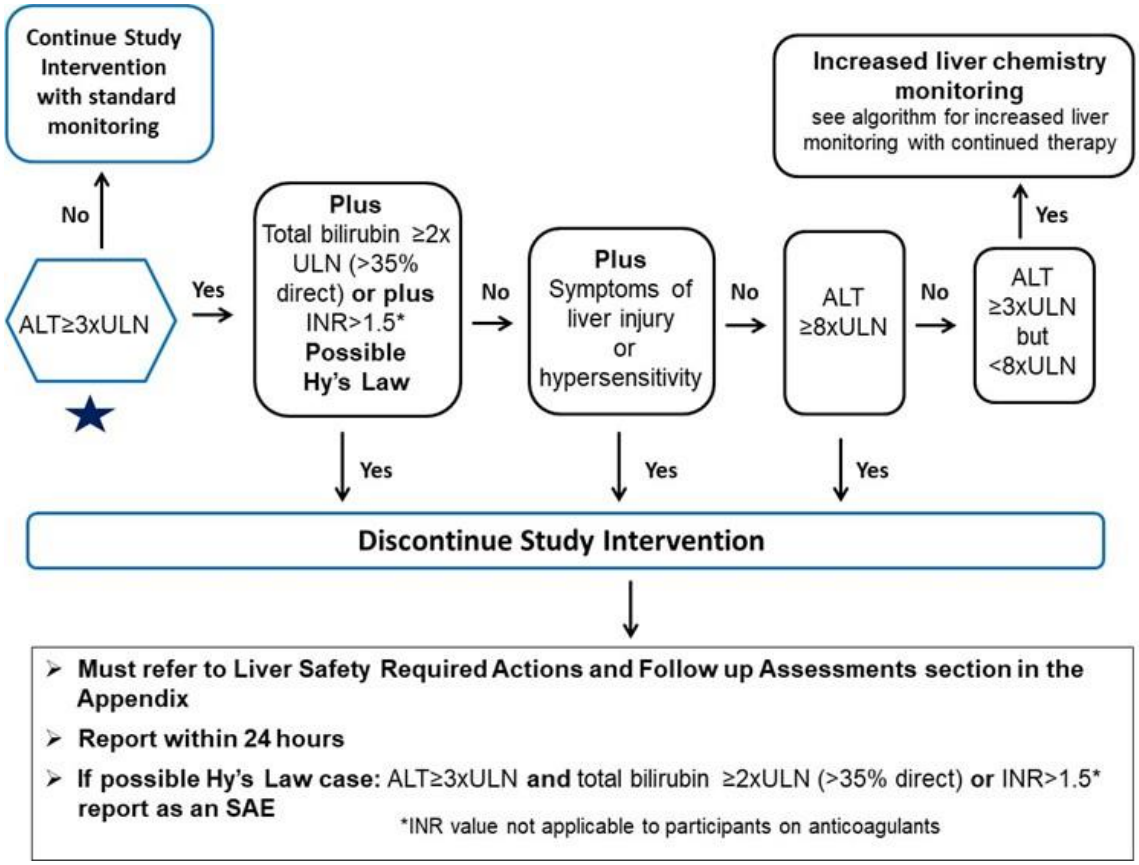
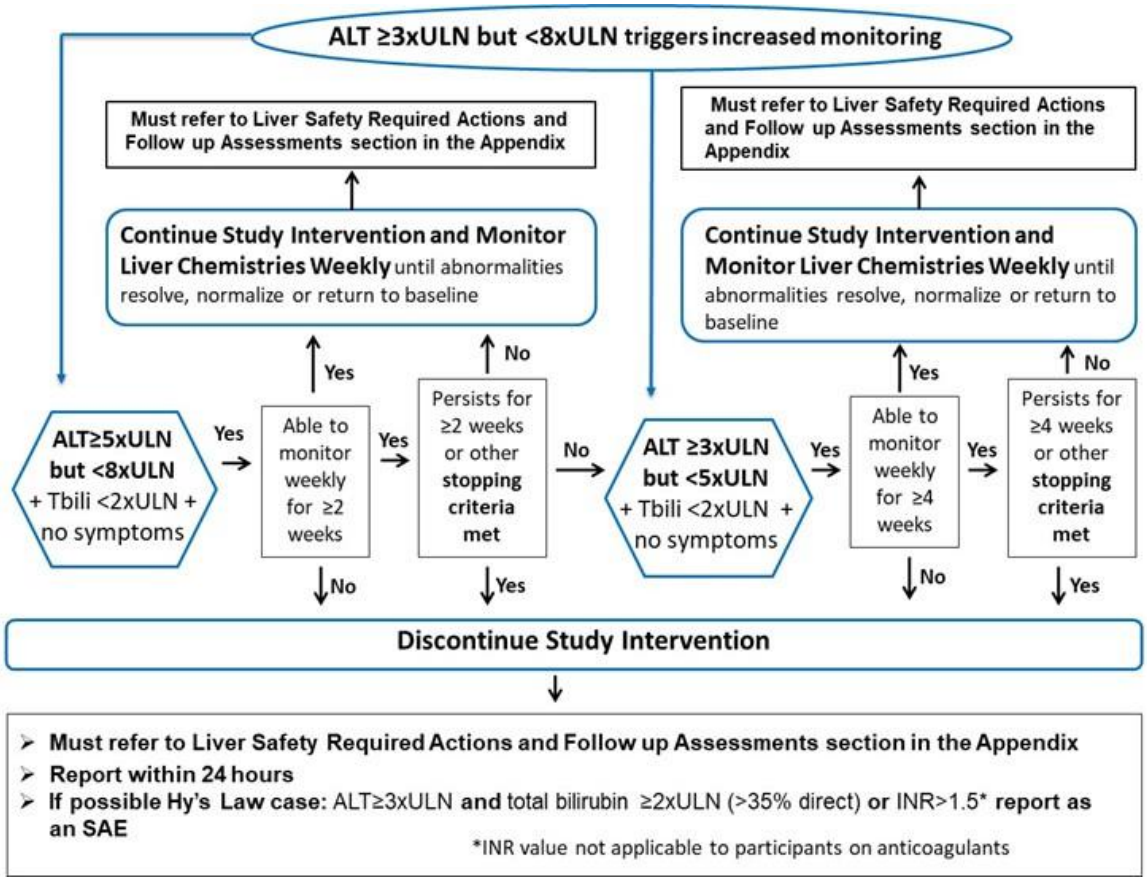


Figure 5 Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



Liver Safety Required actions and Follow up Assessments Section can be found in Appendix 6 and Appendix 7.

8.2.1.1. Study Intervention Restart or Rechallenge after liver stopping criteria met

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

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

Refer to Appendix 6 and Appendix 7 for details.

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

8.2.2. Allergic and Anaphylactic Reaction Stopping Criteria

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

8.2.3. Corneal Event Stopping Criteria

Belantamab mafodotin dose modifications and stopping criteria for treatment-related corneal events should be based on the guidelines of Keratopathy Visual Acuity (KVA) Scale (see Table 13 and Table 14) Grade 4 belantamab mafodotin treatment-related corneal events (Table 13) according to the Keratopathy Visual Acuity (KVA) Scale must be discussed in detail between the Principal Investigator, site qualified eye care specialist such as ophthalmologist/optometrist (Appendix 12) , and GSK Medical Director or delegate, in order to determine whether the participant should be allowed to continue treatment with belantamab mafodotin, or permanently discontinue treatment (Table 13). The decision will be documented in study files, together with individual assessment of risk-benefit.

8.2.4. Infusion-Related Reactions Stopping Criteria

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

Infusion-related reactions should be managed by guidelines provided in Table 11. A participant that experiences a Grade 4 IRR must permanently discontinue study treatment but will continue in the study.

8.3. Participant Discontinuation/Withdrawal from the Study

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

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

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The status of ongoing, withdrawn (from the study), and “lost to follow-up” patients at the time of an OS analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patients current physician, and checking publicly available death registries.

Withdrawn participants will not be replaced.

8.4. Lost to Follow Up

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

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form must be obtained from the participant prior to any study-specific procedures or assessments being performed.

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

Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time.

Study procedures and the timing of each assessment is listed in the SoA (Section 2). Key assessments to be performed are listed below, with more detailed information provided for specific assessments in the SRM, Ocular Reference Manual (ORM) and Q2 Lab Manual:

- Study procedures and their timing are summarized in the SoA (Section 2).
- 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 criterion listed in Section 6.1 and Section 6.2
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Visit Windows:
    - Baseline disease assessments must be completed with 28 days prior to dosing start unless otherwise specified. Refer to SoA (Section 2).
    - Every effort should be made for C1D1 to occur on the same day as the randomisation call is made, or as soon as possible after.
    - 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.
    - Screening pregnancy testing must be completed within 10-14 days (first test) and within 24 hours (second test) prior to first dose.
    - Post screening pregnancy testing should occur within 72h prior to dosing.
    - On study visits, including dosing C2-CX, have a ±3-day window.
    - After C1D1, on-study ocular exams should be performed within 5 days prior to dosing.
    - PFS follow-up visits have a ±3-day window.
    - OS follow-up visits have a ±14-day window and can be conducted by phone call, or other form of communication.
    - CCI [redacted]

The timing and number of planned study assessments, including biomarker assessments, may be altered during the course of the study based on newly available data (e.g., to

obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

For details on possible alternative health care approaches, please refer to Appendix 13

9.1. Efficacy Assessments

Standard disease assessments for RRMM will include the following assessments:

- UPEP, Urine Immunofixation (24 hr urine collection for urine M-protein)
- SPEP, Serum immunofixation for serum M protein
- Calcium corrected for albumin
- Quantitative Ig (IgG, IgM, IgA)
- IgD, IgE (only in participants with IgD or IgE myeloma)
- Serum Kappa, lambda free LC, FLC ratio
- Bone marrow:
  - at screening: biopsy and/or aspirate for baseline analysis (disease assessment, FISH, MRD);
  - at the first time of achieving VGPR, repeated every 6 months for 2 years and then yearly until PD: aspirate to assess MRD
  - at the time of suspected CR for cases of deepening response from VGPR to CR, or achieving CR without prior VGPR, repeated every 6 months for 2 years and then yearly until PD: aspirate to assess MRD
  - at the time of suspected CR: biopsy (preferred) or aspirate to assess % of plasma cells
  - Additional bone marrow testing if CR is achieved: biopsy for immunohistochemistry (IHC) to confirm sCR
- Imaging of extramedullary disease (only in participants with extramedullary disease)
- PET/CT is required for participants after first achieving MRD-by NGS, preferably within 42 days after receiving data showing MRD negativity (Section 2)
- Physical examination (as indicated for palpable/superficial lesions)
- Skeletal surveys at screening and as clinically indicated

Response evaluation will be performed according to the IMWG Uniform Response Criteria for Multiple Myeloma [Kumar, 2016]. Response will be assessed by the Investigators. A pre-specified audit by an Independent Review Committee (IRC) will be used to support the Investigator-assessed responses.

Baseline serum/urine disease assessment and baseline imagining will be completed during screening period (within 28 days prior to the first dose of study treatment). On study serum and urine-based assessments (including M-protein, FLC, SPEP, UPEP ± immunofixation and calcium corrected for albumin) will be performed every 3 weeks from first dose of study intervention as detailed in the SoA (Section 2). Details for the preparation and shipment of samples for central laboratory assessments will be provided in the Lab Manual.

In participants with extramedullary disease, the disease assessments must include imaging (e.g., CT, MRI, or PET-CT) and should be performed as described in the SoA (Section 2). The same modality should be used throughout the study and include physical examination (as indicated for palpable/superficial lesions). Selected target lesion needs to be measured and followed over time. Whole body MRI is also acceptable, if it can be repeated over time. For participants with PD due to extramedullary disease, confirmatory scans are not required. The laboratory parameters do not need to be repeated if the extramedullary disease is the only site of progression. If the last radiographic assessment occurred ≥8 weeks prior to the participants' withdrawal from study treatment, and PD has NOT been documented, a new assessment for extramedullary disease should be obtained at the end of treatment (EOT) visit. If participant continues in PFS follow-up, perform scans for extramedullary disease as clinically indicated. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans when 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). This may be performed at the EOT visit. Digital copies of all scans must be maintained at Investigator site as source document.

Targeted next generation sequencing (NGS) will be used to assess minimal residual disease (MRD) status utilizing a central testing lab. MRD testing should take place as described in Section 2. Response evaluation will be performed according to the IMWG criteria [Kumar, 2016]. For participants who are MRD negative by NGS (10^{-5}), a CT-PET will be performed at the time of confirming MRD negativity.

All response assessments on study must be performed on a calendar schedule and must not be affected by dose interruptions/delays.

For participants who are discontinuing study intervention due to PD, the confirmation 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 initiation of any new anti-myeloma therapy. The assessments will be performed during End of Treatment Visit (Table 4) for the SoA of anti-myeloma activity.

If the last imaging assessment was greater than or equal to 8 weeks prior to the participant's discontinuation from study treatment and progressive disease has not been

documented, a new disease assessment must be obtained at the time of discontinuation from study treatment.

9.1.1. Independent Review Committee

Independent Review Committee (IRC) responses will be utilized to assess efficacy endpoints of the study for a pre-specified random sample, or full IRC if audit meets the required threshold, as supportive information to the investigator-assessed responses. Independent Review Committee (IRC) responses will be utilized to assess efficacy endpoints of the study for a pre-specified random sample, or full IRC review if audit meets the required threshold, as supportive information to the investigator-assessed responses. All laboratory parameters and lesion measurements used to assess participant response will be shared with the IRC and will be used to assess their responses, according to the IMWG criteria. Additional information can be found in Appendix 1 and in the IRC Charter.

9.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 2).

9.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the head, eyes, ears, nose, throat, skin, thyroid, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes, and extremities. Height (only at screening) and weight will also be measured and recorded (see SoA, Section 2).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.2.2. Vital Signs

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

9.2.2.1. Belantamab Mafodotin Infusions

Monitoring intervals: Vital signs must be monitored at designated time points related to drug infusion as specified in the SoA (see Section 2). In general, participants must also be monitored for at least 1 hour after the completion of the first infusion and may be discharged if considered clinically stable and all other study procedures have been completed. For subsequent infusions, participants may be discharged after the infusion has been completed if considered clinically stable and all other study procedures have been completed.

9.2.3. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All ECGs must be performed by qualified personnel at the site after the participant has at least a 5-minute rest.

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

9.2.4. ECOG Performance Status

Participants performance status will be assessed at Screening and then as specified in the SoA (Section 2), using the Eastern Cooperative Oncology Group (ECOG) scale, provided in Appendix 9.

9.2.5. Clinical Safety Laboratory Assessments

Refer to Appendix 2 for a list of clinical laboratory tests to be performed and to the SoA (see Section 2) for the timing and frequency. Details for the preparation and shipment of samples will be provided in the SRM / Lab 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 eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 70 days after the last dose of either study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical director.

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

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SRM.

Asymptomatic elevations of lactate dehydrogenase (LDH) and creatine kinase (CK) and AST have been observed in study BMA117159. Participants with significant elevations (≥x3 ULN) should, where possible, have a sample sent for central testing of CK and LDH isoenzyme levels.

9.2.6. Ocular Examinations and Procedures

Study sites must establish a close collaboration with a qualified eye care specialist such as ophthalmologist/optometrist who will be responsible for assessing participants while they are on study and managing participants who develop belantamab mafodotin treatment-related ocular symptoms or vision changes. Management of such participants must be performed in close communication with the GSK Medical Director and the site's

qualified eye care specialist. Participants will be assessed by a qualified eye care specialist such as ophthalmologist/optometrist at screening/baseline in both arms.

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

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

The ***on treatment*** **and** ***follow-up*** ophthalmic exam should be performed for both eyes (OU) as described below and in the SoA (Section 2):

1. Best corrected visual acuity. (Snellen-equivalent BCVA must be recorded in the eCRF.)
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 fundoscopic exam (if clinically indicated)

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

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

9.2.6.1. Treatment Arm 1 – belantamab mafodotin

Participants will be assessed by a qualified eye care specialist such as ophthalmologist/optometrist (Appendix 12) 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).

- If there are no significant (Grade 2 or above) ocular examinations findings, patient'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 the qualified eye care specialist.
- In case of persistent ocular exam findings, newly developed ocular symptoms or vision changes, the participants will have further ocular exams, at least every cycle until resolution or baseline, or more frequently as clinically indicated by the qualified eye care specialist.

Participants with a belantamab mafodotin treatment-related ocular AEs at the End of Treatment Visit will be followed by the qualified eye care specialist at least every 3 months according the schedule in the SOA (Section 2) until either: resolved to Grade 1 or baseline, or up to 1 year (whichever comes first). These examinations are referred to as "follow-up visits."

CCI

[redacted]

9.2.6.2. Treatment Arm 2 – pom/dex

Examinations should be performed as described above at screening/baseline and then as described in the SoA (Section 2).

9.2.7. Pregnancy Tests (WOCBP only)

Two highly sensitive serum pregnancy tests should be performed at screening. The first test should be performed within 10 – 14 days and the second test within 24 hours before the first dose of study intervention. Subsequent pregnancy tests may be either serum or urine.

For all WOCBP enrolled in Arm 1, belantamab mafodotin, pregnancy tests must be conducted within 72 hours prior to dosing.

For all WOCBP enrolled in Arm 2, pom/dex therapy, pregnancy tests should be conducted weekly during the first 4 weeks of use, then every 4 weeks thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles within 72 hours prior to dosing [e.g. POMALYST PI; Imnovid SmPC].

Additional pregnancy testing should be performed according to the Schedule of Activities (Section 2) during the treatment period, at EoT Visit and at least 70 days after the last dose of study treatment (belantamab mafodotin arm) or at least 4 weeks after the last dose of study treatment (pom/dex treatment arm) and as required locally. Follow-up pregnancy assessment by telephone (for WOCBP only) should be performed 4 months after the last dose of belantamab mafodotin study treatment.

Pregnancy testing and counselling will be performed whenever a menstrual cycle is missed, or when pregnancy is otherwise suspected, or if there is any abnormality in a female participant's menstrual bleeding.

9.2.8. Pomalidomide Risk Evaluation and Mitigation Strategy (REMS) /Pregnancy Prevention/Controlled Distribution Program

Pomalidomide is a thalidomide analogue, which is a known human teratogen. Because of the embryo-fetal risk, pomalidomide is available only through a pregnancy prevention/controlled distribution program.

Participants receiving pomalidomide must register with the appropriate pregnancy prevention/controlled distribution program in place (see SRM for details). Ensure counselling is completed and documented as required by applicable pregnancy prevention program. Acceptable contraception methods need to be aligned to regulatory guidelines/regulations for respective countries and as outlined in the local label (as applicable). Contraception and pregnancy testing timelines and frequencies must be within the regulatory guidelines/regulations for the respective country.

9.3. Adverse Events and Serious Adverse Events

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

Adverse events will be coded using the standard MedDRA and grouped by system organ class. Adverse events will be graded by the investigator according to the NCI-CTCAE, (version 5.0).

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 8).

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

- All SAEs will be collected from the start of intervention until at least 70 days following discontinuation of either Arm 1 or Arm 2 study treatment regardless of initiation of a new myeloma therapy or transfer to hospice at the time points specified in the SoA (Section 2). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study up to and including follow up.

  Note: In China *only*, all SAEs should be collected from the signing of the ICF.

- All AEs will be collected from the start of intervention until at least 70 days following discontinuation of either Arm 1 or Arm 2 study treatment regardless of initiation of a new myeloma therapy or transfer to hospice at the time points specified in the SoA (Section 2).

- 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 case report form (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 Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs 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 (Arm 1 only) via paper forms, emails (preferably), and fax 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 SAEs that are ongoing at the time of the final DCO must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up. Updates to these events will also occur via paper forms directly to GSK (see SRM for details). GSK retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at EOS, if judged necessary.
- Follow up of ocular data after the start of PACT:

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

  - Ocular exam schedule during PACT treatment: Participants without ocular (including corneal) examinations findings, symptoms or vision changes when entering the PACT phase, will be required to have an ocular assessment at least every 3 months, or as clinically indicated, until the end of treatment. For participants who at the time of entering PACT have ocular (including corneal) examinations findings, symptoms or vision changes (or develop these during PACT treatment), the ocular assessment will occur (increase to) every three weeks (and prior to the next belantamab mafodotin infusion if dosing), until resolution (KVA Grade 1 or baseline). After resolution, the ocual exam assessment frequency reduces to at least every 3 months, or as clinically indicated, until the end of treatment.
  - Ocular exam schedule after end of PACT treatment: Participants with treatment-related ocular (including corneal) examination findings, symptoms, or vision changes at the end of PACT treatment have ocular assessments at least every 3 months, or as clinically indicated, for up to 12 months from the end of treatment or until resolution (to KVA Grade 1 or baseline), or withdrawal of consent, whichever comes first. For participants without ocular (including corneal) examination findings, symptoms, or vision changes at the end of PACT treatment no further ocular exams are required.

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

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

9.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

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

9.3.3. 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, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.4). Further information on follow-up procedures is given in Appendix 3.

9.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study 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 a 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.

9.3.5. Adverse Events of Special Interest

Adverse events of special interest (AESI) for belantamab mafodotin are corneal events, thrombocytopenia and infusion-related reactions. The severity of all AESI will be graded utilizing the National Cancer Institute – Common Toxicity Criteria for Adverse Events (version 5.0). Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment are provided in Section 7.6.

9.3.6. Pregnancy

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

The need for a screening pregnancy test depends on whether a female participant is of childbearing potential or non-childbearing potential and as described in Section 2.

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, or 4 weeks for pomalidomide.

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 or 4 weeks for pomalidomide. This applies only to male participants who receive study intervention.

If a pregnancy is reported, the investigator must inform GSK within 24 hours of learning of the pregnancy and must follow the procedures outlined in Appendix 4.

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

9.3.7. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

9.3.8. Management of Hepatitis B+ Participants

Management 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 SoA (Table 6).

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

Table 17 Dose Modification Table for HBV+ Participants

Toxicity	Grade/description of toxicity	Recommendations
Hepatitis B reactivation	Detectable HBV DNA	• Immediate (within 1 week) consult with local specialist to institute/modify treatment and monitoring • Hold study treatment • Contact GSK Medical Monitor promptly - agreement with MM must be obtained prior to further dosing of study treatment • Follow liver monitoring/stopping guidelines per protocol for elevation in liver function tests.

9.4. Treatment of Overdose

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

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

- Contact the Medical Director 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 if requested by the GSK Medical Director (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.
- Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Director based on the clinical evaluation of the participant.

In the event of overdose with pomalidomide, supportive care is advised as indicated in the product information for pomalidomide [e.g. POMALYST PI; Imnovid SmPC].

In the event of overdose with dexamethasone, supportive and symptomatic therapy are advised, which may include gastric lavage or emesis.

9.5. Pharmacokinetics

9.5.1. Blood Sample Collection for Pharmacokinetics

Blood samples for pharmacokinetic (PK) analysis of belantamab mafodotin, total antibody, and cys-mcMMAF will be collected from participants in Arm 1 at the visits indicated in the SOA (Section 2) either via an Enhanced PK schedule (Table 18) or via a Standard PK schedule (Table 19). Participants in Arm 1 will undergo additional PK sampling at timepoints specified in Table 18 for enhanced PK analysis until evaluable samples are available for approximately 25% of participants. These additional assessments will be collected during Cycle 1 and Cycle 3. All North East Asian participants must follow the enhanced PK schedule in Table 18 Table 17.

In addition to the PK schedule outlined in Table 18 and Table 19, for participants of the ocular sub study, a single PK sample will be collected prior to the first infusion following the dosing hold (see Section 9.12).

Following a liver stopping event a blood sample for pharmacokinetic (PK) analysis and a blood sample for sBCMA will be obtained within 70 days after the last belantamab mafodotin dose (see Appendix 6)

Collection of a soluble BCMA (sBCMA) sample (Section 9.8.1) is required for each PK sample.

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

All PK, sBCMA, and ADA samples once collected (regardless of dosing) will be analyzed if the sample date and time have been recorded.

Table 18 Enhanced Pharmacokinetic and sBCMA Collection Schedule

Cycle/Day	Sample Timepoint	Notes
C1D1	Predose	Within 0-30 min prior to SOI (sBCMA also collected in Arm 2)
	EOI	Within 0-30 **after** EOI
	2 h after SOI	Within ±15 min of SOI + 2 h
C1D2	24 h after SOI	Within ±2 h of SOI + 24 h
C1D4	Anytime	Within ±24 h of SOI + 72 h
C1D8 – C1D15	Anytime	One sample on any study day between Day 8 and 15 in the cycle, inclusive
C1D22	Anytime	Collect only if the dose for the next cycle is delayed; collect within ±2 days of Day 22
C2D1	Predose	Within 0-30 min prior to SOI
	EOI	Within 0-30 min **after** EOI
C3D1	Predose	Within 0-30 min prior to SOI
	EOI	Within 0-30 min **after** EOI
	2 h after SOI	Within ± 15 min of SOI + 2 h
C3D2	24 h after SOI	Within ± 2 h of SOI + 24 h
C3D4	Anytime	Within ± 24 h of SOI + 72 h
C3D8 – C3D15	Anytime	One sample on any study day between Day 8 and Day 15 in the cycle, inclusive
C3D22	Anytime	Collect only if the dose for the next cycle is delayed; collect within ± 2 days of Day 22
C4D1, C6D1	Predose	Within 0-30 min prior to SOI
	EOI	Within 0-30 min **after** EOI
C9D1, C12D1	Predose	Within 0-30 min prior to SOI
Every 6 cycles (C18D1, etc.)	Predose	Within 0-30 min prior to SOI
EOT	Anytime	At End of Treatment visit (sBCMA also collected in Arm 2)
FU	Between 6 and 12 weeks after last dose of study treatment and before initiation of new anti-myeloma therapy	Collect one PK, one ADA, and one sBCMA sample. Sample may be collected at any planned follow-up visit
MRD	MRD assessment timepoints	sBCMA only (Arm 1 & Arm 2)
CCI [redacted]		

SOI = start of infusion; EOI = end of infusion; EOT = end of treatment

Table 19 Standard PK and sBCMA Collection Schedule

Cycle/Day	Sample Timepoint	Notes
C1D1	Predose	Within 0-30 min prior to SOI (sBCMA also collected in Arm 2)
	EOI	Within 0-30 min **after** EOI
C1D2	24 h after SOI	Within ± 2 h of SOI + 24 h
C2D1	Predose	Within 0-30 min prior to SOI
	EOI	Within 0-30 min **after** EOI
C3D1	Predose	Within 0-30 min prior to SOI
	EOI	Within 0-30 min **after** EOI
C3D2	24 h after SOI	Within ± 2 h of SOI + 24 h
C4D1, C6D1	Predose	Within 0-30 min prior to SOI
	EOI	Within 0-30 min **after** EOI
C9D1, C12D1	Predose	Within 0-30 min prior to SOI
Every 6 cycles (C18D1, etc.)	Predose	Within 0-30 min prior to SOI
EOT	Anytime	At End of Treatment visit (sBCMA also collected in Arm 2)
FU	Between 6 and 12 weeks after last dose of study treatment and before initiation of new anti-myeloma therapy	Collect one PK, one ADA, and one sBCMA sample. Sample may be collected at any planned follow-up visit
MRD	MRD assessment timepoints	sBCMA only (Arm 1 & Arm 2)
CCI [redacted]		

SOI = start of infusion; EOI = end of infusion; EOT = end of treatment

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

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

9.5.2. Pharmacokinetic Sample Analysis

Plasma analysis will be performed under the control of by GSK or its designee, the details of which will be included in the SRM. Concentrations of belantamab mafodotin, total antibody, and cys-mcMMAF will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site.

Once the plasma has been analyzed for belantamab mafodotin, total antibody, and cys-mcMMAF, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate GSK protocol.

9.6. Pharmacodynamics

Pharmacodynamic biomarker parameters may be evaluated in this study. See Section 9.8 for further details.

9.7. Genetics

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

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

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the SRM/Lab Manual.

9.8. Biomarkers

Biomarker research is part of this study and will involve peripheral blood (serum and plasma) and bone marrow. Soluble BCMA (sBCMA) and cfDNA analysis will be assessed with their relationship to response to belantamab mafodotin. Any blood, serum, and bone marrow 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. 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 2). 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 potentially predictive of response or associated 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/or RNA analysis performed on bone marrow biopsy or aspirate
- Bone marrow biopsy or aspirate may be evaluated for any DNA/RNA changes correlating with response
- Measurements of the serum levels of soluble BCMA (sBCMA)
- Soluble factors, including circulating plasma cell-free DNA (cfDNA).

CCI

[redacted]

9.8.3. RNA Transcriptome Research

Transcriptome studies may be conducted using microarray, 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.

The same samples may also be used to confirm findings by application of alternative technologies.

9.8.4. RNA Expression Research of a Subset of RNA Species

RNA expression studies may be conducted using quantitative reverse transcriptase polymerase chain reaction (RT-qPCR), and/or alternative equivalent technologies, which can facilitate the simultaneous measurement of the relative abundances of RNA species resulting in a RNA expression profile for bone marrow samples. The RNAs assayed may be those involved with the pathogenesis of multiple myeloma or in the participant's response to belantamab mafodotin. In addition, continuing research may identify other proteins or regulatory RNAs that may be involved in the response to belantamab

mafodotin or the pathogenesis of multiple myeloma. The RNAs that code for these proteins and/or regulatory RNAs may also be studied. This will enable the evaluation of changes in RNA expression profiles that may correlate with biological response relating to response to belantamab mafodotin.

9.9. Immunogenicity Assessments

Serum samples for determination of anti-belantamab mafodotin antibodies (anti-drug antibody; ADA) will be taken from all participants in this study at the time-points specified in the SoA (Section 2). Additionally, serum samples should be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. ADA sample collection may be terminated when sufficient data have been collected. These samples will be tested by the Sponsor or Sponsor's designee.

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

The detection and characterization of antibodies to belantamab mafodotin will be performed using validated assays. The anti-belantamab mafodotin antibody assay was designed to detect antibodies to belantamab mafodotin, the unconjugated monoclonal antibody belantamab, and the linker-payload portion of belantamab mafodotin. Plasma samples for the determination of belantamab mafodotin and total antibody plasma concentrations will be collected at the same time points (see SoA) as the immunogenicity samples. The plasma concentration results will enable interpretation of the anti-drug antibody data.

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

9.10. Health Economics

CCI [redacted] will be assessed in this study and reported by participants using a questionnaire to be completed at each study visit. Parameters to be measured include:

- Number of office/outpatient/hospital clinic visits by specialty
- Number of emergency room/urgent care facility visits
- Number and duration of in-patient hospitalization (total nights, including duration by wards [intensive care unit vs. general ward])

For further details, see the SRM. The questionnaire will be administered to participants in different regions based on the availability of translated versions. The data collected in the eCRF may be used to conduct exploratory economic analyses.

9.11. Patient-Related Outcomes

All participants will complete the self-administered version of each questionnaire, unless their vision or other factors prevents them from being able to complete the questionnaire on their own, or due to site restrictions or the PI or site feels it is in the best interest of the participant not to come to the site. Participants who are not able to complete the questionnaire on their own and require assistance should have the questionnaires administered to them in an interview format. The interview may be administered by the site staff (or delegate) or a third party over the telephone. If the Interviewer-Administered format is used, the questionnaires should be read to the participants verbatim, and participant responses should be recorded directly without any interpretation. For further details, refer to the SRM.

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

Participants enrolled under the original protocol and who completed the EORTC IL52 questionnaires will continue to do so. Participant enrolled under protocol amendment 1 will complete the EORTC QLQ-MY20 questionnaire. All participants will complete the CCI [redacted] at the required study visits.

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

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

The PRO-CTCAE will be administered as noted in the SoA (Section 2) to participants in different regions based on the availability of translated versions.

9.11.2. Visual Function Questionnaire

The impact of potential ocular change in vision on function and health-related quality-of-life will be assessed with the use of the OSDI visual function questionnaire. All participants will use the Self-Administered version of the questionnaire, unless their vision prevents them from being able to complete the questionnaire on their own. Participants who are not able to complete the questionnaire on their own and require

assistance must use an Interviewer Administered format. If the Interviewer Administered format is being used, it must be read to the participants verbatim, and participant responses must be recorded directly without any interpretation. For any additional assessments conducted via telephone (either during participation in the treatment period or during Follow-up), the Interviewer Administered format must be used.

The OSDI will be administered as noted in the SoA (Section 2) to participants in different regions based on the availability of translated versions.

9.11.2.1. The Ocular Surface Disease Index

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

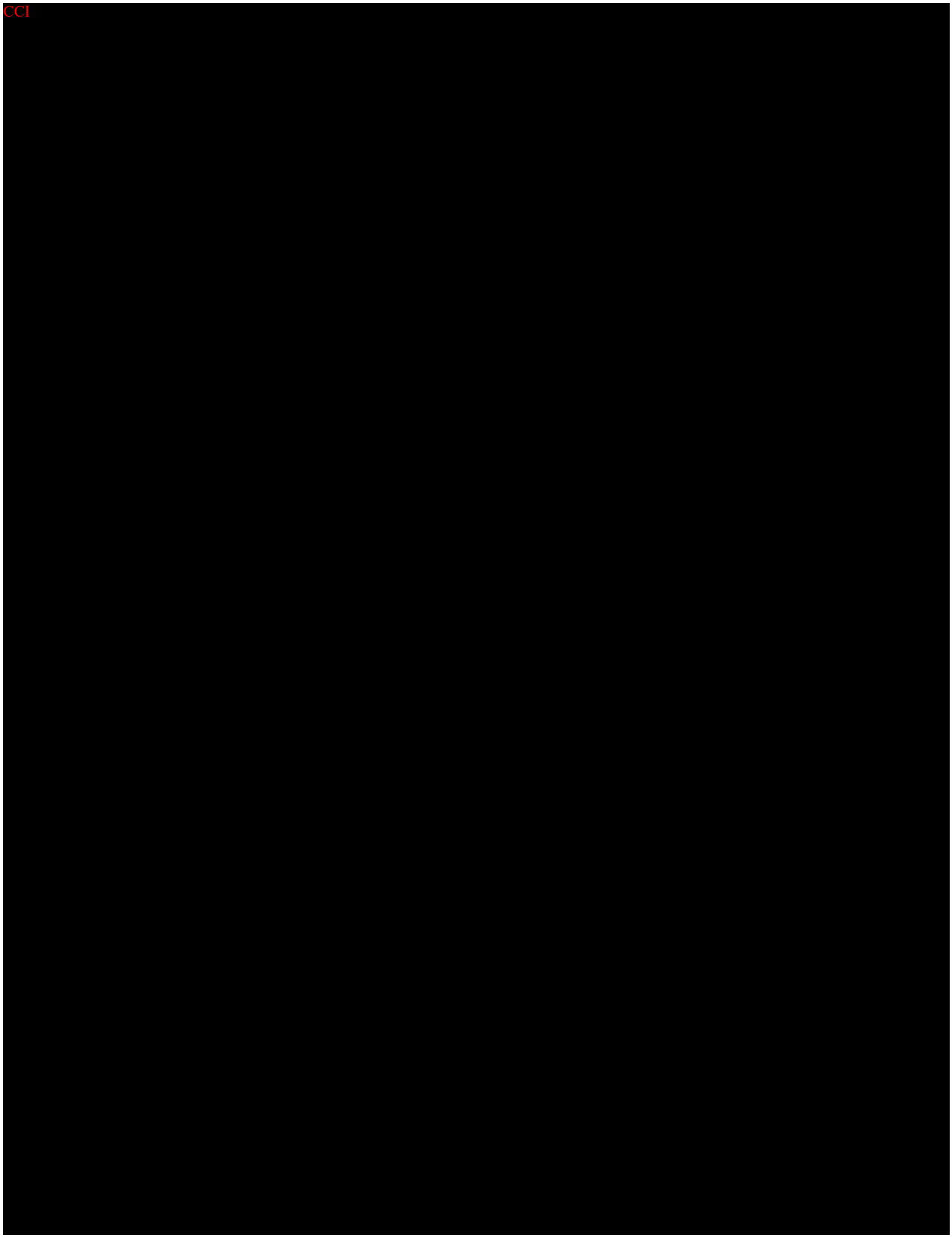
9.11.3. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module (EORTC QLQ-C30)

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

9.11.4. European Organization for Research and Treatment of Cancer Multiple Myeloma Module 20 (EORTC QLQ MY20) and EORTC IL52

The EORTC Quality of Life Questionnaire 20-item Multiple Myeloma module (QLQ-MY20) is a supplement to the QLQ-C30 instrument used in patients with multiple myeloma [Aaronson, 1993; Cocks, 2007]. It includes four scales (Disease Symptoms, Body Image, Future Perspective, and Side Effects. For the EORTC IL52, only the Disease Symptoms domain of the QLQ-MY20 will be administered, which includes bone aches or pain, back pain, hip pain, arm or shoulder pain, chest pain, and pain increasing with activity. For both, the QLQ-C30 and QLQ-MY20, domain scores are averaged and transformed linearly to a score ranging from 0–100. A high score for Disease Symptoms represents a high level of symptomatology or problems [Proskorovsky, 2014].

CCI



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10. STATISTICAL CONSIDERATIONS

10.1. Statistical Hypotheses

Primary endpoint PFS

The primary efficacy analysis will be the comparison of the distribution of PFS between the two treatment groups. Assuming proportional hazards for PFS, the following statistical hypothesis will be tested to address the primary efficacy objective at one-sided alpha level of 2.5%:

$$H_{01}: \Theta_1 \geq 1 \quad \text{VS.} \quad H_{A1}: \Theta_1 < 1$$

where, θ_1 is the PFS HR (belantamab mafodotin arm vs. pom/dex arm).

Key secondary endpoint OS

Assuming proportional hazards for OS, the following statistical hypotheses will be tested at one-sided alpha level of 2.5% if PFS is statistically significant:

$$H_{02}: \Theta_2 \geq 1 \quad \text{VS.} \quad H_{A2}: \Theta_2 < 1$$

where, θ_2 is the OS HR (belantamab mafodotin arm vs. pom/dex arm).

10.2. Sample Size Determination

Primary Endpoint PFS

Based on available data from literature, the median PFS in the pom/dex arm is expected to be around 4 months [San Miguel, 2013]. It is expected that treatment with belantamab mafodotin will result in a 43% reduction in the hazard rate for PFS, i.e. an expected HR of 0.57 (corresponding to an increase in median PFS from 4 months to 7 months under the exponential model assumption).

The final PFS analysis will be conducted after observing approximately 151 events and the first 320 randomized subjects have been followed for a minimum of 4 months. With 151 events, the study has a power of 90% to detect a hazard ratio of 0.57 at 1-sided alpha of 0.025 (corresponding to a critical value of 0.713 for the hazard ratio). This calculation assumes participants randomized to the two treatment arms in a 2:1 ratio. Assuming that enrolment will continue for approximately 20 months at a uniform rate of 16 participants per month, a total of 320 participants will be randomized in a 2:1 ratio to receive single agent belantamab mafodotin or pom/dex. It is estimated that the targeted 151 PFS events will be observed approximately 23 months after the first participant is randomized based on a lognormal cure rate model [Chen, 2016]. These calculations were made using the software package East 6.5 and a proprietary SAS macro.

Power for Analysis of Key Secondary Endpoint OS

OS, as the key secondary endpoint, will be formally statistically tested, provided that the primary endpoint PFS is statistically significant. Based on available data from literature, the median OS in the pom/dex arm is expected to be around 13 months [San Miguel, 2013]. It is hypothesized that treatment with belantamab mafodotin will result in a 32% reduction in the hazard rate for OS, i.e., an expected HR of 0.68 (which corresponds to an increase in median OS to 19 months under the exponential model assumption). In order to ensure 80% power to test the null hypothesis: OS HR = 1, versus the specific alternative hypothesis: OS HR = 0.68, a total of 250 deaths need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, participants randomized to the two treatment arms in a 2:1 allocation ratio, and a group sequential design with a Lan-DeMets (O'Brien-Fleming) alpha spending

function [Lan, 1983] using information fractions of (0.4, 0.7, 1). Based on the same number of participants that are planned to be enrolled in this study to provide sufficient power for the primary endpoint, it is estimated that these 250 deaths will be observed approximately >60 months after the randomization date of the first participant under H_{A2} (assuming a similar loss to follow-up, i.e. 5% per year). Therefore, the cut-off date for the final analysis of OS will be approximately 35 months after the cut-off date for the final analysis of PFS. These calculations were made using the software package East 6.5 and a proprietary SAS macro.

If the number of participants required by local regulatory agencies are not recruited within the planned recruitment target, enrollment may continue in separate cohorts until the country enrollment requirements, as required by local regulatory bodies, have been reached. Additional participants that are enrolled in separate cohorts will not be included in the analysis portion of the study planned for the marketing application, which is based on approximately 151 events. However, these additional participants will be included in country-specific supplemental analyses, as detailed in country specific Statistical Analysis Plan (SAP), requested by the applicable regulatory authorities concerned.

10.3. Populations for Analyses

For purposes of analysis, the populations are defined in Table 20:

Table 20 Analysis Populations

Population	Description
All Screened	The All Screened Population will consist of all participants who sign the ICF to participate in the clinical trial. Participants in this population will be used for screen failure summary.
Intent-to-Treat (ITT)	ITT Population will consist of all randomized participants whether or not randomized treatment was administered. This population will be based on the treatment and strata to which the participant was randomized and will be the primary population for the analysis of efficacy data. Any participant who receives a treatment randomization number will be considered to have been randomized.
mITT (modified ITT)	All participants who have received at least 2 lines of prior therapies; randomized and received at least one dose of study treatment (participant randomized to the belantamab mafodotin arm but received pom/dex will be excluded and vice versa); with measurable disease at baseline.
Safety	All randomized participants who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic	The Pharmacokinetic Population will consist of those participants in Safety Population from whom at least one PK sample has been obtained and analyzed. This population will be the primary population for PK analyses.
[redacted]	

10.4. Statistical Analyses

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

10.4.1. Efficacy Analyses

Analysis of efficacy endpoints will be based on Investigator-assessed confirmed response and dates per IMWG [Kumar, 2016] criteria with the ITT population unless otherwise specified.

The primary analysis based on Investigator-assessed responses will be supported by a pre-specified analysis based on IRC-assessed responses in a randomly selected subset of ITT population. Details of the audit are described in the IRC Audit plan, including sample size calculation for the IRC audit, random sampling process, the methods to summarize and analyse the data from the sample-based IRC assessment, and assessment of the bias from investigator responses. Appropriate subgroup analyses may be performed if data permits, e.g., the primary endpoint PFS may be analyzed by age (<65 years, ≥65 years), sex (Female, Male), ethnicity (Hispanic, non-Hispanic), race groups (American Indian or Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Mixed Race), region (North America, Europe, North-East Asian [consisting of Japan, China and Republic of Korea], etc.), prior anti-myeloma therapy and other baseline characteristics.

The analytical methods planned for each endpoint are described in Table 21.

Table 21 Statistical Analytical Methods - Efficacy

Endpoint	Statistical Analysis Methods
Primary	**PFS** is the primary endpoint of this study; it is defined the time from randomization until the earliest date of PD, or death due to any cause. Determination of dates of PFS event and dates for censoring is provided in the SAP. Final PFS analysis will be conducted at the time of observing approximately 151 PFS events and the first 320 randomized subjects have been followed for a minimum of 4 months. The distribution of PFS for each treatment arm will be estimated using the Kaplan-Meier method. The median, 25th and 75th percentiles of PFS will be estimated and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (1982). The distribution of PFS will be compared between the two treatment arms using log-rank test stratified by randomization stratification factors at one-sided alpha level of 0.025. The proportional hazard assumption will be checked through the Kaplan-Meier plot, log(-log(survival) against log (survival time) plot, Schoenfeld residuals, and evaluation of time dependency of HR by adding an interaction term of time by treatment in the Cox proportional hazard model. HR and corresponding 95% CI will be estimated from Cox proportional hazard model stratified by randomization factors with treatment arm as the sole explanatory variable. If the proportional hazard assumption does not hold, Restricted Mean Survival Time (RMST) may be

Endpoint	Statistical Analysis Methods
	conducted in addition as appropriate. The hypothesis testing decision of the primary endpoint PFS will be based on ITT population, investigator-assessed response per IMWG 2016 and primary censoring rule defined in the SAP. Investigator-assessed response will be supported by IRC-assessed responses in a randomly selected subset of the ITT population. Additional analyses of PFS based on alternative censoring rules will also be performed. The analyses will only include Kaplan-Meier estimates, Cox proportional hazards model stratified by randomization factors. Details are provided in the SAP. Analyses of PFS will also be performed based on mITT population and investigator assessed response. The analyses will only include Kaplan-Meier estimates, Cox proportional hazards model stratified by randomization factors. Details are provided in the SAP. Subgroup PFS analysis by randomization stratification factors will be conducted at final PFS analysis based on ITT population only. Details are provided in the SAP.
Key Secondary	Overall Survival (**OS**), defined as the interval of time from randomization to the date of death due to any cause. Participants who are alive will be censored at the date of last contact. Provided that PFS is significant, OS analysis will be conducted at planned analysis using similar approach as for the final PFS analysis (i.e. Kaplan-Meier estimates, stratified log-rank test, Cox proportional hazards model stratified by randomization factors, and examination of non-proportional hazards effect). The hypothesis testing and boundary crossing decision of the key secondary endpoint OS will be based on ITT population. Analyses of OS will also be performed based on mITT population. The analyses will only include Kaplan-Meier estimates, Cox proportional hazards model stratified by randomization factors. Details are provided in the SAP. Subgroup OS analysis by randomization factors will be conducted at final OS analysis based on ITT population. Details are provided in the SAP.
Secondary	At final PFS/OS analysis, the following secondary analyses will be conducted: **ORR**, defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR, and sCR). The number and percentage of participants with the best confirmed response in the following response categories at will be summarized by treatment arm: sCR, CR, VGPR, PR, overall response (sCR+CR+VGPR+PR), minimal response (MR), stable disease (SD), progressive disease (PD), and not evaluable (NE). The corresponding exact 95% CI for ORR will also be provided. Participants with unknown or missing responses will be treated as non-responders, i.e., these participants will be included in the denominator when calculating percentages of response. The exact 95% CI for the difference will be calculated. **CBR,** defined as the percentage of participants with a confirmed minimal response (MR) or better. **DOR** 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 any cause among

Endpoint	Statistical Analysis Methods
	participants who achieve a response (i.e., confirmed PR or better). Responders without disease progression will be censored at the censoring time point for TTP. Distribution of DOR will be summarized using the Kaplan-Meier method by treatment arm. The median, 25th and 75th percentiles of DOR will be estimated and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (1982). **TTR** is defined as the time between the date of randomization and the first documented evidence of response (PR or better), among participants who achieve a response (i.e., confirmed PR or better). TTR will be summarized descriptively by treatment arm using medians and quartiles in the subset of participants with a confirmed response of PR or better as the Best Overall Response (BOR). **TTP** is defined as the time from randomization until the earliest date of PD, or death due to PD. Determination of dates of TTP event and dates for censoring will be described in the SAP. TTP analysis will be conducted using approaches of Kaplan-Meier estimates, Cox proportional hazards model stratified by randomization factors. **MRD negativity rate** is defined as the proportion of participants who are MRD negative as assessed by NGS. For analysis purposes, participants in the ITT population without MRD assessment will be considered as having positive MRD. The MRD negativity rate will be summarized by treatment arm. Corresponding 95% exact Cis will also be provided. Analyses of ORR, CBR, DoR, TTR, and TTP will be performed based on investigator-assessed response for ITT population.
CCI [redacted]	

10.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population and are described in Table 22.

Table 22 Statistical Analytical Methods - Safety

Endpoint	Statistical Analysis Methods
Secondary	Adverse Events: All adverse events whether serious or non-serious, will be reported from the start of treatment until at least 70 days after the last dose of study treatment, regardless of initiation of a new myeloma therapy, until the participant withdraws consent for study participation.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 Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary [NCI, 2010]. Adverse events will be summarized by frequency and proportion of total participants, by system organ class and preferred term. Separate summaries will be given for all AEs, common (>5%) AEs, treatment-related AEs, SAEs, and AEs leading to dose delays and discontinuation of study treatment and AE of special interest. Adverse events, if listed in the NCI-CTCAE (version 5.0) will be summarized by the maximum grade. Characteristics (e.g., number of occurrences, action taken, grade, etc.) of the following toxicity profile 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 laboratory values and changes from baseline in observed value at each scheduled visit. • The worst-case- toxicity grade in hematology and chemistry result during the treatment will be summarized. Other Safety Measures: Data for vital signs and ophthalmic examination findings will be summarized. For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages. Details will be provided in the SAP.

CCI

CCI

[redacted]

10.4.4. Other Analyses

10.4.4.1. Biomarker Analyses

Biomarker exploratory analyses will be described in the reporting and analysis plan.

10.4.4.2. Pharmacokinetic Analyses

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

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

Plasma belantamab mafodotin, total mAb, and cys-mcMMAF concentration-time data may be combined with data from other studies and will be analyzed using a population pharmacokinetic approach. The initial analysis will use the current population pharmacokinetic model to generate *post hoc* belantamab mafodotin pharmacokinetic parameter estimates for the individual participants in Arm 1 of Study 207495. Based on the individual *post hoc* parameter values, dosing information, and sample collection times, belantamab mafodotin plasma concentrations at the time of sample collection will be predicted for each participant. Model evaluation will consist of comparison of model-predicted and observed concentrations. If necessary, model estimation will be performed. Results of this analysis may be provided in a separate report.

For participants who undergo enhanced pharmacokinetic sampling, noncompartmental analysis to generate selected pharmacokinetic parameter values (Cmax, tmax, AUC(0-τ), Ctrough) may be performed at Cycle 1 and Cycle 3, data permitting.

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

GSK CPMS analysts will have access to a blinded population PK dataset (including, but not limited to, concentration, actual dosing information, demographics, and some vital sign and laboratory information, but excluding adverse event and efficacy information) at several time points (e.g., prior to each interim analysis) throughout the trial for population PK model development/refinement.

North East Asia country PK analyses will be completed at the time of the final analysis for each country-specific expansion cohort and may be provided in a separate report.

10.4.4.3. Pharmacokinetic/Pharmacodynamic Analyses

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

10.5. Planned Analyses

Table 23 summarizes the planned interim and / or final analyses for PFS and OS.

Table 23 Summary of PFS and OS analyses

Analyses Timing from Randomization	Planned PFS analyses	Planned OS analyses
~25 months	PFS final ~151 PFS events and the first 320 randomized subjects have been followed for a minimum of 4 months[c]	OS IA for efficacy[a] ~100 OS events ~40% OS information fraction
~48months	N/A	OS IA for efficacy[a] ~175 OS events ~70% OS information fraction
>60 months	N/A	OS final[b] ~250 OS events

a. Provided that final PFS analysis is significant.
b. If PFS is significant and null hypothesis is not rejected at the 2nd OS IA for efficacy.
c. First dose of 320th subject happens around 21 months

Planned Analyses for Key secondary endpoint OS

The key secondary efficacy endpoint, OS, will be compared between the 2 treatment arms (belantamab mafodotin arm vs pomalidomide/ dexamethasone arm) using a group sequential log-rank test corresponding to three analyses: one interim analysis at the same

time of PFS final (~40% information), one interim analysis at ~70% information and one final at 100% information. The boundary for declaring superiority of belantamab mafodotin arm over pomalidomide/ dexamethasone arm is based on a Lan-DeMets (O'Brien-Fleming) alpha spending function [Lan, 1983] with overall alpha = 0.025, one-tailed, and will be adjusted based on actual observed number of deaths (actual information fraction).

At the first OS interim analysis (~40% OS information fraction), the study will not be stopped regardless of the results. GSK will continue to collect the OS data to conduct the 2nd OS interim analysis to test for efficacy at ~70% OS information fraction.

At the OS interim analysis for efficacy (~70% OS information fraction) (Table 23), assuming 175 events are observed, if the calculated p<0.0073 (corresponding to HR<0.676), it would be considered that the efficacy boundary is crossed and the OS analysis would be significant.

A hierarchical testing procedure will be adopted and the OS interim/final analysis for efficacy will only be performed if the primary efficacy endpoint PFS is statistically significant at PFS final analysis [Bretz, 2009; Li, 2017]. The testing procedures are detailed as follows:

Step 1: Test PFS at the final PFS analysis. If significant, go to Step 2 and overall one-sided alpha of 0.025 will be carried forward to test for OS; if not significant, stop testing;

Step 2: Test OS at the first OS interim analysis (at the same time of PFS final, ~40% OS information fraction) for efficacy (cumulative one-sided alpha spent for OS = 0.0004);

Step 3: Test OS at the 2nd OS interim analysis for efficacy (~70% information fraction). If significant, stop testing; if not significant, go to Step 4 (cumulative one-sided alpha spent for OS = 0.0074);

Step 4: Test OS at the time of the final OS analysis (cumulative one-sided alpha spent for OS = 0.025).

Table 24 Stopping boundaries for OS

Information fraction	N of events	Cum. alpha Spent	Efficacy Boundary (p-value)	Efficacy Boundary (HR)	Boundaries crossing probabilities (incremental)	
					Under H0	Under H1
0.4	100	0.0004	0.0004*	0.491*	0.04%	5.8%
0.7	175	0.0074	0.0073	0.676	0.7%	41.2%
1	250	0.0250	0.0227	0.765	1.8%	33.1%

*: The threshold will be is used for the 1st OS analysis, however, the study will not be stopped for efficacy regardless of the results. GSK will continue to collect the OS data to conduct the 2nd OS interim analysis to test for efficacy at ~70% OS information fraction.

If OS is significant at 70% IF, OS data will continue to be collected until final analysis: defined as all participants have died, are lost to follow up, or withdrawn consent, or for 2 years after the OS analysis at ~70% IF, whichever occurs first. Analysis of OS will be performed using only Kaplan-Meier method and stratified Cox proportional hazards model.

10.5.1. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) consisting of at least 2 physicians and one statistician as defined in the IDMC Charter will review data at defined time points. Additional details, including the list of outputs supporting decision making at the interim analysis, will be provided in the IDMC charter.

The first IDMC safety review meeting is planned when approximately 60 participants have been on study for at least 8 weeks. Subsequent IDMC safety review meeting is planned approximately every 6 months hereafter.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

11.1.1. Regulatory and Ethical Considerations

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

11.1.2. Financial Disclosure

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

11.1.3. Informed Consent Process

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

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

11.1.4. Data Protection

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

11.1.5. Committees Structure

Details on the IDMC structure will be defined in the IDMC charter and as noted in Section 10.5.1.

An IRC will be utilized to perform a pre-specified audit of the investigator-assessed response and progression. Further details on the IRC process will be defined in the IRC charter. Results from the IRC audit will not be provided to the investigative sites.

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

Laboratory data

- Serum M protein electrophoresis (SPEP) and immunofixation results
- 24-hour Urine M protein electrophoresis (UPEP) and immunofixation results
- Serum free light chain (FLC) values including kappa and lambda values, kappa/lambda ratio, difference between kappa and lambda [dFLC]

Imaging data

- Extramedullary lesions identified at Baseline (longest diameter, longest perpendicular diameter, sum of product of diameters [SPD])
- New extramedullary lesions
- Skeletal lytic lesions

Bone marrow aspirate/biopsy data

- Bone marrow plasma cell percentage (BMPC%)
- Absence of plasma cell clonality in bone marrow (per k/l ratio by IHC)
- Minimal Residual Disease (MRD) by NGS (10^{-5})

11.1.6. Dissemination of Clinical Study Data

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

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

provided by trial 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.

11.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, International Conference on Harmonization Good Clinical Practice (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 (except for 15 years in the US, China including Hong Kong SAR (Special Administrative Region)), 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.
- GSK will retain records for 30 Years after date of study report (or date of termination if no report issued).

11.1.8. Source Documents

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

11.1.9. Study and Site Closure

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

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

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

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

11.1.10. Publication Policy

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

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

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

11.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 25 are identified as being performed at either local or central laboratory.
- For response assessments, local laboratory results are only required in the event that the central laboratory results are not available in time for response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Pregnancy testing for WOCBP (for definition see Section 11.4.1) Note that for questionable cases (child-bearing potential), FSH and estradiol will be performed, as needed.
    - Screening Pregnancy (serum) testing, all participants (Section 6.1 [Inclusion Criteria] for screening pregnancy criteria).
    - Post screening for participants in Arm 1, belantamab mafodotin therapy, pregnancy testing (urine or serum as required by local regulations) will be conducted at every cycle during intervention.
    - Post screening for participants in Arm 2, pom/dex therapy, pregnancy tests will be performed weekly during the first month (first cycle) and then once every cycle thereafter in women with regular menstrual cycles, or every 2 weeks in women with irregular menstrual cycles. Pregnancy tests may be either serum or urine.
    - Pregnancy testing (urine or serum as required by local regulations) will be conducted at the end of relevant systemic exposure (at least 70 days [belantamab treatment] or at least 4 weeks [pomalidomide treatment].
    - Additional serum or urine pregnancy tests may be performed at any time during the study, as determined necessary by the investigator or required by local regulations, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 25 Protocol-Required Safety and other Laboratory Assessments, including optional assessment[1]

Laboratory Assessments	Parameters		
Hematology[2]	Platelet Count[8]	*RBC Indices:* MCV MCH Reticulocyte Count MCHC	WBC count with Differential: Neutrophils[8] Lymphocytes Monocytes Eosinophils Basophils
	Red Blood Cell (RBC) Count		
	White Blood Cell (WBC) count (absolute)		
	Hemoglobin[8]		
	Hematocrit		

Laboratory Assessments	**Parameters**			
Clinical Chemistry[2,3]	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)	Total and direct bilirubin[8]
	Creatinine	Sodium	Alanine Aminotransferase (ALT)[8]	Total Protein
	Chloride	Uric Acid	Total bicarbonate or Total CO_2 or CO_2CP	Gamma Glutamyl transferase (GGT)
	Magnesium	Phosphorous	Creatine kinase (CK)	Lactate Dehydrogenase (LDH)
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	Albumin
	Estimated glomerular filtration Rate (eGFR)[8]	Thyroid Stimulating Hormone (TSH)	T4	
Urine Tests[2,8]	• Optional Urine dipstick[5] OR • Spot urine (creatinine/albumin ratio)[5]			
Other Safety Laboratory Tests	• Highly sensitive serum human chorionic gonadotropin (hCG)[2] pregnancy tests (as needed for women of childbearing potential) at screening. Subsequent pregnancy tests may be urine or serum. • Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential; for additional details see Appendix 4)[2] • Hepatitis B surface antigen (HBsAg) – screening ONLY[2,8] • Hepatitis B core antibody (HBcAb) – screening ONLY[2,8] NOTE: Please refer to Table 6 regarding Hepatitis B DNA testing.[2,4] • HBeAG and HBeAb[2] – Japan ONLY • Hepatitis C (Hep C antibody): - screening ONLY[2,8] NOTE: Please refer to Table 7 regarding Hepatitis C RNA testing[2,4]. • LDH and CK isoenzymes[4, 7]			
PK/ADA (not performed at screening)	• Belantamab mafodotin pharmacokinetics (PK)[4] • Anti-Drug Antibodies (ADA)[4] to belantamab mafodotin			
Optional Testing	• Gx[4] • Tissue sample at PD for BCMA (BM biopsy) or bone marrow aspirate for biomarker research[4]			
Biomarker Measurements	• cfDNA (plasma)[4] • soluble BCMA (sBCMA)[4] – serum • Remaining portion of bone marrow sample (biopsy or aspirate) collected at baseline/screening will be used for biomarker research[4] • Remaining portion of optional bone marrow sample (biopsy or aspirate) collected at PD will be used for biomarker research[4]			
Disease Evaluation Laboratory Tests	• Urine Protein Electrophoresis (UPEP)[4,8] • Serum Protein Electrophoresis (SPEP)[4,8] • Urine immunofixation[4] • Serum immunofixation[4] • 24-hour urine collection for M-protein[4,8] • Serum Kappa, lambda free LC, FLC ratio[4,8]			

Laboratory Assessments	Parameters
	• Beta2 microglobulin[4] • IgG[4], IgM[4], IgA[4] (IgD and IgE ONLY for participants with IgD/E myeloma)[4] • Calcium corrected for albumin (serum)[4]
Bone Marrow Aspiration/Biopsy	• MRD testing[4] • Disease assessment (percent plasma cells)[2, 4] • To confirm sCR (IHC)[4,6] • FISH testing to be performed locally at least for: t(4;14), t(14;16), amp(1q), del(1p) and del(17p13). If patient is known to have previously tested positive for t(4;14),or t(14;16), FISH testing for those translocations does not need to be repeated, as results from previous tests are acceptable regardless of when those tests were performed. Other 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. • BCMA IHC assessment[4]
The results of each test performed by a Local Laboratory must be entered into the eCRF. Central laboratory data will be sent directly to GSK.	

1. Other lab tests maybe completed as needed.
2. Performed by local lab.
3. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 6 All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (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).
4. Performed by central lab
5. 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. Albumin/creatinine will be performed at a local lab. If local testing is not available, then central testing will be performed (first void).
6. Results from tests to confirm sCR will be collected and stored by third party vendor.
7. Participants with significant elevations (≥x3 ULN)
8. Assessments critical for eligibility

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

11.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study 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 conditions 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.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of

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

11.3.2. Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent

everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
Is associated with liver injury and impaired liver function defined as: • ALT ≥3 x ULN and total bilirubin* ≥2 x ULN (>35% direct), or • ALT ≥3 x ULN and INR** >1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥3 x ULN and total bilirubin ≥2 x ULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form. Refer to Appendix 6 for liver chemistry follow-up procedures.

11.3.3. Definition of Cardiovascular Events

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

Cardiovascular Events (CV) Definition:
• Deep venous thrombosis/pulmonary embolism • Revascularization

11.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (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 the National Cancer Institute Common Terminology Criteria for Adverse Events (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)[1]. Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2]. Grade 4: Life-threatening consequences; urgent intervention indicated. Grade 5: Death related to AE. [1]Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

AE and SAE Recording

[2] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

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

11.3.5. Reporting of SAE to GSK

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

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical director/SAE coordinator. • 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 services • 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 Study Reference Manual.

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

11.4.1. 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.

For questionable cases (child-bearing status), follicle-stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential only) should be performed at local lab (see Appendix 2).

Women in the following categories are not considered WOCBP:

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

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

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

11.4.2. Contraception Guidance

Use of belantamab mafodotin in pregnant women may cause fetal harm and there is the potential for embryo-fetal risk when prescribing pomalidomide. Pomalidomide is available only through a pregnancy prevention/controlled distribution program.

Participants receiving pomalidomide must register with any pregnancy prevention/controlled distribution program in place locally where applicable (see SRM for details). Acceptable contraception methods need to be aligned to regulatory guidelines/regulations for respective countries and as outlined in the local label (as applicable). Contraception and pregnancy testing timelines and frequencies must be within the regulatory guidelines/regulations for the respective country. See Section 6.1 for further details.

Contraceptives allowed during the study for both treatment arms are presented in Table 26.

Table 26 Contraceptives Allowed During the Study

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b,c] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c, d]
• Intrauterine device (IUD)[d]
• Intrauterine hormone-releasing system (IUS)[c, d]
• 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,c] That Are User Dependent

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • Oral[e]
  • 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. **Consult the local label for additional guidance on contraceptive use when using pomalidomide**. **If local label has stricter requirements, the local label should take precedence.** 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. d) Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia. (Imnovid SmPC). e) **Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended** (Imnovid SmPC). Consult pomalidomide pregnancy prevention program / product information for recommended contraception. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

11.4.3. 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 who becomes pregnant while participating in this study and for 6 months following last dose of belantamab mafodotin treatment (Arm 1) or at least 4 weeks after the last dose of pomalidomide treatment (Arm 2). 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 during the pregnancy and post delivery to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- For Arm 1 follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. For participants in Arm 2, follow-up will be up to 1 year for infant follow-up. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study and for 4 months following last dose of belantamab mafodotin treatment (Arm 1) or 4 weeks after the last dose of pomalidomide treatment (Arm 2).
- 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. For participants in Arm 2, follow-up will be up to 1 year for infant follow-up.
- 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 Appendix 3. While the investigator is not obligated to actively

seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- In compliance with REMS requirements, pregnancy information on any female participant enrolled in Arm 2 (pom/dex therapy) in the US must be reported to Celgene Corporation at 1-888-423-5436 or FDA at 1-800-332-1088 or www.fda.gov/medwatch. Notification to other program which may be in place locally will be detailed in the SRM.

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

11.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention 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 blood sample will be collected 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 interventions 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 relationships between genetic variants in the host and response to belantamab mafodotin. A detailed description of any planned analyses will be documented in a Statistical Analysis Plan (SAP) prior to initiation of analyses. Planned analyses and results of genetic investigations will be reported either as part of the clinical SAP and clinical study report (CSR), or in a separate genetics SAP and report, as appropriate.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to belantamab mafodotin or study interventions 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 interventions 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.

11.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments and Study Intervention Rechallenge Guidelines

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

Liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for 4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• Immediately discontinue study intervention • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study intervention unless allowed per protocol and GSK Medical Governance approval **is granted** (See below) • If restart/rechallenge **not allowed or not granted**, permanently discontinue study intervention and continue participant in the study	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis and a blood sample for sBCMA, if it can be obtained within 70 days after last dose[5] • 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 • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on

Liver Chemistry Stopping Criteria	
for any protocol specified follow up assessments **MONITORING:** **If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u> (bilirubin <2xULN and INR ≤1.5<u>):</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page **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 HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms. • Liver biopsy may be considered and discussed with local specialist if available, for instance: o In patients when serology raises the possibility of autoimmune hepatitis (AIH) o In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In patients with acute or chronic atypical presentation: • If liver biopsy conducted complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention 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, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; and the threshold value stated will not apply to participants receiving anticoagulants

3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; HBsAg and HBcAb; Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody or Hepatitis E RNA, For Hepatitis B patients, obtain Hepatitis B-DNA
5. PK sample and associated sBCMA sample may not be required for participants known to be non-GSK comparator interventions. 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.

Liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical director **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study intervention • For HBV patients, obtain HBV-DNA testing • For HCV patients, obtain HCV-RNA testing • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

11.7. Appendix 7: Liver Safety Drug Restart or Rechallenge Guidelines

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 is obtained, if required 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.

11.7.1. Rechallenge Following Liver Stopping Events that are Possibly Related to Study Intervention

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 one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- hypersensitivity with initial liver injury (e.g. fever, rash, eosinophilia) [Andrade, 2009]
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- ongoing severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR>1.5
- serious adverse event or fatality has earlier been observed with drug rechallenges [Hunt, 2010; Papay, 2009]
- 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 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 intervention administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the rechallenge with study intervention. Documentation of informed consent must be recorded in the study file.
- Study intervention must be administered at the dose specified by GSK.
- Participants approved by GSK for rechallenge with study intervention 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 intervention rechallenge, participant meets protocol-defined liver chemistry stopping criteria, study intervention should be permanently discontinued.
- GSK Medical Director, and the IRB/IEC as required, must be informed of the participant's outcome following study intervention rechallenge.
- GSK to be notified of any adverse events.

11.7.2. Restart Following Transient Resolving Liver Stopping Events Not Related to Study Intervention

Restart refers to resuming study intervention 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, acute viral hepatitis). Furthermore, restart is not permitted following liver stopping event when the underlying cause was alcohol-related hepatitis.

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

- Principal Investigator requests consideration for study intervention 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 <3xULN).

- Possible study intervention-induced liver injury has been excluded by the principal investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study intervention 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 intervention-related liver injury cannot be excluded, the guidance on rechallenge will apply.
- There is no evidence of alcohol-related hepatitis.
- IRB/IEC approval of study intervention restart must be obtained, as required.

If restart of study intervention is approved by GSK in writing:

- The participant must be provided with a clear description of the possible benefits and risks of study intervention administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the study intervention restart. Documentation of informed consent must be recorded in the study file.
- Study intervention must be administered at the dose specified by GSK.
- Participants approved by GSK for restart of study intervention 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 participant meets protocol-defined liver chemistry stopping criteria after study intervention restart, study intervention should be permanently discontinued.
- GSK Medical Director, and the IRB/IEC must be informed of the participant's outcome following study intervention restart.
- GSK to be notified of any adverse events.

11.8. Appendix 8: Abbreviations and Trademarks

Abbreviations

ADA	Anti-drug antibody
ADC	Antibody drug conjugate
ADL	Activities of Daily Living
ADCC	Antibody dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase or Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase or Aspartate transaminase
AUC	Area under the curve
CCI [redacted]	
BCMA	B cell maturation antigen
BCVA	Best corrected visual acuity
BM	Bone marrow
BOR	Best overall response
BP	Blood pressure
BSEP	Bile salt export pump
C	Cycle
C1D1	Cycle 1 Day 1
CBR	Clinical benefit rate
cfDNA	Cell free deoxyribonucleic acid
CI	Confidence interval
CK	Creatine kinase
CL	Clearance
Cmax	Maximum observed concentration
CO_2	Carbon dioxide
CO_2CP	Carbon dioxide combining power
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
CT	Computed tomography
Ctau	Trough concentration
Ctrough	Concentration at trough
CV	Cardiovascular
CV%	Percent coefficient of variation
CYP	Cytochrome P450
cys-mcMMAF	cysteine maleimidocaproyl monomethyl auristatin-F;
CX	Cycle and number (any, unspecified)
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram

ECOG (PS)	Eastern Cooperative Oncology Group (Performance Status)
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
CCI [redacted]	
ER	Endoplasmic reticulum
EMA	European Medicines Agency
EMD	Extramedullary disease
EOI	End of infusion
EORTC IL52	European Organisation for Research and Treatment of Cancer - Disease Symptoms domain of EORTC-QLQ-MY20
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module
EORTC QLQ-MY20	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma Module
EOT	End of treatment
EOS	End of study
EU	European Union
FDA	Food and Drug Administration
FISH	Florescent in situ hybridization
FLC	Free light chain
FSH	Follicle stimulating hormone
FTIH	First Time in Human
g	Gram
GSK	GlaxoSmithKline
GVHD	Graft-Versus-Host Disease
h	Hour
HBcAb	Hepatitis B core antibody
HBeAb	Hepatitis B e antibody
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
CCI [redacted]	
HCV	Hepatitis C virus
HD	High Dose Dexamethasone
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
IA	Interim Analysis
IB	Investigator's Brochure
ICD	Immunogenic cell death
ICF	Informed consent form
ICH GCP	International Conference on Harmonization Good Clinical Practice

IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IF	Information fraction
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IL-#	Interleukin-#
IMWG	International Myeloma Working Group
INR	International normalization ratio
IRC	Independent Review Committee
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRT	Interactive Response Technology
ISS	International Staging System
IV	Intravenous
kg	Kilogram
KVA	Keratopathy Visual Acuity
λz	Terminal phase elimination rate constant
L	Liter
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
mcL	microliter
mcMMAF	maleimidocaproyl monomethyl auristatin-F;
MD	Medical director
MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
μg	Microgram
uL	Microliter
min	Minute
mIU	Milli-international unit
mL	Milliliter
mm	Millimeter
MM	Multiple myeloma
MMAF	Microtubular inhibitor monomethyl auristatin-F
MOA	Mechanism of action
mOS	Median overall survival
MR	Minimal response
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MRP	Multidrug resistance associated protein
MSDS	Material Safety Data Sheet

msec	Millisecond
MTD	Maximum tolerated dose
MUD	Maximum utility dose
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute- Common Toxicity Criteria for Adverse Events
NCI-ODWG	National Cancer Institute - Organ Dysfunction Working Group
NE	Not estimable
NGS	Next generation sequencing
NIH	National Institute of Health (in the United States)
NK	Natural killer (cell)
nm	Nanometer
NR	Not reported
NYHA	New York Heart Association
OATP	Organic-anion-transporting polypeptide
ORR	Overall response rate
OS	Overall survival
OSDI	Ocular Surface Disease Index
OTC	Over the counter
OU	Both Eyes
PACT	Post analysis continued treatment
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PFS2	Progression-free Survival on Subsequent Line of Therapy
pg	Picogram
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic(s)
pmol	Picomole
POEMS	Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes
pom/dex	Pomalidomide plus Low-Dose Dexamethasone
PRO-CTCAE	Patient-Reported Outcome Version of the Common Toxicity Criteria for Adverse Events
PR	Partial response
Q3W	Every three weeks
QID	Four times a day
QTc	Corrected QT interval
RCE	Recurrent corneal erosion(s)
RIBA	Recombinant immunoblot assay
RP2D	Recommended Phase 2 Dose
RNA	Ribonucleic acid
RO	Receptor occupancy

RRMM	Relapsed/refractory multiple myeloma
SAE	Serious adverse event
SAS	Statistical Analysis System
sBCMA	Soluble B cell maturation antigen
sCR	Stringent complete response
sCRS	Severe cytokine release syndrome
SCT	Stem cell transplant
SD	Stable disease
SEB	Staphylococcal enterotoxin B
sec	Second
SoA	Schedule of Activities
SoC	Standard of care
SOC	System organ class
SOI	Start of infusion
SOP	Standard Operating Procedure
SPD	Sum of the Products of the maximal perpendicular Diameters of measured lesions
SPEP	Serum protein electrophoresis
SRM	Study Reference Manual
$t_{1/2}$	Terminal phase half-life
tlast	Last time point where the concentration is above the limit of quantification
TLS	Tumor lysis syndrome
tmax	Time to Cmax
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
TTP	Time to progression
TTR	Time to response
CCI [redacted]	
UK	United Kingdom
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
US	United States
USA	United States of America
USP	United States Pharmacopeia
V	Volume of distribution
VGPR	Very good partial response
WBC	White blood cell

Trademark Information

Trademarks of the GSK group of companies
NONE

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IMNOVID
MedDRA
POMALYST
PureVision

11.9. Appendix 9: ECOG Performance Status

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

Source: Oken, 1982.

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

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

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

where, GFR is expressed in mL/min/1.73 m^2, S_{Cr} is serum creatinine expressed in mg/dL, and age is expressed in years.

The link below will auto-calculate the creatinine clearance:

http://nephron.org/cgi-bin/MDRD_GFR/cgi

11.11. Appendix 11: NYHA Functional Classification System

The New York Heart Association (NYHA) Functional Classification: Class I, II, III or IV Heart Failure [The Criteria Committee of the New York Heart Association (NYHA), 1994] provides a simple way of classifying the extent of heart failure. It places participants in 1 of 4 categories based on the level of limitation experienced during physical activity

NYHA Functional Classification for Heart Failure

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Source: NYHA. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co. 1994. 253-256.

11.12. Appendix 12: Eye Care Specialist's Qualifications and Requirements

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

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

Qualified eye care specialists, including optometrist, will also be able to communicate with patients on the effect of belantamab mafodotin on eye.

11.13. Appendix 13: Home Healthcare and Telemedicine Approaches

Home Healthcare (General Visit):

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

Activities that may be done as part of a home healthcare visit must follow the schedule provided in the SoA (Section 2) and include:

- History-taking to elicit signs and symptoms relevant to clinical features of multiple myeloma, and adverse events of study medications
- 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.
- Delivery/Administration of oral study medication or direct to patient service
- Identification and reporting of concomitant medications.
- Dosing diary review for medication compliance.
- The Home Health visit may be combined with Telemedicine visit with the PI (see below)

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.

It is strongly recommended that all participants should have at least one onsite visit per treatment cycle to also allow assessments that cannot be done via home health to be performed.

The participant should be informed of any potential risks associated with Home Healthcare and sign a revised or additional 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 2) and include:

- Best corrected Visual Acuity (VA)*
- 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.

** Note: Pinhole can be used for assessment of BCVA at patient's home when the examiner does not have the opportunity to perform refraction. Note: Rosenbaum pocket eye screener chart (i.e. near VA chart) should only be assessed if space doesn't allow for distance-chart e.g. in participants' home.*

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.

Remote Patient Reported Outcomes (PRO) Administration

Where applicable country and local regulations and infrastructure allow, remote PRO administration may be permitted. Remote PRO administration is defined administration of protocol PROs by a qualified third party over the telephone. The remote PRO Administrator will use the versions of the PROs designed for verbal administration. The remote PRO Administrator will have access to the electronic PRO portal for the study and input participant responses as the interview is being conducted.

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

11.14. Appendix 14: 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 patient and/or critical data quality need, e.g., to assess patient 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 subject 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 subject 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 patient is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing the 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. Please note that unblinding procedures remain the same as those documented in the protocol and other study-related documents.

11.15. Appendix 15: Country Specific Requirements

Inclusion / Exclusion Criteria:

- In **Republic of Korea**, a participant must be over 19 years of age inclusive, at the time of signing the informed consent.
- In **France** a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.
- In **Germany**, the following additional exclusion criteria applies: Availability of a standard-of-care treatment that, in the Investigator's opinion, represents a superior benefit-risk for the patient than participation in this clinical trial (e.g. triple-drug regimen).
- In **France,** the following additional exclusion criteria applies: Availability of a standard-of-care treatment that, in the Investigator's opinion, represents a superior benefit-risk for the patient than participation in this clinical trial (e.g. anti-CD38 containing regimen for a patient who has not been previously treated with anti-CD38)
- In **Japan**, Hepatitis B participants who are HBsAb+ are eligible for inclusion in this study if after assessing HBeAg, HBeAb, and HBV DNA, HBV DNA is undetectable. If a potential participant is 18 or 19 years of age, signed informed consent from the participants' legally acceptable representative must be obtained, as well as from the participant himself/herself.
- In **China**, Hepatitis B participants who are HBsAb+ are eligible for inclusion in this study if HBV DNA is undetectable.

Adverse Events

- For all studies conducted in **China**, SAEs will be collected from signing of the ICF and NOT from the start of treatment.

Ocular Examinations

- In **France**, all ocular examinations required per protocol will be conducted only by an ophthalmologist.

Other Assessments:

- In **China**, the following assessment with not be performed as a follow-up to bilirubin or INR meeting Liver Chemistry stopping criteria: Serum acetaminophen adduct HPLC assay.

- In **China**, the following samples will not be collected: bone marrow biopsy sample for BCMA IHC, BM aspirate for exploratory endpoints, cfDNA and pharmacogenetic samples.

- In **China**, MRD sample collection and assessment will not be performed until approval from OHGRA is obtained.

C [redacted]

Contraception Guidance:

Of the contraceptive methods defined in Table 26 Contraceptives Allowed During the Study, the following are NOT approved in **Japan** as contraceptive method:

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

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

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

11.16. Appendix 16: Protocol Amendment History

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

Amendment 4: (20-Apr-2022)

Overall Rationale for the Amendment:

This protocol amendment is being introduced following the re-estimation of study completion timeframe based on the current rate of accrual of PFS events being slower than originally anticipated.

This protocol amendment revises the power for PFS Final Analysis from 95.6% to at-least 90%, allowing the PFS final analysis to be triggered when at least 151 events are accrued and the first 320 randomized subjects have been followed for a minimum of 4 months, with an anticipated median follow-up of approximately 10 months by the time 151 PFS events accrue.

The PFS futility Interim Analysis is removed as this would coincide with the updated PFS Final analysis.

The two interim and one final planned OS analyses remain unchanged.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Revised the number of events required for PFS analysis Added clarification around post analysis continued treatment (PACT) phase and definition of end of study	To support delivering PFS analyses projections within a reasonable timeframe To ensure patients benefiting from study treatment will be allowed to continue on study treatment after end of OS Follow-Up
Section 1.2 Schema	Added clarification around PACT phase	To ensure patients benefiting from study treatment will be allowed to continue on study treatment after end of OS Follow-Up
Section 2 Schedule of Activities	Added clarification around PACT phase Updated clarification for disease assessment evaluation window Updated BM biopsy/aspirate collection requirements	To ensure patients benefiting from study treatment will be allowed to continue on study treatment after end of OS Follow-Up To ease testing burden for sites To ease testing burden for sites and to align with program language
Section 5.1 Overall Design	Added clarification around PACT phase and end of study Revised the number of events required for PFS analysis	To ensure patients benefiting from study treatment will be allowed to continue on study treatment after end of OS Follow-Up and country-specific (expansion cohort) analyses To support delivering PFS analyses projections within a reasonable timeframe
Section 5.4 End of Study Definition	Added clarification around PACT phase and end of study	To ensure patients benefiting from study treatment will be allowed to continue on study treatment after end of OS Follow-Up
Section 7.7 Intervention	Added clarification around PACT phase	To ensure patients benefiting from study

Section # and Name	Description of Change	Brief Rationale
after the End of OS Follow-up	and end of study	treatment will be allowed to continue on study treatment after end of OS Follow-Up
Section 8.1 Discontinuation of Study Intervention	Replaced End of Study with End of OS follow-up	Due to change in definition of End of Study
Section 9.1 Efficacy Assessments	Updated clarification for disease assessment evaluation window	To ease testing burden for sites and to align with program language
Section 9.3 Adverse Events and Serious Adverse Events	Added clarification around PACT phase and end of study	To ensure patients benefiting from study treatment will be allowed to continue on study treatment after end of OS Follow-Up
Section 9.5 Pharmacokinetics	Added clarification that PK and accompanying sBCMA sample collection may be terminated when sufficient data have been collected	To ease testing burden for sites
Section 9.8 Biomarkers	Updated BM biopsy/aspirate collection requirements Added clarification that PK and accompanying sBCMA sample collection may be terminated when sufficient data have been collected	To ease testing burden for sites and to align with program language To ease testing burden for sites
Section 9.9 Immunogenicity Assessments	Added clarification that ADA sample collection may be terminated when sufficient data have been collected	To ease testing burden for sites
Section 10.2 Sample Size Determination	Remove PFS IA Revision of power for PFS Final Analysis from 95.6% to at least 90% Revised the number of events and months of follow-up required for PFS analysis	The new proposed PFS Final analysis will supersede the PFS futility Interim Analysis as the two analyses are expected to happen at about the same timeframe. To support delivering PFS analyses projections within a reasonable timeframe To support delivering PFS analyses projections within a reasonable timeframe
Section 10.4 Statistical Analyses	Revised the number of events and months of follow-up required for PFS analysis	To support delivering PFS analyses projections within a reasonable timeframe
Section 10.5 Planned Analyses	Remove PFS IA Revised the number of events and months of follow-up required for PFS analysis	The new proposed PFS Final analysis will supersede the PFS futility Interim Analysis as the two analyses are expected to happen at about the same timeframe. To support delivering PFS analyses projections within a reasonable timeframe
Section 11.2 Appendix 2: Clinical Laboratory Tests	Table 25: Added option regarding testing for Total CO_2 or CO_2CP Updated BM biopsy/aspirate collection requirements	To allow flexibility based on local country practices To ease testing burden for sites and to align with program language

Amendment 3: (21-Oct-2021)

Overall Rationale for the Amendment:

The protocol amendment has been introduced to increase the global enrollment cap (limit) for patients who have received ≤3 prior lines from 40% to 55%. Due to the increasing use of pomalidomide and anti-CD38 antibodies in 3rd and 4th lines of therapy in relapsed/refractory multiple myeloma, the closure of the cap (meeting the limit) for participants with ≤3 prior lines has resulted in the slowing of patient enrollment into the study. There will be no change in the 40% global enrollment cap for participants with prior anti-CD38 treatment, as data in anti-CD38-naive patients are required to meet global evidence needs. There are no changes to overall statistical assumptions for this study.

The removal of the North-East Asia enrolment cap will also support delivering recruitment projections within a reasonable timeframe.

The Inclusion Criteria (IC) 4b has also been updated to align with the International Myeloma Working Group (IMWG) definition of refractory Multiple Myeloma.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Increase in global enrollment cap for patients who have received ≤3 prior lines from 40% to 55% Updated definition of refractory Multiple Myeloma Removal of enrollment cap for North-East Asia countries	To deliver recruitment projections within a reasonable timeframe To align with the International Myeloma Working Group (IMWG) definition of refractory Multiple Myeloma To support delivering recruitment projections within a reasonable timeframe
Section 1.2 Schema	Added expanded definition of refractory multiple myeloma in schematic	To align with the International Myeloma Working Group (IMWG) definition of refractory Multiple Myeloma
Section 2 Schedule of Activities	Updated HBV-DNA and HCV-RNA assessments to include central testing	To ease testing burden for sites
Section 5.1 Overall Design	Increase in global enrollment cap for patients who have received ≤3 prior lines from 40% to 55% Updated definition of refractory Multiple Myeloma Removal of enrollment cap for North-East Asia countries	To deliver recruitment projections within a reasonable timeframe To align with the International Myeloma Working Group (IMWG) definition of refractory Multiple Myeloma To support delivering recruitment projections within a reasonable timeframe
Section 6.1 Inclusion Criteria	Updated definition of refractory Multiple Myeloma	To align with the International Myeloma Working Group (IMWG) definition of refractory Multiple Myeloma
Section 9.9 Immunogenicity	Remove statement that ADA samples will be disposed of three months after	To align with sample retention for sBCMA and PK samples

Section # and Name	Description of Change	Brief Rationale
Assessments	final approved results are provided to the Clinical Study Team	
Section 10.2 Sample Size Determination	Removal of enrollment cap for North-East Asia countries	To support delivering recruitment projections within a reasonable timeframe
Section 10.4 Statistical Analyses	Remove secondary endpoints for mITT	To align with Statistical Analysis Plan

Amendment 2: (20-Sep-2021)

Overall Rationale for the Amendment:

The protocol was amended to update the planned Progression-Free Survival (PFS) futility interim analysis (IA) to be based on the first 120 randomized participants. Due to the fast enrollment rate, enrollment was expected to be near complete by the time of the originally planned PFS futility IA, and a large proportion of study participants would have insufficient follow-up at the time of this IA. The PFS data based on all participants enrolled at the time of the IA would therefore be immature. To support an informed decision-making process, the non-binding PFS futility IA was planned to be based on the first 120 randomized participants, anticipated to occur when approximately 69 events (~35% information fraction) were observed. It was anticipated that participants at the time of this revised IA would have minimum follow-up of ~4.5 months and the data was considered to be mature.

An additional Overall Survival (OS) interim analysis was introduced to allow for the comprehensive reporting of all available information to the Agencies at the time of the primary analysis. Long-term survival data would continue to be collected beyond this interim analysis.

The enrollment cap for North-East Asia countries was increased from 15% to 20% to support recruitment expectations in this region and to enable more patients who meet the eligibility criteria to potentially benefit from study participation.

Per the FDA guidance that allows participants with Hepatitis B, Hepatitis C, and Human Immunodeficiency Virus to be enrolled into clinical trials where they can be monitored appropriately [FDA Guidance Docket Number: FDA-2019-D-0363], eligibility criteria was updated accordingly.

Additional changes were incorporated which align with program revisions and/or updates based on the latest Investigator's Brochure [GSK2857916 IB, GSK Document Number 2013M17518_09, 2021].

Section # and Name	Description of Change	Brief Rationale
Throughout	Administrative updates to add	Editorial changes were made for accuracy,

Section # and Name	Description of Change	Brief Rationale
	clarification and/or remove discrepancies	clarity, conformity, flow, and typographical error corrections
Section 1.1 Synopsis	Updated definition of End of Study Increase in North East Asia enrollment cap from 15% to 20% Update of data collection information after the end of study	To account for change in language around OS follow up To support recruitment expectations in this region and to enable more patients who meet the eligibility criteria to potentially benefit from study participation Decrease burden on patients and sites
Section 2 Schedule of Activities	Table 1, Table 2, Table 3, Table 4: Added clarification around testing for BCMA expression Table 3: Added optional genetic sampling along with requirement of separate informed consent Table 3 and Table 4: Added the row on 'Dispense/return medication diary' and 'Return medication diary' respectively Table 6 & Table 7: Added assessments for Hepatitis C and Hepatitis B	Added per country request To clarify that BM biopsy is the preferred way to collect genetic sampling at PD To remind sites to have participants fill out medication diary. To support the change in hepatitis B and C eligibility criteria and align with FDA guidance
Section 3.4.3 Pharmacokinetics and Pharmacodynamics in Humans	Update background information of belantamab mafodotin PK data	To be consistent with updated information in the investigator's brochure.
Section 3.5.1 Risk Assessment	Table 8: Update in explanation of risks	To align with IB update
Section 5.1 Overall Design	Increase in North East Asia enrollment cap from 15% to 20% Update of data collection information after the end of study	To support recruitment expectations in this region and to enable more patients who meet the eligibility criteria to potentially benefit from study participation Decreased burden on patients and sites
Section 5.4 End of Study Definition	Updated definition to End of Study Update of data collection information after the end of study	To account for change in language around OS follow up Decrease burden on patients and sites
Section 6.2 Exclusion Criteria	Updated Hepatitis B virus (HBV) and Hepatitis C Virus (HCV) eligibility criteria	To support the change in hepatitis B and C eligibility criteria and align with FDA guidance
New Section 7.5.3 Drug Interactions	Updated drug interactions information	To clarify drug interaction information
Section 7.6.2 Dose Modifications	Table 13: Updated footnotes to provide further clarifications on keratopathy grading criteria Addition of criteria to re-baseline BCVA if participant has cataract surgery	To align with program-wide language To support accurate assessment of belantamab mafodotin-associated change in BCVA

Section # and Name	Description of Change	Brief Rationale
Section 7.7 intervention after the End of Study	Update of data collection information after the end of study	Decreased burden on patients and sites
Section 8.3 Participant Discontinuation/Withdrawal from the Study	Added the responsibilities of site personnel on collecting survival data from public sources	Provide clarity on collecting survival data
Section 9.1 Efficacy Assessments	Extend the allowance of PET CT from 21 days to 42 days after MRD negativity results are available	Alignment with program-wide language
Section 9.3.1 Time Period and Frequency for Collecting AE and SAE information	Update of SAE collection information after the end of study	Decreased burden on patients and sites
Section 9.3.6 Pregnancy	Addition of pregnancy data collection information	To align with program language
New Section 9.3.8 Management of Hepatitis B+ Participants	Addition of guidelines for management of Hepatitis B+ Participants and Hepatitis B reactivation	To reflect the change in hepatitis B eligibility criteria
Section 9.5.1 Blood Sample Collection for Pharmacokinetics	Table 18 & Table 19: Clarification on PK and sBCMA collection schedule	Clarity of assessment schedule for sites
Section 10.2. Sample size determination	Addition of 40% Information fraction The percentage of global enrollment cap on North East Asia Countries has been updated to 20% from 15%	Decision to add OS interim analysis to allow for the comprehensive reporting at the time of the primary analysis To support recruitment expectations in this region and to enable more patients who meet the eligibility criteria to potentially benefit from study participation
Section 10.5. Interim Analyses	The non-binding interim PFS futility analysis is to be performed based on the first 120 randomized participants, and when ~69 (~35% information fraction) events are observed in these 120 participants Addition of an OS interim analysis at 40% IF OS follow-up wording updated to add OS interim analysis at the time of PFS final analysis Table 25 Stopping Boundaries for OS is updated	To ensure data for PFS futility IA is sufficiently mature. Decision to add OS interim analysis to allow for the comprehensive reporting at the time of the primary analysis To allow for long-term survival data to be collected in the event of a significant outcome at 2nd OS IA. Addition of 40% IF to reflect additional OS IA
Section 11.2 Appendix 2: Clinical Laboratory Tests	Table 26 Update safety laboratory tests	Addition of Hepatitis B DNA in line with eligibility and with pomalidomide label update
Section 11.6 Appendix 6 Liver Safety: Required Actions and Follow-up Assessments and Study Intervention Rechallenge Guidelines	Addition of assessments for HBV and HCV patients	Updated the assessment table to support the change in hepatitis B and C eligibility criteria
New Section 11.14 Appendix 14 Data management/Monitoring	To provide guidance on remote monitoring	Alignment with program-wide language

Section # and Name	Description of Change	Brief Rationale
Section 11.15 Appendix 15: Country Specific Requirements	Japan: Addition of serology of HBsAb+ from exemption from Hepatitis B exclusion criteria China: Addition of serology of HBsAb+ from exemption from Hepatitis B exclusion criteria	Added per country request Added per country request
New Section 11.16 Appendix 16 Protocol Amendment History	Documentation of previous Protocol Amendment changes and rationale	As per protocol template

Amendment 1: (23-Oct-2020)

Overall Rationale for the Amendment:

The protocol has been amended based on regulatory agency comments. Additional changes were incorporated which align with program revisions and/or updates based on data from the analysis of the Phase II Study 205678 (DREAMM-2) evaluating the efficacy and safety of two doses of belantamab mafodotin monotherapy in patients with relapsed or refractory multiple myeloma who had 3 or more prior lines of treatment, were refractory to a proteasome inhibitor and an immunomodulatory agent and have failed an anti-CD38 antibody.

Section # and Name	Description of Change	Brief Rationale
Throughout	Update of contraception use timeframe to 6 months for males and 4 months for females post-last dose of belantamab mafodotin	Updated to align with FDA guidance "Oncology Pharmaceuticals Reproductive Toxicity and Testing recommendations" and considering the half-life of belantamab mafodotin
Throughout	Updated role of Medical Monitor to Medical Director	Company change in the terminology for description of the lead GSK physician
Throughout	Added qualified eye care specialist to wording related to ophthalmologist/ optometrist and referred to Appendix 12 listing the required qualifications	To ensure consistency in qualification for those completing the ocular examinations and to further outline the necessary qualifications.
Throughout	Addition of DREAMM 2 primary analysis publication reference; clarification of data	Updated reference due to publication of data; Clarification that supporting data was from primary analysis
Throughout	Amended GSK2857916 to belantamab mafodotin	To refer to product by name versus compound number
Throughout	Updated reference to belantamab mafodotin investigator brochure, POMALYST PI and Imnovid SmPC	To refer to the most recent versions
Throughout	C [redacted]	C [redacted]
Throughout	Minor editorial and document formatting revisions	To improve overall clarity and typographical corrections
Throughout	Renumbering of Tables, Figures and Footnotes	As a result of changes within the document
Title Page	Added Study Logo	For easier recognition
Section 1.1 Synopsis	Updated study rationale paragraph	To align with current program level wording based on additional data from DREAMM-2/ 205678 study and in alignment with

Section # and Name	Description of Change	Brief Rationale
		Investigator brochure update
	Added EORTC QLQ-MY20 to HRQOL endpoint	To align with the implementation of EORTC QLQ-MY20 assessment for participants enrolled under the protocol amendment
	C [redacted]	C [redacted]
	Increased global enrollment cap for of participants with ≤3 prior lines and added global enrollment cap for of participants with prior anti-CD38 treatment	To align with change in MM treatment paradigm
	Revised study treatment completion statement	Clarification
	Added sub header for End of Treatment and End of Study; adjusted OS analysis statement	Clarification
	Revision of analyses language in IDMC section	To simplify the wording in the synopsis
Section 1.2 Schema	Renamed Figure 1 and Added PFS2	Clarification
	Added Figure 2: Treatment and Assessment Schema	A visual aid for readers of the protocol
Section 2 Schedule of Activities	Table 1, Table 2 & Table 3 Updated screening period from 21 to 28 days, including imaging	Increase flexibility for completion of Screening activities.
	Table 1, Table 2 & Table 3: Moved optional genetic consent from Table 2 and Table 3 to Table 1	To better reflect flow of activities
	Table 1, Table 2 & Table 3: clarified which assessment are not required to be repeated on C1D1 if performed within 72h prior to dosing and removed 'X' for screening assessment from C1D1 column that do not need to be repeated.	For simplification and to avoid unnecessary repeat of assessments
	Table 1, Table 2, Table 3 & Table 4: Footnote numbering and placement updated throughout the tables. Abbreviations updated	Due to the addition and removal of footnotes and for simplification of footnotes
	Table 1 and Table 2: replaced footnotes with abbreviated instruction where assessment is not done at every visit	For clarification (e.g. Q6W for urinalysis, MRD only for biomarker analysis)
	Table 1: Added collection of Prior anti-myeloma therapy data	To clarify that this data is collected

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	Table 1: Clarification of 'questionable cases' in pregnancy testing footnote	Clarification
	Table 1, Table 2, Table 3 & Table 4: Combined Urinalysis, with Spot Urine and updated information about albumin/ creatinine analysis	Revision of program wording for Urinalysis and assessment of urine protein.
	Table 1, Table 2, Table 3 & Table 4: Removed Assessment of Troponin, BNP and Echocardiogram	Based on cardiac data from earlier studies, cardiac risk was determined to be low and routine monitoring was removed
	Table 1, Table 2, Table 3 & Table 4: Updated and clarified imaging requirements: Removed 'whole body' wording. Clarified when follow-up imaging is and is not required and added a timeframe where applicable. Follow-up requirements for extramedullary disease moved to Section 9.1.	Whole body scan is not a requirement for imaging, and not mandated by the protocol. Added follow-up guidance to minimize need for exposure. Other changes were made to clarify requirements and simplify text.
	Table 1, Table 2 & Table 3: Bone Marrow sample requirements: Updated specimen for BCMA expression; added collection time requirements, added analytical methods used and clarified use of remaining sample for biomarker research	Specimen updated based on assay requirements. Other updates were made for clarity and simplification
	Table 2 & Table 3: Addition of statement that all visits are based of timing from C1D1	Added clarity to ensure visits occur as scheduled post first dose
	Table 2 & Table 3: Added cycle lengths to header	Clarification
	Table 2 & Table 3: Removed 'X' for Physical exam at Q3W visits	Not needed for response assessment, only considered necessary if dosing
	Table 2, Table 3 & Table 4: Update to AE language and requirement to collect AE/SAEs for 70 days post last dose.	Alignment with program level language.
	Table 1, Table 2, Table 3 & Table 4: Revisions to Ocular exam wording, requirements and frequency	Updated based on review of earlier study data and in consultation with ocular experts
	Table 2, Table 3 & Table 4: Updated MRD follow-up and reduced frequency after 2 years.	In line with IMWG Multiple Myeloma guidance
	Table 2, Table 3 & Table 4: Added timeframe for imaging after negative MRD	Clarification
	Table 2, Table 3 & Table 4: Updated	

Section # and Name	Description of Change	Brief Rationale
	requirements on M-protein testing	In line with IMWG Multiple Myeloma guidance
	Table 2, Table 3 & Table 4: EORTC-QLQ-MY20 will be implemented for participants enrolled under protocol amendment 1.	To allow a more comprehensive evaluation of belantamab mafodotin
	Table 2: Changed header of treatment prophylaxis to Supportive Care and simplified footnote	To align with main body of protocol and for simplification
	Table 3, Removal of infusion wording for Arm 2	Arm 2 is an oral product, thus did not apply
	Table 3, Added timeframe and specimen requirements for subsequent pregnancy testing	Clarification
	Table 4: Adjustment of timing for EOT visit	Alignment with program language for EOT.
	Table 4: Addition of wording to clarify end of study	Language added to clarify collection of OS data if final OS analysis occurs at interim OS analysis
	Table 4, Note 25: Inclusion of EORTC IL53 during OS follow-up, and removal of wording after progression for timing	Align with program language with revisions to PRO plans.
	Table 5: C [redacted]	C [redacted]
Section 3.1 Study Rationale	Condensed results section and referenced to Section 3.4	To avoid duplication of text within document
Section 3.3 Antibody-Drug Conjugate Belantamab Mafodotin	Replacement of section with current program language	Clarification on mechanism of action
Section 3.4 Human Experience with Belantamab mafodotin	Section amended with updated data from DREAMM-2/205678 study and in alignment with Investigator brochure update.	New and updated data available. Sub headers added for better navigation.
Section 3.5.1. Risk Assessment	Revisions to wording of risks for Keratopathy, IRR, thrombocytopenia, other hematological effects, nephrotoxicity, pulmonary, other laboratory abnormalities, immunosuppression, fertility and data acquisition	To align with current program level wording based on additional data from DREAMM-2/ 205678 study and in alignment with Investigator brochure update.
	Removal of the risks of potential for cardiotoxicity related to inflammatory response and hepatotoxicity	Based on a comprehensive review of the data from studies BMA117159 and 205678, the risks are considered closed.
Section 4 Objectives	Removal of ECGs from exploratory endpoint	Based on available data, cardiac risk was determined to be low and routine monitoring was removed
	Added EORTC QLQ-MY20 to HRQOL endpoint	To align with the implementation of EORTC QLQ-MY20 assessment for participants

Section # and Name	Description of Change	Brief Rationale
		enrolled under the protocol amendment
	Revision of Endpoint to exploratory Objective of Exploring the relationship between biologic characteristics and response	To summarize all analysis on all biological material collected
	Addition of pharmacogenetics Objective and Endpoint	Was omitted from the exploratory endpoints in the original protocol
	[redacted]	[redacted]
Section 5.1 Overall Design	Updated wording of prior lines	Align with wording for Inclusion Criteria
	[redacted]	[redacted]
	Increased global enrollment cap for of participants with ≤3 prior lines and added global enrollment cap for of participants with prior anti-CD38 treatment	To align with change in MM treatment paradigm
Section 5.2 Scientific Rationale	Removed duplicated wording on DREAMM-1 results and referenced Section 3.4.1 instead.	To simplify and ensure alignment within document
Section 5.3.1 Belantamab Mafodotin – Arm 1	Removed duplicated wording on DREAMM-1 results and referenced Section 3.4.1 instead.	To simplify and ensure alignment within document
Section 5.4 End of Study Definition	Revision to number of deaths required for end of study	To clarify that end of study is also reached if final OS analysis occurs at interim OS analysis, however, in this case, OS data will continue to be collected
	Addition of language to 'End of Study' definition	Language added to clarify how end of study is determined if final OS analysis occurs at interim OS analysis
Section 6.1 Inclusion criteria	Inclusion Criteria #4b, removal of IMWG wording	The reference to the International Myeloma Working Group (IMWG) guidance for definition of disease progression has been removed to allow flexibility to accommodate differences in global standards in determining disease progression prior to study entry.
	Removal of LVEF entry criteria and associated footnote	Based on cardiac data from available studies, cardiac risk was determined to be low and entry criteria was removed
	Deleted Inclusion Criteria #10 from section	Avoid redundancy; Country specific criteria are stated in Appendix 14
Section 6.2 Exclusion criteria	Removal of QT interval exclusion criteria	Based on available data, cardiac risk was determined to be low and entry criteria was removed
	Addition of corneal related exclusion criteria	Update to eligibility criteria to align with program language
Section 6.3 Lifestyle	New sub-header 6.3.1. contact lenses;	Sub-headers are for easier navigation; change

Section # and Name	Description of Change	Brief Rationale
Considerations	Revision to wording for contact lens usage; New sub-header 6.3.2. for Tobacco; New sub-header 6.3.3 for other lifestyle considerations	in contact lens use is aligned with revised program language to allow re-start based on physician review
Section 7.1 Study intervention(s) administered	Added day dose every 21 days for belantamab mafodotin Add footnote for 20mg pomalidomide dose	Clarification Align with other sections of the protocol and label
Section 7.1.1. Supportive Care Guidelines for Belantamab Mafodotin – Arm 1	Revision of language to corneal events and use of steroid eye drops Removed duplicated exam language and referenced Section 9.2.6.1 instead	Revision of program corneal language Simplification
Section 7.1.2: Supportive Care Guidelines for Pom/Dex – Arm 2	Created subsection for Pom/Dex Supportive Care	For added clarity and easier navigation via Table of content
Section 7.3 Measures to Minimize Bias	Added that dosing should occur on same randomization call where possible Amended caps on stratification factors	Clarification In line with Section 5.1
Section 7.5. Concomitant Therapy	Addition of requirements for Concomitant Therapy recording after End of Study treatment	Calrification
Section 7.5.2. Prohibited Medication (s)	Replacement of Section with reference to Arm 2 for allowed steroid use Addition of live or live attenuated vaccines	Clarification Addition of wording due to language associated with dexamethasone
Section 7.6.2.1 Belantamab mafodotin – Arm 1	Revision of introductory wording Table 9: Revision of Recommendations for Serum Creatinine, Urine Dipstick, Thrombocytopenia, Febrile neutropenia, Neutropenia, and Pneumonitis. Table 10: Addition of new footnote to clarify action for dose delay Table 11: Revision of Table header and replaced table with corneal toxicities New Table 12: Dose modification guidelines based on toxicities assessed with Table 10	Update to program language Update to program language. Update to program language Update to program language Update to program language
Section 7.7. Intervention after the End of the Study	Update to post-study treatment options language	Updated language to align with program-level post-study treatment policy
Section 8.1 Discontinuation of Study Intervention	Revision of options for participants who permanently discontinue study treatment Addition of language to OS follow-ups	Clarification of statement To clarify collection of OS data if final OS analysis occurs at interim OS analysis

Section # and Name	Description of Change	Brief Rationale
Section 8.2.1. Liver Chemistry Stopping Criteria	Updated Algorithms Figure 4 and Figure 5 and additional reference made to Appendix 7	In line with GSK update to liver chemistry stopping criteria and creation of Appendix 7
Previous Section 8.2.2. QTc Stopping Criteria	Removal of Section	Based on available data, cardiac risk was determined to be low and stopping criteria were removed
Previous Section 8.2.4. Left Ventricular Ejection Fraction (LVEF) Stopping Criteria	Removal of section	Based on available data, cardiac risk was determined to be low and routine monitoring was removed
Section 8.2.3. Corneal Event Stopping Criteria	Revision of header and language	Update to program language
Section 9 Study Assessments and Procedures	Revision of Language. Visit window updates: Removal of Echocardiogram window; addition of ocular exam window. Added that dosing should occur on same randomization call where possible. Separated instructions for pregnancy testing at screening and post screening.	Based on available data, cardiac risk was determined to be low and routine monitoring was removed; ocular window expanded for flexibility. Other changes were made for clarification
Section 9.1 Efficacy Assessments	Bone Marrow sample: added biopsy for screening, and biopsy or aspirate for disease response. Clarified when PET/CT is recommended for MRD negativity Added which assessment and sample will be collected for what clinical response Addition of language to clarify timeframe for disease assessments; additional wording to clarify length of intervention Added requirements for extramedullary disease assessment	Change in sample type; high assay failure due to hemodilution in bone marrow aspirate. Clarification Clarification Clarification
Section 9.2.3 Electrocardiograms	Removal of reference to QT withdrawal criteria (Section 8.2.2)	Section 8.2.2 removed
Previous Section 9.2.4. Echocardiogram	Removal of section	Based on available data, cardiac risk was determined to be low and routine monitoring was removed
Section 9.2.5 Clinical Safety Laboratory Assessments	Revision of timing of laboratory tests post last dose	Revision of End of Treatment visit and associated collection of laboratory results
Section 9.2.6. Ocular Examinations and Procedures	Revision of language	Update to program language
Section 9.2.6.1. Treatment Arm 1 – belantamab mafodotin	Revision of language	Update to program language
Section 9.2.7 Pregnancy Tests	Updated pregnancy test language and follow-up period in arm 1	Clarification and update to program language

Section # and Name	Description of Change	Brief Rationale
Section 9.2.8 Pomalidomide REMS/Pregnancy prevention/Controlled distribution program	Added counselling requirements	In alignment with REMS
Section 9.3.1. Time Period and Frequency for Collecting AE and SAE information	Update of timing for final collection of AEs and SAEs Rearrangement of paragraph	Update to program language To separate country specific requirements from study requirements
Section 9.3.3. Follow-up of AEs and SAEs	Revision of AE collection period for AEs	Revision of language to ensure all AEs, not just those of clinical interest, are followed until resolution
Section 9.3.5. Adverse Events of Special Interest	Revision of wording from corneal epithelium to corneal events	Revision of program corneal language
Section 9.3.6. Pregnancy	Removal of duplicated language for data collection post pregnancy	For clarification as all details are captured in Appendix 4
Previous Section 9.3.8. Disease Related Events and/or Disease Related Outcomes Not Qualifying as SAEs	Removal of section	Revision based on program decision
Section 9.4. Treatment of Overdose	Revision of timeframe for monitoring and addition of sBCMA sample for related PK sample	Revision of language and addition of sBCMA sample for PK samples
Section 9.5.1 Blood and Sample Collection for Pharmacokinetics	Revised enhanced PK population States that all samples will be tested regardless of dosing Revised who will perform analysis C [redacted]	To ensure 25% of evaluable sample will be available Clarification Clarification C [redacted]
Section 9.8 Biomarkers	Addition of potential sample use for assay development and/or diagnostics test Bone Marrow sample: replaced aspirate with biopsy for BCMA expression sample; clarified aspirate for other testing	Alignment with GSK scope of biomarker research Sample specification updated based on the intended assay
CCI [redacted]		
Section 9.9. Immunogenicity Assessments	Provided definition of ADA and updated who will perform analysis	Clarification
Section 9.11 Patient related Outcomes	Added language to allow interviewer-administered format	For added flexibility

Section # and Name	Description of Change	Brief Rationale
	The full EORTC-QLQ-MY20 will be implemented for participants enrolled under protocol amendment 1.	To allow a more comprehensive evaluation of belantamab mafodotin. For participant enrolled under the original protocol assessment of EORTC IL52 will continue.
CCI [redacted]		
Section 10.2. Sample Size Determination	Revision of calculations and wording	Removal of PFS Efficacy Interim Analysis adjusted the calculations and wording
Section 10.3 Populations for Analysis.	Added Table header to existing Table CCI [redacted]	For completeness CCI [redacted]
Section 10.4.1. Efficacy Analyses	Subgroup analysis correct from 'gender' to 'sex' Table 18: Primary Endpoint, removal of piecewise HR; additional analysis language added Table 18: Key Secondary removal of 250 death observation; additional analysis language added Table 18: TTP analysis not to be conducted with same approach as PFS analysis Table 18: MRD analysis moved from Exploratory to Secondary Table 18: removed MRD from derived analysis CCI [redacted]	In alignment with demographic data collected No longer applies. Provide additional information regarding analysis rules and populations Clarification that death events do not apply to analyses; Provide additional information regarding analysis rules and populations Stringency of analysis not needed as TTP is secondary endpoint Correction Correction CCI [redacted]
Section 10.4.2. Safety Analyses	Added header and numbered safety analysis table Table 19: Revision of AE collection period Table 19: Removal of ECG and ECHO wording	Clarification Revision of program language Assessments no longer apply
CCI [redacted]		
Section 10.4.4.3. Pharmacokinetic/ Pharmacodynamic Analyses	Revision of wording from corneal epithelium to corneal events Moved paragraph of North East Asia PK analysis from Section 10.4.4.3 to Section 10.4.4.2	Revision of program corneal language Correction
Section 10.5. Interim	Table 20: Revision of Table	Internal decision to remove this interim

Section # and Name	Description of Change	Brief Rationale
Analyses		analysis following regulatory agency comments.
	Table 20: Removal of PFS Efficacy information and Cumulative alpha spend	Revision of table to account for removal of PFS Efficacy interim analysis
	Primary Endpoint wording adjusted to account for removal of PFS Efficacy analysis	Revision to account for removal of PFS Efficacy interim analysis
	Key Secondary Endpoint: Addition of references to explain hierarchical testing; revision of stopping criteria during OS analyses; revision to Table 21 and Table 22	Clarifications added based on regulatory agency feedback
Section 10.5.1 IDMC	Addition of safety review timings	Clarification
Section 11	Moved Section of Supporting Documents in front of Reference Section	GSK standard
Section 11.1.7 Appendix 1: Data Quality Assurance	Updated Record retention section	GSK update to record retention
Section 11.2 Appendix 2: Clinical Laboratory Tests	Updated pregnancy testing interval and clarified specimen	Revision of program language
	Table 23: Revision of urinalysis wording; removal of Troponin and BNP and associated footnote	Update based on safety recommendations for program
	Table 23 Updated Biomarker and optional testing sections	Clarification which sample is used for biomarker research
Section 11.3.4. Recording and Follow-up of AE and SAE	Update of NCI-CTCAE version	Correction of Version from 4.03 to 5.0 due to error in original protocol
Section 11.4.2. Appendix 4: Contraception guidance	Added risk of fetal harm for belantamab mafodotin	Clarification
	Table 24: Added that local requirement must be followed if stricter	Clarification
Section 11.4.3. Collection of Pregnancy Information	Added that pregnant female partner follow-up occurs during pregnancy and after delivery	Clarification
	For arm 1: updated follow-up period for pregnancy information of female partner	Revision of program language Addition of information per pomalidomide supplier requirements
	For Arm 2, per requirements associated with Arm 2, follow-up of infant is to be 1 year	
Section 11.6 Appendix 6 Liver Safety: Required actions and Follow-up Assessments and Study	For reference PK sample, a sBCMA sample to be collected and timeframe for collection updated and associated footnotes	Revision of program language

Section # and Name	Description of Change	Brief Rationale
intervention Rechallenge Guidelines	Added headers for different criteria requiring different monitoring and follow-up; Added collection of GGT, GLDH and serum albumin to follow-up assessment; Added guidance on liver biopsy requirements	GSK requirement
Section 11.7, Appendix 7: Liver Safety Drug Restart or Rechallange Guidelines	New Appendix	Added to inform about the process after liver event as described in Appendix 6 occurred
Section 11.12 Appendix 12: Eye Care Specialist's Qualifications and Requirements	New Appendix to define the qualification and requirements - ophthalmologists, optometrists and eye care specialists	To ensure consistency in qualification for those completing the ocular examinations
Section 11.13 Appendix 13: Home Healthcare and Telemedicine Approaches	New Appendix to allow Home Healthcare and Telemedicine Approaches	To allow flexibility in study conduct
Section 11.14 Appendix 14: Country Specific Requirements	Addition of statement applicable to France that only ophthalmologists are to be utilized Included country specific amendments issued for the original protocol and still applicable in the protocol amendment 1 for Japan and China Addition of country specific exclusion criteria for Germany and France Addition of MRD sample requirements for China CCI [redacted]	Added per regulatory agency's request For completeness Added per regulatory agency's request To ensure OHGRA approval is obtained prior to MRD sample collection CCI [redacted]
Section 12 References	Moved reference section to end of protocol Added new references used in the updated Sections and updated IB version and Year	GSK standard For completeness

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