TITLE PAGE

Protocol Title: A Phase III, Multicenter, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of Belantamab Mafodotin in Combination with Pomalidomide and Dexamethasone (B-Pd) versus Pomalidomide plus Bortezomib and Dexamethasone (PVd) in Participants with Relapsed/Refractory Multiple Myeloma (DREAMM 8)

Protocol Number: 207499 Amendment 4

Compound Number: GSK2857916 (Belantamab Mafodotin)

Brief Title: A Phase III Study of Belantamab Mafodotin plus Pomalidomide and Dexamethasone vs. Pomalidomide, Bortezomib and Dexamethasone in Participants with RRMM

Study Phase: Phase 3

Acronym: DREAMM 8

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Approval Date: 28 Sep 2023

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 04	28 Sep 2023	TMF-16737343
Amendment 03	23 Feb 2023	TMF-15201205
Amendment 02	12 Jul 2022	TMF-14683895
Amendment 01	20 Apr 2021	TMF-12460807
Original Protocol	16 Apr 2020	2018N381008_00

Amendment 4: 28 Sep 2023

Where this Protocol Amendment applies:

Protocol Amendment 4 applies to all participants in all countries and all sites.

Overall Rationale for the Amendment 4:

The overall rationale for this protocol amendment is to delay the timing of the Primary PFS analysis, allowing for a longer duration of follow up and increasing OS data maturity at the time of Primary PFS analysis. Consequently, an interim analysis has been included prior to the Primary PFS analysis to allow for the opportunity to test for efficacy early. The delayed Primary PFS analysis and additional interim analysis for PFS result in an increase in the targeted number of PFS events and modified multiplicity strategy. Additional details regarding planned OS interim analyses have been included.

Updated sections of pharmacokinetics and pharmacodynamics in humans; updated benefit:risk assessment to align with the changes made in current belantamab mafodotin Investigator Brochure (IB); administrative updates were made to add clarification and/or remove discrepancies.

All changes are listed in table below.

Section # and Name	Description of Change	Brief Rationale
Headers, cover page, and Protocol Amendment Summary of Changes Table	Headers and cover page were updated with new document number; added an EU CT study number for EU CTR submission; and revised sponsor name from GSK to GlaxoSmithKline Protocol Amendment Summary of Changes Table section was created and populated to include details and rationale for this amendment	Editorial changes to align with the GSK's standard protocol template
Throughout	Administrative updates to add clarification and/or remove discrepancies	Editorial changes were made for accuracy, clarity, conformity, flow, and typographical error corrections
Section 1.1 Synopsis and Section 3 Objectives and Endpoints	Details of endpoint definitions expanded in alignment with definitions in Section 9.	Clarification
Section 1.1 Synopsis Section 6.1 Study Intervention(s) Administered	Clarification of definitions of experimental arm (B-Pd, Arm A) and active comparator arm (PVd, Arm B).	Clarification
Section 1.3 Schedule of Activities	Clarification of disease evaluations of sample collection and immunofixation test in Table 1 and Table 2. PD confirmation based on laboratory parameters must be performed from a different blood or 'urine' collection. Serum immunofixation must be performed each time that M-protein is not quantifiable by SPEP (0 g/dL). Urine immunofixation must be performed each time that M-protein is not quantifiable by UPEP (0 mg/24 h) AND SPEP (0 g/dL).	Clarification
Section 1.3 Schedule of Activities	Addition of a footnote in Table 1 and Table 2 for the frequency of Pregnancy Prevenstion Counselling after EoT. It must be performed in WOCBP at the EoT visit and at least 4 weeks following discontinuation of pomalidomide treatment, whichever comes last.	Clarification
Section 2.3 Human Experience with Belantamab Mafodotin	Updated with results from ongoing DREAMM studies.	Updated and added newly available information from the current IB.
Section 2.4 Benefit:Risk Assessment	Update of Risk Assessment table to reflect current information from the belantamab mafodotin program.	Updated information from the current IB.

Section # and Name	Description of Change	Brief Rationale
Section 3 Objectives and Endpoints and deletion of Section 10.1.11 Third Parties and Sub-Contractors	Deleted footnote regarding list of third parties and sub-contractors with cross-reference to now deleted Section 10.1.11.	Deleted Section 10.1.11 Third Parties and Sub-Contractors to avoid the necessity of protocol amendment due to vendor name change only.
Section 6.4 Study Intervention Compliance	Deleted "intravenously" for dose administration of bortezomib.	Correction of typographical error.
Section 7.2 7.2 Participant Withdrawal from the Study	Added “treatment” after the study. Participants who are withdrawn from the study TREATMENT because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study TREATMENT due to an AE/SAE until the event is resolved or considered clinically stable.	As there is no way a physician will follow up with the participant after they have withdrawn from the study/consent, protocol wording amended to withdrawn from the study TREATMENT instead of withdrawn from study/consent.
Section 7.3 Lost to Follow-up	Added “directly” in below sentence Sponsor personnel will not be DIRECTLY involved in any attempts to collect vital status information.	Clarification
Section 8 Study Assessments and Procedures	Added “Inclusion/exclusion criteria will be assessed during screening until enrollment. A participant is considered enrolled when the investigator or designee has confirmed, through the eligibility form, that all eligibility criteria have been met. Any interval change in the participant's clinical course (e.g., laboratory values, concomitant medications, clinical condition) between enrollment and the first dose of investigational product that could impact the ability of the participant to safely receive their first dose should be jointly discussed between the investigator and medical monitor prior to dosing”. Deleted reticulocyte count from Table 24 List of Clinical Laboratory Assessments.	Clarification of management of safety before the first study drug dose. Reticulocyte count deleted because not included in any planned analyses.
Section 8.2.7 Pregnancy Testing (WOCBP Only)	Clarifying documentation requirement of the pregnancy prevention program. Ensure counselling is completed and documented as required by applicable pregnancy prevention program.	Clarification
Section 9.1 Statistical Hypotheses	Section focused on hypotheses to be tested only. Removed reference to statistical assumptions and significance level for testing. Reordered endpoints to align with multiplicity strategy.	The inclusion of an interim analysis changes the multiplicity strategy, details were previously included in multiple places and are more appropriate to include in Section 9.2 and 9.3.

Section # and Name	Description of Change	Brief Rationale
Section 9.2 Multiple Comparisons and Multiplicity	Modified multiplicity strategy, acknowledging the importance of OS as a key secondary endpoint and accommodating the group sequential design. Further details to be provided in the SAP.	Inclusion of interim analyses and modified multiplicity strategy.
Section 9.3 Sample Size Determination	Sample size for PFS revised. Subsections for key secondary endpoints removed.	To permit a longer follow up, increase OS data maturity at the time of Primary PFS analysis/IA3 and account for PFS interim analysis for efficacy (IA1). Subsections for key secondary endpoints provided no additional value. The decision to revise sample size was independent of the planned sample size re-estimation per Section 9.3.2.
Section 9.5.1 Efficacy Analyses	Flexible wording added when defining subgroup analyses and stratum size. Removed redundant information that is defined in other sections of the protocol or clarified in the SAP. Removed reference to significance level for testing and added clarification of p-values and confidence intervals to be produced. Removed reference to 2L analysis. OS definition revised so that "Participants who are alive will be censored at the date last known alive" instead of at date of last contact.	To align with intent of analyses and provide sufficient information. To avoid repetition. Multiplicity strategy is defined in Section 9.2 and will be clarified in the SAP. A separate 2L analysis will no longer be performed due to increased follow-up for all participants. Intent of OS analysis has not changed, but wording clarified to allow the use of public records if applicable per local laws.
Section 9.6 Interim Analyses	Interim analyses for efficacy included. Tables of Stopping Boundaries for Interim Analysis for PFS Efficacy added. IA for harm (IA1) details clarified. Additional OS analyses considered. Added text to clarify that delegate(s) who are not involved in the study conduct may be unblinded for performing population PK and PKPD dataset preparation in support of planned analyses and PK display review. All other personnel will remain blinded to aggregate data by treatment group until database lock.	Interim analyses added to allow the opportunity to test for efficacy early. Given the revised targeted number of PFS events, clarified IA1 as this was planned under previous protocol assumptions and sample size. If requested, additional OS analyses may be required. To allow for sufficient time to prepare and conduct planned analyses.
Section 9.6.1 Independent Data Monitoring Committee	Section restructured and multiple interim analyses considered for IDMC review.	Addition of interim analyses for efficacy.

Section # and Name	Description of Change	Brief Rationale
Section 9.6.2 Sequence of Interim and Other Planned Analyses	IA for harm (IA1) details clarified. Interim analyses for efficacy included. Primary PFS analysis/IA3 and final analysis events and timing modified. 2L analysis removed.	Given the revised targeted number of PFS events, clarified IA1 as this was planned under previous protocol assumptions and sample size. Interim analyses added to allow the opportunity to test for efficacy early. Primary PFS analysis/IA3 and final analysis events and timing modified to permit a longer follow up and increase OS data maturity. 2L analysis is redundant with the increased follow up for Primary PFS analysis/IA3.
Section 10.1.4 Recruitment Strategy	Added section to clarify study recruitment	To align with EU CTR transition.
Section 10.1.11 Study and Site Start and Closure	Addition of First Act of Recruitment. Updated study/site termination.	To align with EU CTR transition.
Section 10.2.5 Reporting of Serious Adverse Events to GSK or Designee	Removed SAE coordinator.	The role was eliminated.
Section 10.4 Appendix 4: Required Actions, Follow-up Assessments, and Study Treatment Rechallenge Guidelines	Corrected footnote 2 to clarify that ALT ≥3×ULN.	Added "3" due to typographical error in previous amendments.
Section 10.9 Appendix 9: Progression-Free Survival Event and Censoring Rules	Clarifications added to table and footnotes 2, 3, and 5.	Clarification
Section 10.14 Abbreviations, Trademarks and Definitions of Terms	Addition of definitions of specialized terms in clinical study.	Clarification

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase III, Multicenter, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of Belantamab Mafodotin in Combination with Pomalidomide and Dexamethasone (B-Pd) versus Pomalidomide plus Bortezomib and Dexamethasone (PVd) in Participants with Relapsed/Refractory Multiple Myeloma (DREAMM 8)

Brief Title:

A Phase III Study of Belantamab Mafodotin plus Pomalidomide and Dexamethasone vs. Pomalidomide, Bortezomib, and Dexamethasone in Participants with RRMM

Rationale:

Multiple myeloma (MM) is a heterogeneous disease characterized by the clonal proliferation of plasma cells. A variety of drugs and combination treatments have been evaluated and were found effective in treating MM. These include immunomodulatory agents and proteasome inhibitors (PIs) that form the backbone of treatment regimens across all treatment lines.

The treatment paradigm of relapsed/refractory multiple myeloma (RRMM) is rapidly evolving with an increasing use of lenalidomide-based therapy as frontline treatment and pomalidomide in subsequent lines of therapy. Pomalidomide is an immunomodulatory drug with a similar structure to thalidomide and lenalidomide that binds to cereblon (CRBN). It is approved when administered with low-dose dexamethasone (pomalidomide in combination with dexamethasone; Pd) in the United States (US), European Union (EU), and a number of other countries worldwide for patients with RRMM who have received at least 2 prior therapies, including both lenalidomide and bortezomib and have demonstrated disease progression at last therapy. The Pd combination improved median progression-free survival (mPFS) for about 2 months over dexamethasone alone in patients with lenalidomide-resistant MM (4.0 vs. 1.9; hazard ratio [HR] 0.49; 95% confidence interval [CI]: 0.40, 0.61; $p<0.001$). The combination regimens of daratumumab or elotuzumab with Pd were also approved in the US for RRMM in patients who have been previously treated with at least 2 prior therapies including lenalidomide and a proteasome inhibitor.

With the increasing use of lenalidomide in first-line either in combination with other anti-myeloma drugs or as maintenance therapy after autologous stem cell transplant (ASCT), pomalidomide is also emerging as a second-line regimen for the treatment of RRMM. The combination of pomalidomide with twice-weekly bortezomib injected subcutaneously (SC) and low-dose dexamethasone (pomalidomide plus bortezomib and dexamethasone; PVd) given in 21-day cycles (i.e., every 3 weeks [q3w]) showed significantly improved clinical activity in a randomized Phase III trial (OPTIMISMM Study, N=559) in patients previously treated with lenalidomide and 1 to 3 prior lines of therapy. PVd reduced the risk of progression and death by 39% compared with

bortezomib plus dexamethasone (Vd) (HR: 0.61; 95% CI: 0.49, 0.77, p<0.0001) with a mPFS of 11.2 (vs. 7.1) months and an overall response rate (ORR) of 82% (vs. 50%), including 15.7% stringent complete response (sCR)/complete response (CR), 37% very good partial response (VGPR), and 29.5% partial response (PR). The safety profile was consistent with known toxicities associated with other immunomodulators, PIs, and dexamethasone combination regimens, mostly comprising myelosuppression, infections, and neuropathy. Based on these findings, PVd has been approved in the EU for the treatment of patients with at least 1 prior lines of therapy including lenalidomide. It is anticipated that the combination of PVd will become a standard of care (SoC) option for second line treatment of RRMM in other countries/regions.

Belantamab mafodotin is a humanized immunoglobulin G1 (IgG1) antibody-drug conjugate (ADC) that binds specifically to B-cell maturation antigen (BCMA), a target restricted to B-cells at later stages of differentiation, and expressed on tumor cells of all patients with MM. Efficacy and safety results from the first-time-in-human (FTIH) Study BMA117159 (DREAMM-1) have demonstrated that belantamab mafodotin administered as single agent at the 3.4 mg/kg q3w has the potential to be an effective treatment option with a novel mechanism of action (MOA) for patients with RRMM. However, a significant number of patients required dose delays and dose reductions to manage adverse events (AEs); most common AEs include thrombocytopenia and corneal events.

In the pivotal Phase II Study 205678 (DREAMM-2), belantamab mafodotin was further evaluated as monotherapy in RRMM patients at doses of 2.5 mg/kg and 3.4 mg/kg q3w and demonstrated meaningful clinical activity in patients with heavily pretreated RRMM. While both 2.5 and 3.4 mg/kg dose levels have a positive benefit:risk profile, the 2.5 mg/kg dose had a lower incidence of adverse events, less frequent dose delays and reductions, and with similar efficacy as the 3.4 mg/kg dose as measured by ORR, and therefore belantamab mafodotin monotherapy was approved by regulatory authorities at 2.5 mg/kg as an intravenous infusion once every 3 weeks in patients with RRMM.

Nonclinical data with belantamab mafodotin suggest significant added benefit (efficacy and survival) when combined with pomalidomide and/or dexamethasone in an established MM xenograft model. We hypothesize that the combination of belantamab mafodotin with Pd may result in significant additive or synergistic effects with acceptable toxicity profiles, establishing new global standard of care (SoC) regimens.

Belantamab mafodotin at multiple dose levels in combination with Pd every 4 weeks (q4w) is being evaluated for safety and efficacy in patients with RRMM in an ongoing Phase I/II study conducted by the Myeloma Canada Research Network (MCRN 007 or Study 209418).

The present study is evaluating whether the combined activity of belantamab mafodotin at 2.5 mg/kg in Cycle 1 (C1) and 1.9 mg/kg in Cycle 2 onwards (C2+) when administered in combination with Pd could potentially translate into clinically meaningful benefits compared to PVd in RRMM participants who are progressing on or after treatment with a lenalidomide-containing regimen.

Primary and Secondary Objectives and Endpoints:

Objectives	Endpoints
Primary	
To compare the efficacy of B-Pd with that of PVd in participants with RRMM	• Progression-Free Survival (PFS), defined as the time from randomization until the earliest date of PD based on IRC-assessment per IMWG criteria, or death due to any cause.
Key Secondary	
To further compare the efficacy of B-Pd with that of PVd in participants with RRMM	• Overall Survival (OS), defined as the interval of time from randomization to the date of death due to any cause. • Duration of Response (DoR), defined as the time from first documented evidence of PR or better until progressive disease (PD) or death due to any cause. Response will be based on IRC-assessment per IMWG criteria. • MRD negativity rate, defined as the percentage of participants who achieve MRD negative status (as assessed by NGS at 10^{-5} threshold) at least once during the time of confirmed CR or better response based on IRC-assessment per IMWG.

Objectives	Endpoints
Secondary	
To further assess the efficacy of B-Pd in terms of other efficacy outcomes in participants with RRMM	• Overall Response Rate (ORR), defined as the percentage of participants with a confirmed partial response (PR) or better (i.e., PR, VGPR, CR, and sCR) based on IRC-assessment per IMWG criteria. • Complete Response Rate (CRR), defined as the percentage of participants with a confirmed complete response (CR) or better (i.e., CR and stringent complete respone (sCR) based on IRC-assessment per IMWG criteria. • Very Good Partial Response (VGPR) or better rate, defined as the percentage of participants with a confirmed VGPR or better (i.e., VGPR, CR, and sCR) based on IRC-assessment per IMWG criteria. • Time to Best Response (TTBR), defined as the interval of time between the date of randomization and the earliest date of achieving best response among participants with a confirmed PR or better based on IRC-assessment per IMWG. • Time to Response (TTR), 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) based on IRC-assessment per IMWG. • Time to Progression (TTP), defined as the time from randomization until the earliest date of PD based on IRC-assessment per IMWG criteria, or death due to PD. • PFS2, defined as time from randomization to disease progression (investigator-assessed response) after initiation of new anti-myeloma therapy or death from any cause, whichever is earlier. If disease progression after new anti-myeloma therapy cannot be measured, a PFS event is defined as the date of discontinuation of new anti-myeloma therapy, or death from any cause, whichever is earlier.
To evaluate the safety and tolerability of B-Pd	• Incidence of AEs and changes in laboratory parameters • Ocular findings on ophthalmic exam
To describe the exposure to belantamab mafodotin after infusion	• Plasma concentrations of belantamab mafodotin, and cys-mcMMAF
To evaluate the PK of pomalidomide in combination with belantamab mafodotin and dexamethasone, in a subset of participants	• Derived PK parameter values, as data permit
To assess ADAs against belantamab mafodotin	• Incidence and titers of ADAs against belantamab mafodotin

Objectives	Endpoints
To evaluate the safety and tolerability of belantamab mafodotin based on self-reported symptomatic adverse effects when administered in combination with pomalidomide and dexamethasone	• Maximum post-baseline PRO-CTCAE score for each item attribute
To evaluate and compare changes in symptoms and HRQoL	• Change from baseline in HRQoL as measured by EORTC QLQ-C30, EORTC QLQ-MY20* and EORTC IL52*

Abbreviations: ADA=Anti-drug antibody; AE=adverse event; B-Pd=Belantamab mafodotin in combination with pomalidomide and dexamethasone; CR=complete response; CRR=complete response rate; cys-mcMMAF=Cysteine maleimidocaproyl monomethyl auristatin F; DoR=duration of response; EORTC IL52=European Organisation for Research and Treatment of Cancer Item Library 52; 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; HRQoL=Health-related Quality of Life; MRD=Minimal Residual Disease; NGS=next generation sequencing; ORR=Overall Response Rate; OS=Overall Survival; PFS=Progression-free Survival; PFS2=progression-free survival on subsequent line of therapy; PR=partial response; PRO CTCAE=Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PK=Pharmacokinetic(s); PVd=pomalidomide plus bortezomib and dexamethasone; RRMM=Relapsed/refractory multiple myeloma; sCR=Stringent Complete Response; TTBR=time to best response; TTP=Time to Disease 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 participants enrolled under protocol amendment 1.

Overall Design:

This study will evaluate the efficacy and safety of belantamab mafodotin in combination with pomalidomide and dexamethasone (B-Pd) compared with PVd in participants with RRMM previously treated with lenalidomide and at least 1 prior line of therapy.

Disclosure Statement:

This study is a parallel group study with 2 treatment arms and no masking.

Number of Participants:

Approximately 375 participants in Phase III will be screened to achieve approximately 300 participants randomized in a 1:1 ratio between the 2 arms.

If the number of participants required by local regulatory agencies is not recruited within the planned recruitment target, enrollment may continue in separate cohorts until the country enrollment requirements are met, 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. 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:

Following Screening, participants will be stratified based on the number of prior lines of therapy (1 vs. 2 /3 vs. ≥4), prior bortezomib treatment (yes or no) and prior anti-CD38 treatment (yes or no), and centrally randomized in a 1:1 ratio to Treatment Arm A or

Treatment Arm B. No more than 50% of participants with 2 or more prior lines of treatment will be enrolled. It is anticipated that no more than 15% of participants will be enrolled in with 4 or more prior lines of treatment. No cross-over between 2 study arms will be allowed.

Experimental Arm/Treatment Arm A (B-Pd): belantamab mafodotin 2.5 mg/kg in C1 and 1.9 mg/kg in C2+ (IV), pomalidomide 4 mg, and dexamethasone 40 mg, q4w

In Treatment Arm A, belantamab mafodotin will be administered intravenously (IV) at a single dose of 2.5 mg/kg on Day 1 (D1) of Cycle 1 and 1.9 mg/kg in Cycle 2 and beyond (2+) of every 28-day cycle (q4w). Pomalidomide will be taken orally 4 mg per day on Days 1-21 of each 28-day cycle. Dexamethasone will be administered orally at a dose of 40 mg per day on Days 1, 8, 15, and 22 of each 28-day cycle. For participants who are >75 years old or have comorbidities or are intolerant to dexamethasone 40 mg, dexamethasone may be administered at the lower dose of 20 mg in Arm A at the discretion of the investigator.

Active Comparator Arm/Treatment Arm B (PVd): Pomalidomide 4 mg, bortezomib 1.3 mg/m^2, and dexamethasone 20 mg, q3w

In Treatment Arm B, pomalidomide will be administered PO at 4 mg daily on Days 1 to 14 of each 21-day cycle (i.e., q3w), with bortezomib injected SC at 1.3 mg/m^2 on Days 1, 4, 8, and 11 of each 21-day cycle for Cycles 1 through 8 and on Days 1 and 8 of each 21-day cycle for Cycles 9 and beyond (Cycles 9+). Dexamethasone will be administered PO at a dose of 20 mg on the day of and day after bortezomib, q3w or on Days 1, 2, 4, 5, 8, 9, 11, and 12 for Cycles 1 through 8, and then on Days 1, 2, 8, and 9 for Cycles 9+. For participants who are >75 years old or have comorbidities or are intolerant to dexamethasone 20 mg, dexamethasone may be administered at the lower dose of 10 mg on the day of and day after bortezomib in Arm B at the discretion of the investigator.

Treatment will continue in both arms until progressive disease (PD), death, unacceptable toxicity, start of a new anti-myeloma therapy, withdrawal of consent, or end of the study, whichever occurs first. Dose delays or reductions may be required following potential drug-associated toxicities. Participants will be followed for PD and overall survival (OS).

End of Study Definition

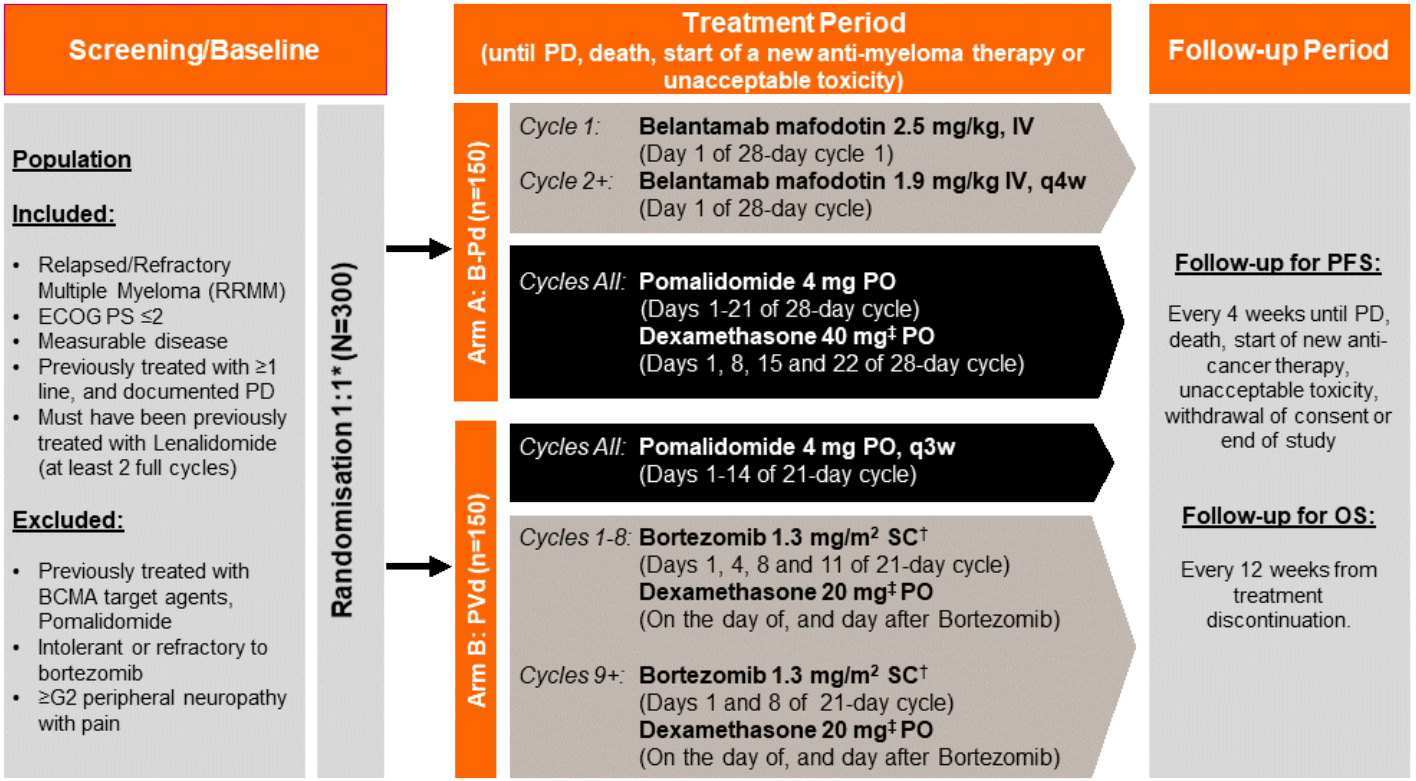
The final analysis data cut-off (DCO) is defined as 5 years from Last Participant First Visit (LPFV), or when all participants have died, withdrawn consent or have been lost to follow-up, whichever occurs first. The final analysis DCO represents the end of data collection. Following the final analysis, DREAMM-8 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 drug in the opinion of their treating physician may continue to receive study drug and only SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases, and pre-specified ocular data will be reported directly to GSK.

End of study is defined as the end of the safety follow-up following the last participant last dose i.e. the completion of the PACT phase.

Data Monitoring/Other Committee: Yes, refer to Section 10.1.6

1.2. Study Schema

Figure 1 Schematic of Study Structure



Abbreviations: PD=progressive disease; RRMM=relapsed/refractory multiple myeloma.
* Stratification: Prior lines of treatment (1 vs. 2 / 3 vs. ≥4), prior bortezomib treatment (yes or no) and prior anti-CD38 treatment (yes or no) . No more than 50% of participants with 2 or more prior lines of treatment will be enrolled. It is anticipated that no more than 15% of participants will be enrolled with 4 or more prior lines of treatment. No cross-over will be allowed.
† SC administration of bortezomib only
‡ Reduce the dose level of dexamethasone by half if age >75 years or have comorbidities or are intolerant to 40 mg dose in Arm A or 20 mg dose in Arm B, respectively.

1.3. Schedule of Activities (SoA)

Table 1 Treatment Arm A - Belantamab Mafodotin in Combination with Pomalidomide and Dexamethasone (B-Pd)

Screening assessments do not need to be repeated on C1D1 if conducted within 72 hours of C1D1 dosing, unless otherwise specified. Study treatment should be initiated within 72 hours after treatment allocation.

Precise timing of treatment cycles may vary due to treatment delays, but participants must still visit for efficacy assessments regularly, regardless of when they receive treatment. The schedule for efficacy assessments is q4w. These are referred to as 'fixed visits' or 'weeks visits' and should be scheduled from C1D1.

Assessments scheduled on days of dosing should be done prior to drug administration unless otherwise specified. All assessments should be carried out even if a participant is not dosed **except for the following**: vital signs, weight, pregnancy test, PK (with the exception of C2D1), and ADA.

The End of Treatment (EoT) Visit will occur within 30 days from the last cycle or prior to initiation of new anti-MM treatment, whichever occurs first. AEs and SAEs will be collected up to at least 70 days after the last dose, either via phone or a follow-up visit.

The progression-free survival (PFS) Follow-up Visit, (for participants who discontinue study treatment for a reason other than PD) should be conducted q4w (±3 days) until confirmed PD, death, unacceptable toxicity, start of a new anti-myeloma therapy, withdrawal of consent, or end of the study, whichever occurs first.

The overall survival (OS) Follow-up Visit will be performed in all participants who come off treatment completely. Participants will be followed for survival and subsequent anti-myeloma therapy by chart review, phone, or any form of communication every 12 weeks (±14 days) until the final analysis. Record the participant's survival status and whether subsequent treatment for disease was given. Participant does not need to attend the site. An exception is participants who have ocular symptoms at EoT who will be followed up for ocular examinations and OSDI questionnaire.

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 A only), and pregnancies will be reported directly to the Sponsor via paper forms (see Section 4.4, Section 6.7 and Section 8.3.1). For participant discontinuing treatment in the PACT phase, no end of treatment visit is required.

Procedure	**Screening**	**On Treatment**						**Follow-up**		
Cycle / Visit		**C1**		**C2 Onward**			**Fixed Visits q4w (Starting at Week 5)**	**EoT Visit**	**PFS Follow-up Visit**	**OS Follow-up Visit[26]**
				C2 Onward	**C2 Only**	**C3 Onward**				
Day		**D1**	**D8, 15, 22**	**D1**	**D8, 15, 22**	**D15**				
Window	**-28 days**	**±3 days (except D8, 15, and 22)**								±14 days
Informed Consent[1]	X									
Baseline Demographics	X									
Medical/Disease History and Characteristics	X									
Body Weight	X	X		X				X		
Height	X									

Procedure	**Screening**	**On Treatment**						**Follow-up**		
Cycle / Visit		**C1**		**C2 Onward**			**Fixed Visits q4w (Starting at Week 5)**	**EoT Visit**	**PFS Follow-up Visit**	**OS Follow-up Visit[26]**
				C2 Onward	**C2 Only**	**C3 Onward**				
Day		**D1**	**D8, 15, 22**	**D1**	**D8, 15, 22**	**D15**				
Window	**-28 days**	**±3 days (except D8, 15, and 22)**								±14 days
Safety										
ECOG Performance Status	X	X		X				X	X	
AEs/SAEs		AEs/SAEs will be collected from the start of study treatment until at least 70 days following EoT, regardless of initiation of new anti-myeloma therapy. SAEs related to study participation or any GSK product are collected from time of consent up to and including any follow-up.								
Concomitant Medications	Concomitant medications will be collected, as reported by the participant or through participant medical record review.									
Physical Examination[2]	X	X		X				X	X	
Ocular Examination[3]	X	X[3]		X				X	X[3]	X[3]
Vital Signs (BP, Heart Rate, Body Temperature)[4,5]	X	X		X				X		
12-Lead ECG[6]	X	As clinically indicated								
Laboratory Assessments[7]										
Hematology[5,8]	X	X	X	X	X	X		X	X	
Clinical Chemistry[8]	X	X	X	X	X	X		X	X	
HbA1c	As clinically indicated									
eGFR[9]	X	X		X				X		
Urinalysis (Dipstick) OR Spot Urine (Albumin/Creatine Ratio)[10]	X	X		X				X		
HbsAg, HbcAb, Hep C Ab, Hep C RNA[11]	X									
Pregnancy Test for WOCBP[12]	X	X		X				X	X	X
Disease Evaluations: Baseline disease assessments completed within 28 days (30 days for imaging) of C1D1 do not need to be repeated on C1D1. For participants who are discontinuing IP due to PD, confirmation based on laboratory parameters must be performed from a different blood or urine collection preferably within 14 days of the original date of the disease progression, preferably before institution of any new anti-myeloma therapy. This may be performed at the EoT Visit.										
β2 Microglobulin	X									
SPEP (Serum Protein Electrophoresis)	X	X					X	X	X	
UPEP (Urine Protein Electrophoresis on 24-hour Collected Urine)	X	X					X	X	X	
Serum Kappa Lambda Free LC, FLC Ratio	X	X					X	X	X	
Serum Immunofixation	X	Serum immunofixation must be performed each time that M-protein is not quantifiable by SPEP (0 g/dL)								
Urine Immunofixation	X	Urine immunofixation must be performed each time that M-protein is not quantifiable by UPEP (0 mg/24 h) AND SPEP (0 g/dL).								
Ca^{2+} Corrected for Albumin (Serum)	X	X					X	X	X	
IgG, IgM, IgA	X	X					X	X	X	

Procedure	**Screening**	**On Treatment**						**Follow-up**		
Cycle / Visit		**C1**		**C2 Onward**			**Fixed Visits q4w (Starting at Week 5)**	**EoT Visit**	**PFS Follow-up Visit**	**OS Follow-up Visit[26]**
				C2 Onward	**C2 Only**	**C3 Onward**				
Day		**D1**	**D8, 15, 22**	**D1**	**D8, 15, 22**	**D15**				
Window	**-28 days**	**±3 days (except D8, 15, and 22)**								±14 days
IgD/IgE[13]	X	X					X	X	X	
Imaging for Extramedullary Disease[14]	X	X					q12w for 1 year then as clinically indicated			
Skeletal Survey[15]	X	X	As clinically indicated							
Response Assessment by IMWG[16]							X	X	X	
PET/CT upon Achieving MRD Negativity by NGS		To be performed once and within 42 days of receiving MRD negative result (by NGS). In participants who achieved CR or better response by the time MRD negative result received.								
Bone Marrow Assessments										
BM Biopsy or Aspirate for BCMA Expression and Biomarker Research	Please refer to Table 3 for detailed schedule for BM collection procedures at all timepoints, including Screening									
BM Aspirate for FISH Testing										
BM Biopsy and/or Aspirate for Disease Assessment										
BM Aspirate for MRD Testing										
BM Biopsy to Confirm sCR by IHC										
Optional BM Sample at PD										
Treatments Administered										
Supportive Medications		Belantamab mafodotin: Premedication should be considered in any participant who experienced an IRR at the first or any subsequent infusion. Pomalidomide: Thromboprophylaxis recommended for the duration of treatment with pomalidomide based on an assessment of the participant's underlying risk factors and local prescribing information								
Belantamab Mafodotin[17]		Day 1 of every 28-day cycle								
Pomalidomide[18]		Days 1 – 21 of every 28-day cycle								
Dexamethasone[19]		Days 1, 8, 15, and 22 of every 28-day cycle								
Pregnancy Prevention Counselling	X	X		X				X[27]	X[27]	X[27]
Ocular Supportive Care for Belantamab Mafodotin										
Preservative-free Artificial Tears		Administered in each eye at least 4-8 times daily beginning on C1D1 until EoT. In the event of ocular symptoms (i.e., dry eyes), the use of artificial tears may be increased up to every 2 hours, as needed.								
Cooling Eye Masks		Apply cooling eye masks as long as tolerated, up to 4 hours								
Health Outcomes[20]										
PRO-CTCAE		X					X	X		
EORTC QLQ-C30		X					X	X	X[21]	X[22]
EORTC IL52[24]		X					X	X	X[21]	X[22]

Procedure	Screening	On Treatment						Follow-up		
Cycle / Visit		C1		C2 Onward			Fixed Visits q4w (Starting at Week 5)	EoT Visit	PFS Follow-up Visit	OS Follow-up Visit[26]
				C2 Onward	C2 Only	C3 Onward				
Day		D1	D8, 15, 22	D1	D8, 15, 22	D15				
Window	-28 days	±3 days (except D8, 15, and 22)								±14 days
EORTC QLQ-MY20[25]		X					X	X	X[21]	X[22]
EQ-5D-3L		X					X (q8w)	X	X[21]	X[22]
PGIS		X					X	X	X[21]	
PGIC							X	X	X[21]	
FACT-GP5		X					X	X		
OSDI[23]		X					X[23]	X	X[23]	X[23]
HCRU		X					X			
PK and ADA										
PK		On-treatment standard and enhanced PK sampling schedule can be found in Section 8.5.1 and Section 8.5.3						X		
ADA		On-treatment ADA sampling schedule can be found in Section 8.6						X		
Biomarkers										
Soluble BCMA	X	On-treatment standard and enhanced sBCMA sampling schedules can be found in Section 8.9.1								
Genetics										
Optional Genetic Sample		X	To be taken at C1D1 from participants who consent to genetic research after randomization. May be taken at another visit if not taken at C1D1.							
Other Follow-Up										
Safety Follow-up Phone Call										X
Subsequent Anti-MM Treatment									X	X

Abbreviations: ADA=anti-drug antibody; AE=adverse event; BCMA=B-cell maturation antigen; BM=bone marrow; BP=blood pressure; C=Cycle; CBC=complete blood count; CR=complete response; CT=computed tomography; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eGFR=estimated glomerular filtration rate; EOI=end of infusion; EORTC IL52=European Organization for Research and Treatment of Cancer Item Library 52; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item core module; EORTC QLQ-MY20=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myloma Module; EoT=End of Treatment; EQ-5D-3L=European Quality of Life 5 Dimensions 3 Level Scale; FACT-GP5=Functional Assessment of Cancer Therapy – General Population; FISH=fluorescence-in-situ hybridization; FLC=free light chain; HbA1c=hemoglobin A1c; HbcAb=Hepatitis B core antibody; HbsAg=Hepatitis B surface antigen; Hep C Ab=Hepatitis C antibody; Hep C RNA=Hepatitis C ribonucleic acid; HCRU=Healthcare Resource Utilization; ICF=Informed Consent Form; Ig=immunoglobulin.; IHC=immunohistochemistry; IMWG=International Myeloma Working Group; IP=Investigational Product; IRR=infusion-related reaction; LC=light chain; MDRD=Modified Diet in Renal Disease; MM=Multiple myeloma; MRD=Minimal Residual Disease; MRI=magnetic resonance imaging; NGS=Next-Generation Sequencing; OS=Overall Survival; OSDI=Ocular Surface Disease Index; PD=progressive disease; PET/CT=positron emission tomography/computed tomography; PFS=progression-free survival; PGIC=Patient Global Impression of Change, PGIS=Patient Global Impression of Severity, PK=Pharmacokinetic(s); PRO=patient-reported outcome; PRO-CTCAE=Patient-Reported Outcomes version of the Common Term Criteria for Adverse Events; q12w=every 12 weeks; q4w=every 4 weeks; q8w=every 8 weeks; SAE=serious adverse event; sBCMA=soluble B-cell maturation antigen; sCR=stringent complete response; SOI=Start of Infusion; SPEP=Serum Protein Electrophoresis; SRM=Study Reference Manual; UPEP=Urine Protein Electrophoresis; VGPR=Very Good Partial Response; WOCBP=Woman of Childbearing Potential.

1. ICF must be signed before any study-specific assessments are performed; the day the informed consent form is signed will be counted as Day 1 and the screening window of 28 days will initiate on this Day 1 as well. Assessments performed as standard of care prior to signing consent need not be repeated if done within the appropriate screening window. A separate informed consent required

for optional samples. For optional samples, a blood sample will be taken at C1D1. The blood sample may be collected at another visit if not taken at C1D1. A redraw can be requested if the sample is not availableor of insufficient quality to perform the analysis.

2. Physical examination assessments are listed in Section 8.2.1. Physical examination must be within 72 hours prior to first dose of study drugs to be administered in that cycle.
3. C1D1 ocular examination does not need to be repeated if within 28 days of Screening examination. On treatment ocular examinations to be performed q4w, prior to dosing, up to the 6th dose of belantamab mafodotin. Ocular examination shall be performed up to 5 days prior to dosing. After the 6th dose of belantamab mafodotin, if there have been no significant ocular exam findings, symptoms or vision changes up to and including the 6th dose, the frequency of ocular examinations may be decreased to every 3 months until EoT. In case of persistent or newly developed ocular symptoms or vision changes, participants will have further ocular examinations, at least every cycle, until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by the eye care specialist. See Section 8.2.6 and for full details of ophthalmic examination procedures. Participants in PFS follow-up will only have ocular examinations if they had signs or symptoms at EoT or as clinically indicated.
4. At the first dose of belantamab mafodotin, vital signs must be assessed within 30 minutes prior to SOI, 15 minutes after SOI, (±10 minutes), within 15 minutes after EOI, and at 1 hour (±10 minutes) after EOI. On subsequent doses of belantamab mafodotin, vital signs must be assessed within 30 minutes prior to SOI and within 15 minutes after EOI. Vital signs should be measured after resting for at least 5 minutes. On days when vital sign time points align with blood sampling time points, it is recommended that vital signs be assessed prior to blood samples being drawn. On days when vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.
5. Hematology and vital signs must be repeated prior to each dose of belantamab mafodotin treatment.
6. Single ECG at Screening..
7. All laboratory assessments with values considered clinically significantly abnormal during participation in the study and up to at least 70 days after the last dose of study treatment should be repeated until the values return to normal or baseline. Refer to Table 24 for a comprehensive list of laboratory assessments. If laboratory assessments are completed within 72 hours prior to the first dose, these assessments need not be repeated on C1D1.
8. Hematology (CBC) and clinical chemistry should be performed weekly for the first 2 cycles (i.e., D1, 8, 15, and 22 for 8 weeks) and as clinically indicated; thereafter, CBC and clinical chemistry laboratory assessments should be performed on D1 and 15 of every 28-day cycle for C3+ and prior to every belantamab mafodotin administration. Testing may be performed up to 72 hours prior to administration of study treatment. Results must be evaluated prior to treatment administration.
9. eGFR as calculated by Modified Diet in Renal Disease (MDRD) formula (Section 10.7).
10. Urine dipstick 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 ≥2+ On Treatment, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local laboratory. If local testing is not available, then central testing will be performed (first void).
11. Hepatitis B virus DNA testing will be done to determine a participant's eligibility if HBcAb and/or HBsAg is positive. Hepatitis C virus RNA testing will be done to determine participant eligibility if Hepatitis C Ab-positive. This will be performed at a local laboratory or, if not available, then at a central laboratory. For additional procedures during Screening and upon enrolment for participants who have a history of Hepatitis B and/or Hepatitis C, please refer to Table 4 and Table 5, respectively.
12. Perform only in women of childbearing potential (WOCBP), see Appendix 3 for definition. A serum pregnancy test must be performed at Screening. Two negative serum pregnancy tests must be obtained prior to initiating treatment; the first test should be performed within 10-14 days of C1D1, but the second must be performed within 24 hours of C1D1. After the first dose, pregnancy test will be done weekly during the first month, then every cycle thereafter (or every 2 weeks in females with irregular menses). Subsequent pregnancy test on dosing days may be either serum or urine test. Each pregnancy test must be performed within 24 hours prior to dosing. Final pregnancy test (serum or urine) must be performed in WOCBP at the EoT Visit and at 2 weeks (in females with irregular menses) and 4 weeks following treatment discontinuation, and repeated at least 70 days after last dose. Follow-up pregnancy assessment by phone (for WOCBP only) should be performed 4 months after the last dose of belantamab mafodotin.
13. Only in participants with IgD/IgE myeloma.
14. Imaging is only required for participants with extramedullary disease by either CT, MRI, or PET/CT. Screening assessment may be performed up to 30 days prior to C1D1. Subsequently imaging should be performed every 12 weeks within the first 12 months (at Weeks 13, 25, 37, and 49, ±7 days); thereafter only if clinically indicated, per local guidance. The same modality should be used throughout the study as was done at Baseline. Selected target lesion should be measured and followed over time. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, MRI scans, or dedicated CT scans, where applicable. For participants with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the sum of the products of the maximal perpendicular diameters of measured lesions. Digital copies of all scans must be maintained at investigator site as source document. Participants undergoing PET/CT should have all blood samples taken before the PET/CT is performed.

For participants with PD due to extramedullary disease, confirmation scans are not required. The laboratory assessments 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 participant's withdrawal from study treatment, and PD has NOT been documented, a new assessment for extramedullary disease should be obtained at EoT. If participant continues in PFS follow-up, perform scans for extramedullary disease as clinically indicated. Optional tissue sample from extramedullary tumor may be collected at PD (Table 3).

15. Imaging of bones for lytic lesions by method aligned with institutional guidance (e.g., X-ray, CT, or MRI). Survey results within 30 days prior to C1D1 date are acceptable. At later cycles, repeat as clinically indicated, or if worsening clinical symptoms suggest PD, by the same method used as at Screening. Sites shall maintain an archive of all study-related images/scans as source documentation.
16. Response to treatment will be assessed q4w (±3 days) regardless of dosing, based on laboratory assessments and imaging (if applicable), using IMWG criteria [Kumar, 2016].
17. Belantamab mafodotin 2.5 mg/kg will be administered on Day 1 of Cycle 1 and 1.9 mg/kg in Day 1 of C2 onwards every 28-day cycle as an IV infusion over at least 30 minutes (see Pharmacy Manual for details). A window of ±3 days is acceptable for administration of study treatment after C1D1. Refer to Section 6.6.1 and Section 6.7.1 for instructions on dose delays and dose modification guidelines.
18. Pomalidomide 4 mg PO daily on Days 1-21 of each 28-day cycle to be taken after the 1hr rest period after belantamab mafodotin. Platelet count must be ≥50,000 per μL to initiate new cycle. Refer to Section 6.6.1 and Section 6.7.1 for instructions on dose delays and dose modification guidelines.
19. Dexamethasone 40 mg PO on Days 1, 8, 15, and 22 of every 28-day cycle. For participants who are >75 years, have comorbidities, or are intolerant to 40 mg, the dose of dexamethasone can be reduced to 20 mg in Arm A. Refer to Section 6.6.1 and Section 6.7.1 for instructions on dose delays and dose modification guidelines. On days where only pomalidomide and dexamethasone are taken at home, they should be taken in the morning approximately at the same time each day. On belantamab mafodotin dosing days, dexamethasone should be administered 1 to 3 hours prior to the first administration of belantamab mafodotin. Participant diaries will be used to keep a record of self-administered oral study treatment(s) at home.
20. PRO-CTCAE, EORTC QLQ-C30, EORTC QLQ-MY20, EORTC IL52, FACT-GP5, PGIS, and PGIC, should be collected q4w regardless of treatment and at EoT. EQ-5D3L should be collected q8w regardless of treatment and at EoT. All PROs should be administered prior to any assessments being performed and prior to results being provided to the participant. PRO collection will start at C1D1 with the exception of the PGIC which will start at Week 5.
21. EORTC QLQ-C30, EORTC QLQ-MY20, EORTC IL52, EQ-5D-3L, PGIS, and PGIC will be administered q8w after EoT whilst in PFS follow-up.
22. EORTC QLQ-C30, EORTC QLQ-MY20, EORTC IL52, and EQ-5D-3L should be administered at 12, 24, and 48 weeks in the OS follow-up. For participants in OS follow-up not attending the site, they can be administered via a phone call in an interview format.
23. OSDI should be collected prior to any treatment administration on C1D1, then q4w up to Week 21 and thereafter q8w post Week 21 until EoT. Participants in Arm A with no ocular signs at the EoT ocular assessment will have no further OSDI collection. Participants in Arm A with ocular signs at the EoT ocular assessment will have OSDI collected q12w until resolution to Grade 1 or baseline or more frequently as clinically indicated by the eye care specialist. For participants in OS follow-up not attending the site, they can be administered via a phone call in an interview format.
24. Only applicable for participants enrolled under the original protocol.
25. Only applicable for participants enrolled under protocol amendment 1.
26. GSK may request that updated survival data be collected on all treated/randomized participants outside the protocol window noted in the SoA. At the time of the request, the site will determine survival status for each participant by the method agreed with the participant, unless the participant has withdrawn consent for survival follow up. Where permitted, data from publically available death registers will be used for participants withdrawn from study or lost to follow-up prior to death.
27. Final Pregnancy Prevention Counselling must be performed in WOCBP at the EoT visit and/or at least 4 weeks following discontinuation of pomalidomide treatment, whichever comes last.

Table 2 Treatment Arm B – Pomalidomide Plus Bortezomib and Dexamethasone (PVd)

Screening assessments do not need to be repeated on C1D1 if conducted within 72 hours of C1D1 dosing, unless otherwise specified. Study treatment should be initiated within 72 hours after treatment allocation.

Precise timing of treatment cycles may vary due to treatment delays, but participants must still visit for efficacy assessments regularly, regardless of when they receive treatment. The schedule for efficacy assessments is q4w. These are referred to as 'fixed visits' or 'weeks visits' and should be scheduled from C1D1.

Assessments scheduled on days of dosing should be done prior to drug administration unless otherwise specified. All assessments should be carried out even if a participant is not dosed **except for the following**: vital signs, weight, and pregnancy test.

The end of treatment (EoT) Visit will occur within 30 days from the last cycle or prior to initiation of new anti-MM treatment, whichever occurs first. AEs and SAEs will be collected up to at least 70 days after the last dose, either via phone or a follow-up visit.

The progression-free survival (PFS) Follow-up Visit (for participants who discontinue study treatment for a reason other than PD) should be conducted q4w (±3 days) until confirmed PD, death, unacceptable toxicity, start of a new anti-myeloma therapy, withdrawal of consent, or end of the study, whichever occurs first.

The overall survival (OS) Follow-up Visit will be performed in all participants who come off treatment completely. Participants will be followed for survival and subsequent anti-myeloma therapy by chart review, phone, or any form of communication every 12 weeks (±14 days) until the final analysis. Record the participant's survival status and whether subsequent treatment for disease was given. Participant does not need to attend the site.

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 A only), and pregnancies will be reported directly to the Sponsor via paper forms (see Section 4.4, Section 6.7 and Section 8.3.1). For participant discontinuing treatment in the PACT phase, no end of treatment visit is required.

Procedure	**Screening**	**On Treatment**					**Follow-up**		
Cycle / Visit		**C1-8**		**C9 Onward**		**Fixed Visits q4w Starting Week 5**	**EoT Visit**	**PFS Follow-Up Visit**	**OS Follow-Up Visit[26]**
Day		**D1**	**D4, 8, 11**	**D1**	**D8**				
Window	**-28 days**	**±3 days (except D4, 8, and 11)**							**±14 days**
Informed Consent[1]	X								
Baseline Demographics	X								
Medical/Disease History and Characteristics	X								
Body Weight	X	X		X			X		
Height	X								
Safety									
ECOG Performance Status	X	X		X			X	X	
AEs/SAEs		AE/SAEs will be collected from the start of study treatment until at least 70 days following EoT, regardless of initiation of new anti-myeloma therapy. SAEs related to study participation or any GSK product are collected from time of consent up to and including any follow-up.							
Concomitant Medications	Concomitant medications will be collected, as reported by the participant or through participant medical record review.								

Procedure	Screening	On Treatment					Follow-up		
Cycle / Visit		C1-8		C9 Onward		Fixed Visits q4w Starting Week 5	EoT Visit	PFS Follow-Up Visit	OS Follow-Up Visit[26]
Day		D1	D4, 8, 11	D1	D8				
Window	**-28 days**	**±3 days (except D4, 8, and 11)**							**±14 days**
Physical Examination[2]	X	X		X			X	X	
Ocular Examination[3]	X	X[3]		X			X		
Vital Signs (BP, Heart Rate, Body Temperature)[4,5]	X	X		X			X		
12-Lead ECG[6]	X	As clinically indicated							
Laboratory Assessments[7]									
Hematology[5,8]	X	X	X	X	X		X	X	
Clinical Chemistry[8]	X	X	X	X	X		X	X	
HbA1c	As clinically indicated								
eGFR[9]	X	X		X			X		
Urinalysis (Dipstick) OR Spot Urine (Albumin/Creatinine Ratio)[10]	X	X		X			X		
HbsAg, HbcAb, Hep C Ab, Hep C RNA[11]	X								
Pregnancy Test for WOCBP[12]	X	X		X			X	X	X
Disease Evaluations: Baseline disease assessments completed within 28 days (30 days for imaging) of C1D1 do not need to be repeated on C1D1. The efficacy assessments need to be completed q4w starting Week 5. For participants who are discontinuing IP due to PD, confirmation based on laboratory parameters must be performed from a different blood or urine collection preferably within 14 days of the original date of the PD, preferably before institution of any new anti-MM therapy. This may be performed at the EoT Visit.									
β2 Microglobulin	X								
SPEP (Serum Protein Electrophoresis)	X	X (C1D1)				X	X	X	
UPEP (Urine Protein Electrophoresis on 24-hour Collected Urine)	X	X (C1D1)				X	X	X	
Serum Kappa Lambda Free LC, FLC Ratio	X	X (C1D1)				X	X	X	
Serum Immunofixation	X	Serum immunofixation must be performed each time that M-protein is not quantifiable by SPEP (0 g/dL)							
Urine Immunofixation	X	Urine immunofixation must be performed each time that M-protein is not quantifiable by UPEP (0 mg/24 h) AND SPEP (0 g/dL).							
Ca^{2+} Corrected for Albumin (Serum)	X	X (C1D1)				X	X	X	
IgG, IgM, IgA	X	X (C1D1)				X	X	X	
IgD/IgE[13]	X	X (C1D1)				X	X	X	
Imaging for Extramedullary Disease[14]	X	X (C1D1)				q12w for 1 year then as clinically indicated			

Procedure	**Screening**	**On Treatment**					**Follow-up**		
Cycle / Visit		**C1-8**		**C9 Onward**		**Fixed Visits q4w Starting Week 5**	**EoT Visit**	**PFS Follow-Up Visit**	**OS Follow-Up Visit[26]**
Day		**D1**	**D4, 8, 11**	**D1**	**D8**				
Window	**-28 days**	**±3 days (except D4, 8, and 11)**							**±14 days**
Skeletal Survey[15]	X	X (C1D1)		As clinically indicated					
Response Assessment by IMWG[16]						X	X	X	
PET/CT upon Achieving MRD Negativity by NGS		To be performed once and within 42 days of receiving MRD negative result (by NGS). In participants who achieved CR or better response by the time MRD negative result received.							
Bone Marrow Assessments	Please refer to Table 3 for detailed schedule for BM collection procedures at all timepoints, including Screening								
BM Biopsy or Aspirate for BCMA Expression and Biomarker Research									
BM Aspirate for FISH Testing									
BM Biopsy and/or Aspirate for Disease Assessment									
BM Aspirate for MRD Testing									
BM Biopsy to Confirm sCR by IHC									
Optional BM Sample at PD									
Treatments Administered									
Supportive Medications		Bortezomib: Antiviral prophylaxis recommended for the duration of treatment with bortezomib in accordance with local prescribing information. Pomalidomide: Thromboprophylaxis recommended for the duration of treatment with pomalidomide based on an assessment of the participant's underlying risk factors and local prescribing information.							
Pomalidomide[17]		Days 1 –14 of each 21-day cycle							
Bortezomib[18]		Cycles 1-8: Days 1, 4, 8, and 11 of each 21-day cycle, Cycle 9+: Day 1 and 8 of each 21-day cycle							
Dexamethasone[19]		Cycles 1-8: Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle Cycle 9+: Days 1,2 ,8, and 9 of each 21-day cycle							
Pregnancy Prevention Counselling	X	X		X			X[27]	X[27]	X[27]
Health Outcomes[20]									
PRO-CTCAE		X				X	X		
EORTC QLQ-C30		X				X	X	X[21]	X[22]
EORTC IL52[24]		X				X	X	X[21]	X[22]
EORTC QLQ-MY20[25]		X				X	X	X[21]	X[22]
EQ-5D-3L		X				X (q8w)	X	X[21]	X[22]
PGIS		X				X	X	X[21]	
PGIC						X	X	X[21]	

Procedure	Screening	On Treatment					Follow-up		
Cycle / Visit		C1-8		C9 Onward		Fixed Visits q4w Starting Week 5	EoT Visit	PFS Follow-Up Visit	OS Follow-Up Visit[26]
Day		D1	D4, 8, 11	D1	D8				
Window	**-28 days**	**±3 days (except D4, 8, and 11)**							**±14 days**
FACT-GP5		X				X	X		
OSDI[23]		X				X	X[23]		
HCRU		X				X			
Biomarkers									
Soluble BCMA	X	sBCMA sampling schedule can be found in Section 8.9.1							
Optional Genetics									
Optional Genetic Sample		X	To be taken at C1D1 from participants who consent to genetic research after randomization. May be taken at another visit if not taken at C1D1.						
Other Follow-Up									
Safety Follow-up Phone Call									X
Subsequent Anti-MM Treatment								X	X

Abbreviations: AE=adverse event; BCMA=B-cell maturation antigen; BM=bone marrow; BP=blood pressure; C=Cycle; CR=complete response; CT=computed tomography; D=Day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eGFR=estimated glomerular filtration rate; EORTC IL52=European Organization for Research and Treatment of Cancer Item Library 52; EORTC QLQ-C30=European Organization 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; EQ-5D-3L=European Quality of Life 5 Dimensions 3 Level Scale; FACT-GP5=Functional Assessment of Cancer Therapy – General Population; FISH=fluorescence-in-situ hybridization; FLC=free light chain; HbA1c=hemoglobin A1c; HbcAb=hepatitis B core antibody; HbsAg=hepatitis B surface antigen; Hep C Ab=Hepatitis C antibody; Hep C RNA=Hepatitis C ribonucleic acid; HCRU=Healthcare Resource Utilization; ICF=Informed Consent Form; Ig=immunoglobulin.; IHC=immunohistochemistry; IMWG=International Myeloma Working Group; IP=Investigational Product; LC=light chain; MDRD=Modified Diet in Renal Disease; MM=multiple myeloma; MRD=Minimal Residual Disease; MRI=Magnetic Resonance Imaging; NGS=next-generation sequencing; OS=Overall Survival; OSDI=Ocular Surface Disease Index; PD=progressive disease; PET/CT=positron emission tomography/computed tomography; PFS=progression-free survival; PGIC=Patient Global Impression of Change, PGIS=Patient Global Impression of Severity; PRO=patient-reported outcome; PRO-CTCAE=Patient-Reported Outcomes version of the Common Term Criteria for Adverse Events; PVd=pomalidomide plus bortezomib and dexamethasone; q12w=every 12 weeks; q4w=every 4 weeks; q8w=every 8 weeks; QTcF=QT interval corrected using Fridericia's formula; SAE=serious adverse event; sBCMA=soluble B-cell maturation antigen; sCR=stringent complete response; SPEP=serum protein electrophoresis; UPEP=Urine Protein Electrophoresis; VGPR=Very Good Partial Response; WOCBP=Woman of Childbearing Potential.

1. ICF must be signed before any study-specific assessments are performed; the day the informed consent form is signed will be counted as Day 1 and the screening window of 28 days will initiate on this Day 1 as well. Assessments performed as standard of care prior to signing consent need not be repeated if done within the appropriate screening window. A separate informed consent required for optional samples. For optional samples, a blood sample will be taken at C1D1. The blood sample may be collected at another visit if not taken at C1D1. A redraw can be requested if the sample is not available of insufficient quality to perform the analysis.
2. Physical examination assessments are listed in Section 8.2.1. Physical examination must be within 72 hours prior to first dose of study drugs to be administered in that cycle.
3. C1D1 ocular examination does not need to be repeated if within 28 days of the Screening examination. On treatment ocular examinations to be performed every 6 months (± 4 weeks window) or as clinically indicated and at the EoT. See Section 8.2.6 for full details of ophthalmic examination procedures
4. Vital signs must be assessed within 30 minutes before and within 15 minutes after each dose of bortezomib. Vital signs should be measured after resting for at least 5 minutes.
5. Hematology and vital signs must be repeated prior to each dose of PVd treatment.
6. Single ECG at Screening

7. All laboratory assessments with values considered clinically significantly abnormal during participation in the study up to at least 70 days after the last dose of study treatment should be repeated until the values return to normal or baseline. Refer to Table 24 for a comprehensive list of laboratory assessments. If laboratory assessments are completed within 72 hours prior to the first dose, these assessments need not be repeated on C1D1.
8. Hematology and clinical chemistry must be repeated prior to each dose of bortezomib on D1, 4, 8, and 11 of each 21-day cycle for C1 to 8 and then on D1 and 8 of each 21-day cycle for C9+. If laboratory assessments are completed within 72 hours prior to the first dose, these assessments need not be repeated on C1D1. Results must be evaluated prior to treatment administration. Refer to Table 24 for a comprehensive list of laboratory assessments.
9. eGFR as calculated by Modified Diet in Renal Disease (MDRD) formula (Section 10.7).
10. Urine dipstick 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 ≥2+ On Treatment, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local laboratory. If local testing is not available, then central testing will be performed (first void).
11. Hepatitis B virus DNA testing will be done to determine a participant's eligibility if HBcAb and/or HBsAg is positive. Hepatitis C virus RNA testing will be done to determine participant eligibility if Hepatitis C Ab-positive. This will be performed at a local laboratory or, if not available, then at a central laboratory. For additional procedures during Screening and upon enrolment for participants who have a history of Hepatitis B and/or Hepatitis C, please refer to Table 4 and Table 5, respectively.
12. Perform only in women of childbearing potential (WOCBP), see Appendix 3 for definition. A serum pregnancy test must be performed at Screening. Two negative serum pregnancy tests must be obtained prior to initiating treatment; the first test should be performed within 10-14 days of C1D1, but the second must be performed within 24 hours of C1D1. After the first dose, pregnancy test will be done weekly during the first month, then every cycle thereafter (or every 2 weeks in females with irregular menses). Subsequent pregnancy test on dosing days may be either serum or urine test. Each pregnancy test must be performed within 24 hours prior to dosing. Final pregnancy test (serum or urine) must be performed in WOCBP at the EoT Visit and at 2 weeks (in females with irregular menses) and 4 weeks following treatment discontinuation, and repeated at least 70 days after last dose. Follow-up pregnancy assessment by phone (for WOCBP only) should be performed 7 months after the last dose of bortezomib.
13. Only in participants with IgD/IgE myeloma.
14. Imaging is only required for participants with extramedullary disease by either CT, MRI, or PET/CT. Screening assessment may be performed up to 30 days prior to C1D1. Subsequent imaging should be performed every 12 weeks within the first 12 months (at Weeks 13, 25, 37, and 49, ±7 days); thereafter only if clinically indicated, per local guidance. The same modality should be used throughout the study as was done at Baseline. Selected target lesion should be measured and followed over time. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, MRI scans, or dedicated CT scans, where applicable. For participants with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the sum of the products of the maximal perpendicular diameters of measured lesions. Digital copies of all scans must be maintained at investigator site as source document. Participants undergoing PET/CT should have all blood samples taken before the PET/CT is performed.
    For participants with PD due to extramedullary disease, confirmation scans are not required. The laboratory assessments 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 participant's withdrawal from study treatment, and PD has NOT been documented, a new assessment for extramedullary disease should be obtained at EoT. If participant continues in PFS follow-up, perform scans for extramedullary disease as clinically indicated. Optional tissue sample from extramedullary tumor may be collected at PD (Table 3).
15. Imaging of bones for lytic lesions by method aligned with institutional guidance (e.g., X-ray, CT, or MRI). Survey results within 30 days prior to C1D1 date are acceptable. At later cycles, repeat as clinically indicated, or if worsening clinical symptoms suggest PD, by the same method used as at Screening. Sites shall maintain an archive of all study-related images/scans as source documentation.
16. Response to treatment will be assessed q4w (±3 days) regardless of dosing, based on laboratory assessments and imaging (if applicable), using IMWG criteria [Kumar, 2016].
17. Pomalidomide administration 4 mg PO daily on Days 1-14 of each 21-day cycle. Platelet count must be ≥50,000 per μL to initiate a new cycle. Refer to Section 6.6.2 and Section 6.7.2 for instructions on dose delays and dose modification guidelines.
18. Bortezomib 1.3 mg/m^2 (SC only). Bortezomib administered on Days 1, 4, 8, and 11 of every 21-day cycle in Cycles 1 to 8 and then on Days 1 and 8 of every 21-day cycle in Cycles 9 and beyond (C9+). Refer to Section 6.6.2 and Section 6.7.2 for instructions on dose delays and dose modification guidelines.
19. Dexamethasone 20 mg PO will be given on D1, 2, 4, 5, 8, 9, 11 and 12 of every 21-day cycle for C1 to 8 and on D1, 2, 8 and 9 of each 21-day cycle for C9+. For participants who are >75 years, have comorbidities, or are intolerant to 20 mg, the dose of dexamethasone can be reduced to 10 mg in Arm B. Refer to Section 6.6.2 and Section 6.7.2 for instructions on dose delays and dose

modification guidelines. On days where only pomalidomide and dexamethasone are taken at home, they should be taken in the morning approximately at the same time each day. Participant diaries will be used to keep record of self-administered oral study treatment(s) at home.

20. PRO-CTCAE, EORTC QLQ-C30, EORTC QLQ-MY20 EORTC IL52, FACT-GP5, PGIS, and PGIC should be collected q4w regardless of treatment and at EoT. EQ-5D3L should be collected q8w regardless of treatment and at EoT. All PROs should be administered prior to any assessments being performed and prior to results being provided to the participant. PRO collection will start at C1D1 with the exception of the PGIC which will start at Week 5.
21. EORTC QLQ-C30, EORTC QLQ-MY20, EORTC IL52, EQ-5D-3L, PGIS, and PGIC will be administered q8w after EoT whilst in PFS follow-up.
22. EORTC QLQ-C30, EORTC QLQ-MY20, EORTC IL52 and EQ-5D-3L should be administered at 12, 24, and 48 weeks in the OS follow-up. For participants in OS follow-up not attending the site, they can be administered via a phone call in an interview format.
23. OSDI should be collected prior to any treatment administration on C1D1, then q4w up to Week 21 and thereafter q8w weeks post Week 21 until EoT, and at EoT. EQ-5D-3L should be administered q8w on treatment. During PFS/OS follow-up, there will be no collection of OSDI in Arm B.
24. Only applicable for participants enrolled under the original protocol.
25. Only applicable for participants enrolled under protocol amendment 1.
26. GSK may request that updated survival data be collected on all treated/randomized participants outside the protocol window noted in the SoA. At the time of the request, the site will determine survival status for each participant by the method agreed with the participant, unless the participant has withdrawn consent for survival follow up. Where permitted, data from publically available death registers will be used for participants withdrawn from study or lost to follow-up prior to death.
27. Final Pregnancy Prevention Counselling must be performed in WOCBP at the EoT visit and/or at least 4 weeks following discontinuation of pomalidomide treatment, whichever comes last.

Table 3 Bone Marrow Aspirate and/or Biopsy and tissue sample Collection (Treatment Arm A and Treatment Arm B)

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

BCMA = B-cell maturation antigen; BM = bone marrow; CR = complete response; DNA = deoxyribonucleic acid; FISH = fluorescence in situ hybridization; EMD = extramedullary diseases; MRD = Minimal Residual Disease; PD = Progressive disease; RNA = ribonucleic acid; sCR = Stringent Complete Response; VGPR = Very Good Partial Response.

a. These assessments will be performed at a local laboratory.
b. These assessments will be performed at a central laboratory.
c. For Disease assessment: BM aspirate and/or biopsy as per institutional practice.
d. For sCR in participants achieving a CR, a bone marrow core biopsy is required to confirm sCR by IHC for absence of clonal cells. Only 1 bone marrow procedure required for CR and sCR assessment. If IHC testing cannot be performed at a local lab, the samples can be sent to the central lab.
e. FISH testing to be performed locally at least for: t(4;14), t(14;16), amp(1q), del(1p) and del(17p13). If participant is known to have tested positive for t(4;14) or t(14;16) on previous tests, FISH for those translocations does not need to be repeated and results from previous tests are acceptable regardless of when those 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.
f. MRD sample to be collected at the time of first achieving confirmed response of VGPR or better (i.e. achieving CR without prior VGPR), and repeated every 6 months (±1 month) until PD. In case of deepening of response from VGPR to CR, MRD sample should be collected at the time of CR assessment and then repeated every 6 months until PD.
g. BM core biopsy or aspirate samples are collected at Screening for BCMA expression and biomarker research. When medically feasible and consistent with institutional practice, a BM core biopsy is the preferred samples for these exploratory analyses. If a BM biopsy is not obtainable, then an aspirate should be collected for BCMA expression and biomarker research. Any remaining biopsy and/or aspirate sample may be used for biomarker research (which may include, but not be limited to, immune cell characterization and/or profiling and/or DNA/RNA analyses).
h. Optional BM (core biopsy or aspirate) or tissue sample (if from extramedullary tumor, BM sample is not required in case of EMD relapse) for BCMA expression and biomarker research may be collected at PD. When medically feasible and consistent with institutional practice, BM core biopsy is the preferred sample to be collected for BCMA expression and biomarker research at PD. If BM biopsy is not obtainable, then an aspirate may be collected for BCMA expression and biomarker research. Any remaining biopsy and/or aspirate sample may be used for biomarker research (which may include, but not be limited to immune cell characterization and/or profiling and/or DNA/RNA analyses). Separate consent is required for this optional sample at PD.

Table 4 Additional procedures for Participants with positive serology for HBV at Baseline

HBV Study Assessments	During Screening /Prior to starting treatment	During Treatment	EoT	Notes
HBV related Liver Imaging[3]	X[1]	X[1]	X[1]	1. Liver imaging (specific test per standard of care at local institution) in **HBsAg+ participants** to rule-out/identify cirrhosis, focal hepatic lesions, and/or biliary abnormalities at baseline. Repeat imaging at one year after starting treatment if still on treatment and twice yearly thereafter as long as participant remains on study treatment or as clinically indicated. 2. HBV-DNA testing prior to the start of belantamab mafodotin and subsequently every 3 months, or if LFT elevations requiring increased monitoring or stopping criteria occurs, or for any clinical suspicion of hepatitis reactivation. 3. For **HBsAg+ participants**, appropriate antiviral treatment per local guidance (e.g. tenofovir or entecavir) is started before starting belantamab mafodotin, continues through to completion of belantamab mafodotin therapy and should not be stopped unless advised by local hepatology or virology services.. 4. Only for Japan: HBsAg+ participants only
HBV-DNA testing	X[2]	X[2]	X[2]	
Prevention of HBV reactivation	X[3]	X[3]	X[3]	
HBeAg and HBeAb testing	X[4]			

HBeAg = Hepatitis B e antgen; HBeAb = Hepatitis B e antibody; HBsAg = Hepatitis B surface antigen; HBV = Hepatitis B; LFT = Liver Function Test

Please refer to Section 8.2.8 for management of participants with positive serology for HBV.

Table 5 Additional schedule of procedures: HCV+ Participants

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

HCV= Hepatitis C virus; LFT = Liver Function Test

2. INTRODUCTION

2.1. Study Rationale

Multiple myeloma (MM) is a heterogeneous disease characterized by the clonal proliferation of plasma cells. A variety of drugs and combination treatments have been evaluated and found effective in treating MM [NCCN, 2018; Moreau, 2017]. These include immunomodulatory agents and proteasome inhibitors (PIs) that form the backbone of treatment regimens across all treatment lines. Combining active agents with lenalidomide plus dexamethasone or bortezomib plus dexamethasone (Vd) treatment can yield improved patient outcomes with acceptable toxicity profiles, establishing new global standard of care (SoC) regimens [Raza, 2017; Palumbo, 2016; Reeder, 2009; Richardson, 2010].

Lenalidomide is widely used in first-line either in combination with other anti-myeloma drugs or as maintenance therapy after autologous stem cell transplant (ASCT). Pomalidomide, an immunomodulatory drug with a similar structure to thalidomide and lenalidomide, that binds to cereblon (CRBN), is also emerging as a regimen in subsequent settings. Pomalidomide when administered with low-dose dexamethasone (pomalidomide in combination with dexamethasone; Pd) is approved by the United States Food and Drug Administration and European Medicines Agency (EMA) for patients with relapsed/refractory multiple/myeloma (RRMM) who have received at least 2 prior therapies including lenalidomide and bortezomib and have demonstrated disease progression after their last therapy. Pd improved median progression-free survival (mPFS) for about 2 months over dexamethasone alone in patients with lenalidomide-resistant MM (4.0 vs. 1.9; hazard ratio [HR] 0.49; 95% confidence interval [CI]: 0.40, 0.61; $p<0.001$). The combination regimens of daratumumab or elotuzumab with Pd were also approved in the United States (US) for RRMM in patients who have been previously treated with at least 2 prior therapies including lenalidomide and a PI [POMALYST USPI, 2019; Darzalex USPI, 2018; Empliciti, 2018].

The combination of pomalidomide with twice-weekly bortezomib injected subcutaneously (SC) and low-dose dexamethasone (PVd) given in 21-day cycles (q3w) showed significantly improved clinical activity in a randomized Phase III trial (OPTIMISMM Study, n=559) in patients previously treated with lenalidomide and 1 to 3 prior lines of therapy [San Miguel, 2013; Paludo, 2017; Richardson, 2019]. PVd reduced the risk of progression and death by 39% compared with bortezomib and dexamethasone (Vd) (HR: 0.61; 95% CI: 0.49, 0.77, $p<0.0001$) with a mPFS of 11.2 (vs. 7.1) months and an overall response rate (ORR) of 82% (vs. 50%), including 15.7% sCR/CR, 37% VGPR, and 29.5% PR. The safety profile was consistent with known toxicities associated with other immunomodulators, PIs, and dexamethasone combination regimens, mostly comprising myelosuppression, infections and neuropathy. Based on these findings, PVd has been approved in the EU for treatment of patients with at least 1 prior line of therapy including lenalidomide. It is anticipated that the combination of PVd will become a SoC option for second-line (2L) treatment of RRMM in other countries/regions as well.

Belantamab mafodotin, a humanized immunoglobulin G1 (IgG1) antibody-drug conjugate (ADC) that targets B-cell maturation antigen (BCMA), has demonstrated

strong single-agent activity in two clinical studies (DREAMM-1 and DREAMM-2) conducted in heavily pre-treated patients with RRMM [Trudel, 2018; Trudel, 2019; Lonial, 2020]. Based on the results from the pivotal Phase II Study 205678 (DREAMM-2), belantamab mafodotin was approved by regulatory authorities at 2.5 mg/kg as an intravenous (IV) infusion once every 3 weeks in patients with RRMM.

Nonclinical data demonstrated that the activity of belantamab mafodotin is enhanced by lenalidomide in cultured myeloma cell lines and patient myeloma cells [Tai, 2014; Tai, 2015]. Additional, nonclinical data with belantamab mafodotin suggest significant added benefit (efficacy and survival) when combined with pomalidomide and/or dexamethasone in an established MM xenograft model [GSK Document Number RPS-CLIN-051778, IB V11, 2023].

Belantamab mafodotin at multiple dose levels in combination with Pd q4w is being evaluated for safety and efficacy in patients with RRMM in an ongoing Phase I/II study conducted by the Myeloma Canada Research Network (MCRN 007 or Study 209418, see Section 2.3.4). The Sponsor performed an analysis for an abstract submission (cut-off date of 01 February 2020). A total of 18 patients were included in this report, of which 11 patients received belantamab mafodotin at 1.92 mg/kg dose level, and 7 patients at 2.5 mg/kg dose level. Preliminary data showed that the B-Pd combination at both dose levels resulted in early signs of clinical activity, and the observed safety profile of B-Pd was consistent with the safety profile of belantamab mafodotin and pomalidomide/dexamethasone.

Responses obtained in the belantamab mafodotin 2.5 mg/kg cohort were deep and rapid, with PR or VGPR responses achieved within the first 2 cycles. However, all 7 patients treated in the belantamab mafodotin 2.5 mg.kg cohort experienced Grade 2 or 3 ocular toxicities within 2 cycles of therapy, requiring dose interruptions or dose reductions of belantamab mafodotin from 2.5 mg/kg to 1.92 mg/kg q4w. Despite these dose modifications, all 7 patients achieved deep responses (best overall response 6 VGPR and 1 sCR).

The dose cohort of 1.92 mg/kg q4w was better tolerated with less frequent dose interruptions of belantamab mafodotin. However, the efficacy observed thus far (4 SD, 2 PR and 4 VGPR) appears inferior than the efficacy observed in the dose cohort of 2.5 mg/kg q4w.

We hypothesize that the combination of belantamab mafodotin with Pd may result in significant additive or synergistic effects, which could potentially translate into better benefits compared to PVd in RRMM participants who are progressing on or after the treatment with a lenalidomide-containing regimen. While there is some overlap in the pattern of identified toxicities (primarily hematologic), the safety and tolerability of this combination will be further explored in this randomized trial. This study will evaluate the efficacy and safety of belantamab mafodotin at 2.5 mg/kg in C1 q4w and 1.9 mg/kg in C2+ q4w when administered in combination with Pd versus PVd q3w in participants with RRMM.

Further information on the effects of belantamab mafodotin is available in the Investigator's Brochure (IB) [GSK Document Number RPS-CLIN-051778, IB V11, 2023]

2.2. Background

2.2.1. Clinical Management of Multiple Myeloma and Relapsed/Refractory Multiple Myeloma

MM is an incurable malignancy that accounts for 1.8% of all new cancers and 13% of all hematologic malignancies [SEER CSR, 2015]. Worldwide, approximately 103,000 new cases are diagnosed annually [Cowan, 2018] and in the United States (US), 32,110 new cases and 12,960 deaths are estimated to occur in 2019 [Siegel, 2019].

A variety of drugs and combination treatments have been evaluated and found effective in treating MM [Moreau, 2017; Fonseca, 2017; NCCN, 2018]. However, most, if not all, patients treated with currently approved treatment regimens inevitably relapse and require subsequent treatments [Moreau, 2015; Jagannath, 2008, Richardson, 2003, Richardson, 2006].

Bortezomib is approved in the US, EU and a number of other countries worldwide for the treatment of MM and is the most frequently used PI [VELCADE USPI, 2019 ; VELCADE SmPC, 2021]. Bortezomib is often given in combination with dexamethasone as this has been shown to result in improved ORRs in MM [Kropff, 2005; Kroemer, 2013; Dimopoulos, 2015]. Multiple studies have demonstrated that adding a third agent to bortezomib/dexamethasone leads to improved patient outcomes, with acceptable safety profiles [Paludo, 2017; Palumbo, 2016; Raza, 2017; Reeder, 2009; Richardson, 2010]. European Society for Medical Oncology and National Comprehensive Cancer Network guidelines recommend triplet combination regimens as the induction therapy for fit patients with MM eligible for ASCT, and as the increasingly preferred therapy for RRMM patients [Moreau, 2017; NCCN, 2018].

Immunomodulatory agents are an important cornerstone of treatment for patients with RRMM, including lenalidomide and more recently pomalidomide. The treatment paradigm of relapsed MM is rapidly evolving with increasing use of lenalidomide-based therapy as frontline treatment and pomalidomide in subsequent settings.

2.2.1.1. Pomalidomide in Combination with Dexamethasone (Pd) for Relapsed/Refractory Multiple Myeloma Treatment

Pd is approved by in the US, EU and a number of other countries for patients with RRMM who have received at least 2 prior therapies including both lenalidomide and bortezomib and have demonstrated disease progression on their last therapy [POMALYST USPI, 2019; Imnovid SmPC, 2019].

The combination regimen of Pd has been previously studied in patients with relapsed or refractory MM to lenalidomide and bortezomib in the Phase III trial MM-003, which compared Pd with high-dose dexamethasone (HD) [San Miguel, 2013]. The median OS was significantly longer with Pd than with HD alone (12.7 vs. 8.1 months; HR: 0.74;

p=0.0285). Pd improved the mPFS by about 2 months over HD alone in patients with lenalidomide-resistant MM (4.0 vs. 1.9; HR 0.49; 95% CI: 0.40, 0.61; p<0.001). An ORR of 31% was achieved with Pd (CR: 1%; VGPR: 5%; PR: 26%). The most common Grade 3 to 4 hematological AEs were neutropenia (48% vs. 16%), anemia (33% vs. 37%), and thrombocytopenia (22% vs. 26%). Serious adverse events (SAEs; defined as fatal, life-threatening, requiring hospitalization or resulting in disability or incapacity) occurred in 61% and 53% of participants in the Pd 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. The combination regimens of daratumumab or elotuzumab with Pd were also approved in the US for RRMM in patients who have been previously treated with at least 2 prior therapies including lenalidomide and a PI [POMALYST USPI, 2019; Darzalex USPI, 2018; Empliciti USPI, 2018].

2.2.1.2. Pomalidomide Plus Bortezomib and Dexamethasone (PVd) for Relapsed/Refractory Multiple Myeloma Treatment

Lenalidomide is widely used in first-line either in combination with other anti-myeloma drugs or as maintenance therapy after ASCT. Pomalidomide is also emerging as a second-line regimen for the treatment of RRMM. PVd (pomalidomide with twice-weekly bortezomib injected SC and low-dose dexamethasone) given in 21-day cycles (i.e., q3w) showed significantly improved clinical activity in a randomized Phase III trial (OPTIMISMM Study, N=559) in patients previously treated with lenalidomide and 1 to 3 prior lines of therapy [San Miguel, 2013; Paludo, 2017; Richardson, 2019]. PVd reduced the risk of progression and death by 39% compared with Vd (HR: 0.61; 95% CI: 0.49, 0.77, p<0.0001) with mPFS of 11.2 (vs. 7.1) months and an ORR of 82% (vs. 50%), including 15.7% sCR/CR, 37% VGPR, and 29.5% PR. The safety profile was consistent with known toxicities associated with other immunomodulators, PIs, and dexamethasone combination regimens, mostly comprising myelosuppression, infections, and neuropathy. Based on these clinical results [Richardson, 2019], PVd has received the endorsement from the EMA's Committee for Medicinal Products for Human Use (CHMP) and has been approved by EMA for treatment of RRMM patients with at least 1 prior line of therapy. It is anticipated that the combination of PVd will become a SoC option for second-line treatment of RRMM in other countries/regions as well.

2.2.2. Role of B-Cell Maturation Antigen in 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; Jiang, 2011; Usmani, 2013; Varfolomeev, 2004]. BCMA is widely expressed on malignant plasma cells in MM and to a lesser degree in other B-cell malignancies [Tai, 2015; Tai, 2006]. The restricted expression

profile of BCMA to B cells at later stages of differentiation, and the expression on tumor cells of all patients with MM (GSK internal data) make it a very good target for a therapeutic antibody with direct cell killing activity, which 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 shown to associate with response to therapy and OS [San Miguel, 2013; Sanchez, 2012].

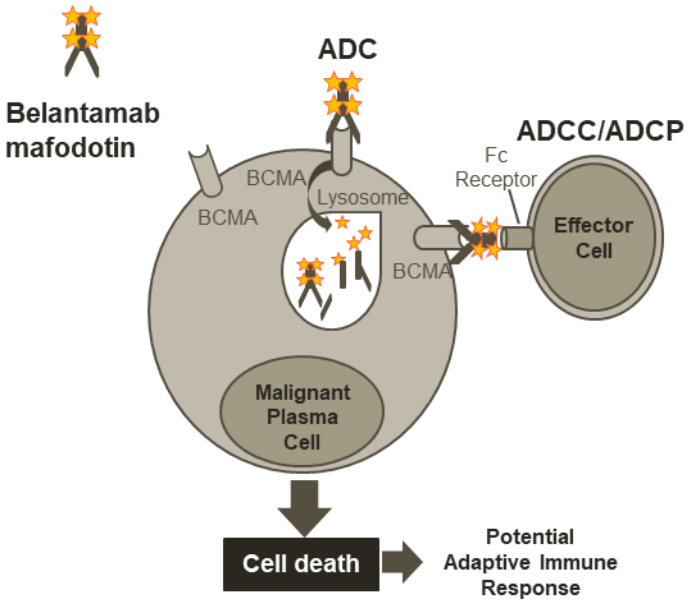
BCMA has been validated as a therapeutic target in MM in nonclinical studies [Tai, 2014; Tai, 2015], and more recently in the clinic, where notable results were demonstrated with chimeric antigen T-cell therapy (CAR-T) [Cohen, 2016; Ormhøj, 2017], and with belantamab mafodotin monotherapy in heavily pre-treated MM patients [Trudel, 2018; Trudel, 2019; Lonial, 2020].

2.2.3. Antibody-Drug Conjugate Belantamab Mafodotin

Belantamab mafodotin is a humanized immunoglobulin G1 (IgG1) antibody-drug conjugate (ADC) that binds specifically to BCMA and competes with its natural ligands: APRIL and BAFF. The parent antibody (belantamab) is produced in an afucosylated form to enhance antibody-dependent cellular cytotoxicity (ADCC) and is conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF), resulting in an ADC molecule. In addition, when MM cells expressing BCMA are exposed to belantamab mafodotin, immunogenic cell death (ICD) markers are induced. Exposure of dendritic cells to tumor cells undergoing ICD is expected to result in an antigen-specific T-cell response, enhancing the patient's own immune response against the MM tumor. The inhibition of BCMA-dependent signaling has also been demonstrated in vitro, but it is uncertain if it contributes to in vivo anti-tumor activity due to the lower concentrations achievable in humans (Figure 2).

Altogether, these mechanisms enable belantamab mafodotin to deliver potent anti-tumor activity by targeting both dividing and non-dividing tumor cells. These mechanisms of action (MoAs) clearly differentiate belantamab mafodotin from existing approved treatments for MM [GSK Document Number RPS-CLIN-051778, IB V11, 2023].

Figure 2 Mechanism of Action of Belantamab Mafodotin



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

2.2.4. Nonclinical Pharmacology of Belantamab Mafodotin

Anti-tumor activity has been observed for belantamab mafodotin in vitro and in vivo. In vitro, belantamab mafodotin demonstrated both ADC and ADCC against all MM cell lines tested, including those with low BCMA expression, and against primary multiple myeloma samples. Further, belantamab mafodotin activity was demonstrated under conditions designed to mimic the human target cells and microenvironment in the bone marrow, including in the presence of physiological concentrations of BCMA ligands, in the presence of shed BCMA (sBCMA), at a large range of BCMA expression levels, and at concentrations of belantamab mafodotin hypothesized to be achievable in humans. Monotherapy treatment with belantamab mafodotin significantly inhibited tumor growth in xenograft models of female mice bearing human MM NCI-H929, OPM2, and MM1Sluc cells [GSK Document Number RPS-CLIN-051778, IB V11, 2023].

Previous work has demonstrated that combining belantamab mafodotin with existing myeloma therapies can enhance the apoptotic and ADCC activities in MM cell lines and MM patient samples [Tai, 2014; Tai, 2015].

Additional studies have been performed to evaluate the anti-tumor activity of belantamab mafodotin in combination with bortezomib, pomalidomide and/or dexamethasone in 2 established MM xenograft mouse models. Belantamab mafodotin had significant tumor growth inhibition efficacy and provided survival advantage when administered to the OPM-2 and MOLP-8 MM xenograft models as a monotherapy. Belantamab mafodotin combination therapy with pomalidomide or bortezomib provided additional benefit compared to each single agent by significantly increasing survival in both mouse models. In the OPM-2 model, belantamab mafodotin combination therapy with bortezomib also led to significant increases in tumor growth inhibition. Combining belantamab mafodotin

with dexamethasone in double or triple combinations did not provide significant added benefit when compared to single agents or double combinations, respectively [GSK Document Number RPS-CLIN-051778, IB V11, 2023].

2.3. Human Experience with Belantamab Mafodotin

2.3.1. Studies with Belantamab Mafodotin Monotherapy

Belantamab mafodotin has demonstrated strong single-agent activity in 2 clinical studies conducted in heavily pre-treated participants with RRMM (Trudel, 2018; Trudel 2019; Lonial, 2020).

In the FTIH study BMA117159 (NCT02064387, DREAMM-1), as of 27 February 2019 safety cut-off, a total of 73 participants with RRMM received at least 1 dose of belantamab mafodotin (Trudel, 2018; Trudel, 2019). The administration schedule was once q3w IV. Final data from BMA117159 demonstrated a manageable safety profile with thrombocytopenia and corneal events being the most frequently reported AEs. Thirty-eight (38) patients were treated in the dose-escalation Part 1 and 35 patients in the dose-expansion Part 2 at the 3.4 mg/kg. The majority of patients (29/38 [76%] in Part 1 and 20/35 [57%] in Part 2) had received 5 or more prior lines of therapy. All patients in Part 2 experienced at least 1 AE. The most common events occurring in ≥30% of patients were corneal events, thrombocytopenia (including the preferred term platelet count decreased), nausea, fatigue, anemia, and aspartate aminotransferase increased. In Part 2, Grade 3 to 4 AEs were reported in 29/35 patients (83%) and SAEs were reported in 17/35 (49%) patients. The most common SAEs were lung-associated infections, pneumonia, pyrexia, and infusion-related reaction (IRR).

Thrombocytopenia/platelet count decreased was reported in a total of 40/70 patients (55%) in the All-Patients Treated (APT), and 22/35 patients (63%) in Part 2. Belantamab mafodotin may cause transient worsening of thrombocytopenia in some patients, but in most cases these events are resolved during between-dosing intervals. In the Part 2 MM population, 2 serious bleeding events were reported: intracranial hemorrhage in a patient with a history of an intracranial bleeding in the setting of disease progression, and hematuria in a patient with a large bladder mass in the setting of progressive disease (PD).

Corneal events are the most frequently reported AEs associated with belantamab mafodotin in the clinic, which include keratopathy (microcyst-like superficial deposits in the corneal epithelium), blurred vision, dry eyes and photophobia. These findings are consistent with those previously reported with other antibody drug conjugates utilizing monomethyl auristatin F in terms of manifestation and incidence of events [Eaton, 2015]. In Part 2 of BMA117159 (n=35 patients treated at 3.4 mg/kg q3w), corneal events were reported in 24/35 (69%) patients, most commonly blurred vision (18/35; 51%), dry eye (13/35; 37%) and photophobia (10/35; 29%). Nineteen (19; 54%) patients experienced Grade 1 or 2 corneal events; 5 (14%) patients had Grade 3 events. The median duration of corneal events for patients with a resolution date (n=16) was 35 days (range 5–442). Corneal events led to dose reduction in 16 (46%) patients, and dose interruptions or delays in 17 (49%) patients [Trudel, 2018; Trudel, 2019].

In Part 2 of BMA117159 (n=35), belantamab mafodotin demonstrated an ORR of 60.0% (95% CI: 42.1%, 76.1%), sCR of 6%, CR of 9%, VGPR of 40%, and PR of 6%, with RRMM [Trudel, 2018; Trudel, 2019]. The median duration of response (DoR) was 14.3 months (95% CI: 10.6 months, NR). The mPFS in this population was 12.0 months (95% CI: 3.1 months, NR). For patients refractory to both immunomodulators 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 months, Not Estimable [NE]) [Lonial, 2020]. In Study BMA117159, the maximum clinical benefit (by ORR) was observed at the 3.4 mg/kg dose level, but a significant number of patients required dose delays and dose reductions to manage AEs.

In the Phase II pivotal Study 205678 (NCT03525678, DREAMM-2), belantamab mafodotin was further evaluated as monotherapy in RRMM patients at doses of 2.5 mg/kg and 3.4 mg/kg q3w. It was a two-arm, randomized study in patients who have failed at least 3 prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and who are refractory to an immunomodulator and a PI (97 in the 2.5 mg/kg cohort and 99 in the 3.4 mg/kg cohort) [Lonial, 2020]. The DREAMM-2 study final analysis was completed and the results are presented in the final Study Report (October 2022). However, there are participants continuing treatment in PACT (Post-Analysis Continued Treatment) phase.

As of the cut-off date of 31 March 2022, the ORR was 32% (97.5% CI: 21.7%,43.6%) in the 2.5 mg/kg cohort and 35% (97.5% CI: 24.8%, 47.0%) in the 3.4 mg/kg cohort. The median DoR was 12.5 months (95% CI: 4.2 months, 19.3 months) at 2.5 mg/kg and 6.2 months (95% CI: 4.8 months, 18.7 months) at 3.4 mg/kg. The mPFS in this population was 2.8 months (95% CI: 1.6 months, 3.6 months) and 3.9 months (95% CI: 2.0 months, 5.8 months), respectively and the median OS was 15.3 months (95% CI: 9.9 months, 19.2 months) at 2.5 mg/kg and 14.0 months (95% CI: 10.0 months, 18.1 months) at 3.4 mg/kg. Positive clinical activity was also demonstrated at the 3.4 mg/kg lyophilized dose (ORR 52% [97.5% CI: 28.9%, 74.5%]).

2.3.2. Safety

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

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

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

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 final analysis report (data as of 31 March 2022), events in the Eye disorders System Organ Class occurred in 98% of participants treated with belantamab mafodotin 2.5 mg/kg (n=95). The most common ocular AEs were keratopathy (71%, changes in corneal epithelium identified on eye exam, with or without symptoms), blurred vision (23%), and dry eye (15%). Belantamab mafodotin can cause keratopathy with or without vision impairment. In the safety population treated with belantamab mafodotin 2.5 mg/kg (n=95), median time to onset for the first occurrence of a keratopathy event was 28 days.

Dose modifications, specifically dose delays, appear to be the most important mitigation strategy. Concomitant use of preservative-free artificial tear drops might also be beneficial, although they are not expected to prevent the occurrence of the epitheliopathy. Participants with a history of dry eye symptoms prior to starting belantamab mafodotin were more likely to develop keratopathy compared with participants without a history of dry eye symptoms. Therefore, active management of dry eye symptoms prior to and during treatment is recommended (i.e., administration of preservative-free artificial tears). Permanent treatment discontinuations due to corneal events were rare and occurred in <5% of participants.

The ocular sub-study of DREAMM-2 provided no evidence that corticosteroid eye drops are an effective mitigation strategy for keratopathy/corneal events.

Thrombocytopenia

In DREAMM-2 (data as of 31 March 2022), 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. Grade 3 or higher events occurred in 22% of participants, and 1% overall were considered SAEs. The median time to onset of the first thrombocytopenic event was 25.5 days and the median time to resolution was 21.5 days.

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

IRRs are expected for biologic agents. The majority of IRRs were non-serious and between grade 1 and grade 2 in severity. In DREAMM-2, IRRs occurred in 21% of participants receiving belantamab mafodotin 2.5 mg/kg. Symptoms of IRRs have included chills, asthenia, hypertension, lethargy, pyrexia, nausea, diarrhea, tachycardia, hypotension, and vomiting. 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% to 27% of participants. One participant (2.5 mg/kg cohort) discontinued treatment due to IRRs (Grade 3 IRRs at first and second infusion).

2.3.3. Pharmacokinetics and Pharmacodynamics in Humans

The pharmacokinetics (PK) and pharmacodynamics (PD) of belantamab mafodotin (ADC, including complex) and total monoclonal antibody (total mAb; including complex), and cysteine maleimidocaproyl monomethyl auristatin F (cys-mcMMAF) were investigated in 291 participants with RRMM following IV administration at doses from 0.03 to 4.6 mg/kg q3w in DREAMM-1 (n=73) and at doses of 2.5 or 3.4 mg/kg q3w in DREAMM-2 (n=218).

Maximum plasma concentration (Cmax) of belantamab mafodotin and total monoclonal antibody were observed at or shortly after the end of infusion (EOI), whereas 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 PK were well described by a linear, 2-compartment population model, with a time-varying decrease in clearance in a population PK analysis. At Cycle 1, belantamab mafodotin had a systemic clearance of 0.924 L/day, steady-state volume of distribution of 10.8 L, and an elimination half-life of 12 days in participants with RRMM in DREAMM-2. Over time, clearance was reduced by 28%, with an elimination half-life of 14 days. The time to 50% change in clearance was approximately 50 days.

No clinically significant differences in the PK 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 (estimated glomerular filtration rate [eGFR] ≥30 ml/min/1.73m^2) or mild hepatic impairment (National Cancer Institute Organ Dysfunction Working Group classification). Higher serum levels of β_2-microglobulin, immunoglobulin (Ig) G, and sBCMA and lower levels of albumin were associated with more advanced MM or a higher MM disease burden. Higher baseline IgG and sBCMA levels and lower baseline albumin levels were associated with higher belantamab mafodotin clearance leading to lower average and trough concentrations (Ctau) of belantamab mafodotin. Higher baseline IgG and sBCMA levels were associated with higher cys-mcMMAF central volume of distribution leading to lower cys-mcMMAF Cmax.

In nonclinical studies, cys-mcMMAF had limited metabolic clearance. In vitro data suggested that belantamab mafodotin and cys-mcMMAF are unlikely to perpetrate a drug-drug interaction or to be a victim of a drug-drug interaction with inhibitors or inducers of cytochrome P450 enzymes (CYP). Cys-mcMMAF was an in vitro substrate of organic anion transporting polypeptides (OATPs) OATP1B1 and OATP1B3, multidrug resistance associated proteins (MRP) MRP1, MRP2, and MRP3, a borderline substrate of bile salt export pump, 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 DREAMM-1 and DREAMM-2. All subjects exhibited reductions in free sBCMA concentration at EOI compared to baseline at Cycle 1, with a return to near-baseline level by 7 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 DREAMM-2 and/or DREAMM-1found that ocular safety endpoints were most strongly associated with belantamab mafodotin exposure, while efficacy endpoints had a weaker association with belantamab mafodotin exposure. Both safety and efficacy endpoints were associated with patient characteristics. Belantamab mafodotin Ctau was associated with probability of corneal events and keratopathy and cys-mcMMAF Cmax was associated with probability of thrombocytopenia. Probability of occurrence of dry eye, blurred vision, neutropenia and IRR 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.

In addition, the pharmacokinetics of belantamab mafodotin were further investigated in monotherapy from 217 participants with RRMM following IV administration of 2.5 mg/kg q3w in DREAMM-3; in combination with lenalidomide/dexamethasone (n=45) or bortezomib/dexamethasone (n=107) in participants with RRMM following IV administration at doses ranging from 1.9 mg/kg to 3.4 mg/kg in DREAMM-6; in combination with nirogacestat (n=44, SubStudy 3) in participants with RRMM following IV administration at doses ranging from 0.95 mg/kg in DREAMM-5; and in combination with lenalidomide/bortezomib/dexamethasone (n=90) in transplant ineligible newly diagnosed MM participants following IV administration at doses ranging from 1.0 mg/kg to 1.9 mg/kg in DREAMM-9. Overall, the pharmacokinetics of belantamab mafodotin were similar in these earlier line patient populations to that observed in later line RRMM patients receiving belantamab mafodotin monotherapy.

Additional information related to belantamab clinical PK, PD, and exposure-response relationships can be found in the IB [GSK Document Number RPS-CLIN-051778, IB V11, 2023].

2.3.4. Study 209418: Belantamab mafodotin in combination with pomalidomide and dexamethasone

Study 209418 (or MCRN007) is an ongoing Phase I/II, dose-escalation study conducted by the MCRN to evaluate the safety and efficacy of belantamab mafodotin given IV q4w in combination with pomalidomide and dexamethasone (B-Pd) in patients with RRMM. The study consists of two parts: Part 1 is dose-finding and Part 2 is the expansion phase.

All patients receive multiple dose levels of belantamab mafodotin administered IV q4w in combination with pomalidomide and dexamethasone in a 28-day treatment cycle. Pomalidomide is administered at 4 mg QD on Days 1 to 21 of a 28-day cycle and dexamethasone at 40 mg QD (participants ≤75 years old) or 20 mg QD (participants >75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle. Treatment will be administered until disease progression or unacceptable toxicity.

In the original protocol, as of the data cut-off on 01 February 2020, 7 patients received belantamab mafodotin at 2.5 mg/kg dose when administered in combination with Pd q4w (2.5 mg/kg in Cycle 1 followed by 1.9 mg/kg in Cycle 2+ q4w) and 11 patients received 1.92 mg/kg in Study 209418. Briefly, both doses of belantamab mafodotin were shown to be tolerable with demonstrated clinical activity when administered in combination with Pd in each 28-day cycle. The 1.92 mg/kg q4w belantamab mafodotin dosing regimen was associated with less frequent dose interruptions and reductions and a lower incidence of AEs (including corneal events) compared with 2.5 mg/kg q4w. Additional preliminary blinded data, based on the instream data (cut-off date of 15 July 2021), a total of 60 patients were included in this report, of which the following dosing levels/schedules were explored: 1.92 mg/kg q4w (n=12), 2.5 mg/kg q4w (n=7), 2.5 mg/kg in cycle 1 followed by 1.9 mg/kg in cycle 2+ Q4W (n=5), 2.5 mg/kg q8w (n=12), 2.5 mg/kg q12w (n=11), 2.5 mg/kg SPLIT (n=8) and 3.4 kg/mg SPLIT (n=5) (i.e. one half dose was given on D1 and D8 of each 28-day cycle).

The overall safety profile for belantamab mafodotin in combination with Pd remains consistent with known toxicities of each component, and no new safety concerns were identified. The most frequently reported AEs were corneal and haematological toxicities and most events resolved (or were resolving) following protocol defined monitoring and dose modifications.

As of 15 July 2021, 54 of 60 participants in Study 209418 were evaluable for efficacy response, and across all cohorts the ORR was 87% (10 PR, 24 VGPR, and 13 CR). In the cohort of 2.5 mg/kg in cycle 1 followed by 1.92 mg/kg in cycle 2+; ORR was 100% (1 PR, 2 VGPR and 2 CR) with a VGPR or better rate achieved by 80% of participants. The rationale of the selected belantamab mafodotin dosing regimen in DREAMM-8 is supported by a clinically significant positive predictive impact on reduction in corneal toxicity with minimal predictive negative impact on efficacy.

2.4. Benefit:Risk Assessment

Information regarding the known and expected benefits and adverse reactions associated with belantamab mafodotin are provided in the Investigator Brochure [GSK Document

Number RPS-CLIN-051778, IB V11, 2023]. A summary of risk assessment for potential overlapping toxicities with the combination of B-Pd are described below.

Details on risks for pomalidomide, dexamethasone and bortezomib can be found in respective prescribing information; see Pharmacy Manual.

2.4.1. Summary of Risk Assessment for the Combination Therapy of B-Pd (Arm A)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential overlapping toxicities for belantamab mafodotin/pomalidomide/dexamethasone (Treatment Arm A)		
Thrombocytopenia	**Belantamab mafodotin:** Belantamab mafodotin may cause transient thrombocytopenia in some participants, which for most cases recovered between doses. In study 205678, which included participants treated with belantamab mafodotin 2.5 mg/kg, thrombocytopenia was noted in 38% of participants and ranged between Grade 1 to 4 in severity. **Pomalidomide:** May cause thrombocytopenia and anemia.	Routine monitoring of hematologic panels as outlined in the SoA. Supportive therapy per local medical practice (*e.g.*, platelet transfusion, growth factors). Dose modification guidelines are outlined in Section 6.6.1 and Section 6.7.1.
Pneumonitis	**Belantamab mafodotin:** Non-clinical safety experiments have demonstrated the presence of progressive microscopic changes in the lungs (prominent alveolar macrophages associated with eosinophilic material; mixed perivascular/neutrophilic 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. **Pomalidomide:** Interstitial lung disease and related events, including cases of pneumonitis, have been observed with pomalidomide.	Monitoring for clinical signs and symptoms related to pulmonary toxicity. If a participant experiences new or worsening pulmonary symptoms, (e.g., cough, dyspnea) without obvious etiology, appropriate diagnostic evaluation should be performed (see protocol Section 6.7) and further treatment with belantamab mafodotin delayed. 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 Table 13 and Table 19.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hepatotoxicity	**Belantamab mafodotin:** Nonclinical safety studies have identified the liver as a target organ for toxicity, with increased liver weights and/or raised hepatobiliary enzymes and transaminases observed in both rat and monkey. These changes in the liver were without clinical consequence in the shorter duration studies and in the rat 13-week study. In the monkey 13-week study, progression of liver toxicity to include minimal multifocal hepatocellular necrosis was observed at all doses administered (≥3 mg/kg/week). Elevated liver enzymes including AST, ALT, GGT and bilirubin have been observed in clinical trials with belantamab mafodotin. **Pomalidomide:** Hepatic failure, including fatal cases and elevated levels of alanine aminotransferase (ALT) and bilirubin reported.	Only participants with well-preserved liver function per the inclusion/exclusion criteria will be allowed on study. Participants with Hepatitis B and C may be enrolled if meeting entry and agreeing to monitoring/treatment criteria. See Table 4 and Table 5 and exclusion criteria in Section 5.2. Liver function tests will be monitored per SoA. Liver stopping criteria outlined in Section 7.1.1
Increased Infections due to immunosuppression or neutropenia	**Belantamab mafodotin:** In non-clinical 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. Neutropenic events, including febrile neutropenia have been observed with belantamab mafodotin. **Pomalidomide:** Neutropenia was reported, rate of Grade 3-4 neutropenia was 46% and febrile neutropenia was 8%. **Dexamethasone:** Patients who are on corticosteroids are more susceptible to infections or exacerbation of latent infections than healthy individuals. Chickenpox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids.	Patients with an active infection will be excluded. Monitoring for infections and immediate treatment of immunosuppression according to standard practice. Routine monitoring of hematologic panels as outlined in the SoA. Supportive therapy per local medical practice (*e.g.* growth factors). Prophylactic antibiotics, per local institutional guidance, in participants with Grade 3-4 neutropenia. Immediate hospitalization of participants with febrile neutropenia. Dose modification guidelines are outlined in Section 6.6.1 and Section 6.7.1
Keratopathy (changes to the corneal epithelium,	**Belantamab mafodotin:** Changes in the corneal epithelium on ocular examination have been frequently observed with belantamab mafodotin and were most commonly associated with keratopathy (changes in the	Active monitoring of the corneal epithelium and visual acuity as outlined in the SoA. Evaluation and management by an eye care professional.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
potentially resulting in vision changes)	corneal epithelium upon examination), blurred vision, dry eyes, photophobia, and changes in visual acuity. Participants with a history of dry eye were more prone to develop changes in the corneal epithelium. Based on available follow-up data, visual acuity returned to, or near baseline in most cases. **Dexamethasone:** Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.	Dose modification guidelines are outlined in Section 6.6.1, Section 6.7.1, and Section 7.1.
Embryo-Fetal Toxicity	**Belantamab mafodotin:** 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. **Pomalidomide:** Pomalidomide is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. Pomalidomide is available only through a pregnancy prevention/controlled distribution program	Pregnancy testing outlined in the SoA. Contraception requirements detailed in Section 10.3. Participants receiving pomalidomide must register with any pregnancy prevention/controlled distribution program in place locally (see SRM for details).
Risks related to belantamab mafodotin not listed under potential overlapping toxicities		
Infusion-Related Reactions (IRRs)	IRRs were reported in participants treated with belantamab mafodotin. Most IRRs were Grade 1-2 and manageable with medical treatment.	Close monitoring for signs of IRR. Consider premedication for IRR. If an IRR occurs, follow the guidance in Section 7.1.3.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Nephrotoxicity	Non-clinical safety experiments have demonstrated primary glomerular injury and tubular degeneration/regeneration (in rat and monkey). These 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 13-week monkey 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 1 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, and in such cases appropriate monitoring and dose modification should be considered.	Kidney function monitoring including albumin/creatinine ratio. Education of participants on the need to maintain adequate urinary output. Dose modification guidelines for increased serum creatinine and urinary albumin/creatinine ratio are outlined in Section 6.7.1.
Risks related to Study Procedures		
BM Aspiration/Biopsy	Pain, infection, bleeding may occur after the procedure.	Participants will be treated according to institution's practice.
Incidental Findings During Imaging Data Acquisition	During the acquisition of imaging data (*e.g.*, MRI, CT, PET-CT), non-MM disease or clinically relevant abnormalities could be found by the radiographer performing the examinations.	Copies of all medical images that include non-MM disease clinically relevant abnormalities will be stored at the site.

Abbreviations: ADA=Anti-Drug Antibody; AE=Adverse Event; ALT=Alanine Aminotransferase; AST=Aspartate Aminotransferase; BCMA=B Cell Maturation Antigen; BM=bone marrow; CK=Creatine Kinase; CT=Computed Tomography; cys-mcMMAF=Cysteine Maleimidocaproyl Monomethyl Auristatin F; DRESS=Drug Reaction With Eosinophilia And Systemic Symptoms; GGT=Gamma-glutamyl transferase; IRR=Infusion Related Reaction; LDH=Lactate Dehydrogenase; MM=Multiple Myeloma; MRI=Magnetic Resonance Imaging; PET/CT=Positron Emission Tomography/Computed Tomography; PML=Progressive Multifocal Leukoencephalopathy; PRES=Posterior Reversible Encephalopathy Syndrome; PVd=Pomalidomide Plus Bortezomib And Dexamethasone; RPLS=Reversible Posterior Leukoencephalopathy Syndrome; SJS=Stevens Johnson Syndrome; SoA=Schedule Of Activities; SRM=Study Reference Manual; TEN=Toxic Epidermal Necrolysis; TLS=Tumor Lysis Syndrome; TTP/HUS=Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome; ULN=Upper Limit Of Normal; VZIG=Varicella Zoster Immune Globulin.

1. Refer to belantamab mafodotin Investigator's Brochure and to local prescribing information for pomalidomide, bortezomib, and dexamethasone for further information.

2.4.2. Benefit Assessment

As of 27 February 2019, results from the FTIH Study BMA117159 (DREAMM-1) indicated that belantamab mafodotin monotherapy administered at 3.4 mg/kg (n=35) is active in the RRMM population and demonstrated an ORR of 60.0% (95% CI: 42.1%, 76.1%) and mPFS of 12.0 months (95% CI: 3.1 months, NR). In the Phase II pivotal Study 205678 (DREAMM-2), belantamab mafodotin was further evaluated as monotherapy in RRMM patients at doses of 2.5 mg/kg and 3.4 mg/kg q3w (97 in the 2.5 mg/kg cohort and 99 in the 3.4 mg/kg cohort) [Lonial, 2020]. As per the inclusion criteria, all patients were refractory to immunomodulatory drugs and PIs, and had previously received an anti-CD38 monoclonal antibody. As of 31 January 2020, the ORR was 31% (97.5% CI: 21.7%,43.6%) in the 2.5 mg/kg cohort and 35% (97.5% CI: 24.8%, 47.0%) in the 3.4 mg/kg cohort. The combination treatment of a highly active drug belantamab mafodotin with Pd is relatively safe with early signs of clinical activity as measured by objective response in an ongoing Phase I/II study conducted by the MCRN (Study 209418). Responses obtained in 7 participants with 2.5 mg/kg belantamab mafodotin with Pd, were achieved deep responses (best overall response 6 VGPR and 1 sCR). Based on this data, it is reasonable to hypothesize that such a combination will benefit MM patients, who are refractory to currently available treatments.

This Phase III study is being performed to evaluate the efficacy and safety of belantamab mafodotin in combination with pomalidomide and dexamethasone (B-Pd) vs pomalidomide plus bortezomib and dexamethasone (PVd), an emerging SoC, for participants with RRMM who have been previously treated with at least 1 prior therapy, including lenalidomide. The study population enrolled in this study has a high unmet medical need. Participants failing multiple lines of prior treatments do not have many therapeutic options left, and if a response can be achieved with currently available drugs, it is usually of short duration.

2.4.3. Overall Benefit:Risk Conclusion

Considering the observed clinical activity of belantamab mafodotin as a single agent and when combined with Pd in patients with RRMM and based on the emerging data from B-Pd in 209418 (MCRN 007), it is reasonable to assume that B-Pd may offer additional benefit over PVd to patients with RRMM by improving progression-free survival. Although there were overlapping toxicities, it is anticipated that belantamab mafodotin toxicities will be manageable. Considering the measures taken to minimize risks to participants in this study, the potential risks identified in association with belantamab mafodotin when combined with Pd are justified by the anticipated benefits that may be afforded to participants with MM.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To compare the efficacy of B-Pd with that of PVd in participants with RRMM	• Progression-Free Survival (PFS), defined as the time from randomization until the earliest date of PD based on IRC-assessment per IMWG criteria, or death due to any cause.
Key Secondary	
To further compare the efficacy of B-Pd with that of PVd in participants with RRMM	• Overall Survival (OS), defined as the interval of time from randomization to the date of death due to any cause. • Duration of Response (DoR), defined as the time from first documented evidence of PR or better until progressive disease (PD) or death due to any cause. Response will be based on IRC-assessment per IMWG criteria. • MRD negativity rate, defined as the percentage of participants who achieve MRD negative status (as assessed by NGS at 10^{-5} threshold) at least once during the time of confirmed CR or better response based on IRC-assessment per IMWG.
Secondary	
To further assess the efficacy of B-Pd in terms of other efficacy outcomes in participants with RRMM	• Overall Response Rate (ORR), defined as the percentage of participants with a confirmed partial response (PR) or better (i.e., PR, VGPR, CR, and sCR) based on IRC-assessment per IMWG criteria. • Complete Response Rate (CRR), defined as the percentage of participants with a confirmed complete response (CR) or better (i.e., CR and stringent complete response (sCR)) based on IRC-assessment per IMWG criteria. • Very Good Partial Response (VGPR) or better rate, defined as the percentage of participants with a confirmed VGPR or better (i.e., VGPR, CR, and sCR) based on IRC-assessment per IMWG criteria. • Time to Best Response (TTBR), defined as the interval of time between the date of randomization and the earliest date of achieving best response among participants with a confirmed PR or better based on IRC-assessment per IMWG. • Time to Response (TTR), 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) based on IRC-assessment per IMWG. • Time to Progression (TTP), defined as the time from randomization until the earliest date of PD based on

Objectives	Endpoints
	IRC-assessment per IMWG criteria, or death due to PD. • PFS2, defined as time from randomization to disease progression (investigator-assessed response) after initiation of new anti-myeloma therapy or death from any cause, whichever is earlier. If disease progression after new anti-myeloma therapy cannot be measured, a PFS event is defined as the date of discontinuation of new anti-myeloma therapy, or death from any cause, whichever is earlier.
To evaluate the safety and tolerability of B-Pd	• Incidence of AEs and changes in laboratory parameters • Ocular findings on ophthalmic exam
To describe the exposure to belantamab mafodotin after infusion	• Plasma concentrations of belantamab mafodotin, and cys-mcMMAF
To evaluate the PK of pomalidomide in combination with belantamab mafodotin and dexamethasone, in a subset of participants	• Derived PK parameter values, as data permit
To assess ADAs against belantamab mafodotin	• Incidence and titers of ADAs against belantamab mafodotin
To evaluate the safety and tolerability of belantamab mafodotin based on self-reported symptomatic adverse effects when administered in combination with pomalidomide and dexamethasone	• Maximum post-baseline PRO-CTCAE score for each item attribute
To evaluate and compare changes in symptoms and HRQoL	• Change from baseline in HRQoL as measured by EORTC QLQ-C30, EORTC QLQ-MY20* and EORTC IL52
Exploratory	
To further evaluate the safety and tolerability of belantamab mafodotin when administered in combination with pomalidomide and dexamethasone	• Changes in safety assessments, including vital signs
To further characterize the PK profile of belantamab mafodotin when administered in combination with pomalidomide and dexamethasone	• Derived PK parameter values for belantamab mafodotin and cys-mcMMAF, as data permit
To evaluate self-reported ocular symptomatic AEs of belantamab mafodotin when administered in combination with pomalidomide and dexamethasone	• Changes from baseline in symptoms and related impacts as measured by OSDI
To further evaluate and compare changes in HRQoL and symptoms	• Change from baseline in HRQoL as measured by EQ-5D-3L • Change from baseline in PGIS and change over time in PGIC
To further evaluate the impact of side effects on QoL	• Change from baseline in FACT-GP5
To further explore the efficacy in terms of MRD-negativity	• Sustained MRD negativity rate: defined as the percentage of participants who achieve MRD negative status assessed by NGS at 10^{-5} threshold at least twice, a minimum of 12 months apart and

Objectives	Endpoints
	with no MRD positive result in between, during the time of confirmed CR or better response. • Imaging plus MRD-negativity rate, defined as the percentage of participants who achieve MRD negative status assessed by NGS at 10^{-5} threshold and have no evidence of disease on PET-CT at least once during the time of confirmed CR or better response
To evaluate and compare nonprotocol-specified HCRU	• Out-patient visits by physician specialty • Emergency room visits • Home healthcare visits • Inpatient hospitalizations (including duration by wards (intensive care unit vs. general ward)
To explore the exposure-response relationship between belantamab mafodotin exposure and clinical endpoints in participants treated with B-Pd	• Belantamab mafodotin exposure (e.g., concentration, C_{max}, or AUC) vs. efficacy and safety endpoints (e.g., PFS, ORR, CRR, corneal events)
To explore the relationship between clinical response and biologic characteristics including, but not limited to, BCMA expression on tumor cells and sBCMA concentrations	• Assess various tumor and blood-based biomarkers at baseline and on-treatment, by analysis of DNA, RNA and/or protein, including but not limited to evaluating baseline BCMA expression and/or immune status in tumor sample and in the tumor microenvironment and/or serum soluble BCMA levels, and their relationship to response to belantamab mafodotin
To explore the effect of host genetic variation on the response to belantamab mafodotin and disease under study as well as related drug classes and diseases	• Effect of host genetic variation in 1 or more candidate genes or across the genome on response to belantamab mafodotin and disease under study as well as related drug classes and diseases

Abbreviations: ADA=anti-drug antibody; AE=adverse event; AUC=area under the concentration time curve; BCMA=B-cell maturation antigen; BM=Bone marrow; B-Pd=Belantamab mafodotin in combination with pomalidomide and dexamethasone; CR=Complete Response; CRR=Complete Response Rate; C_{max}=maximum plasma concentration; cys-mcMMAF=cysteine-maleimidocaproyl monomethyl auristatin F; DoR=Duration of Response; EORTC IL52=European Organisation for Research and Treatment of Cancer Item Library 52; 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; EQ-5D-3L=European Quality of Life 5 Dimensions 3 Level Scale; FACT-GP5=Functional Assessment of Cancer Therapy – General Population; HCRU=Healthcare Resource Utilization; HRQoL=Health-Related Quality of Life; MRD=Minimal Residual Disease; NGS=next-generation sequencing; ORR=Overall Response Rate; OS=Overall Survival; OSDI=Ocular Surface Disease Index; PFS=Progression-free Survival; PFS2=Progression-free Survival on subsequent line of therapy; PGIC=Patient Global Impression of Change, PGIS=Patient Global Impression of Severity; PK=Pharmacokinetic(s); PR=Partial Response; PRO-CTCAE=Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PVd=pomalidomide plus bortezomib and dexamethasone; QoL=quality of life; RRMM=relapsed/refractory multiple myeloma; sBCMA=soluble B-cell maturation antigen; sCR=stringent complete response; TTBR=time to best response; TTP=time to disease 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 participants enrolled under protocol amendment 1.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase III, multicenter, open-label, randomized study evaluating the efficacy and safety of B-Pd vs. PVd in participants with RRMM.

The study will include a Screening Period, a Treatment Period, and a Follow-up Period.

During the 28-day Screening Period, participants will be evaluated for study eligibility per protocol as defined in the Inclusion / Exclusion criteria (Section 5.1 and Section 5.2). Eligible participants must have a confirmed diagnosis of MM, been previously treated with at least 1 prior line of therapy including lenalidomide and must have documented disease progression during, or following, the most recent line of therapy.

Following Screening, participants will be stratified based on the number of prior lines of therapy (1 vs. 2 / 3 vs. ≥4), prior bortezomib treatment (yes or no) and prior anti-CD38 treatment (yes or no), and centrally randomized in a 1:1 ratio to either arm, as described in Section 6.1. Based on the emerging data and anti-CD38 such as daratumumab approval in the front-line setting, prior anti-CD38 exposure has been selected as a stratification factor, replacing ISS status. No more than 50% of participants with 2 or more prior lines of treatment will be enrolled. It is anticipated that no more than 15% of participants will be enrolled in with 4 or more prior lines of treatment. No cross-over between 2 treatment arms will be allowed.

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 enrolment requirements are met, as requested by local regulatory authorities. Additional participants that are enrolled in separate cohorts will not be included in the analysis portion of the study planned for the marketing application. However, these additional participants will be included in country-specific supplemental analyses, as detailed in the country-specific Statistical Analysis Plan (SAP).

During the Treatment Period, safety and disease assessments will be performed regularly according to the schedule of activities (SoA) (Section 1.3) for each arm. Treatment will continue in both arms until PD, death, unacceptable toxicity, start of a new anti-myeloma therapy, withdrawal of consent, or end of study, whichever occurs first. Dose interruptions or reductions may be required following potential drug-associated toxicities (see Section 6.6 and Section 6.7).

For participants who discontinue study treatment for reasons other than PD, disease evaluations will continue to be performed every 4 weeks (±3 days) until confirmed PD (documented), death, start of a new anti-myeloma therapy, withdrawal of consent, loss to follow-up or end of the study, whichever occurs first. In case of PD, participants will be followed to ascertain subsequent anti-myeloma therapy, progression free survival on the subsequent line of therapy (PFS2), and survival status every 12 weeks (q12w) (±14 days) until withdrawal of consent, loss to follow-up, death or the end of the study as defined in Section 4.4.

Following the DCO (data cut-off) date for the final analysis (See Section 4.4), DREAMM-8 will move into the post analysis continued treatment (PACT) phase. This includes the global study population and participants in any country-specific expansion cohorts. 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 A only) will be reported directly to GSK.

The end of study is defined as the end of the safety follow-up following the last participant last dose i.e. the completion of the PACT phase.

Note: In its most common usage, the start of a cycle is defined by when a participant takes the first dose of a drug for the given cycle. But because this study is assessing 3 drugs given in combination, within the context of this protocol "cycle" refers to a planned cycle of doses for the 3 drugs, as per their individual planned dosing schedules. If administration of 1 or 2 of the drugs are delayed for any reason, the dosing of the other drug(s) should continue within the cycle as per the planned dosing schedule. If drug(s) that were delayed can be administered again during an ongoing planned cycle, dosing would resume according to what day it is relative to Day 1 of the planned cycle, and only the remaining planned doses for that cycle would be given. For example, if belantamab mafodotin is administered on Day 1 of a 28-day cycle, but pomalidomide and dexamethasone were both delayed until Day 8, pomalidomide would then be given on Days 8-21, and dexamethasone would be given on Days 8, 15, and 22. Dosing would then resume on Day 1 of the next planned cycle as per the planned dosing schedule.

4.2. Scientific Rationale for Study Design

Immunomodulatory drugs and PIs have been a cornerstone in the treatment of MM for many years [Kumar, 2014, Kumar, 2008, Richardson, 2007]. Combining active agents with lenalidomide/dexamethasone or bortezomib/dexamethasone treatment may yield improved patient outcomes with acceptable toxicity profiles, establishing new global SoC regimens.

With the increasing use of lenalidomide in first-line either in combination with other anti-myeloma drugs or as maintenance therapy after ASCT, pomalidomide is also emerging as a second-line regimen for RRMM. PVd (pomalidomide with twice-weekly bortezomib injected SC and low-dose dexamethasone) showed clinical activity when given in 21-day cycles (i.e., q3w) in a randomized Phase III trial (OPTIMISMM Study, N=559) in patients previously treated with lenalidomide and 1 to 3 prior lines of therapy [San Miguel, 2013; Paludo, 2017; Richardson, 2019]. PVd reduced the risk of progression and death by 39% compared with Vd (HR: 0.61; 95% CI: 0.49, 0.77, $p<0.0001$) with mPFS of 11.2 (vs. 7.1) months and an ORR of 82% (vs. 50%), including 15.7% sCR/CR, 37% VGPR, and 29.5% PR. The safety profile was consistent with known toxicities associated with other immunomodulatory agents, mostly comprising myelosuppression, infections, and neuropathy [Richardson, 2019]. Based on these findings, PVd has been approved by

EMA for treatment of patients with at least 1 prior lines of therapy including lenalidomide and thus has been selected as the control arm for the study. It is anticipated that the combination of PVd will become a SoC option for second line treatment of RRMM in other countries/regions as well.

Belantamab mafodotin has demonstrated strong single-agent activity in two clinical studies (DREAMM-1 and DREAMM-2) conducted in heavily pre-treated participants with RRMM (Trudel, 2018; Trudel, 2019; Lonial, 2020). In the Phase II Study 205678 (DREAMM-2), belantamab mafodotin was further evaluated as monotherapy in RRMM patients at doses of 2.5 mg/kg and 3.4 mg/kg q3w. The belantamab mafodotin dose of 2.5 mg/kg q3w has been recommended as the monotherapy dose for RRMM due to its lower incidence of AEs, less frequent dose delays and reductions, and with similar efficacy as the 3.4 mg/kg dose as measured by ORR. Additional nonclinical studies have been performed to evaluate the anti-tumor activity of belantamab mafodotin in combination with bortezomib, pomalidomide or dexamethasone in two established MM xenograft mouse model. Belantamab mafodotin combinations with pomalidomide or bortezomib provided additional benefit compared to each single agent by significantly increasing survival in both mouse models [GSK Document Number RPS-CLIN-051778, IB V11, 2023].

Based on the nonclinical data available for the belantamab mafodotin/pomalidomide combination and the clinical data for belantamab mafodotin monotherapy, it is therefore hypothesized that B-Pd may result in significant additive or synergistic effect, which could potentially translate into better clinical benefits compared to PVd in RRMM participants who are progressing on or after treatment with a lenalidomide-containing regimen. It is expected that due to its unique MOA, belantamab mafodotin will significantly improve mPFS and may be able to overcome the resistance to previously used drugs in the RRMM population. Initial safety and efficacy data of belantamab mafodotin at multiple dose levels in combination with Pd q4w has been evaluated in an ongoing Phase I/II study conducted by the MCRN (Study 209418, see Section 2.3.4). Preliminary data showed that B-Pd has resulted in early signal of clinical activity. The observed safety profile of B-Pd is consistent with the safety profile of belantamab mafodotin and pomalidomide.

The two-arm design for Study 207499 will enable a comparison of the efficacy and safety between B-Pd q4w and PVd q3w in participants previously treated with lenalidomide and with at least 1 prior line of therapy. The belantamab mafodotin dose of 2.5 mg/kg will be administered in C1 followed by 1.9 mg/kg in C2+ in combination with Pd q4w in participants with RRMM. The primary endpoint for Study 207499 is PFS, defined as the time from the date of randomization until the earliest date of documented disease progression (assessed by a blinded IRC), or death, whichever occurs first. Studies have shown a strong correlation between improvements in PFS and resultant OS benefits in MM, including RRMM [Dimopoulos, 2016; Cartier, 2015]. PFS is an acceptable regulatory endpoint with supporting OS data, with the advantages of requiring shorter duration of follow-up and not being confounded by subsequent treatments. Progression-free survival as a primary endpoint has supported registration of several therapies for MM including lenalidomide-based therapy and the recent regulatory approvals of

carfilzomib and daratumumab combination regimens [Krypolis SmPC, 2019; Darzalex USPI, 2018].

The study will evaluate the duration of response (DoR), minimal residual disease (MRD) negativity rate and OS (defined as the time from the date of randomization until the date of death due to any cause), as well as a comprehensive panel of secondary endpoints (Section 3) including response rates. An Independent Data Monitoring Committee (IDMC) will review data from the interim analysis (IA) (see Section 9.6.1).

4.3. Justification for Dose

4.3.1. Belantamab Mafodotin Dose

Belantamab mafodotin has demonstrated strong single-agent activity in 2 clinical studies (DREAMM-1 and DREAMM-2) conducted in heavily pre-treated participants with RRMM (Trudel, 2018; Trudel, 2019; Lonial, 2020). The belantamab mafodotin monotherapy dose in RRMM has been selected to be 2.5 mg/kg when administered on a q3w schedule. This is based on the results from Study 205678 (DREAMM-2) that evaluated 2 doses of belantamab mafodotin (2.5 and 3.4 mg/kg) administered q3w until disease progression in patients 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 (n=218). Belantamab mafodotin monotherapy has generally been well tolerated, with manageable toxicities. The most frequent AEs (≥30% of participants) were corneal examination findings, cough, increased AST, thrombocytopenia/decreased platelet count, nausea, anemia, diarrhea, pyrexia, and chills (Section 2.3.1).

Belantamab mafodotin at multiple dose levels q4w is currently being evaluated in combination with Pd in the Phase I/II Study 209418 conducted by the Myeloma Canada Research Network in RRMM participants who have failed at least one prior line of therapy. Based on the dose escalation criteria, both 1.92 mg/kg and 2.5 mg/kg doses of belantamab mafodotin have been considered to be safe with early signs of clinical activity when administered in combination with Pd in each 28-day cycle. The observed safety profile of B-Pd is consistent with the safety profile of belantamab mafodotin and pomalidomide/ dexamethasone (see Section 2.3.4).

Based on the totality of the data, the dosing regimen will be belantamab mafodotin 2.5 mg/kg initial dose in Cycle 1 followed by 1.9 mg/kg in Cycle 2 and beyond (C2+) when combined with Pd q4w, for maximizing the tolerability and potential efficacy while limiting the dose delays/interruptions.

Doses may be modified for Grade 2 or higher corneal events based on the KVA scale from 1.9 mg/kg q4w to Dose Level -1 of 1.9 mg/kg every other cycle (every 8 weeks) or in the event of a Grade 4 corneal event on KVA scale to Dose Level -2 of 1.4 mg/kg q8w (Protocol Section 6.7.1). The flexibility of an every other cycle dosing schedule as well as the reduced dose of 1.4 mg/kg may improve tolerability and is anticipated to still allow for meaningful target engagement given the reduction of belantamab mafodotin clearance and disease burden over time.

In conjunction with the Dose Level –1 and Dose Level –2 a more aggressive toxicity management to prevent high-grade corneal events has been included. Using a time-course model developed with data from the DREAMM-2 study, different dose modification schedules were simulated to predict impact on corneal events over time. Results suggested dose modification at Grade 2 vs. Grade 3 corneal event has the potential to decrease the occurrence and duration of time at Grade 3 or higher corneal events. Therefore, the dose modification for corneal events (KVA scale) will occur at the first Grade 2 or greater event.

4.3.2. Pomalidomide Dose

Pomalidomide is a thalidomide analogue indicated, in combination with dexamethasone, for patients with MM who have received at least 2 prior therapies including lenalidomide and a PI and have demonstrated disease progression from their last therapy [POMALYST USPI, 2019; Imnovid SmPC, 2019].

In treatment Arm A, pomalidomide will be administered at the approved dosing regimen for use in combination with dexamethasone, i.e., PO at 4 mg daily on Days 1 to 21 of repeated 28-day cycles [POMALYST USPI, 2019; Imnovid SmPC, 2019]. In treatment Arm B, pomalidomide will be administered per the dosing schedule used in the PVd treatment arm of the OPTIMISMM trial, i.e., PO at 4 mg daily on Days 1 to 14 of repeated 21-day cycles [Richardson, 2019].

4.3.3. Bortezomib Dose

Bortezomib is a proteasome inhibitor approved for use in patients with MM. In Arm B, bortezomib will be administered at the approved dose regimen at 1.3 mg/m^2 SC on Days 1, 4, 8, and 11 of every 21-day cycle for Cycles 1 through 8 and then on Days 1 and 8 for Cycles 9+ [VELCADE USPI, 2019; VELCADE SmPC, 2021].

At least 72 hours should elapse between consecutive doses of bortezomib.

4.3.4. Dexamethasone Dose

Dexamethasone will be administered according to the regimen approved for use in combination with pomalidomide or bortezomib [POMALYST USPI, 2019; Imnovid SmPC, 2019; VELCADE USPI, 2019; VELCADE SmPC,, 2021].

In Arm A, dexamethasone will be administered PO at a dose of 40 mg per day on Days 1, 8, 15, and 22 of each 28-day cycle. For participants who are >75 years old or have comorbidities or are intolerant to 40 mg, dexamethasone may be administered at the lower dose of 20 mg in Arm A at the discretion of the investigator. Refer to Section 6.6.1 and Section 6.7.1 for instructions on dose delays and dose modification guidelines.

In Arm B, dexamethasone will be administered PO at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of every 21-day cycle for the first 8 cycles and on Days 1, 2, 8, and 9 of every 21-day cycle for Cycles 9+. For participants who are >75 years or have comorbidities or are intolerant to 20 mg, the dexamethasone dose may be lowered to 10 mg on day of and day after bortezomib in Arm B at the discretion of the investigator. Refer to Section 6.6.2 and Section 6.7.2 for instructions on dose delays and dose modification guidelines.

4.4. End of Study Definition

A final DCO representing the end of data collection, prior to the end of study (EOS), is defined as 5 years from Last Participant First Visit (LPFV), or when all participants have died, withdrawn consent or have been lost to follow-up, whichever occurs first. Following the final analysis 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 study treatment may continue to receive study treatment 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 the EOS definition is reached. Any participants within an expansion cohort will have the option to move into the PACT phase following the global or country-specific planned final analysis DCO date, whichever is later.

The end of study is defined as the end of the safety follow-up following the last participant last dose i.e. the completion of the PACT phase.

5. STUDY POPULATION

The study will enroll adult participants with RRMM who have been previously treated with lenalidomide and at least 1 prior line of therapy, and who have documented disease progression during, or after, their most recent therapy. No more than 50% of participants with 2 or more prior lines of treatment will be enrolled. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Full criteria are included below.

5.1. Inclusion Criteria

General Eligibility

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 Section 10.1.3, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in this protocol.
2. Male or female, 18 years or older (at the time consent is obtained).

   Note: In the Republic of Korea, a participant must be over 19 years of age inclusive at the time of signing the informed consent.
3. Have a confirmed diagnosis of multiple myeloma as defined by the International Myeloma Working Group (IMWG) criteria [Rajkumar, 2016].

Diagnosis and Disease Status

4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (Section 10.6).
5. Have been previously treated with at least 1 prior line of MM therapy including a lenalidomide-containing regimen (lenalidomide must have been administered for at least 2 consecutive cycles) and must have documented disease progression during or after their most recent therapy.

   Note: Participants treated with lenalidomide ≥10 mg daily for at least 2 consecutive cycles are eligible.

   Participants intolerant or refractory to bortezomib at 1.3 mg/m^2 dose twice weekly dosing schedule are not eligible.
6. Must have at least ONE aspect of measurable disease, defined as one the following:
   a. Urine M-protein excretion ≥200 mg/24 h, or
   b. Serum M-protein concentration ≥0.5 g/dL (≥5.0 g/L), or
   c. Serum free light chain (FLC) assay: involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum free light chain ratio (<0.26 or >1.65) only if patient has no measurable urine or serum M spike.

7. Have undergone autologous stem cell transplant (ASCT) or are considered transplant ineligible. Participants with a history of ASCT are eligible for study participation provided the following eligibility criteria are met:
   a. ASCT was >100 days prior to the first dose of study medication
   b. No active bacterial, viral, or fungal infection(s) present
8. All prior treatment-related toxicities (defined by National Cancer Institute -Common Terminology Criteria for Adverse Events [NCI-CTCAE] v5.0) must be Grade ≤1 at the time of enrolment, except for alopecia.

Organ System Function

9. Adequate organ system functions as defined by the laboratory assessments listed in Table 6.

Table 6 Adequate Organ System Function Based on Safety Assessments

Organ System and Laboratory Tests	Laboratory Values
Hematologic[1]	
Absolute neutrophil count (ANC)	≥1.5×10^9/L
Hemoglobin	≥8.0 g/dL
Platelets	≥75×10^9/L
Hepatic	
Total bilirubin	≤1.5×ULN; (isolated bilirubin >1.5×ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
ALT	≤2.5×ULN
Renal	
eGFR[2]	≥30 mL/min/1.73 m^2
Urine dipstick OR Albumin/creatinine ratio (from spot urine)	Negative/trace (if ≥1+ only eligible if confirmed ≤500 mg/g (56 mg/mmol) by albumin/creatinine ratio (spot urine from first void) ≤500 mg/g (56 mg/mmol)

Abbreviations: ALT=Alanine Aminotransferase; ANC=Absolute Neutrophil Count; eGFR=Estimated Glomerular Filtration Rate; ULN=Upper Limit Of Normal; MDRD=Modified Diet In Renal Disease.
Note: Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may re-test the participant and the subsequent within range Screening result may be used to confirm eligibility.
1. Without growth factor support, blood transfusion or platelet stimulating agents within 14 days of assessment, excluding erythropoietin.
2. As calculated by MDRD formula (Section 10.7).

Contraception

10. Female Participants:

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

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

Is not a woman of childbearing potential (WOCBP)

or

Due to pomalidomide being a thalidomide analogue with a risk for embryofetal toxicity and prescribed under a pregnancy prevention/controlled distribution programme, WOCBP participants will be eligible if they commit either to abstain continuously from heterosexual sexual intercourse or use two methods of reliable birth control (one method that is highly effective plus an additional barrier method) [Section 10.3], beginning at least 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. Thereafter, WOCBP participants must use one contraceptive method that is highly effective (with a failure rate of <1% per year) for a further 3 months for WOCBP in Arm A, and 6 months for WOCBP in Arm B.

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

Two negative pregnancy tests must be obtained prior to initiating pomalidomide therapy in Arm A and Arm B. The first test should be performed within 10 to 14 days and the second test within 24 hours prior to taking pomalidomide therapy.

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.

Additional requirements for pregnancy testing during and after study intervention are provided in Section 10.3 and the SoA.

All WOCBP must agree not to donate eggs (ova, oocytes) for the purpose of reproduction during this period.

11. Male Participants:

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

    Male participants are eligible to participate if they agree to the following from the time of first dose of study treatment until 6 months (Arm A) and 4 months (Arm B) after the last dose of study treatment to allow for clearance of any altered sperm:

    Refrain from donating sperm

    plus either:

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

    or

    Must agree to use contraception/barrier as detailed below

Agree to use a male condom, even if they have undergone a successful vasectomy and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Section 10.3 when having sexual intercourse. Male participants should also use a condom with pregnant females.

12. 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.

5.2. Exclusion Criteria

A participant will not be eligible for inclusion in this study if any of the following criteria are met:

Prior or Concomitant Therapies

1. Active plasma cell leukemia at the time of Screening. Symptomatic amyloidosis, active POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma proliferative disorder, and skin changes).
2. Participants after prior allogeneic SCT.

   Note: Participants who have undergone syngeneic transplant will be allowed only if no history of or no currently active graft versus host disease (GvHD).
3. Systemic anti-myeloma therapy (including chemotherapy and systemic steroids) or use of an investigational drug within 14 days or five half-lives (whichever is shorter) preceding the first dose of study drug; Prior treatment with an anti-MM monoclonal antibody drug within 30 days of receiving the first dose of study drugs.
4. Plasmapheresis within 7 days prior to the first dose of study drug.
5. Received prior treatment with or intolerant to pomalidomide.
6. Received prior BCMA targeted therapy.
7. Intolerant to bortezomib or refractory to bortezomib (i.e., participant experienced progressive disease during treatment, or within 60 days of completing treatment, with a bortezomib-containing regimen of 1.3 mg/m^2 twice weekly).

Prior or Concomitant Diseases or Conditions

8. Evidence of cardiovascular risk including any of the following:
   a. Evidence of current clinically significant untreated arrhythmias, including clinically significant ECG abnormalities including 2nd degree (Mobitz Type II) or 3rd degree atrioventricular (AV) 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 (Section 10.8).
   d. Uncontrolled hypertension
9. Any major surgery within the last 4 weeks.

10. Previous or concurrent invasive malignancy other than multiple myeloma, except:
    a. The disease must be considered medically stable for at least 2 years; or
    b. The participant must not be receiving active therapy, other than hormonal therapy for this disease.
11. Known immediate or delayed hypersensitivity reaction or idiosyncratic reaction to belantamab mafodotin or drugs chemically related to belantamab mafodotin, or any of the components of the study treatment.
12. Evidence of active mucosal or internal bleeding.
13. Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice.

    Note: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) is acceptable if participant otherwise meets entry criteria).
14. Active infection requiring treatment.
15. Known human immunodeficiency virus (HIV) infection, unless the participant can meet all of the following criteria:
    - Established anti-retroviral therapy (ART) for at least 4 weeks and HIV viral load <400 copies/mL
    - CD4+ T-cell (CD4+) counts ≥350 cells/μL
    - 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 6.5.2):
16. Patients with Hepatitis B will be excluded unless the following criteria can be met, Table 7:

Table 7 Hepatitis B criteria

Serology*	Screening	During Study Treatment
HbcAb+, HbsAg-	• HBV DNA undetectable	• Monitoring per protocol (Section 8.2.8) • Antiviral treatment instituted if HBV DNA becomes detectable
HBsAg+ at screen or within 3 months prior to first dose	• HBV DNA undetectable • Highly effective antiviral treatment started at least 4 weeks prior to first dose of study treatment • Baseline imaging per protocol • Participants with cirrhosis are excluded • Japan only: must test HBeAg and HBeAb Eligibility verification should be evaluated and agreed with a	• Antiviral treatment maintained throughout study treatment • Monitoring and management per protocol (Section 8.2.8)

Serology*	Screening	During Study Treatment
	hepatologist (after they record the approval in the patient medical record).	

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
Note: Presence of isolated Hep B surface antibody (HBsAb), indicating previous vaccination, will not exclude a participant
*Japan only: Patients with serology of HBcAb+ and/or HBsAb+ AND HbsAg- are eligible if HBV DNA is undetectable. see Appendix 10 for country-specific requirements.

17. Positive hepatitis C antibody (Hep C Ab) test result or positive hepatitis C RNA (Hep C RNA) test result at Screening or within 3 months prior to first dose of study treatment unless the participant can meet the following criteria:
    - RNA test negative
    - Successful anti-viral treatment (usually 8 weeks duration) is required, followed by a negative HCV RNA test after a washout period of at least 4 weeks.
18. Intolerance or contraindications to anti-viral prophylaxis.
19. Presence of active renal conditions (e.g., infection, severe renal impairment requiring dialysis or any other condition that could affect participant's safety). Participants with isolated proteinuria resulting from MM are eligible, provided they fulfil criteria given in Table 6
20. Ongoing Grade 2 peripheral neuropathy with pain within 14 days prior to randomization or ≥ Grade 3 peripheral neuropathy.
21. Active or history of venous and arterial thromboembolism within the past 3 months.
22. Contraindications to or unwilling to undergo protocol-required anti-thrombotic prophylaxis.
23. Current corneal disease except for mild punctate keratopathy.
24. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions (including laboratory abnormalities) that could interfere with participant's safety, obtaining informed consent or compliance to the study procedures.
25. Pregnant or lactating female.

5.3. Lifestyle Considerations

Following lifestyle restrictions applies while the participants are in the study:

- Contact lenses are prohibited for participants on Treatment Arm A, while they are receiving belantamab mafodotin treatment. Contact lens use may be restarted after a qualified eye care specialist (see Appendix 11) confirms there are no other contraindications. Use of bandage contact lenses is permitted during study treatment as directed by the treating eye care specialist.
- Killed or inactivated vaccines may be administered; however, the response to such vaccines cannot be predicted.

- Participants must fast for at least 2 hours before and 1 hour after pomalidomide dosing in Cycle 1 Day 1 only.
- Because corticosteroids may increase blood glucose concentrations, dose adjustments of antidiabetic agents may be required.
- Participants must not donate blood when receiving pomalidomide, during dose interruptions, and for 28 days following discontinuation of pomalidomide, as transfused blood might be given to a pregnant female whose fetus must not be exposed to the drugs.

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

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. 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. Rescreening of a participant more than once requires discussion with the Medical Director. Rescreened participants must be assigned a new unique participant number that is different from the initial number.

6. STUDY INTERVENTION

6.1. Study Intervention(s) Administered

Refer to the Pharmacy Manual for further details on preparation, handling, and administration instructions for study interventions. A summary of the identity and characteristics of the individual components of the Study Treatment is shown in Table 8.

Table 8 Study Treatment(s) Administered

Treatment Arm	Arm A (Experimental arm): B-Pd	Arm B (Active Comparator arm): PVd
Intervention Name	Belantamab Mafodotin Pomalidomide Dexamethasone	Pomalidomide Bortezomib Dexamethasone
Treatment Cycle	28-day cycle (q4w)	21-day cycle (q3w)
Dose Formulation	Belantamab Mafodotin: lyophilized powder Pomalidomide: capsule Dexamethasone: tablet	Pomalidomide: capsule Bortezomib: solution Dexamethasone: tablet
Route of Administration	Belantamab Mafodotin: IV Pomalidomide: PO Dexamethasone: PO	Pomalidomide: PO Bortezomib: SC Dexamethasone: PO
IV Dosing Instructions	Belantamab mafodotin: Reconstitute belantamab mafodotin lyophilized powder 100 mg/vial with 2.0 mL of sterile WFI, dilute with saline before use. Dilute belantamab mafodotin in normal 0.9% saline to the appropriate concentration for the dose. Doses of belantamab mafodotin are to be administrated as an IV infusion via an infusion pump. See the Belantamab Mafodotin IB for compatible administration materials.	N/A

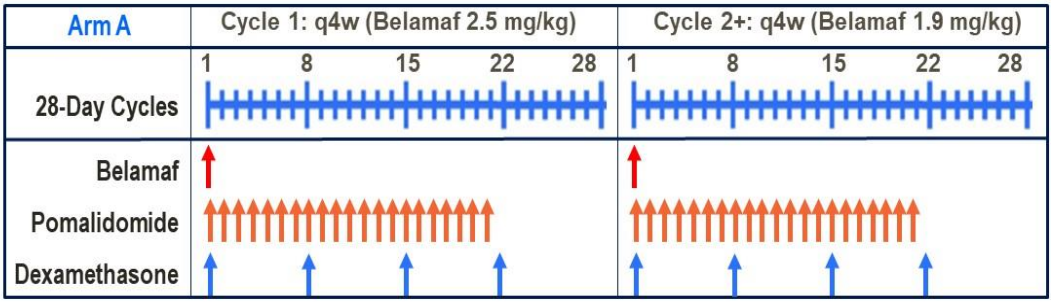
Abbreviations: B-Pd=Belantamab Mafodotin In Combination With Pomalidomide And Dexamethasone; IB=Investigator's Brochure; PVd=Pomalidomide Plus Bortezomib And Dexamethasone; q3w=Every 3 Weeks; q4w=Every 4 Weeks; WFI=Water For Injection.

For both treatment arms, when participants self-administer pomalidomide and dexamethasone at home, compliance 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 Case Report Form (CRF). A record of the number of pomalidomide capsules and dexamethasone tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.1.1. Treatment Arm A Dosing Schedule

The dosing schedule for Treatment Arm A (B-Pd) is depicted in Figure 3.

Figure 3 Summary of Dosing Schedule for Treatment Arm A (B-Pd)



Abbreviations: B-Pd=Belantamab Mafodotin In Combination with Pomalidomide and Dexamethasone; Belamaf=Belantamab mafodotin; q4w=every 4 weeks.

Belantamab mafodotin will be administered intravenously (IV) over at least 30 minutes at a single dose of 2.5 mg/kg dose on Day 1 (D1) of Cycle 1 and 1.9 mg/kg on Day 1 of Cycle 2+ in each 28-day cycle until confirmed PD or unacceptable toxicity. The dose to be administered is based on actual body weight calculated at Baseline. However, 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.

Pomalidomide will be taken orally 4 mg per day on Days 1 to 21 of each 28-day cycle until disease progression, death, unacceptable toxicity, withdrawal of consent, initiation of another anti-myeloma therapy or end of study, whichever occurs first. On Cycle 1 Day 1, pomalidomide should be administered as close as possible to the end of the 1-hour rest period after administration of belantamab mafodotin and no later than 4 hours after the end of the rest period after administration of belantamab mafodotin. On subsequent pomalidomide and belantamab mafodotin co-administration days such as Cycle 2 Day 1, Cycle 3 Day 1, and thereafter, pomalidomide should be administered after the end of the 1-hour rest period after administration of belantamab mafodotin.

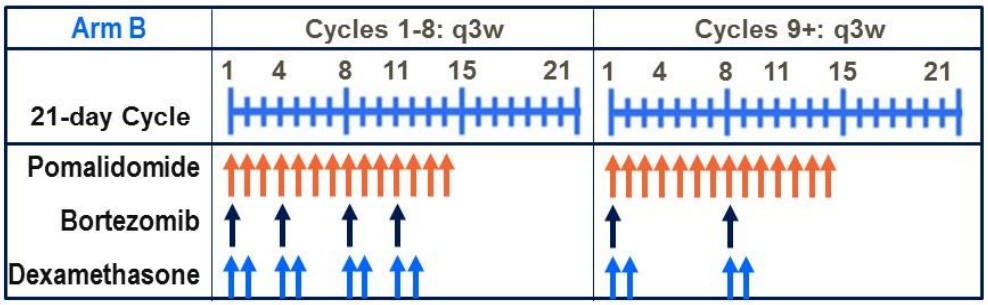
Dexamethasone will be administered orally at a dose of 40 mg per day on Days 1, 8, 15, and 22 of each 28-day cycle. For participants who are >75 years old or have comorbidities or are intolerant to 40 mg, dexamethasone may be administered at the lower dose of 20 mg in Arm A at the discretion of the investigator.

Efficacy assessments will be performed every 4 weeks (±3 days), irrespective of dosing. Detailed guidelines for dose interruption and reduction are provided in Section 6.6.

6.1.2. Treatment Arm B Dosing Schedule

The dosing schedule for Treatment Arm B (PVd) is depicted in Figure 4.

Figure 4 Summary of Dosing Schedule for Treatment Arm B (PVd)



Abbreviations: PVd=Pomalidomide Plus Bortezomib and Dexamethasone; q3w=Every 3 Weeks.

Pomalidomide will be administered PO at 4 mg daily on Days 1 to 14 of each 21-day cycle, with bortezomib injected SC at 1.3 mg/m^2 on Days 1, 4, 8, 11, of each 21-day cycle for Cycles 1 through 8, and on Days 1, 8, of each 21-day cycle for Cycles 9+ until disease progression, death, unacceptable toxicity, withdrawal of consent, initiation of another anti-myeloma therapy or end of study, whichever occurs first.

Dexamethasone will be administered PO at a dose of 20 mg on the day of and day after bortezomib, of each 21-day cycle or on Days 1, 2, 4, 5, 8, 9, 11, 12, of each 21-day cycle for Cycles 1 through 8 and then on Days 1, 2, 8, 9, q3w for Cycles 9+ (Section 1.3). For participants who are >75 years old or have comorbidities or are intolerant to 20 mg, dexamethasone may be administered at the lower dose of 10 mg on the day of and day after bortezomib in Arm B at the discretion of the investigator.

Efficacy assessments will be performed every 4 weeks (±3 days), irrespective of dosing. If either pomalidomide or bortezomib is permanently discontinued due to an AE, the participant will be allowed to continue on the study with the remaining doublet in PVd treatment regimen. Detailed guidelines for dose interruption and reduction are provided in Section 6.6.

6.1.3. Belantamab Mafodotin

6.1.3.1. Belantamab Mafodotin Pre/Post-Medication

Premedication is not required prior to infusion unless deemed medically appropriate by the investigator. Premedication should be considered in any participant who experienced an infusion-related reactions (IRRs) at first or any subsequent infusion with belantamab mafodotin.

IRRs should be managed by guidelines provided in Section 7.1.3. A participant that experiences a Grade 4 IRR associated with belantamab mafodotin should be permanently withdrawn from the study.

6.1.3.2. Corneal Supportive Care Guidelines

Corneal events, which commonly manifest as superficial microcystic keratopathy, have been observed with ADCs, including those conjugated to MMAF.

Further information regarding corneal events associated with belantamab mafodotin, including prophylactic measures are in Section 6.1.3.3. See the SoA (Section 1.3) for guidance on required monitoring for corneal toxicity.

Sites are required to establish a close collaboration with an eye care specialist who will be responsible for assessing participants on Treatment Arm A and managing those who develop corneal events in close communication with Medical Director and possibly a GSK ophthalmologist.

Participants on Treatment Arm A will be assessed by a qualified eye care specialist at Screening/Baseline and then q4w prior to dosing of any study medications, at the start of new treatment cycle, 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 ocular examinations findings, patient's symptoms or vision changes up to and including the sixth dose exam, participants may have their ophthalmologic examinations decreased to once every 3 months. If a participant subsequently develops a change in visual acuity or other ocular symptoms, the participant should be promptly evaluated by a qualified eye care specialist. In case of persistent ophthalmic examination findings, newly developed ocular symptoms or vision changes, the participants will have further ophthalmologic examinations, at least every cycle until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by the qualified eye care specialist.

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

Participants on Treatment Arm B will be assessed by a qualified eye care specialist every 6 months (± 4 weeks) and as clinically indicated and at the End of Treatment (EoT) (see ocular reference manual for further details).

Participants who have corneal signs per Keratopathy Visual Acuity (KVA) scale present at end of treatment will continue to be followed every 3 months for up to 12 months, until they return to their baseline, or are deemed clinically stable by a qualified eye care specialist , whichever comes first. The definition of "clinically stable" may include any Grade 1 finding for mild keratopathy or a one-line change in vision due to intervisit variability, which is well defined/understood. Once clinically stable, an event will not be followed up further and no repeat examination is necessary.

Treatment-related corneal events are to be graded according to the KVA scale. Dose modification guidelines and stopping criteria for belantamab mafodotin treatment-related corneal events based on the KVA scale and KVA scale are provided in Table 15.

6.1.3.3. Ocular Prophylaxis for Treatment Arm A

Ocular prophylaxis should be instituted for all participants on Treatment Arm A as detailed in the SoA. Ocular prophylaxis is provided in Table 9:

Table 9 Prophylactic Measures for Corneal Toxicity Associated with Belantamab Mafodotin

Prophylactic Measure[1]	Dose and Administration	Timing
Preservative-free artificial tears	Must administer in each eye at least 4 to 8 times daily	Administer daily beginning on Cycle 1 Day 1 until End of Treatment.
Cooling eye mask	May apply cooling eye mask to both eyes for approximately 1 hour or as much as tolerated by the participant	At the start of each belantamab mafodotin infusion administration in the first hour for up to 4 hours, as tolerated

1. Dose modifications and treatment for ocular toxicities are discussed in Section 6.6.

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.

Corticosteroid eye drops are not required but can be used if clinically indicated per discretion of an eye-care specialist. Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops (if administered together). If steroid eye drops are deemed medically necessary and prescribed, intraocular pressure must be monitored if used for >7 days.

In the event of ocular symptoms (i.e., dry eyes), the use of artificial tears may be increased up to every 2 hours, as needed.

On Treatment Arm A, contact lenses are prohibited while the participant is on study treatment. Contact lens use may be restarted after a qualified eye care specialist confirms there are no other contraindications.

Use of bandage contact lenses is permitted during study treatment as directed by the treating qualified eye care specialist.

6.1.4. Pomalidomide

Pomalidomide will be taken PO 4 mg per day in both arms on Days 1 to 21 of each 28-day cycle (Arm A) or Days 1 to 14 of each 21-day cycle (Arm B). Pomalidomide capsules should be swallowed whole with water; the capsules should not be opened, broken, or chewed. Pomalidomide 4 mg PO or any reduced dose should be taken in the morning approximately at the same time each day and may be taken at home. Pomalidomide will be administered according to institutional instructions.

If considered appropriate based on an assessment of a participant's underlying risk factors, prophylactic anti-thrombotic agents may be prescribed by the investigator.

Refer to the Pharmacy Manual for further details on preparation, handling, and administration.

6.1.4.1. Dosing for Participants with Hepatic Impairment

Pomalidomide is metabolized primarily by the liver. Following single dose administration, the area under the concentration time curve (AUC) of pomalidomide increased 51%, 58%, and 72% in participants with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to participants with normal liver function.

Therefore, participants with normal hepatic function will receive 4 mg daily dose but participants with mild or moderate hepatic impairment require a 25% reduction in pomalidomide dose while participants with severe hepatic impairment should be receiving pomalidomide at a 50% reduced dose. See the pomalidomide label for further details.

6.1.4.2. Dosing for Participants with Renal Impairment

Participants with mild to severe renal impairment not requiring dialysis do not require a dose adjustment and should be treated per the recommended pomalidomide dose.

In patients with severe renal impairment requiring dialysis, the AUC of pomalidomide increased by 38% and the rate of SAE increased by 64% relative to patients with normal renal function; therefore, dose adjustment by at least 25% is recommended. For these participants, pomalidomide should be administered after the completion of hemodialysis on dialysis days because exposure of pomalidomide could be significantly decreased during dialysis. See the pomalidomide label for further details.

6.1.5. Bortezomib

In Arm B, bortezomib 1.3 mg/m^2 SC will be administered on Days 1, 4, 8, and 11 of every 21-day cycle for Cycles 1 through 8 and then on Days 1 and 8 of every 21-day cycle for Cycles 9+. In participants who experience a local injection site reaction, bortezomib will be delayed until the injection site reaction has resolved and the participant is considered clinically stable.

Bortezomib dosing is based on the participant's body surface area (BSA), which is calculated using a nomogram [West, 2000]. The reconstituted concentration of bortezomib for subcutaneous administration (2.5 mg/mL) is greater than the reconstituted concentration of bortezomib for intravenous administration (1 mg/mL). Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered.

Dose modifications may be required for safety. Refer to Section 6.7 for more information.

At least 72 hours should elapse between consecutive doses of bortezomib.

Sites for each SC injection (thigh, abdomen, or per institutional guidance) should be rotated. New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.

If local injection site reactions occur following administration of bortezomib SC, a less concentrated solution (1 mg/mL instead of 2.5 mg/mL) may be administered SC.

Refer to the Pharmacy Manual for further details on preparation, handling, and administration.

6.1.5.1. Dose Calculation

After determining the participant's BSA in m^2, use the following equations to calculate the total volume (mL) of reconstituted bortezomib to be administered:

For subcutaneous administration (2.5 mg/mL concentration):

[bortezomib dose (mg/m^2) × participant BSA (m^2)] ÷ [2.5 mg/mL] = Total bortezomib volume (mL) to be administered

6.1.5.2. Dosing for Participants with Hepatic Impairment

Participants with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended bortezomib dose. During study treatment, participants with moderate or severe hepatic impairment should be receiving bortezomib at a reduced dose (see Section 6.7.2 for dose reductions). See the bortezomib label for further details.

6.1.5.3. Dosing for Participants with Renal Impairment

No clinically significant differences in the pharmacokinetics of bortezomib were observed based on renal impairment (including patients administered bortezomib after dialysis). Dosing adjustments of bortezomib in participants with renal impairment are therefore not necessary. However, since dialysis may reduce bortezomib concentrations, bortezomib should be administered after the dialysis procedure. See the bortezomib label for further details.

6.1.6. Dexamethasone

In Arm A, dexamethasone will be administered orally at a dose of 40 mg per day on Days 1, 8, 15, and 22 of each 28-day cycle. For participants who are >75 years old or have comorbidities or are intolerant to 40 mg, dexamethasone may be administered at the lower dose of 20 mg in Arm A at the discretion of the investigator.

In Arm B, dexamethasone 20 mg PO will be given on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle for the first 8 cycles and then on Day 1, 2, 8, and 9 for Cycles 9+. Dexamethasone should be taken at the same time of the day and may be taken at home.

For participants who are >75 years old or have comorbidities or are intolerant to 20 mg, dexamethasone may be administered at the lower dose of 10 mg on the day of and day after bortezomib in Arm B at the discretion of the investigator.

Refer to the Pharmacy Manual for further details on preparation, handling, and administration contained in package inserts.

6.2. 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 Pharmacy Manual.

Precaution will be taken to avoid direct contact with the study interventions. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the Medical Director and/or GSK study contact.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Interactive Response Technology System

This is an open-label study. All participants will be centrally randomized using a central Interactive Response Technology (IRT) system. 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.

Randomization list will be done centrally using a randomization schedule generated by the GSK Clinical Statistics Department in RandALL NG or by the Contract Research Organization, which will assign participants in a 1:1 ratio to Treatment Arm A and Treatment Arm B. As this is an open-label study, no blinding of treatment identity is needed for either Treatment Arm A or Treatment Arm B.

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

Cenduit Study-specific User Guide and Clinical Support Helpdesk contact information will be provided to sites.

Study intervention will be dispensed at the study visits summarized in SoA. Returned study intervention should not be re-dispensed to the participants.

6.3.2. Stratification

Factors used for randomization include number of prior lines of therapy (1 vs. 2 /3 vs. ≥4), prior bortezomib treatment (yes or no), and prior anti-CD38 treatment (yes or no).

ISS status (I vs II/III) was a randomization factor but was replaced by prior anti-CD38 treatment (yes or no) in Protocol Amendment 1.

Refer to Section 9.5 for further details on how these randomization factors will be considered within the statistical analyses.

No more than 50% of participants with 2 or more prior lines of treatment will be enrolled. It is anticipated that no more than 15% of participants will be enrolled with 4 or more prior lines of treatment. No cross-over will be allowed.

6.4. 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. 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. For orally administered doses, study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

Belantamab mafodotin will be intravenously administered to participants at the site. Bortezomib will be subcutaneously administered to participants at the site. Administration will be documented in the source documents and reported in the CRF.

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

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

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

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

6.5.1. Permitted Concomitant Therapies

Participants should receive full supportive care during the study, including transfusions of blood products, growth factors, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, as appropriate.

- While the participants are receiving treatment with pomalidomide in either arm of the study, thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the participant's underlying risks, in accordance with local prescribing information.
- Antiviral prophylaxis is recommended in accordance with local prescribing information in participants being treated with bortezomib.
- Concomitant therapy with bisphosphonates is allowed and recommended.
- Concomitant prophylactic treatment for tumor lysis syndrome (according to local standards) in participants with high tumor load should be considered
- Concomitant treatment or prophylaxis using monoclonal antibodies for serious conditions unrelated to MM, such as COVID, may be permitted after discussion with the GSK Medical Director. The preference is that doses are not given on the same day while on belantamab mafodotin treatment (applicable for all treatment cycles).

Participants may receive local irradiation for pain or stability control. Appropriate imaging should be performed to establish presence of new lesions, which would constitute disease progression.

While on study, a participant who is diagnosed with an unrelated malignancy that can be addressed by local therapy can 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.

6.5.2. Prohibited Concomitant Therapies

Chronic treatment with oral steroids other than treatment specified in the SoA is prohibited while the participant is on study, with the exception of low-dose prednisolone (≤10 mg/day) as substitution in participants with adrenal insufficiency. A short course (7 days) of steroids is allowed to manage an AE. Steroids may be used to treat IRRs. Inhaled, intranasal, topical and topical ophthalmic steroids are not prohibited.

Other prohibited therapies 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 protease 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.
- Administration of live or live-attenuated vaccines are contraindicated 30 days prior to the first dose of study treatment and while on study. Use of live or live-attenuated vaccines is further contraindicated for at least 70 days following the last dose of belantamab mafodotin.

For participants receiving belantamab mafodotin:

- Elimination pathways for belantamab mafodotin and cys-mcMMAF have not been characterized in humans. Cys-mcMMAF was not an inhibitor, an inducer, or a good substrate of cytochrome P450 enzymes in vitro. Cys-mcMMAF was shown to be a substrate of P-glycoprotein (P-gp), OATP1B1, and OATP1B3 transporters in vitro.
- Caution should be exercised when belantamab mafodotin is combined with strong inhibitors of P-gp, and strong inhibitors of OATP1B1 and OATP1B3 should be avoided unless considered medically necessary. See the SRM for more information.
- For participants receiving anti-HIV and anti-microbials:

  Anti-HIV and anti-microbials that are OATP inhibitors (list provided in SRM;) and thus prohibited unless considered medically necessary. Preferably alternative antimicrobials and anti-HIV drugs would need to be prescribed to these patients.

Pomalidomide is predominantly metabolized by CYP1A2 and CYP3A4 and is a P-gp substrate. In vitro pomalidomide was neither an inducer nor inhibitor of CYP, nor an inhibitor of transporter proteins P-gp. Co-administration of pomalidomide with a strong CYP1A2 inhibitor, fluvoxamine, approximately doubled pomalidomide exposure. Thus, concomitant use of strong CYP1A2 inhibitors with pomalidomide should be avoided. If a strong CYP1A2 inhibitor must be used, reduce pomalidomide dose by 50%. For further information see the prescribing information.

Bortezomib is a substrate of CYP3A4, CYP2C19 and CYP1A2. Caution should be exercised when bortezomib is combined with CYP3A4 or CYP2C19 substrates. Participants should be closely monitored when bortezomib is administered in

combination with potent CYP3A4 inhibitors for signs of bortezomib toxicity and consider reducing bortezomib dose. Strong CYP3A4 inducers may decrease exposure which may reduce bortezomib toxicity. For further information see the prescribing information.

6.6. Dose Modification and Delay

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

After Cycle 1 Day 1, dose modifications may be made for individual participants based on safety findings.

Dosing delays are also permitted for medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, participant vacation, and/or holidays) but not for participant's decision to delay treatment. For dose delays or interruptions lasting >1 cycle, the Medical Director should be contacted to discuss restarting treatment.

For potential overlapping toxicities, such as hematologic toxicity, the investigator should use their clinical judgement on which agent should be dose-reduced first, or for severe toxicities, more than one agent can be held/ dose modified. Whenever possible, step-wise dose modification is recommended first in order to minimize the potential to compromise treatment efficacy.

The reason for any dose delay must be documented in the participant's electronic Case Report Form (eCRF) and clinic record. Where safety findings cannot be ascribed solely to one study treatment, follow the guidance provided in Table 14.

Efficacy and safety assessments must remain the same as scheduled for the study regardless of dose delay/interruption or modification. In any dosing delay scenario, response assessments should be carried out q4w (±3 days) in Arm A and at q3w±3 days (for safety) or q4w±3 days (for efficacy) in Arm B as described in the SoA (see Section 1.3). For treatment delays within the treatment window, subsequent treatment dates will not be adjusted.

6.6.1. Guidance on Dose Delays for Treatment Arm A (B-Pd)

Table 10 summarizes the guidance on dose interruptions/delays for Treatment Arm A.

Table 10 Dose Delays for B-Pd in Treatment Arm A

Scenario	Actions for belantamab mafodotin	Actions for Pd
1. Delay of only belantamab mafodotin	After Cycle 1, a window of ± 3 days is acceptable for belantamab mafodotin dosing, but subsequent dosing dates will not be adjusted. Outside this window, treatment should be given on D1 of the next planned cycle, q4w.	Continue Pd according to the regimen outlined in the SoA.
2. Delay of only pomalidomide	Continue belantamab mafodotin according to the schedule, q4w as outlined in the SoA.	If pomalidomide treatment cannot be administered as planned, when a participant is ready to resume treatment, pomalidomide may be restarted at the appropriate time in the planned dosing regimen. If the participant is unable to receive pomalidomide on D1-21 of a given cycle, treatment could resume on D1 of next cycle, and missed pomalidomide doses will not be made up. Dexamethasone should be administered on the planned treatment day.
3. Delay of only dexamethasone	Continue belantamab mafodotin according to the schedule, q4w as outlined in the SoA.	If participant is ready to resume treatment, dexamethasone may be restarted at the appropriate time in the planned dosing regimen (e.g., on Days 1, 8, 15, 22 q4w). If the participant is unable to receive dexamethasone on D22 of a given cycle, treatment could resume on D1 of next cycle, and missed dexamethasone doses will not be made up. Pomalidomide should be administered on the planned treatment day.
4. Delay of Pd components in Arm A	Continue belantamab mafodotin according to the schedule, q4w as outlined in the SoA if Pd are delayed.	Follow Pd delay guidelines as outlined above for pomalidomide only delay (Scenario 2) or dexamethasone only delay (Scenario 3).
5. Delay of both belantamab mafodotin and Pd	Follow belantamab mafodotin only delay guidelines as outlined above (Scenario 1).	Follow Pd delay guidelines as outlined above for pomalidomide only delay (Scenario 2) or dexamethasone only delay (Scenario 3).
6, Permanent discontinuation of belantamab mafodotin	N/A	Pd will be allowed to continue according to the schedule, q4w as outlined in the SoA.
7. Permanent discontinuation of either pomalidomide or dexamethasone or both	Continue belantamab mafodotin according to the schedule, q4w as outlined in the SoA.	If either pomalidomide or dexamethasone is permanently discontinued, the remaining drug in Pd combination will be allowed to continue in Arm A.

Abbreviations: B-Pd=Belantamab Mafodotin In Combination with Pomalidomide And Dexamethasone; N/A=Not Applicable; Pd=Pomalidomide In Combination with Dexamethasone; q4w=Every 4 Weeks; SoA=Schedule of Activities.

6.6.2. Guidance on Dose Delays for Treatment Arm B (PVd)

Table 11 summarizes the guidance on dose interruptions/delays for Treatment Arm B.

Table 11 Dose Delays for PVd in Treatment Arm B

Scenario	Actions for Pomalidomide	Actions for Bortezomib	Actions for Dexamethasone
1. Delay of only pomalidomide	If pomalidomide treatment cannot be administered as planned, when a participant is ready to resume treatment, pomalidomide may be restarted at the appropriate time from D1 to D14 of any 21-day cycle in the planned dosing regimen. If the participant is unable to receive pomalidomide on D1-14 of a given cycle, treatment could resume on D1 of next cycle, and missed pomalidomide doses will not be made up.	Continue bortezomib according to the regimen outlined in the SoA.	Continue dexamethasone according to the regimen outlined in the SoA.
2. Delay of only bortezomib	Continue pomalidomide according to the regimen outlined in the SoA.	If bortezomib treatment cannot be administered as planned, when a participant is ready to resume treatment, bortezomib may be restarted at the appropriate time (e.g., on Days 1, 4, 8, or 11, q3w) in the planned dosing regimen. If the participant is unable to receive bortezomib on D11 of a given cycle, treatment could resume on D1 of next cycle, and missed bortezomib doses will not be made up.	Continue dexamethasone according to the regimen outlined in the SoA.
3. Delay of only dexamethasone	Continue pomalidomide according to the schedule, q3w as outlined in the SoA.	Continue bortezomib according to the regimen outlined in the SoA.	If participant is ready to resume treatment, dexamethasone may be restarted at the appropriate time in the planned dosing regimen (e.g., on Days 1, 2, 4, 5, 8, 9, 11, 12, of each 21-day cycle (q3w) for C1-8 and then then on Days 1, 2, 8, 9, q3w for C9+). If the participant is unable to receive dexamethasone on D15 of a given cycle,

Scenario	Actions for Pomalidomide	Actions for Bortezomib	Actions for Dexamethasone
			treatment could resume on D1 of next cycle, and missed dexamethasone doses will not be made up.
4. Delay of Pd components in Arm B	Follow the guidelines as outlined above for pomalidomide only delay (Scenario 1).	Continue bortezomib according to the regimen outlined in the SoA.	Follow the guidelines as outlined above for dexamethasone only delay (Scenario 3).
5. Delay of Vd components in Arm B	Continue pomalidomide according to the schedule, q3w as outlined in the SoA.	Follow the guidelines as outlined above for bortezomib only delay (Scenario 2).	Follow the guidelines as outlined above for dexamethasone only delay (Scenario 3).
6. Delay of both pomalidomide and bortezomib	Follow the guidelines as outlined above for pomalidomide only delay (Scenario 1).	Follow the guidelines as outlined above for bortezomib only delay (Scenario 2).	Continue dexamethasone according to the regimen outlined in the SoA.
7, Permanent discontinuation of pomalidomide	N/A	Continue bortezomib according to the schedule, q3w as outlined in the SoA.	Continue dexamethasone according to the regimen outlined in the SoA.
8. Permanent discontinuation of bortezomib	Continue pomalidomide according to the schedule, q3w as outlined in the SoA.	N/A	Continue dexamethasone according to the regimen outlined in the SoA.
9. Permanent discontinuation of either pomalidomide and bortezomib or dexamethasone alone	Continue the remaining drug(s) according to the schedule, q3w as outlined in the SoA	Continue the remaining drug(s) according to the schedule, q3w as outlined in the SoA	Continue the remaining drug(s) according to the schedule, q3w as outlined in the SoA

Abbreviations: D=Day; N/A=Not Applicable; PVd=Pomalidomide Plus Bortezomib And Dexamethasone; q3w=Every 3 Weeks; SoA=Schedule of Activities; Vd=Bortezomib Plus Dexamethasone.

6.7. Dose Reductions Due to Toxicity

6.7.1. Guidance on Dose Reductions in Treatment Arm A (B-Pd)

After Cycle 1, participants may have their dose delayed or reduced for toxicities according to the recommendations. See Section 4.3 for the justification of dose. See Table 13 for dose modification guidelines for belantamab mafodotin-related AEs, Table 14 for guidelines for drug-related otherwise specified AEs, and Table 15 for dose modification guidelines for corneal-related AEs associated with belantamab mafodotin based on the KVA scale.

- Belantamab mafodotin will be administered at 2.5 mg/kg on D1 of Cycle 1 and then followed at 1.9 mg/kg on Day 1 of Cycle 2+ q4w.
- Belantamab mafodotin dose may be reduced only for corneal toxicities, based on KVA scale, from 1.9 mg/kg q4w to Dose Level -1 of 1.9 mg/kg every other cycle (or

every 8 weeks). For Grade 4 corneal AEs, reduce to Dose Level -2 of 1.4 mg/kg q8w. Belantamab mafodotin dose modification for other treatment-related toxicity is described in Table 13 and Table 14.

- If the participant cannot tolerate belantamab mafodotin at the lowest dose level, subsequent doses may be delayed/interrupted or discontinued. If belantamab mafodotin treatment is delayed/interrupted, the participant may continue Pd therapy.

Table 12 Belantamab Mafodotin Dose Levels for Corneal Toxicities Management: Treatment Arm A

Dose Level	Belantamab Mafodotin Dose
Dose Level -1*	1.9 mg/kg IV q8w *(Only for Grade 2 and Grade 3; Corneal toxicities based on KVA Scale)*
Dose Level -2*	1.4 mg/kg IV q8w *(Only for Grade 4 Corneal toxicities based on KVA Scale)*

*: Dose modifications are permitted for Corneal toxicities based on KVA Scale, see Table 15

Table 13 Dose Modifications Guidelines for Belantamab Mafodotin Treatment-Related Adverse Events

Toxicity	Grade/Symptoms	Recommendations for Belantamab Mafodotin
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 pre-held dose • If confirmed on re-test and no clear evidence of disease progression ○ Interrupt treatment with belantamab mafodotin ○ Repeat testing within 4 weeks ○ If spot urine <2000 mg/g (224 mg/mmol), may restart belantamab mafodotin at same dose level ○ 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[b]

Toxicity	**Grade/Symptoms**	**Recommendations for Belantamab Mafodotin**
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) Graded according to NCI-CTCAE criteria	Grade 3	• No bleeding: continue treatment with at the same dose level
		• With bleeding: withhold the dose, continue treatment after recovery at the same dose level • Consider additional supportive treatment (e.g., transfusion), as clinically indicated and per local practice.
	Grade 4	• Withhold the dose. Consider restarting at the same dose level 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 >25x109/L continuing treatment at the same dose level may be considered after discussion with the Medical Director
Afebrile Neutropenia Graded according to NCI-CTCAE criteria	Grade ≥3 (Defined as ANC <1.0x109/L)	• If noted on Day 1 of any cycle, withhold belantamab mafodotin dose • Resume belantamab mafodotin at pre-held dose once neutropenia recovers to Grade ≤ 2 (ANC ≥ 1.0x109/L) on Day 1 of the subsequent cycle. • Prophylactic antibiotics, per physician discretion and local institutional guidance. Consider growth factors. • Local guidance must be followed for hematological monitoring, if more conservative than the protocol SoA specifications. • In cases of frequent recurrent neutropenia (ANC <1.0x109/L), consider at the same dose level of belantamab mafodotin

Toxicity	Grade/Symptoms	Recommendations for Belantamab Mafodotin
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 <1.0×10^9/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 at the same dose level of belantamab mafodotin, if neutropenia was drug-related.
Infusion reaction2 Graded according to NCI-CTCAE criteria	Grade 2	• Stop the infusion, provide medical treatment and continue at a reduced 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 premedicated.
	Grade 4	• Permanently discontinue
Pneumonitis Graded according to NCI-CTCAE criteria	Grade 2	• Withhold treatment with belantamab mafodotin • Upon recovery to Grade 1, restart treatment at the same dose level. • Rechallenge with the same dose must be discussed with the GSK Medical Director
	Grade 3-4	• Permanently discontinue treatment with belantamab mafodotin

Abbreviations: ANC=absolute neutrophil count; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events v05; SoA=schedule of activities; TLS=tumor lysis syndrome; ULN=upper limit of normal.

1. GSK Medical Director may consult GSK's renal safety panel about plans to continue therapy.
2. If symptoms resolve within 1 h of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated at the next scheduled dose.

Table 14 General Dose Modification and Management Guidelines for Drug-Related Adverse Events Not Otherwise Specified

Severity	Management	Follow-up
Grade 1	• Administer symptomatic treatment as appropriate • Continue study drug(s)[2]	• Provide close follow-up to evaluate for increased severity, no dose modification necessary
Grade 2	• Administer symptomatic treatment • Investigate etiology • Consider consulting subspecialist, and/or diagnostic procedure	Symptoms resolved in ≤7 days: • Continue after resolution at the current dose Symptoms ongoing >7 days or worsening: • Delay study drug3, or consider at the same dose level • If recovery takes >3 weeks, consult GSK Medical Director • 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 restarting at the same dose level • Consider consultation with GSK Medical Director. • 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 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 MM it is agreed that benefits outweigh the risks for a given participant

1. Graded according to NCI-CTCAE v5.0 criteria.
2. Treatment-related decisions can be made based on local laboratory results if central results are not available or delayed.
3. In case a dose is delayed, the participant should wait for the next scheduled dose to resume treatment.

Table 15 KVA Scale and Dose Modification Guidelines for Belantamab Mafodotin Treatment-Related Corneal Events Based on KVA Scale

KVA Scale	Grade 1	Grade 2	Grade 3	Grade 4
Corneal Events				
Corneal examination finding(s)	Mild superficial keratopathy[1]	Moderate superficial keratopathy[2]	Severe superficial keratopathy[3]	Corneal epithelial defect[4]
Change in Snellen-equivalent BCVA[5,6,7]	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
Recommended Dosage Modifications per KVA scale				
Recommended Dosage Modifications[8]	Continue treatment at current dose.	Withhold treatment and allow to recover to Grade ≤1. The participant should restart at a lower dose, as follows: · If toxicity was identified prior to dosing Cycle 2, then the participant should be dosed at 1.9 mg/kg every 4 weeks thereafter, as planned. · If toxicity was identified Cycle 2+, the participant should be dosed at 1.9 mg/kg every 8 weeks thereafter.	Follow the instructions provided for Grade 2.	Hold treatment and allow to recover to Grade ≤1. Participant may be restarted following benefit/risk assessment and discussion between the eye care specialist, the investigator, and the Sponsor. If restart is approved, participant should be restarted at 1.4 mg/kg every 8 weeks.

Abbreviations: BCVA=Best-Corrected Visual Acuity; KVA=Keratopathy Visual Acuity.

1. Mild superficial keratopathy=mild superficial punctate keratopathy (documented worsening from baseline), **with or without** symptoms.
2. Moderate superficial keratopathy=any/or a combination of: moderate superficial punctate keratopathy, patchy microcyst like deposits, subepithelial haze (peripheral), or a new peripheral stromal opacity.
3. Severe superficial keratopathy=any/or a combination of: severe superficial punctate keratopathy, diffuse microcyst like deposits involving the central cornea, subepithelial haze (central), or a new central stromal opacity.

4. Corneal epithelial defect such as corneal ulcers. Corneal ulcer by definition means an epithelial defect with underlying stromal infiltration.
5. Changes in visual acuity due to treatment-related corneal findings.
    - For participants who have BCVA worse than 20/20 in either eye at baseline, dose modification for that eye will be determined by the worsening of vision from baseline only (not by absolute BCVA at the visits).
    - If a participant has a baseline BCVA of 20/200 or worse in an eye, then belantamab mafodotin related changes in vision in the other eye will drive the dose modification. If a participant has baseline BCVA of 20/200 or worse in both the eyes, then the decision to delay or reduce belantamab mafodotin dose will be based on Principal Investigator's assessment of benefit vs. risk based on corneal examination findings following a discussion with the qualified eye care specialist such as ophthalmologist/optometrist.
    - Dose modification should be based on the most severe grade. If eyes differ in severity, dose modification guideline should be applied based on the more severe eye.
6. 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.
7. If a participant has cataract surgery during the study the BCVA should be re-baselined (after the BCVA stabilizes if there are no corneal findings but prior to any further belantamab mafodotin administration) and subsequent visual acuity must then be assessed from this new "best" baseline value (see details in Ocular Study Reference Manual).
8. Dose modification should be based on the most severe finding. If eyes differ in severity, dose modification guideline should be applied based on the more severe eye. Dose reductions of belantamab mafodotin will be triggered by Grade 2 or worse events of ocular exam findings or decrease in BCVA on day of dosing.

In Arm A, pomalidomide and dexamethasone dose reductions will be permitted in each 28-day treatment cycle (i.e., q4w). Permitted dose level -1, level -2, and level -3 reductions for pomalidomide and dexamethasone in Arm A are shown in Table 16 and Table 17.

Table 16 Permitted Dose Reductions for Pomalidomide

Starting Dose Level	Dose Level -1	Dose Level -2	Dose Level -3
4 mg	3 mg	2 mg	1 mg

Table 17 Permitted Dose Reductions for Dexamethasone in Arm A

Starting Dose Level	Dose Level -1	Dose Level -2
40 mg (≤75 years of age)	20 mg	12 mg
20 mg (>75 years of age)	12 mg	8 mg

See Table 19 for dose modifications guidelines for pomalidomide-related AEs and Table 21 for dexamethasone-related AEs. If recovery from toxicities is prolonged beyond 21 days in 28-day cycles, then the dose of dexamethasone will be decreased by 1 dose level.

6.7.2. Guidance on Dose Reductions in Treatment Arm B (PVd)

Pomalidomide dose reduction will be permitted in each 21-day treatment cycle (i.e., q3w). Permitted dose level -1, level -2 and level -3 reductions for pomalidomide are shown in Table 18. Detailed dose modification guidelines for pomalidomide-related AEs are described in Table 19.

Table 18 Permitted Dose Reductions for Pomalidomide

Starting Dose Level	Dose Level -1	Dose Level -2	Dose Level -3
4 mg	3 mg	2 mg	1 mg

Table 19 Dose Modifications Guidelines for Hematologic and Other Toxicities associated with Pomalidomide Plus Dexamethasone

Toxicity	Dose Modification
Neutropenia	
ANC <500 per μL (<0.5×10^9/L) or febrile neutropenia (fever ≥38.5°C and ANC <1000 per μL [<1×10^9/L]) ANC return to ≥500 per μL	Interrupt pomalidomide treatment, follow CBC weekly Resume pomalidomide treatment at 3 mg daily
For each subsequent drop <500 per μL (<0.5×10^9/L) Return to ≥500 per μL	Interrupt pomalidomide treatment Resume pomalidomide treatment at 1 mg less than the previous dose
Thrombocytopenia	
Platelet count <25,000 per μL (<25×10^9/L) Platelet count returns to ≥50,000 perμL (≥50×10^9/L)	Interrupt pomalidomide treatment, follow CBC weekly Resume pomalidomide treatment at 3 mg daily
For each subsequent drop <25,000 perμL (<25×10^9/L) Return to ≥50,000 perμL (≥50×10^9/L)	Interrupt pomalidomide treatment Resume pomalidomide treatment at 1 mg less than the previous dose
Cutaneous reactions	
Grade 2–3	Consider dose interruption or discontinue pomalidomide
Grade 4	Permanently discontinue pomalidomide
Hypersensitivity	
Angioedema and anaphylaxis reactions	Permanently discontinue pomalidomide
For other non-hematologic toxicities judged to be related to pomalidomide	
Grade 3-4	Hold pomalidomide treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to Grade ≤2

Abbreviations: ANC=Absolute Neutrophil Count; CBC=Complete Blood Count.

- To initiate a new cycle of pomalidomide, the neutrophil count must be ≥500 per μL, the platelet count must be ≥50,000 per μL (≥50×10^9/L).
- In case of neutropenia, the physician should consider the use of growth factors.
- If adverse reactions occur after dose reductions to 1 mg, then the medicinal product should be discontinued.
- Concomitant use of strong CYP1A2 inhibitors (e.g., ciprofloxacin, enoxacin and fluvoxamine) should be avoided. If strong inhibitors of CYP1A2 must be used, reduce pomalidomide dose by 2 dose levels.

Dexamethasone dose reduction in Arm B will be permitted in each 21-day treatment cycles (i.e., q3w). If recovery from toxicities is prolonged beyond 14 days in 21-day cycles, then the dose of dexamethasone will be decreased by 1 dose level. Dose modification guidelines are described in Table 21 for dexamethasone-related AEs.

Permitted dose level -1 and level -2 reductions for dexamethasone in Arm B are shown in Table 20.

Table 20 Permitted Dose Reductions for Dexamethasone in Arm B

Starting Dose Level	Dose Level -1	Dose Level -2
20 mg (≤75 years of age)	12 mg	8 mg
10 mg (>75 years of age)	—	8 mg

Table 21 Dose Modifications Guidelines for Dexamethasone-Related AEs

Toxicity	Dose Modification
Dyspepsia Grade 1-2 Dyspepsia Grade ≥3	Maintain dose and treat with H2 receptor blockers or equivalent. Decrease by 1 dose level if symptoms persist. Interrupt dose until symptoms are controlled. Add H2 blocker or equivalent and decrease 1 dose level when dose restarted.
Edema Grade ≥3	Use diuretics as needed and decrease by 1 dose level.
Confusion or mood alteration Grade ≥2	Interrupt dose until symptoms resolve. When dose restarted decrease by 1 dose level.
Muscle weakness Grade ≥2	Interrupt dose until muscle weakness Grade ≤1. Restart with decrease by 1 dose level.
Hyperglycemia Grade ≥3	Decrease dose by 1 dose level. Treat with insulin or oral hypoglycemic agents as needed
Acute pancreatitis	Discontinue dexamethasone treatment.
Other Grade ≥3 dexamethasone-related AEs	Stop dexamethasone dosing until AE resolves to Grade ≤2. Resume with 1 dose level decrease.

Abbreviations: AE = adverse event; H2 = histamine H2 receptor.

Bortezomib dose reduction will be permitted in each 21-day treatment cycle (q3w). Detailed dose modification guidelines are described in Table 23 for bortezomib-related AEs.

Permitted dose level -1 and level -2 reductions for bortezomib in Arm B are shown in Table 22.

Table 22 Permitted Dose Reductions for Bortezomib in Arm B

Starting Dose Level	Dose Level -1	Dose Level -2
1.3 mg/m^2	1.0 mg/m^2	0.7 mg/m^2

Table 23 Dose Modification Guidelines for Hematologic and Other Toxicities Associated with Bortezomib Plus Dexamethasone in Arm B

Toxicity	Grade[1]	Recommendations
Hematological Toxicity[2]	Grade ≥4	• Withhold bortezomib therapy until symptoms of toxicity have resolved. • Bortezomib may then be reinitiated with 1 dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2).
Non-hematological toxicities (excluding peripheral neuropathy)[2]	Grade ≥3	• Withhold bortezomib therapy until symptoms of toxicity have resolved to Grade 1 or baseline. Then, bortezomib may be reinitiated with 1 dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). • For bortezomib-related neuropathic pain and/or peripheral neuropathy, hold or modify bortezomib as outlined below.
Peripheral neuropathy[3]	Grade 1	• Asymptomatic, without pain or loss of function: no action needed • With pain: reduce bortezomib dose to 1 mg/m^2
	Grade 2	• Moderate symptoms; limiting instrumental ADL[4] • With no pain: reduce bortezomib dose to 1 mg/m^2 • With pain: withhold bortezomib therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 once per week.
	Grade 3	• Severe symptoms; limiting self-care ADL[5] • Withhold bortezomib therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 once per week.
	Grade 4	• Life-threatening consequences; urgent intervention indicated. • Discontinue bortezomib

Abbreviations: ADL=activities of daily living; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events.

1. Grading based on NCI-CTCAE v5.0, 27 November 2017.
2. Criteria and Recommendations taken from Table 2 of Bortezomib Approved Labelling.
3. Criteria and recommendations for peripheral neuropathy are taken from Section 2.7 and Table 5 of Bortezomib Approved Labelling.
4. Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using phone, managing money, etc.
5. Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

6.8. Continued Access to Study Intervention after the Final Analysis and the End of the Study

Study participants that continue to benefit from study intervention beyond the final analysis DCO date will continue to have access to study intervention until the end of the study as defined in Section 4.4. There is no planned intervention following the end of the study.

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

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

Participants who have not died, withdrawn consent or have been lost to follow-up and who continue to receive treatment at the time of the final analysis may continue to receive the same study drug(s) as received up until final analysis DCO date if in the opinion of their treatment physician, they are continuing to derive clinical benefit from continued treatment, and they do not meet any protocol-defined treatment discontinuation criteria (See Section 7.1). This includes the global study population and participants in any country-specific expansion cohorts. Any participants within an expansion cohort will have the option to move into the PACT phase following the global or country-specific planned final analysis DCO date, whichever is later. Study treatment will continue until a protocol defined treatment discontinuation criterion, as assessed by the investigator, has been met (see Section 7.1)

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 (Arm A only), overdoses and pregnancy while receiving study drugs. 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 in accordance with Section 8.3.1. Pre-specified ocular data (Arm A only) will be reported as outlined in Section 8.3.1.

During the PACT phase, recording and follow up of SAEs, AEs leading to treatment discontinuation, overdose, pregnancy and pre-specified ocular data (Arm A only) will be done via paper forms

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- Confirmed disease progression, as defined by IMWG criteria [Kumar, 2016]
- Unacceptable toxicity to the combination
- Note: see below for advice on unacceptable toxicity for individual agents.
- Participant has met any of the protocol defined safety stopping criteria.
- Pregnancy

Discontinuation of Individual Components of Combination Regimens

At the discretion of the investigator, participant who must permanently discontinue any of the individual agents may continue with the rest of the study treatment until protocol-defined treatment discontinuation criteria are met. Before discontinuing study treatment strictly due to disease progression, sites must contact the GSK Medical monitor to confirm progression meets IMWG criteria [Kumar, 2016]. The GSK Medical monitor will review the central laboratory results as well as imaging results (if applicable) to confirm progressive disease as per IMWG criteria. If progressive disease criteria are not met, the investigator retains the decision to determine if treatment should be discontinued. However, the reason for treatment discontinuation should only be documented as disease progression if IMWG criteria for confirmed disease progression are met.

In addition, 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
- Participant is lost to follow-up
- The study is closed or terminated

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

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

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

Participants who permanently discontinue study treatment for reasons other than disease progression will remain in the study and will be followed for PFS according to the protocol schedule described in Section 1.3 until (whichever occurs first):

- New anti-myeloma therapy is initiated
- Disease progression
- Death
- Withdrawal of consent
- Loss to follow-up
- End of study

Participants with documented disease progression whilst on treatment, or during PFS follow-up, will be followed for PFS2 and OS until death, withdrawal of consent, loss to follow-up or DCO at final analysis (as described in Section 4.4), whichever occurs first.

Participants who have treatment-related ocular AEs at the EoT should be followed to resolution, as described in the SoA and Section 8.2.6 before discontinuing from the study.

The primary reason for discontinuation of any of the individual components of the combination regimen study treatment must be documented independently in the medical record and within the clinical study database.

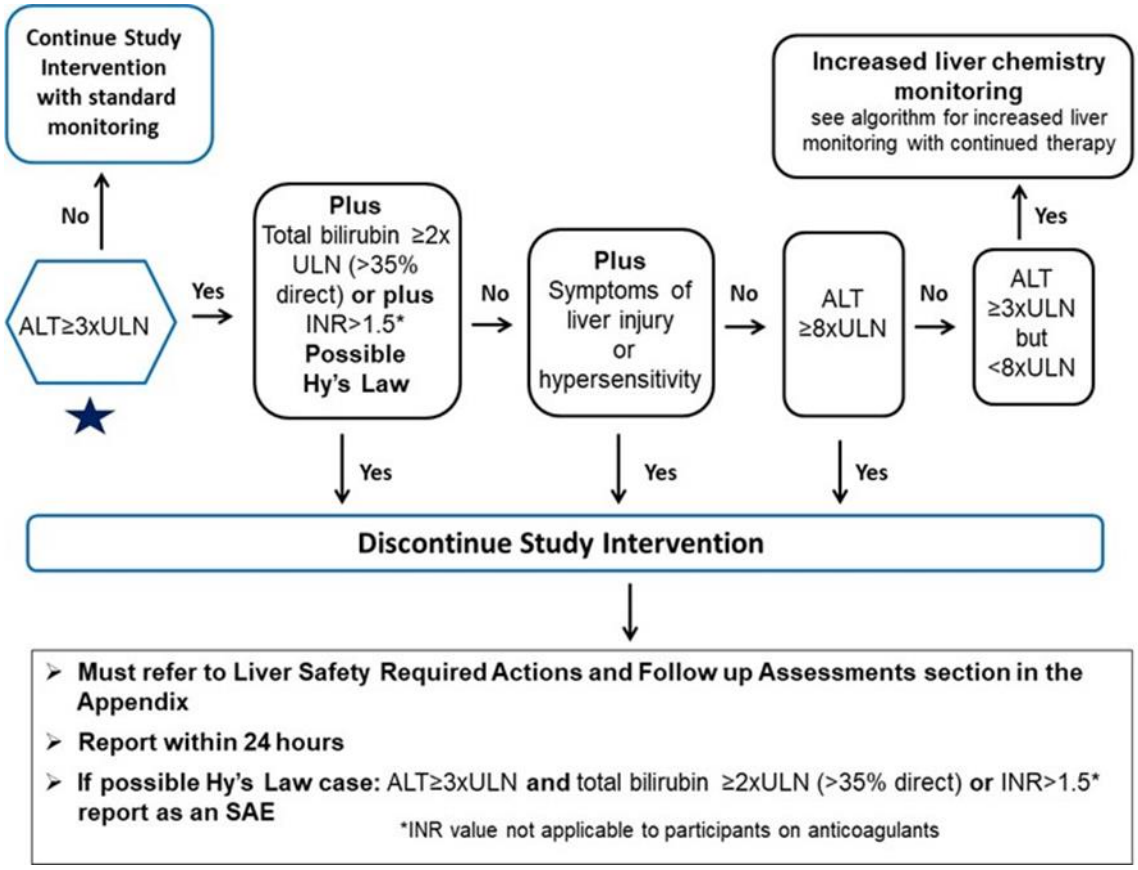
All participants must be followed for survival, up to DCO at final analysis as defined in the protocol. Discontinuation of study treatment does not impact a participant's participation in the study. The participant should comply to the protocol schedule of assessments and data collection should continue.

If the participant does not agree to continue in-person visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the participant, a contact with a relative or treating physician, or collecting information from medical records. The approach taken should be recorded in the medical records. A participant who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

7.1.1. Liver Chemistry Stopping Criteria

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

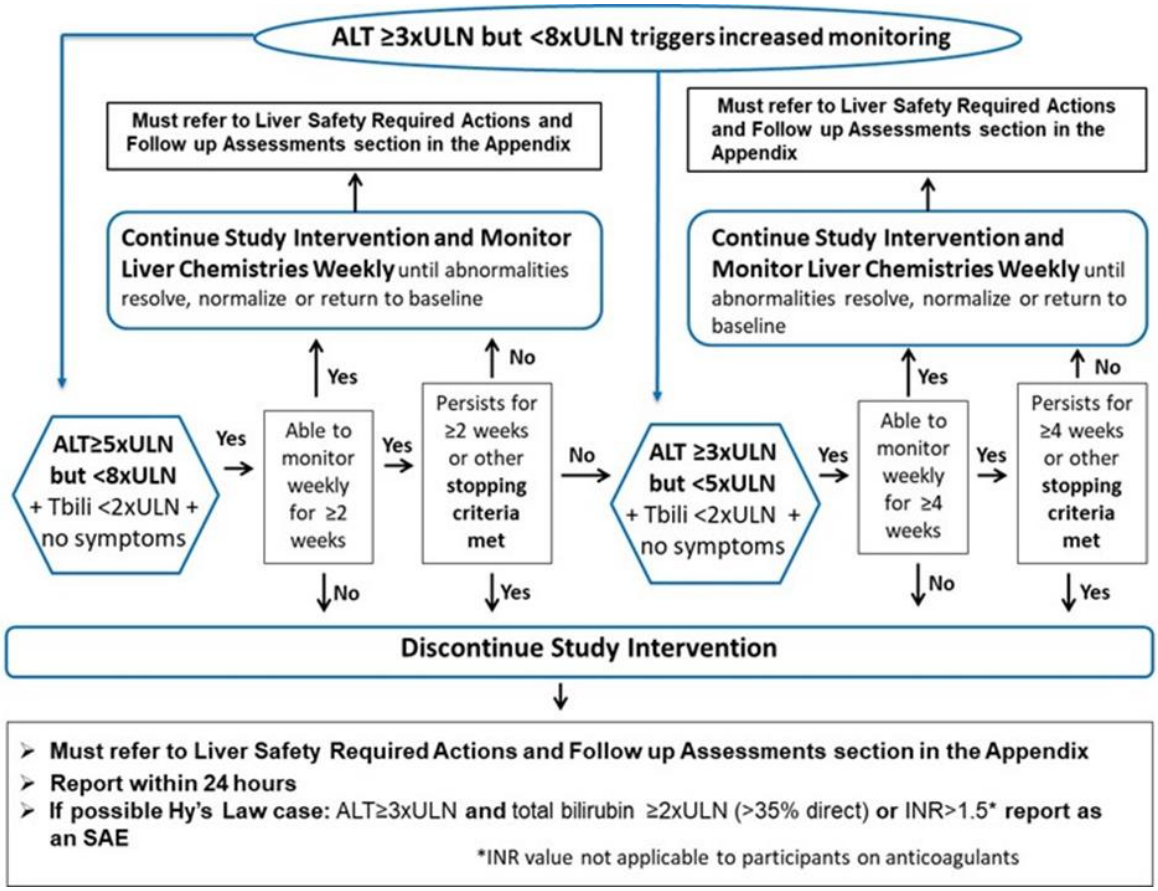
Figure 5 Liver Stopping and Monitoring Event Algorithm



Abbreviations: ALT=Alanine Aminotransferase; INR=International Normalized Ratio; SAE=Serious Adverse Event; ULN=Upper Limit of Normal

Refer to Section 10.4 for required Liver Safety Actions and Follow-Up Assessments and for required process for study intervention restart/rechallenge, if considered for the participant.

Figure 6 Liver Monitoring Event Algorithm with Continued Therapy for ALT≥3×ULN but <8×ULN



Abbreviations: ALT=Alanine Aminotransferase; INR=International Normalized Ratio; SAE=Serious Adverse Event; Tbili=Total Bilirubin; ULN=Upper Limit of Normal.

Refer to Section 10.4 for required Liver Safety Required Actions and Follow-up Assessments and for required process for study intervention restart/rechallenge, if considered for the participant.

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

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

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

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

Refer to Section 10.4 and the SRM for full guidance.

7.1.2. Corneal Event Stopping Criteria

Belantamab mafodotin dose delay/interruption and stopping criteria are to be based on the Keratopathy Visual Acuity (KVA) Scale (Table 15).

Participants who develop Grade 4 corneal events according to the KVA scale must be discussed in detail between the treating qualified eye care specialist (Section 10.11), the GSK Medical Director and possibly a third party ophthalmologist, in order to determine whether the participant can be allowed to continue treatment with belantamab mafodotin, or permanently discontinue treatment (Section 6.7.1). The decision will be documented in study files, together with individual assessment of risk-benefit.

7.1.3. Infusion-Related Reactions Stopping Criteria

7.1.3.1. Belantamab Mafodotin

Premedication is not required prior to first 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. For infusion reactions of any grade/severity, immediately interrupt the belantamab mafodotin infusion and manage symptoms. Once reaction symptoms resolve, resume the infusion at a reduced rate. Premedication may be required with subsequent infusions (Section 6.1.3.1).

A participant that experiences a Grade 4 IRR associated with belantamab mafodotin should be permanently withdrawn from the study.

7.1.4. Allergic Reactions and Anaphylactic Reactions Stopping Criteria

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

7.2. Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons. This is expected to be uncommon. The primary reason for participant withdrawal from the study will be documented in the clinical study database.

- At the time of withdrawal from the study treatment, if possible, an (end of treatment) EoT Visit should be conducted and data collected, as shown in the SoA (Section 1.3). See SoA for data to be collected at the End of Treatment Visit.
- If a participant wishes to withdraw from study at the time of treatment discontinuation they should be asked as to whether they are willing to continue with survival follow up (which can be conducted by telephone). If a full study withdrawal including survival follow up is requested then this should be documented in the patients notes and within the clinical study database.
- 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.
- Participants who are withdrawn from the study treatment because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study treatment due to an AE/SAE until the event is resolved or considered clinically stable (see Section 10.2.4).
- Withdrawn participants will not be replaced.

Survival Follow Up (for OS Analyses)

- Assessments for survival should be made every 12 weeks (±14 days) following disease progression until the final analysis DCO. Survival information may be obtained via telephone contact with the participant, participant's family or by contact with the participant's current physician.
- Survival data will be collected up to the time of the final analysis (i.e. when the final OS analysis will be performed, see Section 9.6.2). Participants should be contacted in the weeks prior to the data cut off for each analysis of survival to provide complete survival data. An additional contact would not be required if a scheduled survival follow up visit/call was conducted within this timeline.
- Prior to the DCO for each planned analysis, a full OS sweep will be conducted. During the OS sweep, each surviving participant, or a close relative, will be contacted for a full collection of survival data, to provide the most accurate data for use in OS analyses. During this time, dates of deaths may also be obtained from public records such as death registries. This data will be collected in the clinical database.
- If, for any reason, a participant is unable to have disease progression documented per IMWG criteria (this is expected to be rare), then OS follow up information will still continue to be collected as per SoA.

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status of the participant is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be directly involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.11.

8. STUDY ASSESSMENTS AND PROCEDURES

A signed, written ICF must be obtained from the participant prior to any study-specific procedures or assessments being performed. The timing of each assessment is listed in the SoA (Section 1.3).

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, it is recommended that the assessments 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. Detailed procedures for obtaining each assessment are provided in the SRM.

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Demographic and baseline assessments will include year of birth, sex, race, and ethnicity.
- Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.1 and Section 5.2.

- Immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Inclusion/exclusion criteria will be assessed during screening until enrollment. A participant is considered enrolled when the investigator or designee has confirmed, through the eligibility form, that all eligibility criteria have been met. Any interval change in the participant's clinical course (e.g., laboratory values, concomitant medications, clinical condition) between enrollment and the first dose of investigational product that could impact the ability of the participant to safely receive their first dose should be jointly discussed between the investigator and medical monitor prior to dosing.
- 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 (Section 1.3).
- Survival follow-up can be conducted by chart review, phone call, or any other form of communication as laid out in the SoA.
- Visit windows:
  - Baseline disease assessments must be completed with 28 days prior to dosing start unless otherwise specified. Refer to the SoA in Section 1.3.
  - Screening assessments performed within the permitted time need not be repeated on Cycle 1 Day 1 unless otherwise specified.
  - Safety laboratory assessments completed within 72 hours of first dose do not need to be repeated on Cycle 1 Day 1.
  - Pregnancy testing must be completed within 24 hours prior to first dose.
  - Imaging must be completed within 30 days prior to first dose.
  - During study treatment, ±7-day window is acceptable for imaging.
  - On study q3w or q4w visits have a ±3-day window.
  - Ocular examinations to performed within 5 days prior to dosing after Cycle 1 Day 1
  - PFS follow-up visits have a ±3-day window.
  - OS follow-up visits have a ±14-day window.
  - For other assessments, please refer to SoA (Section 1.3)

A list of clinical laboratory assessments required during the study is included in Table 24.

Table 24 List of Clinical Laboratory Assessments

Hematology[1]		
Platelet count RBC count WBC count (absolute) Hemoglobin Hematocrit	**RBC Indices**: MCV MCH MCHC	**Automated WBC Differential**: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry[1]		
Potassium Creatinine Chloride Glucose Total bicarbonate (or Total CO_2 or CO_2CP) Sodium Calcium Magnesium Phosphorous eGFR	Aspartate aminotransferase (AST) Total and direct bilirubin Alanine aminotransferase (ALT) Uric acid Gamma glutamyl transferase (GGT) Albumin Alkaline phosphatase Total protein Creatine kinase (CK) Lactate dehydrogenase (LDH)	
Urinalysis[1]		
Optional urine dipstick[2]		
Spot urine (from first void) for albumin/creatinine ratio[3]		
Other Laboratory Tests		
Blood glucose; HbA1c[1]; Pregnancy test (urine or blood)[1]; FSH[1] and estradiol[1] (as needed in women of non-childbearing potential only); Hepatitis B surface antigen (HBsAg)[1], Hepatitis B core antibody (HBcAb)[1], Hepatitis C antibody, Hep C RNA test[1,3] (optional), LDH and CK isoenzymes[4], [1]. Note: Hep C RNA testing is optional but may be done to determine participant eligibility if Hep C Ab positive. Please refer to Table 5 regarding Hep C RNA testing. HBV-DNA testing will be done to determine participant's eligibility if HBcAb positive or HBsAg positive. • Please refer to Table 4 regarding HBV-DNA testing during the study. HBeAg and HBeAb – Japan ONLY (please refer to Table 4, Table 7 and Appendix 10)		
PK and ADA[4]		
Belantamab mafodotin pharmacokinetics (PK) and pomalidomide PK (Arm A only) Anti-drug antibodies (ADA) to belantamab mafodotin		
Disease Evaluation Laboratory Tests[4]		
UPEP	Serum immunofixation	Ca^{2+} corrected for albumin (serum)
SPEP	Urine immunofixation	IgG, IgM, IgA, IgD/IgE[5]

Serum kappa/lambda FLC ratio	24-hr urine collection for M protein	Beta-2 microglobulin
Biomarker Measurements[4]		
sBCMA (serum)		
Optional Testing[4]		
Optional genetic sample for pharmacogenomics (PGx)[6]; Optional bone marrow sample[6] (BM or tissue) for BCMA expression and biomarker research may collected at PD.		

Abbreviations: ADA=Anti-Drug Antibody; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; BCMA-B-cell maturation antigen; BM=bone marrow;; CK=creatine kinase; CO2=carbon dioxide; CO2CP=carbon dioxide combining power; eGFR=Estimated Glomerular Filtration Rate; FISH=Fluorescence-in-situ Hybridization; FLC=free light chain; FSH=Follicle-Stimulating Hormone; GGT=gamma-glutamyl transferase; HbsAg=Hepatitis B surface antigen; HbA1c=hemoglobin A1c; HbcAb=Hepatitis B core antibody; HBV-DNA=Hepatitis B virus-deoxyribonucleic acid; Hep C Ab=hepatitis C antibody; Hep C RNA=Hepatitis C RNA; Ig=immunoglobulin; IHC=immunohistochemistry; LDH=lactate dehydrogenase; MCH=Mean Corpuscular Hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=Mean Corpuscular Volume; MRD=Minimal Residual Disease; PD=Progressive disease; PK=Pharmacokinetic(s); RBC=Red blood cell; sBCMA=soluble B-cell maturation antigen; sCR=Stringent complete response; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis; WBC=White blood cell.

1. To be performed at local laboratory.
2. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be conducted 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.
3. If not available locally it can be performed centrally.
4. To be performed at a central laboratory.
5. Only for participants with IgD/E myeloma.
6. Informed consent for optional sub-studies (e.g., genetic research) must be obtained before collecting a sample.

8.1. Efficacy Assessments

The primary endpoint of this study is PFS. Efficacy assessments will be performed every 4 weeks (±3 days), irrespective of dosing. Standard disease assessments for RRMM will include the following assessments:

- Urine protein electrophoresis (UPEP), urine immunofixation, 24-hour collection for urine M-protein
- Serum protein electrophoresis (SPEP), serum M-protein, serum immunofixation
- Calcium corrected for albumin
- IgG, IgM, IgA
- IgD, IgE (only in participants with IgD or IgE myeloma)
- Serum kappa, lambda free light chain (FLC) ratio
- Bone marrow (aspirate and/or biopsy) at Screening and to confirm CR. Additional BM testing if CR is achieved: biopsy for immunohistochemistry (IHC) to confirm sCR and aspirate for MRD assessment (Section 8.1.2).
- PET/CT required once when participants achieve MRD-negative status (Section 8.1.2).

- Imaging of extramedullary disease (in participants with extramedullary disease)
- 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 criteria [Kumar, 2016].

Baseline serum/urine disease assessment will be completed during Screening Period (within 28 days prior to the first dose of study treatment) and baseline imaging within 30 days prior to the first dose of study treatment. On study serum and urine-based assessments (M-protein, FLC, ± immunofixation) will be performed every 4 weeks. Details for the preparation and shipment of samples for central laboratory assessments will be provided in the laboratory manual.

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

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

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

For participants who are discontinuing study intervention due to PD, the confirmation 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 suspected disease progression, preferably before institution of any new anti-myeloma therapy. The assessments to be performed during EoT Visit are described in the SoA. If the last imaging assessment was greater than or equal to 8 weeks prior to the participant's discontinuation from study treatment and PD has not been documented, a new disease assessment must be obtained at the time of discontinuation from study treatment. 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.

8.1.1. Response Evaluation

Response will be assessed according to the IMWG criteria [Kumar, 2016] by the investigator and response will also be assessed by an independent review committee (IRC, CCI [redacted]

8.1.2. Minimal Residual Disease Assessment and PET/CT Imaging

Targeted next-generation sequencing (NGS)-based clonoSEQ assay will be used to assess MRD status at the sensitivity threshold of 10^{-5}, utilizing a central testing laboratory. MRD testing should take place when a participant first achieves a confirmed response of VGPR or better, and repeated every 6 months until disease progression. In case of

deepening response from VGPR to CR, an MRD sample should be collected at the time of CR assessment and repeated every 6 months until PD. Response evaluation will be performed according to the IMWG Uniform Response Criteria for Multiple Myeloma [Kumar, 2016]. To assess no evidence of underlying disease by imaging, PET/CT will be performed once and within 42 days of the investigaor receiving confirmation of MRD negativity in participants who achieved CR or better response.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Safety assessments include the following:

- Complete physical examinations, including height (cm) and weight (kg)
- Vital signs (blood pressure, body temperature, pulse rate)
- Ocular examinations
- ECOG performance status
- Clinical chemistry, hematology, and other laboratory tests (Table 24)
- Serum beta-human chorionic gonadotropin (β-HCG) pregnancy test for female participants of childbearing potential only
- 12-lead ECG at Screening
- Anti-drug-antibodies, pharmacokinetic testing for belantamab mafodotin
- Patient-Reported Outcome version of Common Terminology Criteria for Adverse Events (PRO-CTCAE, [Babb, 1998; Basch, 2014]): 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.
- Visual Functioning Questionnaire: The visual function questionnaire will include select items from the Ocular Surface Disease Index (OSDI) [Schiffman, 2000].

8.2.1. Physical Examinations

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

8.2.2. ECOG Performance Status

Participant performance status will be assessed at Screening and then as specified in the SoA, using the ECOG scale (Section 10.6).

8.2.3. Vital Signs

Vital sign measurements must include systolic and diastolic blood pressure, temperature, and pulse rate. Vital signs must be measured after resting for at least 5 minutes. Vital signs must be measured more frequently if warranted by the clinical condition of the participant. On days when vital sign time points align with blood sampling time points, it is recommended that 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.

8.2.3.1. Vital Sign Measurement

For Treatment Arm A, vital signs are to be measured at the following time points at the time of first belantamab mafodotin infusions:

- Within 30 minutes prior to start of infusion (SOI)
- 15 minutes after SOI (± 10 minutes)
- Within 15 minutes after EOI
- At 1 hour (± 10 minutes) after EOI

On subsequent dosing days, vital signs must be assessed pre-dose (within 30 minutes prior to SOI) and within 15 minutes after EOI, and as clinically indicated.

For Treatment Arm B, vital signs must be assessed within 30 minutes before and within 15 minutes after each dose of bortezomib.

8.2.4. Electrocardiogram

12-lead ECGs must be obtained at Screening as specified in the SoA. The ECG machine should automatically calculate the heart rate and measure pulse rate, QRS, QT, and QTc (as QTcF) intervals. At each assessment, a 12-lead ECG must be performed by qualified personnel at the site after the participant has at least a 10 -minute rest.

8.2.5. Clinical Safety Laboratory Assessments

Clinical laboratory assessments including hematology, clinical chemistry, urinalysis, and additional parameters to be performed are listed in Table 24; refer to the SoA for the timing and frequency (Section 1.3). Details for the preparation and shipment of samples for central laboratory assessments will be provided in the laboratory manual.

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

All laboratory assessments with values that are significantly abnormal during participation in the study or within 70 days after the last dose of study treatment must be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology must be identified, and the Sponsor notified.

Asymptomatic elevations of lactate dehydrogenase (LDH) and creatine kinase (CK) and AST have been observed in study BMA117159 (DREAMM-1). Participants with elevations of LDH, CK and/or AST should, where possible, have a sample sent for central testing of CK and LDH isoenzyme levels.

8.2.6. Ophthalmic Assessments

Study sites must establish a close collaboration with a qualified eye care specialist (see Section 10.11) who will be responsible for assessing participants while they are on study and managing participants who develop corneal changes associated with belantamab mafodotin. Management of participants with corneal findings must be performed in close communication with the Medical Director and the coordinating qualified eye care specialist.

Participants will be assessed by a qualified eye care specialist at Screening/Baseline in both arms.

A full Screening/Baseline ophthalmic examination for all participants must include:

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

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

This should include:

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

5. Dilated funduscopic examination (if clinically indicated)

The EoT and last follow-up ophthalmic examination should match the Screening/Baseline examination.

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

8.2.6.1. Treatment Arm A: B-Pd

On-study ocular examinations are to be performed by a qualified eye care specialist at Screening/Baseline and then prior to each dose of belantamab mafodotin for the first 6 doses (the schedule of assessment window should be within 5 days prior to dosing, all efforts should be made to schedule as close to belantamab mafodotin dosing as possible). If there has been no change in vision and no ocular exam findings, or ocular symptoms consistent with toxicity up to and including the sixth dose exam, participants may have their ophthalmologic examinations decreased to once every 3 months. If a participant subsequently develops vision changes or other ocular symptoms, the participant should be promptly evaluated by a qualified eye care specialist.

In case of persistent or newly developed ocular symptoms or vision changes, the participants will have further ophthalmologic examinations, at least every cycle until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by the eye care specialist.

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

Participants who have treatment-related ocular AEs present at End of Treatment will continue to be followed 3-monthly for up to 12 months, until they return to their baseline, or are deemed clinically stable by a qualified eye care specialist, whichever comes first. Clinically stable is defined as changes less than or equal to Grade 1 for both Ophthalmic Examination Findings and Visual Acuity. These examinations are referred to as “follow-up visits.”

8.2.6.2. Treatment Arm B: PVd

Examinations should be performed as described above at Screening/Baseline, every 6 months (± 4 weeks window), and as clinically indicated, while on study (referred to as On-treatment) and EoT, as shown in the SoA (Section 1.3).

8.2.7. Pregnancy Testing (WOCBP Only)

The need for a Screening pregnancy test depends on whether a female participant is of childbearing potential or non-childbearing potential. See Appendix 3 for definitions.

Two negative serum pregnancy tests must be obtained prior to initiating treatment; the first test should be performed within 10 to 14 days prior to Cycle 1 Day 1, but the second must be performed within 24 hours of Cycle 1 Day 1. Participants with positive pregnancy test result must be excluded from the study. The study participant will not

receive any study treatment until the study doctor has verified the results of both pre-treatment pregnancy tests are negative.

Participants with negative pregnancy test result must agree to use two methods of reliable birth control (one method that is highly effective) [Section 10.3], beginning at least 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. Thereafter, WOCBP participants must use one contraceptive method that is highly effective (with a failure rate of <1% per year) for a further 3 months for WOCBP in Arm A, and 6 months for WOCBP in Arm B.

After the first dose, pregnancy tests will be done weekly during the first 28 days, then every cycle thereafter or every 2 weeks in females with irregular menses. Additionally, pregnancy testing will be done at treatment discontinuation and at 2 weeks (in females with irregular menses) and 4 weeks following treatment discontinuation. Subsequent pregnancy testing on dosing days may be either by serum or urine testing. Each pregnancy test must be performed within 24 hours prior to dosing.

Pregnancy testing should be performed at the EoT Visit and a follow-up pregnancy assessment by phone should be performed 4 and 7 months after the last dose of belantamab mafodotin (Arm A) and bortezomib (Arm B), respectively.

Participants receiving pomalidomide must register with any pregnancy prevention/controlled distribution program in place locally (see SRM for details). Ensure counselling is completed and documented as required by applicable pregnancy prevention program.

8.2.8. 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 the schedule in SoA Table 4.
- Participants who experience clinically significant elevations in liver chemistry should follow liver event monitoring and stopping criteria (Section 7.1.1), and careful evaluation should be immediately initiated for evaluation of etiology including HBV DNA testing.
- **Participants who develop detectable HBV DNA levels during study treatment should be reviewed by local specialist(s) immediately (within 1 week) and appropriate therapy and monitoring instituted.**
- **Study treatment should be withheld, and GSK Medical Director should be contacted for any participant who develops detectable HBV DNA levels.**

Table 25 Dose Modification Table for HBV+ Participants

Toxicity	Grade/description of toxicity	Actions Required
Hepatitis B reactivation	Detectable HBV DNA	• Immediate consult with local specialist to institute/modify treatment • 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.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.2.

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 (Section 7).

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

All SAEs will be collected from the start of study treatment until at least 70 days after discontinuing all study interventions regardless of initiation of a new cancer therapy or transfer to hospice, at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study up to and including any follow-up.

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

All AEs will be collected from the start of treatment until at least 70 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice at the time points specified in the SoA.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.2. 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 A only) via paper forms, emails (preferably), and fax which will be reported directly to GSK. 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. 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 cycle (and prior to the next belantamab mafodotin infusion if dosing), until resolution (KVA Grade 1 or baseline). After resolution, the ocular 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 cycles 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.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.2.

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

8.3.3. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 8.3.7), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.2.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor or designee of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor or designee has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor or designee will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor or designee will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Details of all pregnancies will be collected after the start of study treatment and for 4 months following the last dose of belantamab mafodotin (Arm A) and 7 months following the last dose of bortezomib (Arm B).

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 (Arm A) and 4 months following the last dose of bortezomib (Arm B).

If a pregnancy is reported, the investigator must inform GSK or designee within 24 hours of learning of the pregnancy and must follow the procedures outlined in Section 10.3.

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

8.3.6. Cardiovascular and Death Events

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported.

For any CV events detailed in Section 10.2.3, whether or not they are considered SAEs, and all deaths, specific CV and Death sections of the CRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific CV section of the CRF within 1 week of receipt of a CV Event data query prompting its completion.

8.3.7. Adverse Events of Special Interest

AESIs for study treatments are corneal events, thrombocytopenia and IRRs. Severity of AESIs will be graded using NCI-CTCAE v5.0 except for corneal events that are assessed and graded by KVA scale (see Table 15). Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in Section 6.6. Dose modifications for belantamab mafodotin corneal events will be based on the KVA scale, provided in Table 15.

8.4. Treatment of Overdose

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

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

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

- Contact the 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 the absence of an overdose.

- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.
- Obtain an additional plasma sample for PK analysis and a blood sBCMA sample if requested by the Medical Director (determined on a case-by-case basis).
- 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.

There is no known specific antidote for pomalidomide, bortezomib or dexamethasone overdose.

Pomalidomide

No specific information is available on the treatment of overdose with pomalidomide. Hemodialysis can remove pomalidomide from circulation [POMALYST USPI, 2019].

Bortezomib

In the event of an overdose of bortezomib, the participant's vital signs should be monitored, and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or inotropic agents) and body temperature [VELCADE SmPC, 2021].

Dexamethasone

It is difficult to define an excessive dose of a corticosteroid as the therapeutic dose will vary according to indication and patient requirements. Exaggeration of corticosteroid related adverse effects may occur. Treatment should be symptomatic and supportive as necessary [Dexamethasone SmPC, 2018].

8.5. Pharmacokinetics

8.5.1. Belantamab Mafodotin Pharmacokinetic Sample Collection

In Treatment Arm A, Enhanced and Standard PK sample collections will be obtained. Blood samples for PK analysis of belantamab mafodotin (ADC and cys-mcMMAF will be collected at the time points indicated in the SoA and Table 26 and Table 27 below. Each PK sample must be collected as close as possible to the planned time relative to the dose administered to the participant on PK sampling days. The actual date and time of each blood sample collection will be recorded on the eCRF.

Approximately 20% of participants in Treatment Arm A will undergo additional belantamab mafodotin PK sampling (Enhanced PK Cohort) according to the schedule in Table 26. For all remaining participants on Treatment Arm A, the samples will be collected as detailed in Table 27 (Standard PK Cohort). In addition, participants from Korea and Japan will have PK sampling following the Enhanced PK schedule. PK-associated sBCMA samples should be collected at all PK time points (according to either the standard or enhanced schedules, see also Section 8.9.1 Table 29 and Table 30).

Soluble BCMA samples must be collected at all PK time points (according to either the standard or enhanced schedule). All PK, sBCMA, and antidrug antibody (ADA) samples

once collected (regardless of dosing) may be analyzed if the sample date and time have been recorded.

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

Table 26 Enhanced PK Collection Schedule

Dose/Day[1]	Timing	Comments
Dose1 D1	Pre-dose	Within 30 min prior to SOI
	EOI	0-30 min after EOI
	2 h after SOI	2 h (±15 min) after C1D1 SOI
Dose1 D2	24 h after SOI on C1D1	24 h (±2 h) after Dose1 SOI
Dose1 D4	Any time	72 h (±24 h) after Dose 1 SOI
Dose1 D8-15	1 sample between C1D8 and C1D15	Any time between D8 and D15
Dose2 D1[2]	Pre-dose	Within 30 min prior to SOI If Dose 2 belantamab mafodotin is delayed, 1 PK sample must also be taken at Dose1 D29
	EOI	0-30 min after EOI
4th and 6th belantamab mafodotin dose	Pre-dose	Within 30 min prior to SOI
	EOI	0-30 min after EOI
9th and 12th belantamab mafodotin dose	Pre-dose	Within 30 min prior to SOI
Every 6 subsequent doses	Pre-dose	Within 30 min prior to SOI; starting at the 18th dose of belantamab mafodotin (e.g., Dose18 D1, Dose24 D1, Dose30 D1 and so on, until the last sample at EoT)

Abbreviations: C=Cycle; D=Day; EOI=End of infusion; EoT=End of Treatment; Pd=Pomalidomide in combination with dexamethasone; PK=pharmacokinetic(s); SOI=Start of infusion.

1. This PK sample is tied to the dose of belantamab mafodotin. This may not correspond to the cycle of treatment e.g., in the event that belantamab mafodotin is held whilst Pd continues.
2. If Dose 2 belantamab mafodotin is delayed, a PK and sBCMA sample must also be taken on Dose1 D29. Then at time of actual Dose 2 collect a PK and sBCMA sample at pre-dose and EOI.

Table 27 Standard PK Collection Schedule

Dose/Day1	Timing	Notes
Dose1 D1	Pre-dose	Within 30 min prior to SOI
	EOI	0-30 min after EOI
Dose1 D2	24 h after SOI	24 h (±2 h) after Dose1 SOI
Dose2 D1[3]	Pre-dose	Within 30 min prior to SOI If Dose 2 belantamab mafodotin is delayed, 1 PK sample must also be taken at Dose1 D29.

Dose/Day1	Timing	Notes
	EOI	0-30 min after EOI
4th and 6th belantamab mafodotin dose	Pre-dose	Within 30 min prior to SOI
	EOI	0-30 min after EOI
9th and 12th belantamab mafodotin dose	Pre-dose	Within 30 min prior to SOI
Every 6 subsequent doses	Pre-dose	Within 30 min prior to SOI; starting at the 18th dose of belantamab mafodotin (e.g., Dose18 D1, Dose24 D1, Dose30 D1 and so on, until the last PK sample at EoT).

Abbreviations: C=Cycle; D=Day; EOI=end of infusion; EoT=End of Treatment; Pd=pomalidomide in combination with dexamethasone; PK=pharmacokinetic(s); SOI=start of infusion.

2. This PK sample is tied to the dose of belantamab mafodotin. This may not correspond to the cycle of treatment e.g., in the event that belantamab mafodotin is held whilst Pd continues.
3. If Dose 2 belantamab mafodotin is delayed, a PK and sBCMA sample must also be taken on Dose1 D29. Then at time of actual Dose 2 collect a PK and sBCMA sample at pre-dose and EOI.

Details on PK blood sample collection including blood volumes, processing, storage, and shipping procedures are provided in the Clinical Laboratory Manual.

8.5.2. Belantamab Mafodotin Pharmacokinetic Sample Analysis

Plasma PK analysis will be performed under the control of GSK. Concentrations of belantamab mafodotin (ADC) 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 (ADC) and cys-mcMMAF, any remaining plasma may be analyzed for other compound-related entities and the results may be reported under a separate GSK protocol.

The actual date and time of each blood sample collection will be recorded on the eCRF.

8.5.3. Pomalidomide Pharmacokinetic Sample Collection and Analysis

PK samples for pomalidomide will be collected in approximately 20 participants in Arm A at the selected time points indicated in Table 27 and in the SoA (Section 1.3) to confirm the anticipated lack of impact of belantamab mafodotin on pomalidomide PK [Li, 2015]. Participants getting pomalidomide PK samples collected must fast for at least 2 hours before to 1 hour after pomalidomide dosing in Cycle 1 Day 1 only.

Plasma analysis will be performed under the control of GSK. Concentrations of pomalidomide will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site.

Table 28 PK Sampling Schedule for Pomalidomide in Arm A

Cycle/Day	Timing	Notes
C1D1	Pre-dose	Within 30 min prior to start of pomalidomide PO
	1 h after pomalidomide PO	(±15 min)
	2 h after pomalidomide PO	(±15 min)
	3 h after pomalidomide PO	(±15 min)
	4 h after pomalidomide PO	(±15 min)
	6 h after pomalidomide PO	(±15 min)
	24 h after pomalidomide PO	(± 1 h) and before pomalidomide administration on C1D2
C1D4	Pre-dose	Within 30 min prior to dosing of pomalidomide PO
C2D1	Pre-dose	Within 30 min prior to dosing of pomalidomide PO

Abbreviations: C=Cycle; D=Day; PK=pharmacokinetic(s).

8.5.4. Bortezomib and Dexamethasone

No PK sampling or analysis is required for bortezomib or dexamethasone in either Treatment Arm A or B.

8.6. Belantamab Mafodotin Immunogenicity

Serum samples for the analysis of anti-belantamab mafodotin antibodies will be collected prior to each belantamab mafodotin infusion (at Doses 1, 2, 4, 6, 9 and 12 at the same time as the pre-infusion belantamab mafodotin PK samples are taken); for treatment beyond 12 doses, collect samples for ADA analysis prior to each infusion every 6th dose of belantamab mafodotin (Dose 18, Dose 24, Dose 30, and so on, until PD). A final ADA sample will be drawn at the EoT Visit. ADA sample collection may be terminated when sufficient data have been collected. These samples will be tested by the Sponsor or Sponsor's designee.

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

The detection and characterization of antibodies to belantamab mafodotin will be performed using validated assays. The anti-belantamab mafodotin antibody assay was designed to detect antibodies to belantamab mafodotin, the unconjugated monoclonal antibody and the linker-payload portion of belantamab mafodotin. Anti-belantamab mafodotin antibody samples will be disposed three months after final approved results are

provided to the Clinical Study Team or its designee or upon documented study termination.

ADA sample collection may be reduced or terminated when sufficient data have been collected.

8.7. Pharmacodynamics

See Section 8.9 for details of biomarkers to be collected.

8.8. Genetics

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the optional genetics analysis component of the study. Participation in this part of the study is optional and all enrolled participants will be given the opportunity to contribute samples. Participation may be declined without effect on medical care during the clinical study. A separate consent signature is required for participation in genetic research.

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.

Information regarding genetic research is included in Section 10.5. In approving the clinical protocol, the IRB/IEC and, where required, the applicable regulatory agency, are also approving the genetic research described in Section 10.5 unless otherwise indicated. Where required by regulatory authorities, approval of the genetic assessments can occur after approval is obtained for the rest of the study. In that case, written approval will indicate that approval of the genetic assessments is being deferred and the study, except for genetic assessments, can be initiated. If genetic assessments are not approved, they will not be conducted.

8.9. Biomarkers

Biomarker research is part of this study and will involve peripheral blood (serum and plasma), bone marrow samples, or tumor biopsies. Samples will be collected at the time points indicated in the SoA. Biomarker samples, including bone marrow and samples for sBCMA, once collected (regardless of dosing) could be analyzed as long as date and time information has been recorded.

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. The relationship of protein, DNA and/or RNA biomarkers in blood, bone marrow, or tumor tissue samples to response to belantamab mafodotin and AEs may be evaluated. Unless stated otherwise, these investigations may be performed irrespective of whether a response to belantamab mafodotin is observed.

Additionally, any blood, serum, plasma, and/or bone marrow samples collected during this study may be used to measure novel biomarkers to identify factors associated with

the biological and clinical responses to belantamab mafodotin. Novel biomarkers may be identified and measured by DNA, RNA, and/or protein analysis, and may involve use of sequencing of DNA and/or RNA.

If relevant, this approach may be extended to include the identification of biomarkers associated with AEs. 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.

Biomarkers assessed in this study may include but not be limited to those mentioned in sub-Sections 8.9.1 to Sections 8.9.3.

8.9.1. Soluble B-Cell Maturation Antigen

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

sBCMA will be measured in both Arm A and Arm B.

For Arm A, sBCMA samples should be collected at all PK time points for all participants, according to either the enhanced (Table 29) or standard (Table 30) PK schedules. Additionally, sBCMA samples will be collected independent from PK samples and dosing, from approximately 100 participants from treatment arm B (Table 31). The actual date and time of each blood sample collection will be recorded on the eCRF. The sBCMA samples once collected (regardless of dosing) may be analyzed if the sample date and time have been recorded.

Serum analysis for sBCMA will be performed under the control of GSK (further details are included in the SRM). Raw data will be archived at the bioanalytical site.

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

Details on sBCMA blood sample collection including blood volumes, processing, storage, and shipping procedures are provided in the laboratory manual.

Table 29 Treatment Arm A sBCMA Blood Collections, Associated with the Enhanced PK Collection Schedule

Dose/Day	Timing	Comments
Screening	Screening	Any time during Screening
Dose1 D1	Pre-dose	Within 30 min prior to SOI
	EOI	0-30 minutes after EOI
	2 h after SOI	2 h (±15 min) after C1D1 SOI
Dose1 D2	24 h after SOI on C1D1	24 h (±2 h) after Dose1 SOI
Dose1 D4	Any time	72 h (±24 h) after Dose 1 SOI

Dose/Day	Timing	Comments
Dose1 D8-15	1 sample between C1D8 and C1D15	Any time between D8 and D15
Dose2 D1[1]	Pre-dose	Within 30 min prior to SOI If Dose 2 belantamab mafodotin is delayed, 1 sample must also be taken at Dose1 D29
	EOI	0-30 min after EOI
4th and 6th belantamab mafodotin dose	Pre-dose	Within 30 min prior to SOI
	EOI	0-30 min after EOI
9th and 12th belantamab mafodotin dose	Pre-dose	Within 30 min prior to SOI
Every 6 subsequent doses	Pre-dose	Within 30 min prior to SOI; starting at the 18th dose of belantamab mafodotin (e.g., Dose18 D1, Dose24 D1, Dose30 D1 and so on, until the last sample at EoT)
EoT	Any time	EoT Visit

Abbreviations: C=Cycle; D=Day; EOI=End of infusion; EoT=End of Treatment; Pd=Pomalidomide in combination with dexamethasone; PK=Pharmacokinetic(s); sBCMA=Soluble B-cell maturation antigen; SOI=Start of infusion; VGPR=Very Good Partial Response.

Note: PK-associated sBCMA samples are tied to the dose of belantamab mafodotin. This may not correspond to the cycle of treatment e.g., in the event that belantamab mafodotin is held whilst Pd continues.

1. If Dose 2 belantamab mafodotin is delayed, a PK and sBCMA sample must also be taken on Dose1 D29. Then at time of actual Dose 2 collect a PK and sBCMA sample at pre-dose and EOI.

Table 30 Treatment Arm A sBCMA Blood Collections, Associated with the Standard PK Collection Schedule

Dose/Day	Timing	Notes
Screening	Screening	Any time during Screening
Dose1 D1	Pre-dose	Within 30 min prior to SOI
	EOI	0-30 min after EOI
Dose1 D2	24 h after SOI	24 h (±2 h) after Dose1 SOI
Dose2 D1[1]	Pre-dose	Within 30 min prior to SOI If Dose 2 belantamab mafodotin is delayed, 1 sample must also be taken at Dose1 D29.
	EOI	0-30 min after EOI
4th and 6th Belantamab Mafodotin dose	Pre-dose	Within 30 min prior to SOI
	EOI	0-30 min after EOI
9th and 12th Belantamab Mafodotin dose	Pre-dose	Within 30 min prior to SOI
Every 6 subsequent doses	Pre-dose	Within 30 min prior to SOI; starting at the 18th dose of belantamab mafodotin (e.g., Dose18 D1, Dose24 D1, Dose30 D1 and so on, until the last PK sample at EoT).
EoT	Any time	EoT Visit

Abbreviations: C=Cycle; D=Day; EOI=End of infusion; EoT=End of Treatment; Pd=pomalidomide in combination with dexamethasone; PK=Pharmacokinetic(s); sBCMA=soluble B-cell maturation antigen; SOI=Start of infusion.
Note: PK-associated sBCMA samples are tied to the dose of belantamab mafodotin. This may not correspond to the cycle of treatment e.g., in the event that belantamab mafodotin is held whilst Pd continues.
1. If Dose 2 belantamab mafodotin is delayed, a PK and sBCMA sample must also be taken on Dose1 D29. Then at time of actual Dose 2 collect a PK and sBCMA sample at pre-dose and EOI.

Table 31 Treatment Arm B sBCMA Blood Collection (Approximately 100 Participants)

Dose/Day[1]	Timing	Comments
Screening	Screening	Any time during Screening
Dose1 D1	Pre-dose	Within 30 min prior to start of dosing
	End of Dose	Within 30 min after end of dosing
EoT	Any time	EoT visit

Abbreviations: C=Cycle; D=Day; EoT=End of Treatment; .

8.9.2. Tumor-Related Biomarkers

Bone marrow samples will be collected during this study at the time points indicated in the SoA to evaluate the relationship of protein, DNA and/or RNA biomarkers in the bone marrow to response to belantamab mafodotin. Biomarkers assessed in bone marrow or other samples may include, but not be limited to BCMA expression on multiple myeloma cells, immune cell characterization and/or profiling and/or DNA/RNA analyses.

Bone marrow or other samples collected during this study may be used to evaluate the relationship of BCMA expression, measured by protein and/or RNA, on multiple myeloma cells in the bone marrow to response to belantamab mafodotin.

Bone marrow or other samples collected during this study may be used to interrogate the relationship of genetic alterations, transcriptional profile, and/or protein expression in bone marrow cells, including multiple myeloma cells and cells in the bone marrow microenvironment, with response to belantamab mafodotin. These studies may include genomic and/or RNA transcriptomic analysis, and may involve use of sequencing of DNA, RNA, and/or alternative equivalent technologies.

8.9.3. RNA Transcriptome Research

Transcriptome studies for bone marrow or other samples may be conducted using microarray, RNA sequencing (RNAseq), and/or alternative equivalent technologies, to evaluate the correlation of changes in transcriptome profiles with responses to belantamab mafodotin.

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

8.10. Patient-Reported Outcomes

Patient-reported outcomes (PROs) should be done at the start of the visit before any assessments and before any results are discussed. 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. Participants who are not able to complete the questionnaire on their own and require assistance should have the PROs administered to them in an interview format. The questionnaires should be read to the participants verbatim, and participant responses should be recorded directly without any interpretation. For any additional assessments conducted via phone (either during participation in the Treatment Period or during follow-up), an interview format should be used where a site staff member administers the questionnaires over the phone.

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

PRO questionnaires should be completed by participants at the start of study visits before receiving any results and before discussing their health status with the study staff.

Participants enrolled under the original protocol and who completed the EORTC IL52 questionnaire will continue to do so. Participants enrolled under protocol amendment 1 will complete the EORTC QLQ-MY20 questionnaire. All participants will complete the PRO-CTCAE, EORTC QLQ-C30, OSDI, EQ-5D-3L, FACT-GP5, PGIS and PGIC at the required study visits.

8.10.1. Patient-Reported Outcomes 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 CTCAE, the standard lexicon for AE 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 selection of items from the PRO-CTCAE v1. 0 item library will be administered to participants.

8.10.2. Health-Related Quality of Life

Five health-related quality of life (HRQoL) assessments will be performed in this study.

8.10.2.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-Item Core Module (EORTC QLQ-C30)

The EORTC QLQ-C30 is a 30-item questionnaire containing both single- and multi-item measures [Aaronson, 1993]. These include 5 functional scales (Physical, Role, Cognitive, Emotional, and Social Functioning), 3 symptom scales (Fatigue, Pain, and Nausea/Vomiting), a Global Health Status/quality of life (QoL) scale, and 6 single items (Constipation, Diarrhea, Insomnia, Dyspnea, Appetite Loss, and Financial Difficulties). Scores for each scale and single-item measure are averaged and transformed linearly to a score ranging from 0–100. A high score for functional scales and for Global Health Status/QoL represent better functioning ability or HRQoL, whereas a high score for symptom scales and single items represents significant symptomatology [Proskorovsky, 2014].

8.10.2.2. European Organization for Research and Treatment of Cancer 20-item Multiple Myeloma Module (EORTC QLQ-MY20) and the Item Library 52 (EORTC IL52; the Disease Symptoms Domain of the EORTC QLQ-MY20)

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire myeloma module (EORTC QLQ-MY20) is a supplement to the EORTC QLQ-C30 instrument used in patients with MM [Aaronson, 1993; Cocks, 2007]. It includes four scales (Disease Symptoms, Body Image, Future Perspective, and Side Effects). Participants enrolled under amendment 1 will complete the full EORTC QLQ-MY20. Participants enrolled under the original protocol will complete the Disease Symptoms domain of the EORTC QLQ-MY20, which includes bone aches or pain, back pain, hip pain, arm or shoulder pain, chest pain, and pain increasing with activity. The Disease Symptom domain of the EORTC QLQ-MY20 will be referred to as the European Organization for Research and Treatment of Cancer Item Library 52 (EORTC IL52). As with the EORTC QLQ-C30, EORTC QLQ-MY20 domain scores are averaged and transformed linearly to a score ranging from 0 to 100. A high score for Disease Symptoms represents a high level of symptomatology or problems [Proskorovsky, 2014].

8.10.2.3. EuroQol Questionnaire (EQ-5D-3L)

The EQ-5D-3L is a standardized instrument for use as a measure of health utility. It is designed for self-completion or interview administration and is cognitively simple, taking only a few minutes to complete.

The EQ-5D-3L self-assessment questionnaire has 2 parts. The first part consists of 5 items covering 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a 3-point Likert scale (no problems, some or moderate problems, and unable or extreme problems). Respondents are asked to choose one level that reflects their "own health state today" for each of the 5 dimensions. Respondents can be then classified into one of 243 distinct health states. The second part is a 20-cm visual analogue scale (EQ-VAS) that has endpoints labelled "best imaginable health state" and "worst imaginable health state" anchored at 100 and 0, respectively. Respondents are asked to indicate how they rate their own health by drawing a line from an anchor box to that point on the EQ-VAS which best represents their own health on that day. EQ-5D-3L health states are converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. The formula is based on the valuation of EQ-5D health states from general population samples.

8.10.2.4. Functional Assessment of Cancer Therapy – General Population (FACT-GP5)

The FACT-G (now in Version 4) is a 27-item compilation of general questions divided into 4 primary QoL domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being [Cella, 1993]. It is considered appropriate for use with participants with any form of cancer and has also been used and validated in other chronic illness condition (for example, HIV/AIDS and multiple sclerosis) and in the general population (using a slightly modified version).

The FACT-GP5 item is a single item from the FACT-G, which assesses how bothersome the side effects of treatment are for cancer patients. The recall period is the past 7 days, and the item has a 5-category response scale ranging from “0=Not at all” to “4=Very much”. This item is being included to assess the overall tolerability of treatment from the participant’s perspective.

8.10.2.5. Patient Global Impression Items

The Patient Global Impression of Severity (PGIS) assesses global impression of symptoms severity at baseline and subsequent timepoints. The second question, the Patient Global Impression of Change (PGIC) serves to rate the global change in symptoms at subsequent time points. In addition to evaluating symptom severity and change, these questions serve as anchors to establish thresholds of clinically meaningful change for the questionnaires in the study [Guy, 1976].

8.10.3. Ocular Surface Disease Index

The impact of potential ocular toxicity on function and health-related quality of life will be assessed with the use of the Ocular Surface Disease Index (OSDI). The OSDI is a 12-

item questionnaire designed to assess both the frequency of dry eye symptoms and their impact on vision-related functioning [Dougherty, 2011; Schiffman, 2000]. 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. The OSDI will be completed by the participants at the times shown in the SoA.

8.11. Non-protocol Specified Healthcare Resource Utilization

Non-protocol specified healthcare resource utilization will collect the frequency, reason, and dates of healthcare contact reported by participants at each visit. These data will be collected in the participant record and in the eCRF.

Parameters to be measured include:

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

The data collected may be used to conduct exploratory economic analyses.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

9.1.1. Primary Endpoint

The following primary hypothesis will be tested, comparing the distribution of PFS between the two treatment groups:

$$H_0: \theta \geq 1 \qquad VS. \qquad H_1: \theta < 1$$

where, θ is the PFS HR (B-Pd vs. PVd).

9.1.2. Key Secondary Overall Survival Endpoint

The key secondary OS analysis will be the comparison of the distribution of OS between the two treatment groups. The following hypothesis will be tested:

$$H_0: \theta \geq 1 \qquad VS. \qquad H_1: \theta < 1$$

where, θ is the OS HR (B-Pd vs. PVd).

9.1.3. Key Secondary Duration of Response Endpoint

The following hypothesis will be tested:

$$H_0: \mu_1 - \mu_0 \leq 0 \qquad VS. \qquad H_1: \mu_1 - \mu_0 > 0$$

where μ_1 is the restricted mean duration of response (RMDOR) for participants in Arm A (B-Pd). and μ_0 is the RMDOR for participants in Arm B (PVd).

9.1.4. Key Secondary Minimal Residual Disease Negativity Endpoint

A key secondary objective of the study is to compare the proportion of participants with MRD negativity between the two treatment groups. The following hypothesis will be tested:

$$H_0: P_1 \leq P_0 \quad VS. \quad H_1: P_1 > P_0$$

where, P_0=proportion of participants with MRD negativity Arm B (PVd)

P_1=proportion of participants with MRD negativity Arm A (B-Pd).

9.2. Multiple Comparisons and Multiplicity

The objective of the study is to compare the efficacy of Treatment A (B-Pd) versus Treatment B (PVd) and will consist of evaluating one primary and three key secondary endpoints (OS, DoR, and MRD Negativity). The analyses will be performed as defined in Section 9.6.2. The study will provide multiplicity control for multiple hypotheses as well

as interim analyses (planned interim analyses are defined in Section 9.6). The global family-wise error rate (FWER) is strongly controlled at 2.5% (one-sided).

Evaluation of primary and key secondary endpoints will be structured in terms of two families of hypotheses. The first family will be based on the primary endpoint PFS, and the second family will be based on the three key secondary endpoints OS, DoR, and MRD Negativity. Testing of the second family of hypotheses is conditional on the successful rejection of the null hypothesis for the first family. If successful, the full alpha will be propagated to the second family of hypotheses. For the second family, a weighted Bonferroni procedure will be applied across OS and DoR. Alpha will be split between the endpoints, with a larger proportion assigned to OS initially. Testing of MRD will be conditional on the successful rejection of the null hypothesis for OS, aligned with a step-down (or hierarchical) testing procedure [Bretz, 2009; Li, 2017]. Details regarding alpha allocation and propagation will be defined in the SAP.

PFS will be tested across 3 planned analyses; an analysis for harm (IA1), an analysis for efficacy (IA2), and the Primary PFS analysis/IA3. A gamma beta-spending function with parameter of -3 is used to define a non-binding boundary for IA1. The Lan DeMet approach that approximates the O'Brien and Fleming spending function [Lan, 1983] will be used to maintain an overall one-sided 2.5% type I error when testing PFS across IA2 and the Primary PFS analysis/IA3, since these analyses provide the opportunity to make a claim of efficacy. The efficacy boundaries (see Section 9.6) will be adjusted based on the actual number of PFS events observed at the time of analysis.

OS will be tested across 4 planned analyses: IA2, Primary PFS analysis/IA3, IA4, and the final analysis. The Lan DeMet approach that approximates the O'Brien and Fleming spending function [Lan, 1983] will be used. The efficacy boundaries will be adjusted based on the actual number of OS events observed at the time of analysis. Additional analyses of OS may be performed upon requests or to provide updated data to the health authorities. The details of these analyses including the associated alpha-adjustment, if any, will be described in the SAP.

Further details regarding the multiplicity strategy will be provided in the SAP.

9.3. Sample Size Determination

9.3.1. Primary Endpoint

Based on data from the OPTIMISMM study [Richardson, 2019], the median PFS in the PVd arm is expected to be around 12 months. It is expected that treatment with B-Pd will lead to a 40% reduction in the risk of progression or death, i.e., an expected PFS HR of 0.6, which corresponds to an increase in median PFS from 12 months to 20 months under the exponential assumption.

The primary PFS analysis will be conducted after observing approximately 173 PFS events, in the randomized participants contributing to the analysis. To ensure >90% power to test the null hypothesis: PFS HR=1, vs. the specific alternative hypothesis: PFS HR=0.6, a total of approximately 173 PFS events are needed. The calculation assumes a comparison of PFS by log-rank test at 1-sided alpha level of 2.5%, an interim analysis for

harm and an interim analysis for efficacy (see Section 9.2 and 9.6). Assuming a total of approximately 302 participants will be randomized in a 1:1 ratio to receive B-Pd or PVd and a uniform enrolment rate of 11.2 participants per month, enrolment will continue for approximately 27 months. It is estimated that the targeted 173 PFS events will be observed approximately 35 months from the first participant randomized under H1 assuming an annual dropout rate of 5%. These calculations were conducted using EAST v6.5.

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. However, these additional participants will be included in country-specific supplemental analyses, requested by the applicable regulatory authorities, as detailed in the country-specific SAP.

9.3.2. Sample Size Re-Estimation

A sample size re-estimation may be considered at the time of the interim analysis for harm to ensure adequate power to demonstrate the treatment effect. The key idea is to evaluate conditional power (CP) at the interim look at approximately 25% information fraction. If the CP is either too low or too high, we do not alter the number of events for the final analysis. However, if conditional power falls in a range that we deem promising, then the number of events may be increased, subject to a pre-determined upper limit [Mehta, 2011]. Further details will be described in the SAP and IDMC charter. Adequate firewalls will be maintained to ensure the integrity of the study.

9.4. Populations for Analyses

For the purpose of this analysis, the following populations are defined:

Population	Description
All Screened	**The All Screened Population will consist of all participants who sign the ICF to participate in the clinical trial. Participants in this population will be used for screen failure summary.**
Intent-to-Treat (ITT)	ITT Population will consist of all randomized participants whether or not randomized treatment was administered. This population will be based on the treatment to which the participant was randomized and stratified 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.
Modified ITT	Participants who met all three criteria below will be included: • Have received at least 1 line of prior therapy including a lenalidomide-based therapy • Randomized and received at least one dose of planned study treatment – Participant randomized to the belantamab mafodotin arm but received bortezomib will be excluded or vice versa

Population	Description
	– Participant randomized but never treated will be excluded • With measurable disease at baseline
Safety	All randomized participants who receive at least 1 dose of study intervention (any component). Participants will be analyzed according to the intervention they actually received. For Arm A: B-Pd, if participants are incorrectly dosed with bortezomib at >50% of dosing visits then they will be assigned to Arm B: PVd as their actual treatment. Similarly, for Arm B: PVd, if participants are incorrectly dosed with belantamab mafodotin at >50% of dosing visits then they will be assigned to Arm A: B-Pd as their actual treatment. Data should be reported according to the actual treatment.
Belantamab mafodotin Pharmacokinetic (PK)	The belantamab mafodotin Pharmacokinetic Population will consist of those participants in the Safety Population from whom at least 1 belantamab mafodotin PK sample was obtained, analyzed and was measurable (Non-quantifiable [NQ] values will be considered as non-missing values). This population will be the primary population for PK analyses related to belantamab mafodotin.
Pomalidomide Pharmacokinetic (Pom PK)	The Pomalidomide Pharmacokinetic Population will consist of those participants in the Safety Population from whom at least 1 pomalidomide PK sample was obtained, analyzed, and was measurable (Non-quantifiable [NQ] values will be considered as non-missing values). This population will be the primary population for pomalidomide PK analyses.

Abbreviations: ICF=Informed Consent Form; ITT=Intent-to-Treat; PK=pharmacokinetic(s).

9.5. Statistical Analyses

9.5.1. Efficacy Analyses

An independent-review committee (IRC, CCI [redacted] will be utilized to assess response and disease progression per IMWG criteria (See Section 10.1.6). Analysis of efficacy endpoints will be based on IRC-assessed confirmed response and dates according to IMWG criteria [Kumar, 2016] (with the exception of PFS2 which will be based on investigator-reported disease progression) with the Intent-to-Treat (ITT) Population, unless otherwise specified.

The analytical methods planned for each endpoint are described in Table 32.

Based on Amendment 01 as depicted in the table below, the study would have two stratification cohorts per randomization, with the first having stratification according to A*B*C for 12 strata and the second having stratification according to A*B*D for 12 strata; and so in all, it has 24 strata since Cohort 1 vs. Cohort 2 is also a stratification factor as a consequence of Cohort 2 having a revised structure for stratification that differs from the initial structure for stratification for Cohort 1.

Prior to Amendment 01 **[Stratification Cohort 1]**	**After Amendment 01** **[Stratification Cohort 2]**
A: number of prior lines of therapy (1 vs. 2/3 vs. ≥4)	**A:** number of prior lines of therapy (1 vs. 2/3 vs. ≥4)
B: prior bortezomib treatment (yes or no)	**B:** prior bortezomib treatment (yes or no)
C: ISS status (I vs II/III)	**D:** Prior anti-CD38 treatment (yes or no)

Since stratification produces balance of the randomized treatment groups for the corresponding factors for stratification, there is no bias to analysis from its ignoring of a factor for stratification. Also, adjustment for all strata can lead to some strata being entirely non-informative by having 0 events for an endpoint like PFS or only including participants from one of the two treatment groups. The strata are at least minimally informative by when each stratum include at least one participant for each of the two treatment groups and at least one participant with an event and at least one participant with no event and follow-up at least as long as at least one participant with the event. Usually the strata should be somewhat more informative than minimally informative, with this implying that each stratum should have approximately 10 participants and approximately 5 participants with a PFS event (or event appropriate per the endpoint).

Based on the above, primary analyses for all stratified analyses will be stratified by two randomization factors; number of prior lines of therapy and prior bortezomib treatment. As appropriate (refer to Table 32) and detailed in the SAP, sensitivity analyses will be performed at the time of Primary PFS analysis considering all 4 randomization factors as possible stratification factors, using a prespecified pooling of strata so that each stratum has approximately 10 participants and approximately 5 participants with a PFS event (or event appropriate per the endpoint). For the primary endpoint of PFS, an additional supportive analysis will be performed as defined in Table 32.

Appropriate subgroup analyses may be performed if data permits, e.g., the primary endpoint PFS may be analyzed by age (e.g., <65 years, ≥65 years), gender (Female, Male), ethnicity (Hispanic, non-Hispanic) and race groups (e.g., American Indian or Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Mixed Race – groups may be combined to provide sufficiently large groups for comparison), region (e.g., North America, Europe, North East Asia [consisting of Japan, China and Republic of Korea], Rest of World), prior anti-myeloma therapy, randomization factors and other baseline characteristics. Further details will be provided in the SAP.

Table 32 Statistical Analytical Methods: Efficacy

Endpoint	Statistical Analysis Methods
Primary	**PFS** is the primary endpoint of this study; it is defined as the time from randomization until the earliest date of PD based on IRC-assessment per IMWG criteria [Kumar, 2016], or death due to any cause. Determination of dates for PFS event and dates for censoring is described in Section 10.9. 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 [Brookmeyer 1982). 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. The distribution of PFS will be compared between the two treatment arms using log-rank test stratified by two randomization factors, number prior lines of therapy and prior bortezomib use. A one-sided p-value will be produced. HR and corresponding two-sided 95% CI will be estimated from Cox proportional hazard model stratified by these two randomization factors with treatment arm as the sole explanatory variable. If the proportional hazard assumption does not hold, restricted mean survival time may be conducted in addition as appropriate. Sensitivity analyses will be performed using a stratified log-rank test, considering stratification by all 4 randomization factors (including all factors used prior to and following protocol amendment 1). However, a prespecified pooling of strata strategy will be applied so that each stratum has informative information (e.g. approximately 10 participants and approximately 5 participants with a PFS event). As a supportive analysis, HR and corresponding two-sided 95% CI will be estimated from Cox proportional hazard model stratified by number prior lines of therapy and prior bortezomib use with treatment, ISS status and prior anti-CD38 treatment as explanatory variables. The same pre-specified pooling strategy as used for the log-rank test will be applied. Details will be provided in the SAP. Additional sensitivity analyses will be conducted using alternative PFS censoring rules as described in Section 10.9 and using investigator-assessed responses and dates. These will be defined in the SAP. Appropriate subgroup PFS analyses may be performed if data permits.
Key Secondary	**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 last known alive. OS will be compared using a similar approach for PFS. Estimates of milestone OS rates and associated two-sided 95% confidence intervals will be provided. The distribution of OS 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 two-sided 95% confidence intervals will be estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982]. The distribution of OS will be compared between the two treatment arms using log-rank test stratified by two randomization factors, number prior lines of therapy, and prior bortezomib use. A one-sided p-value will be produced. HR and corresponding two-sided 95% CI will be estimated from Cox proportional hazard model stratified by these two randomization factors with treatment arm as the sole explanatory variable. If the proportional hazard assumption does not hold, restricted mean survival time may be conducted in addition as appropriate. **DoR** is defined as the time from first documented evidence of PR or better until progressive disease (PD) or death due to any cause. For the primary analysis of DoR, all participants will be included in the analysis regardless of response status, to enable a valid statistical comparison between the two arms. Response will be based on IRC-assessment per IMWG criteria [Kumar, 2016]. DoR will be analyzed based on the restricted mean DoR (RMDOR) using a non-

Endpoint	Statistical Analysis Methods
	parametric approach [Huang , 2022]. Using this approach, non-responders will have an observed DoR of zero. Comparison of RMDOR between the two treatment arms will be based on a one-sided Z test at the overall 2.5% level of significance. The RMDOR and the corresponding two-sided 95% confidence interval will be calculated for each arm. The difference in the RMDOR and the associated one-sided p-value will be provided. Sensitivity analysis will be conducted using investigator-assessed responses. A supplementary analysis will be conducted based on a conventional DoR analysis, where DoR will be 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 participants who achieve a response (i.e., confirmed PR or better) based on IRC-assessment per IMWG criteria [Kumar, 2016]. 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 [Brookmeyer 1982]. **MRD** negativity rate, defined as the percentage of participants who achieve MRD negative status (as assessed by NGS at 10^{-5} threshold) at least once during the time of confirmed CR or better response based on IRC-assessment per IMWG [Kumar, 2016]. For analysis purposes, participants with a confirmed CR or better response who do not achieve MRD negative status (including missing/inconclusive assessment(s)) and participants without a confirmed CR or better response will be considered as having non-negative MRD. MRD negativity rate will be summarized by treatment arm. Corresponding 95% exact CIs will also be provided. MRD negativity rate will also be compared between treatment arms using the Cochran Mantel Haenszel test stratified by the two randomization factors: number of prior lines of therapy and prior bortezomib use. A sensitivity analysis will be performed, with MRD negativity rate defined similarly, but instead using investigator confirmed response according to IMWG. Supplementary analyses may be performed based on participants with VGPR or better, using investigator-assessed and IRC-assessed confirmed response, separately. An additional sensitivity analysis will be performed using the stratified Cochran Mantel Haenszel test, considering stratification by all 4 randomization factors. However, a prespecified pooling of strata strategy will be applied so that each stratum has informative information. Further details are provided in the SAP.
Secondary	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) based on IRC-assessment per IMWG criteria [Kumar, 2016]. 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 two-sided 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 two-sided 95% CI for the difference will be calculated. Sensitivity analysis will be conducted using investigator-assessed responses. **CRR**, defined as the percentage of participants with a confirmed CR or better (i.e., CR, and sCR) based on IRC-assessment per IMWG criteria [Kumar, 2016]. The number and percentage of participants with CR or better as the Best Overall Response (BOR) will be summarized by treatment arm. The corresponding exact 95% CI for CRR 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 complete response. The exact 95% CI for the difference will be calculated.

Endpoint	Statistical Analysis Methods
	VGPR or better rate, defined as the percentage of participants with a confirmed Very Good Partial Response (VGPR) or better (i.e. VGPR, CR, and sCR) based on IRC-assessment per IMWG criteria [Kumar, 2016]. **TTBR** is defined as the interval of time between the date of randomization and the earliest date of achieving best response among participants with a confirmed PR or better based on IRC-assessment per IMWG [Kumar, 2016]. TTBR 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 BOR. **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) based on IRC-assessment per IMWG [Kumar, 2016]. 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 BOR. Sensitivity analysis will be conducted using investigator-assessed responses. **TTP** is defined as the time from randomization until the earliest date of PD based on IRC-assessment per IMWG criteria [Kumar, 2016], 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 similar approach as for the PFS analysis. **PFS2**, defined as time from randomization to disease progression (investigator-assessed response) after initiation of new anti-myeloma therapy or death from any cause, whichever is earlier. If disease progression after new anti-myeloma therapy cannot be measured, a PFS event is defined as the date of discontinuation of new anti-myeloma therapy, or death from any cause, whichever is earlier. Distribution of PFS2 for each treatment arm will be estimated using the Kaplan-Meier method. PFS2 will be compared using similar approach for PFS.
Exploratory	Exploratory analyses will be described in the SAP. For example, To further evaluate the safety and tolerability of belantamab mafodotin when administered in combination with pomalidomide and dexamethasone (i.e., changes in safety assessments, including vital signs) To further characterize the pharmacokinetic profile of belantamab mafodotin when administered in combination with pomalidomide and dexamethasone (i.e., derived PK parameter values for belantamab mafodotin and cys-mcMMAF, as data permit) To evaluate self-reported ocular symptomatic AEs of belantamab mafodotin when administered in combination with pomalidomide and dexamethasone (i.e., changes from baseline in symptoms and related impacts as measured by OSDI) To further evaluate and compare changes in health-related quality of life (HRQoL) and symptoms (i.e., change from baseline in HRQoL as measured by EQ-5D-3L; and change from baseline in PGIS and change over time in PGIC) To further evaluate the impact of side effects on QoL (i.e., change from baseline in FACT-GP5) To evaluate and compare nonprotocol-specified healthcare resource utilization (HCRU) (i.e., out-patient visits by physician specialty; emergency room visits; home healthcare visits; and inpatient hospitalizations (including duration by wards (intensive care unit vs. general ward)) To explore the exposure-response relationship between belantamab mafodotin exposure and clinical endpoints in participants treated with B-Pd (i.e., belantamab mafodotin exposure (e.g., concentration, C_{max}, or AUC) vs. efficacy and safety endpoints (e.g., PFS, ORR, CRR, corneal events)) To explore the relationship between biologic characteristics and clinical response (i.e., Baseline BCMA expression levels in bone marrow and/or tumor tissue, baseline serum soluble BCMA levels and/or immune characteristics relative to clinical response; changes from baseline in sBCMA levels; at MRD assessments and at end of treatment). Pharmacodynamic and/or biomarker exploratory analyses will be described in the SAP or biomarker reporting and analysis plan

Endpoint	Statistical Analysis Methods
	To further explore the efficacy in terms of sustained MRD negativity rate, defined as the percentage of participants who achieve MRD negative status assessed by NGS at 10^{-5} threshold at least twice, a minimum of 12 months apart and with no MRD positive result in between, during the time of confirmed CR or better response based on IRC-assessed response according to IMWG. Participants who do not achieve sustained MRD negative status and participants without a confirmed CR or better response will be considered as not achieving sustained MRD negativity. To further explore the efficacy in terms of imaging plus MRD-negativity rate, defined as the percentage of participants who achieve MRD negative status assessed by NGS at 10^{-5} threshold and have no evidence of disease on PET-CT at least once during the time of confirmed CR or better response, based on IRC-assessed response according to IMWG. Participants who do not meet the criteria will be considered as non-imaging plus MRD-negative, i.e. participants meeting any of the following: 1) do not achieve MRD negative status (including missing/inconclusive assessment) at least once during the time of confirmed CR or better response, or 2) do not have no evidence of disease on PET-CT at least once during the time of confirmed CR or better response, or 3) participants without a confirmed CR or better response. To explore the effect of host genetic variation on the response to belantamab mafodotin and disease under study as well as related drug classes and diseases

Abbreviations: AE=Adverse Event; AUC=Area Under The Concentration Time Curve; BCMA=B-Cell Maturation Antigen; BM=Bone Marrow; BOR=Best Overall Response; B-Pd=Belantamab Mafodotin In Combination With Pomalidomide And Dexamethasone; Cmax=Maximum Plasma Concentration; CR=Complete Response; CRR=Complete Response Rate; Cys-Mcmmaf=Cysteine-Maleimidocaproyl Monomethyl Auristatin F; DoR=Duration Of Response; EoT=End Of Treatment; FACT-GP5=Functional Assessment Of Cancer Therapy – General Population; HCRU=Healthcare Resource Utilization; HR=Hazard Ratio; HRQoL=Health-Related Quality Of Life; IMWG=International Myeloma Working Group; ITT=Intent-To-Treat; MR=Minimal Response; MRD=Minimal Residual Disease; NE=Not Evaluable; NGS=Next-Generation Sequencing; ORR=Overall Response Rate; OS=Overall Survival; OSDI=Ocular Surface Disease Index; PD=Progressive Disease; PFS2=Progression-Free Survival On Subsequent Line Of Therapy; PGIC=Patient Global Impression Of Change; PGIS=Patient Global Impression Of Severity; PK=Pharmacokinetic(S); PR=Partial Response; QoL=Quality Of Life; SAP=Statistical Analysis Plan; sBCMA=Soluble B-Cell Maturation Antigen; sCR=Stringent Complete Response; SD=Stable Disease; TTBR=Time To Best Response; TTP=Time To Disease Progression; TTR=Time To Response; VGPR=Very Good Partial Response.

9.5.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Table 33 Statistical Analytical Methods: Safety

Endpoint	Statistical Analysis Methods
Secondary	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, until the participant withdraws consent for study participation, or until the participant starts subsequent anti-myeloma therapy, whichever occurs first. AEs will be recorded using standard medical terminology and graded according to the NCI-CTCAE (v5.0) with exception of corneal events, which will be graded using the scale detailed in Table 15. For AE reporting, the verbatim term used in the CRF by investigators to identify AEs will be coded using the latest version of MedDRA coding dictionary [NCI, 2017]. AEs 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. AEs, if listed in the NCI-CTCAE (v5.0) or detailed in Section 10.9 will be summarized by the maximum grade. Characteristics (e.g., number of occurrences, action taken, grade, etc.) of the following safety 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 change 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. For each selected item from the PRO-CTCAE library: Maximum PRO-CTCAE score at post-baseline for each item attribute will be summarized by counts and proportions. Supportive analyses will be provided: proportion of PRO-CTCAE scores for attributes (frequency, severity and/or interference) will be presented with stacked bar charts by visit. Proportion of patients with a maximum score of 3 or 4 for each item attribute (severe or very severe, frequently or almost constantly, quite a bit or very much) will also be reported. Proportions will be based on the number of patients with available data and subject with missing response will be excluded from analysis.
Exploratory	Other Safety Measures: Data for vital signs, ECGs, 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 SAP.

Abbreviations: AE=Adverse Event; CRF=Case Report Form; ECG=Electrocardiogram; MedDRA=Medical Dictionary for Regulatory Activities; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; SAP=Statistical Analysis Plan; SAE=Serious Adverse Event.

9.5.3. Pharmacokinetic Analyses

Belantamab Mafodotin:

Concentration-time data: Linear and semi-logarithmic individual concentration-time profiles and mean and/or median profiles (when appropriate) may be plotted for belantamab mafodotin and cys-mcMMAF. Concentrations of belantamab mafodotin and cys-mcMMAF will be listed for each participant and summarized (when appropriate) by planned time point.

Derived pharmacokinetic parameters: Plasma belantamab mafodotin and/or cys-mcMMAF concentration-time data may be combined with data from other studies and analyzed using a population pharmacokinetic approach. The initial analysis will use the population pharmacokinetic model at the time of the analysis to generate post hoc belantamab mafodotin pharmacokinetic parameter estimates for the individual participants in Treatment Arm A. Summary exposure measures (e.g., C_{max}, AUC) will also be computed. Results of this analysis may be provided in a separate report.

Concentration-time data from the participants with enhanced PK schedule may also be analyzed using standard noncompartmental approach.

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.

Pomalidomide:

Concentration-Time Data: Linear and semi-logarithmic individual concentration-time profiles and mean and/or median profiles (when appropriate) will be plotted for pomalidomide. Concentrations of pomalidomide will be listed for each participant and summarized (when appropriate) by planned time point.

Derived PK Parameters: Pomalidomide PK in the presence of belantamab mafodotin may be analyzed using standard noncompartmental methods, data permitting, or analyzed using a published population PK model [Li, 2015]. Results of the population PK analysis may be provided in a separate report.

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

9.5.4. Pharmacokinetic/Pharmacodynamic Analyses

If deemed appropriate and if data permit, exposure-response relationships between belantamab mafodotin exposure (e.g., dose, dose intensity, concentration, $C_{max,}$ or AUC) and clinical activity and/or toxicity (e.g., response, corneal event) may be explored using population methods. If data permit, the effects of covariates may be explored. Results may be reported separately.

9.5.5. Other Analyses

PK, pharmacodynamic, and biomarker exploratory analyses will be described in the SAP or biomarker reporting and analysis plan. The population PK, pharmacodynamic, and biomarker exploratory analyses may be presented separately from the main Clinical Study Report (CSR). PRO analyses will be described in the reporting and analysis plan or PRO reporting and analysis plan and may be presented separately from the main CSR.

9.6. Interim Analyses

Four interim analyses (IAs) are planned for the study, including an interim analysis at the time of Primary PFS analysis (Table 34). Additional analyses of OS may be performed upon request or to provide updated data to the health authorities. The details of these analyses, including the associated alpha-adjustment, if any, will be described in the SAP.

Table 34 Summary of Planned Interim Analyses

	Purpose	Timing
Interim analysis for harm (IA1)	Harm (inferior efficacy)	~35 PFS events (25% PFS information fraction) (~8 months under H1)
IA2	Efficacy	~145 PFS events (~84% PFS information fraction)
Primary PFS analysis/ IA3	Efficacy. This will also be the planned primary analysis of PFS.	~173 PFS events (~100% PFS information fraction) if PFS does not demonstrate statistical significance at IA2 OR ~130 OS events (~60% OS information fraction) if PFS demonstrates statistical significance at IA2
IA4	Efficacy.	~163 OS events (~75% OS information fraction)

Abbreviations: IA=interim analysis; PFS=progression-free survival.

The IA for harm (IA1) is planned at the time of approximately 35 of the 139 targeted PFS events (25% information) have been observed (expected around 8 months from the date of first participant randomized in the study under H1). The interim analysis will allow for stopping early for harm (inferior efficacy). It is expected that 212 participants have been enrolled at the time of IA. A non-binding gamma spending function with parameter -3 will be used to calculate the boundary based on actual observed number of PFS events.

Table 35 shows the stopping boundary for the IA assuming 35 PFS events are observe. The stopping boundaries will be revised based on the observed PFS events included in the IA data. Further details of the interim analysis will be provided in the IDMC charter.

Table 36 provides a summary of boundary crossing probabilities for harm under a range of underlying true hazard ratios.

Boundary crossing probabilities for each of the planned PFS analyses for efficacy based on the revised targeted 173 PFS events are provided in Table 37. The boundaries will be revised based on the observed number of PFS events at the time of analysis.

If PFS demonstrates statistical significance at IA2 (see Section 9.2), the rationale for Primary PFS analysis will be driven by the requirements for OS (PFS will not be retested). The timing of subsequent analyses will be determined based on the OS information fraction. Details of the boundaries and boundary crossing probabilities for

each of the planned OS analyses will be provided in the SAP. OS boundaries will be based on the observed number of OS events at the time of analysis.

In addition, safety data will be reviewed periodically starting from when ~60 participants have been followed for 8 weeks, and then every 6 months or as requested by the IDMC thereafter.

GSK CPMS analysts or delegate(s) not involved in the study conduct 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 interim and primary PFS analyses) throughout the trial for population PK model development/refinement. Additionally, designated representatives not involved with study conduct may be unblinded for performing population PK and PKPD datasets preparation in support of planned analyses and PK display review. All other personnel will remain blinded to aggregate data by treatment group until database lock.

Table 35 Stopping Boundaries for Interim Analysis for Harm (based on 139 targeted PFS events)

Information Fraction	N of Events	Cum. α Spent	Cum. β Spent	Boundary (p-value)	Boundary (HR)	Boundaries Crossing Probabilities for (Harm) (Incremental)	
						Under H0	Under H1
0.25	35	0	0.009	0.805	1.337	0.195	0.009
1	139	0.025	0.148	0.025	0.717	0.78	0.141

Abbreviations: HR=hazard ratio; N/A=not applicable. Per protocol, null hypothesis H0: θ≥1 vs alternative hypothesis H1: θ<1 where θ is the PFS HR (B-Pd vs PVd). To calculate the boundary crossing probabilities, it has been assumed that under H0: HR=1 and under H1: HR=0.6.

Table 36 Boundary Crossing Probabilities for Harm at the Interim Analysis Under a Range of Underlying True Hazard Ratios

Information Fraction	N of Events	Boundary (p-value)	Boundary (HR)	Underlying True HR	Boundaries Crossing Probabilities (Harm)
0.25	35	0.805	1.337	0.6	0.9%
				0.7	2.8%
				0.8	6.3%
				0.9	11.7%
				1	19.1%
				1.1	27.4%
				1.2	36.4%
				1.3	46.0%
				1.4	54.6%

Abbreviations: HR=hazard ratio; N/A=not applicable.

Table 37 Stopping Boundaries for Interim Analyses for PFS Efficacy (based on 173 targeted PFS events)

Information Fraction	N of Events	Cum. α Spent	Boundary (p-value)	Boundary (HR)	Boundaries Crossing Probabilities (Incremental)	
					Under H0	Under H1
0.838	145	0.014	0.014	0.695	0.014	0.812
1	173	0.025	0.021	0.734	0.01	0.1

Abbreviations: HR=hazard ratio; N/A=not applicable. Per protocol, null hypothesis H0: $\theta \geq 1$ vs alternative hypothesis H1: $\theta < 1$ where θ is the PFS HR (B-Pd vs PVd). To calculate the boundary crossing probabilities, it has been assumed that under H0: HR=1 and under H1: HR=0.6.

9.6.1. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) consisting of at least 2 physicians and 1 statistician as defined in the IDMC Charter will review data from the interim analyses (as appropriate) and periodic safety review. Safety data will be reviewed periodically starting from when ~60 participants have been followed for 8 weeks, and then every 6 months or as requested by the IDMC thereafter. Descriptive summaries of efficacy (response rates, number of PFS/OS events) may be included in the safety reviews to support the benefit:risk assessment. Further details are provided in the IDMC charter.

Ad hoc meetings may be convened at the discretion of the IDMC or if requested by the Sponsor. Additional details will be provided in the IDMC Charter.

9.6.2. Sequence of Interim and Other Planned Analyses

All planned analyses are listed in Table 38, below.

Table 38 Details of Planned Analyses

Analysis	Reason/impact	Timing	Endpoints included	Data to be used
Safety review by IDMC	Safety review	Reviewed periodically starting from when ~60 participants have been followed for 8 weeks, and then every 6 months or as requested by the IDMC thereafter.	Key safety (AEs, SAEs, AESIs, deaths, ocular, exposure, dose modifications, laboratory parameters), descriptive efficacy summaries (e.g. response rates, counts of PFS/OS events) and study population summaries.	All data available at the time of the data cut
Interim analysis for harm (IA1)	Harm (inferior efficacy) based on PFS and potential sample-size re-estimation	~35 PFS events (25% PFS information fraction) (~8 months under H1)	Key safety, study population and PFS. Additional analyses may be performed to support decision making if requested by IDMC.	All data available at the time of the data cut
IA2	Efficacy	~145 PFS events (84% information fraction) (~31 months under H1 to observe ~145 PFS events)	Minimally, key safety, study population and PFS. Additional analyses may be performed to support decision making if requested by IDMC. All endpoints may be included if PFS is statistically significant.	All data available at the time of the data cut
Final analysis	To ensure OS data is more mature and provide updated efficacy and safety	~217 OS events (~100% OS information fraction)	Minimally, updated key safety, study population summaries and OS.	All data

All endpoints will be analyzed as per Section 9.5.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, Informed Consent Form (ICF), Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval before implementation of changes made to the study design, as per national requirements, 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/IEC
  - 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 Clinical Trials Directive 2001/20/EC, and all other applicable local regulations

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study 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.
- In case of unexpected pregnancy, participant must be informed that investigator such as [date of birth, sex] of the baby will be collected as part of safety follow-up. Consent for the baby may be obtained from the participant and/or their partner as per local regulations.
- If partners of male participants become pregnant during the study, consent will need to be obtained or notification given as per local regulation to the partner before collecting their PI such as [e.g. LMP, year of birth] or the investigator such as [date of birth, sex] of their baby as part of safety follow-up.

10.1.4. Recruitment Strategy

- Recruitment will be performed by the investigators at the participating sites. The Sponsor will NOT participate in recruitment of participants to the study. The Sponsor will prepare informational material such as infographics, pamphlets, poster and a patient letter to be distributed to the sites to support the investigators in the recruitment process. In addition, the study will be published in public databases such as ClinicalTrials.gov.

10.1.5. 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.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.

10.1.6. Committee Structure

- Periodic safety and interim analyses will be reviewed by an Independent Data Monitoring Committee (IDMC). Details of interim analyses are included in Section 9.6. Additional information will be included in the IDMC charter.
- An independent-review committee (IRC, CCI [redacted]) will be utilized to assess response and disease progression per IMWG criteria. The IRC will remain blinded to all treatment arm assignments, as no treatment information will be provided to the IRC members. Data required for IRC-assessment (e.g. laboratory, imaging and bone marrow data) will be reviewed and adjudicated in-stream. Further details on the IRC process will be defined in the IRC charter. Results from the IRC will not be provided to the investigative sites.

10.1.7. Publication Policy

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

10.1.8. Dissemination of Clinical Study Data

- Disclosure of Clinical Study Reports (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 United States 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 CSR. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.9. Data Quality Assurance

- All participant data relating to the study will be recorded on printed Case Report Form (CRF) or electronic Case Report Form (eCRF) 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.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- 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.
- Quality Tolerance Limits (QTLs) will be predefined in the QTL plan to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and

important deviations from the QTLs and remedial actions taken will be summarized in the CSR.

- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism) 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. Detailed information about study data collection and management process including systems used can be found in a group of documents which govern various processes used by the CRO.
- 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, 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 CSR/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- When copies of source documents are shared externally for review by a central reader mechanism (e.g., endpoint adjudication committee; expert reader), documents are stored by the external body for agreed timeframe according to the charter or contract.

10.1.10. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Copies of documents are shared with external third parties contracted by GSK for review by a central reader mechanism (e.g. endpoint adjudication committee; expert reader). The non-exhaustive list of documents shared to inform the central reader may include, imaging reports, pathology reports, etc. Participant names or any information which would make the participant identifiable or is not essential for the central reader mechanism will be redacted by the investigator sites prior to transfer. Details of the list of documents and the redaction procedure are provided in the site manual or equivalent. These documents will be used by the third party solely for the purpose indicated within this protocol.

10.1.11. Study and Site Start and Closure

First Act of Recruitment

The start of study is defined as first subject first visit (FSFV) at a country-level.

Study/Site Termination

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:

For study termination

- Discontinuation of further study intervention development.

For site termination

- 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 or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
- Total number of participants included earlier than expected

If the study is prematurely terminated or temporarily suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or temporary suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of Adverse Event

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses must be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Definition of Serious Adverse Event

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).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. 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.
c. 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 fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE must be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. 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.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment must be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events must usually be considered serious. – Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
g. Is associated with liver injury and impaired liver function defined as: • Alanine aminotransferase (ALT) ≥3×upper limit of normal (ULN) and total bilirubin* ≥2×ULN (>35% direct), or • ALT≥3×ULN and international normalized ratio (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×ULN and total bilirubin ≥2×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 Section 10.4 for liver chemistry follow-up procedures.

10.2.3. Definition of Cardiovascular Events

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

10.2.4. Recording and Follow-Up of Adverse Events and Serious Adverse Events

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 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)*. • Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**. • Grade 4: Life-threatening consequences; urgent intervention indicated. • Grade 5: Death related to AE. *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the phone, managing money, etc. **Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

In addition to reporting eye disorders using CTCAE criteria, corneal events associated with belantamab mafodotin must also be graded according to the guidelines provided in Table 15.

Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.

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

Follow-up of AE and SAE

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

10.2.5. Reporting of Serious Adverse Events to GSK or Designee

SAE Reporting to GSK or Designee 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 review and verify the relationship of each SAE to Investigational Product/study participation (causality) and documented in source.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).
- Contacts for SAE reporting can be found in the Study Reference Manual (SRM).

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

10.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

10.3.1. Definitions

Woman of childbearing potential (WOCBP):

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

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

Women in the following categories are not considered WOCBP:

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

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

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

1. 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 hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea confirmation with more than 1 FSH measurement is required [in questionable cases a blood sample with simultaneous FSH >40 MIU/mL and estradiol <40 pg/mL (<147 pmol/L) is confirmatory].
    - Females on HRT and whose menopausal status is in doubt will be required to use 1 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 enrolment.

10.3.2. Contraception Guidance

CONTRACEPTIVES[1] ALLOWED DURING THE STUDY
Highly Effective Methods[2] That Have Low User Dependency:
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[3]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• 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[2] That Are User Dependent:
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[3] – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[3] – 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.

Abbreviations: CTFG=Clinical Trial Facilitation Group; IUD=intrauterine device; IUS=intrauterine hormone-releasing system; LAM=lactational amenorrhea method

1. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
2. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
3. 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.

10.3.3. 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 the last dose of belantamab mafodotin (Arm A) and 4 months

following the last dose of bortezomib (Arm B), by phone for WOCBP partners only. This applies only to male participants who receive study treatment.

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

Female participants who become pregnant:

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study and for 4 months following the last dose of belantamab mafodotin (Arm A) or 7 months from the last dose of bortezomib (Arm B).
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event (AE) or serious adverse event (SAE), any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 10.2. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating will discontinue study treatment.

10.4. Appendix 4: Liver Safety: Required Actions, Follow-up Assessments, and Study Treatment Rechallenge Guidelines

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

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥8×ULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥5×ULN but <8×ULN persists for ≥2 weeks
ALT ≥3×ULN but <5×ULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥3×ULN and total bilirubin ≥2×ULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥3×ULN and INR>1.5</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥5×ULN but <8×ULN and cannot be monitored weekly for ≥2 weeks
ALT ≥3×ULN but <5×ULN and cannot be monitored weekly for ≥4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥3×ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions, Monitoring, and Follow-Up Assessments</th></tr>
<tr><th>Actions</th><th>Follow-Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event form and complete SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow-up assessments as described in the Follow-Up Assessment column
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING)
<u>MONITORING</u>:
If ALT ≥3×ULN AND total bilirubin ≥2×ULN or INR >1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within 24 hours
• Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline
• A specialist or hepatology consultation is recommended
For all other criteria (bilirubin <2×ULN and INR ≤1.5)<u>:</u>
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within 24-72 hours
• Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline
<u>RESTART/RECHALLENGE</u>:</td><td>• Viral hepatitis serology[4]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend
• Blood sample for belantamab mafodotin pharmacokinetic (PK) analysis (Arm A only) and a blood sample for sBCMA (Arm A and Arm B), obtained within 70 days after last dose of belantamab mafodotin; blood sample for pomalidomide PK to be obtained within 48 hours of last pomalidomide dose[5]
• CPK and LDH, GGT, glutamate dehydrogenase [GLDH], and serum albumin
• Fractionate bilirubin, if total bilirubin≥2×ULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter medications
• Record alcohol use on the liver event alcohol intake form
If ALT ≥3×ULN AND total bilirubin ≥2×ULN or INR >1.5 obtain the following in addition to the assessments listed above:</td></tr>
</table>

Liver Chemistry Stopping Criteria – Liver Stopping Event	
• **Restart/rechallenge is allowed per protocol but do not resume study intervention unless GSK approval is granted;** If restart/rechallenge is **not granted**, permanently discontinue study intervention and continue participant in the study for any protocol specified follow-up assessments. Refer to Restart/Rechallenge guidelines in Appendix 4.	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins) • Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week. (e.g., where the participant has been resident in the clinical unit throughout) **Note: not required in China** • Liver imaging (ultrasound, magnetic resonance imaging, or computed tomography) to evaluate liver disease; complete Liver Imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance: – In participants when serology raises the possibility of autoimmune hepatitis (AIH) – In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention – In participants with acute or chronic atypical presentation: • If liver biopsy conducted complete liver biopsy form.
Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5×ULN and <8×ULN **and** total bilirubin <2×ULN or INR ≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3×ULN and <5×ULN **and** total bilirubin <2×ULN or INR ≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK Medical 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, total bilirubin and INR) until they resolve, stabilize or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5×ULN and <8×ULN to ≥3×ULN but <5×ULN (total bilirubin <2×ULN and INR ≤1.5), continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3×ULN and bilirubin <2×ULN and INR ≤1.5, monitor participants twice monthly until liver chemistries resolve or return to within baseline.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=serum creatine phosphokinase; DILI=drug-induced liver injury; GGT=gamma-glutamyl transferase; Ig=immunoglobulin; INR=international normalized ratio; LDH=lactate dehydrogenase; PK=pharmacokinetic(s); SAE=serious adverse event; sBCMA=soluble B-cell maturation antigen; SRM=Study Reference Manual; ULN=upper limit of normal.

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 ≥3×ULN **and total** bilirubin ≥2×ULN. 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 ≥3×ULN **and** total bilirubin ≥2×ULN (>35% direct bilirubin) or ALT ≥3×ULN **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)**; the INR threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: hepatitis A IgM antibody; hepatitis B surface antigen and hepatitis B core antibody (IgM); hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR or hepatitis D RNA virus (where needed) [Le Gal, 2005].
5. Record the date/time of the PK/sBCMA blood sample draw and the date/time of the last dose of study intervention (belantamab mafodotin and pomalidomide) prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated or a PK/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. A sample for sBCMA should be collected at the time of PK sample collection.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

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

10.4.1. 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 (IRB)/Independent Ethics Committee (IEC) approval, if required, is obtained and
- Separate Informed Consent Form 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.

10.4.1.1. Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment

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

Risk factors for a fatal drug rechallenge outcome include:

- Hypersensitivity with initial liver injury (e.g., fever, rash, eosinophilia) [Andrade, 2009]
- Jaundice or bilirubin >2x ULN with initial liver injury (direct bilirubin >35% of total)
- Ongoing severe liver injury defined by: ALT ≥3×ULN, bilirubin ≥2×ULN (direct bilirubin >35% of total), or INR >1.5.
- SAEs or fatality has earlier been observed with drug rechallenges [Hunt, 2010; Papay, 2009].
- Evidence of drug-related pre-clinical liability (e.g., reactive metabolites; mitochondrial impairment)

Rechallenge refers to resuming study treatment following study treatment 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 favorable.

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

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

If the rechallenge is approved by GSK in writing:

- The participant must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study file.

- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, participant meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- GSK Medical Director and the IRB/IEC as required, must be informed of the participant's outcome following study treatment rechallenge.
- GSK to be notified of any adverse events (AEs), as per Section 10.2.

10.4.1.2. Restart Following Transient Resolving Liver Stopping Events NOT Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g., biliary obstruction, pancreatic events, hypotension, 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 treatment restart can be considered where:

- Principal Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5×baseline and ALT <3×ULN).
- Possible study treatment-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 treatment has an identified genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate), the presence of the marker should be excluded. If study treatment-related liver injury cannot be excluded, the guidance on rechallenge as stated in previous section, Section 10.4.1, will apply.
- There is no evidence of alcohol-related hepatitis.
- IRB/IEC approval of study treatment restart must be obtained, as required.

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

- The participant must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study file.
- Study treatment must be administered at the dose specified by GSK.

- Participants approved by GSK for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If participant meets protocol-defined liver chemistry stopping criteria after study treatment restart, study treatment should be permanently discontinued.
- GSK Medical Director and the IRB/IEC must be informed of the participant's outcome following study treatment restart.
- GSK to be notified of any AEs, as per Section 10.2.

References

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

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

Papay JI, Clines D, Rafi R, et al. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

10.5. 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 Institutional Review Board/Independent Ethics Committee allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to belantamab mafodotin or multiple myeloma (MM) 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 MM. Genetic research may consist of the analysis of 1 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 CSR 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 MM continues but no longer than 15 years after the Last Participant Last Visit (LSLV) or other period as per local requirements.

10.6. Appendix 6: Eastern Cooperative Oncology Group (ECOG) Functional Status

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

[Oken, 1982]

10.7. Appendix 7: Modified Diet in Renal Disease Formula

The Modified Diet in Renal Disease (MDRD) formula for calculating the estimated glomerular filtration rate (eGFR) is as follows:

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

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

The following link will auto-calculate the creatinine clearance:

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

10.8. Appendix 8: New York Heart Association Classification

The New York Heart Association (NYHA) Functional Classification: Class I, II, III, or IV Heart Failure [New York Heart Association, 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:

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.

10.9. Appendix 9: Progression-Free Survival Event and Censoring Rules

Situation	Date of Event (Progression/Death) or Censored	Event (Progression/Death) or Censored
No (or inadequate) Baseline assessments[1] and the participant has not died (if the participant has died follow the rules for death indicted at the bottom of the table)	Randomization	Censored
No adequate post-Baseline assessments and the participant has not died (if the participant has died follow the rules for death indicted at the bottom of the table)	Randomization	Censored
Progression documented at scheduled visits and Progression documented without extended loss-to-follow-up time[4]	Date of assessment of progression	Event
Progression documented between scheduled visits and Progression documented without extended loss-to-follow-up time[4]	Date of assessment of progression (S1) min (Date of next scheduled visit, date of death)	Event (S1) Event
With post-Baseline assessment but no progression (or death)	Date of last 'adequate' assessment of response[2]	Censored
No adequate post-Baseline assessment before start of new anti-myeloma therapy (prior to documented disease progression or death)	Randomization (S2) Date of starting new anti-myeloma therapy	Censored (S2) Event
With adequate post-Baseline assessment and new anti-myeloma treatment started (prior to documented disease progression or death)[3]	Date of last 'adequate' assessment of response[2] (on or prior to starting anti-myeloma therapy) (S2) Date of starting new anti-myeloma therapy	Censored (S2) Event
Death before first scheduled assessment (or death at Baseline or without any adequate assessments)	Date of death	Event
Death between adequate assessment visits	Date of death	Event
Death without extended loss-to-follow-up time[4]	Date of death	Event

Situation	Date of Event (Progression/Death) or Censored	Event (Progression/Death) or Censored
Death or progression after missing two or more scheduled assessments[4]	Date of randomization if no post-baseline assessments, or date of last 'adequate' assessment of response[2] (prior to missed assessments): since disease assessment is every 4 weeks, a window of 63 days (8 weeks + 7-day window) will be used to determine whether there is extended time without adequate assessment. If the time difference between PD/death and max(last adequate disease assessment, randomization) is more than 63 days, PFS will be censored at the last adequate disease assessment prior to PD/death. (S3) Date of death or progression	Censored (S3) Event
(S4) Treatment discontinuation due to clinical PD[5] before PD or death	(S4) Date of treatment discontinuation	(S4) Event

Abbreviations: CR=Complete Response; FLC=Free Light Chain; MR=Minimal Response; PD=Progressive Disease; PR=Partial Response; sCR=Stringent Complete Response; SD=Stable Disease; VGPR=Very Good Partial Response.
Note: (S1) (S2) (S3) (S4) Rules To Be Applied For PFS Sensitivity Analysis.
Event or censored are based on confirmed responses.

1. Adequate baseline assessment is defined as at baseline, a patient has at least one of the following measurements: Serum M-protein ≥0.5 g/dL (≥5 g/L) or b. Urine M-protein ≥200 mg/24h or c. Serum FLC assay: Involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum free light chain ratio (<0.26 or >1.65)
2. An adequate assessment is defined as an assessment where the response is sCR, CR, PR, VGPR, MR or SD. If the adequate assessment occurred on the same date as new anti-myeloma therapy, it is assumed that the assessment occurred first.
3. If PD or death and new anti-myeloma therapy occur on the same day, assume the progression or death was documented first; e.g., the outcome is progression or death and the date is the date of the assessment of progression or death. If anti-myeloma therapy is started prior to any adequate assessments, censoring date should be the date of randomization.
4. Extended loss-to-follow-up time = 8 weeks + 7 day window = 63 day window; Without extended loss-to-follow-up time is defined as: <= 63 days; after an extended loss-to-follow-up time is defined as: >63 days.
5. Treatment discontinuation of any component due to physician decision = clinical relapse or where physician decision indicates clinical progression.

10.10. Appendix 10: Country Specific Requirements

Inclusion Criteria:

- In the **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 **Israel**, participants must have prior treatment with daratumumab, if available, cannot get access to daratumumab for any reason, or cannot tolerate daratumumab.
- In **Japan**, Hepatitis B participants who are HbsAg- (e.g. HBsAb+/HbsAg-, HBcAb+/HbsAg-, HBcAb+/HBsAb+/HbsAg-) are eligible for inclusion in this study if HBV DNA is undetectable. A patient with HBsAg+ are eligible if HBV DNA is undetectable after assessing HBeAg, HBeAb and HBV DNA, and if a hepatologist agrees with the participation into this study.

Adverse Events:

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

Other Assessments:

- In **China**, the following assessment will not be performed as a follow-up to bilirubin or INR meeting Liver Chemistry stopping criteria: Serum acetaminophen adduct assay.
- In **China**, the following samples will not be collected: bone marrow biopsy sample for BCMA IHC, BM aspirate for exploratory endpoints, and pharmacogenetic samples
- In **China**, MRD sample collection and assessment will not be performed until approval from Human Genetic Resource Administration of China (HGRAC) is obtained

Contraception Guidance:

Of the contraceptive methods defined in Section 10.3.2 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

10.11. Appendix 11: Eye Care Specialist's Qualifications and Requirements

For examiners with a degree in ophthalmology or optometry, those involved in eye evaluations in the protocol will, at a minimum, be able to provide comprehensive eye care to participants, which includes everything from routine check-ups to treatment and ongoing management of visual disease.

Specifically, qualified eye care specialists must be able to:

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

10.12. Appendix 12: 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 schedule of activities (SoA) (Section 1.3) and include:

- Collection of blood and urine samples including:
  - Safety assessments which may include routine blood and urine sampling
  - Pharmacokinetic and anti-drug antibody 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. Refer to the Study Reference Manual/Laboratory Manual for sample collection and storage requirements.
- Measurement of vital signs (BP, heart rate, body temperature) and weight
- Physical examination
- Administration of pre/post-medication
- Identification and reporting of concomitant medications.
- Dosing diary review for medication compliance.
- Identification and reporting of adverse events (AEs)/serious adverse events (SAEs).

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

The participant should be informed of any potential risks associated with Home Healthcare and sign a revised Informed Consent Form (ICF) if required. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) should be informed and/or approve of this change in approach and the process documented in study files.

Home Healthcare (Ophthalmologic Examination)

Where applicable country and local regulations and infrastructure allow, protocol-required eye examinations 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 examinations, must follow the schedule provided in the SoA (Section 1.3) and include:

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

The participant should be informed of any potential risks associated with Home Healthcare Ophthalmologic examinations and sign a revised ICF, if required. IRB/IEC should be informed and/or approve of this change in approach and the process documented in study files.

Telemedicine

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

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

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

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

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

Remote Patient -Reported Outcomes Administration

Where applicable country and local regulations and infrastructure allow, remote patient reported outcome (PRO) administration may be permitted. Remote PRO administration is defined administration of protocol PROs by a qualified third party over the phone. 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 ICF if required. IRB/IEC should be informed and/or approve of this change in approach and the process documented in study files.

10.13. Appendix 13: 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 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.

10.14. Appendix 14: List of Abbreviations, Trademarks, and Definitions of Terms

Abbreviations

2L	Second-line
ADA	Anti-Drug Antibody
ADC	Antibody-Drug Conjugate
ADCC	Antibody-Dependent Cellular Cytotoxicity
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APRIL	A Proliferation-Inducing Ligand
APT	All-Patients Treated
AST	Aspartate Aminotransferase
ASCT	Autologous Stem Cell Transplant
AUC	Area Under The Concentration Time Curve
B-Pd	Belantamab Mafodotin In Combination With Pomalidomide And Dexamethasone
BAFF	B-Cell Activating Factor
BCMA	B-Cell Maturation Antigen
BCVA	Best-Corrected Visual Acuity
BM	Bone Marrow
BOR	Best Overall Response
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CI	Confidence Interval
CIOMS	Council For International Organizations Of Medical Sciences
CIRT	Cenduit Interactive Response Technology
CK	Creatine Kinase
C_{max}	Maximum Plasma Concentration
CO_2	Carbon dioxide
CO_2CP	Carbon dioxide combining power
CONSORT	Consolidated Standards Of Reporting Trials
CPK	Serum Creatine Phosphokinase
CR	Complete Response
CRBN	Cereblon
CRF	Case Report Form
CRR	Complete Response Rate
CSR	Clinical Study Report
CT	Computed Tomography
Ctau	Trough Concentration
CTCAE	Common Terminology Criteria For Adverse Events
CV	Cardiovascular
CV%	Percent Coefficient Of Variation
CYP	Cytochrome P450 Enzymes
Cys-mcMMAF	Cysteine-Maleimidocaproyl Monomethyl Auristatin F
DILI	Drug-Induced Liver Injury

DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic acid
DoR	Duration Of Response
DREAMM	Driving Excellence In Approaches To Multiple Myeloma
DRESS	Drug Reaction With Eosinophilia And Systemic Symptoms
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EMD	Extramedullary diseases
EOI	End of infusion
EORTC IL52	European Organisation for Research and Treatment of Cancer Item Library 52
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
EoS	End of Study
EoT	End of Treatment
EU	European Union
FACT-GP5	Functional Assessment of Cancer Therapy – General Population
FDA	Food and Drug Administration
FISH	Fluorescence-In-Situ Hybridization
FLC	Free Light Chain
FSH	Follicle-Stimulating Hormone
FTIH	First-Time-In-Human
FWER	Family-Wise Error Rate
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HbsAg	Hepatitis B Surface Antigen
HbA1c	Hemoglobin A1c
HBV-DNA	Hepatitis B Virus-Deoxyribonucleic Acid
HbcAb	Hepatitis B Core Antibody
Hep C Ab	Hepatitis C Antibody
Hep C RNA	Hepatitis C RNA
HBeAb	Hepatitis B e antibody
HBeAg	Hepatitis B e antigen
HCRU	Healthcare Resource Utilization
HD	High-Dose Dexamethasone
HGRAC	Human Genetic Resource Administration of China
HIPAA	Health Insurance Portability And Accountability Act
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	International Council For Harmonisation Of Technical Requirements For Pharmaceuticals For Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgG1	Immunoglobulin G1
IHC	Immunohistochemistry
IMWG	International Myeloma Working Group
IP	Investigational Product
IRB	Institutional Review Board
IRC	Independent Review CommitteE
IRR	Infusion-Related Reaction
IRT	Interactive Response Technology
ISS	International Staging System
ITT	Intent-to-Treat
IV	Intravenous/Intravenously
kg	Kilogram
KVA	Keratopathy Visual Acuity
LDH	Lactate Dehydrogenase
LPFV	Last Participant First Visit
LSLV	Last Participant Last Visit
LVEF	Left Ventricular Ejection Fraction
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCRN	Myeloma Canada Research Network
MCV	Mean Corpuscular Volume
MDRD	Modified Diet In Renal Disease
MedDRA	Medical Dictionary For Regulatory Activities
mg	Milligram
MM	Multiple Myeloma
MMAF	Monomethyl Auristatin-F
MOA	Mechanism Of Action
mPFS	Median Progression-Free Survival
MR	Minimal Response
MRD	Minimal Residual Disease
MRP	Multidrug Resistance Associated Protein
MRI	Magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria For Adverse Events
NEA	North East Asian
NGS	Next-Generation Sequencing
NYHA	New York Heart Association
OATP	Organic Anion Transporting Polypeptide
ORR	Overall Response Rate
OS	Overall Survival
OSDI	Ocular Surface Disease Index
PACT	Post Analysis Continued Treatment
Pd	Pomalidomide In Combination With Dexamethasone
PD	Progressive Disease
PDy	Pharmacodynamic(S)
PET/CT	Positron Emission Tomography/Computed Tomography

PFS	Progression-Free Survival
PFS2	Progression-Free Survival On Subsequent Line Of Therapy
PGIC	Patient Global Impression Of Change
PGIS	Patient Global Impression Of Severity
P-gp	P-Glycoprotein
PI	Proteasome Inhibitor
PK	Pharmacokinetic(S)
PML	Progressive Multifocal Leukoencephalopathy
PO	Oral/Orally
POEMS	Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Plasma Proliferative Disorder, And Skin Changes
PR	Partial Response
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	Patient-Reported Outcome
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PVd	Pomalidomide Plus Bortezomib And Dexamethasone
q12w	Every 12 Weeks
q3w	Every 3 Weeks
q4w	Every 4 Weeks
q8w	Every 8 Weeks
QoL	Quality Of Life
QRS	Electrocardiogram Q, R, And S Waves
QT	Electrocardiogram Q And T Waves
QTc	Corrected QT Interval
QTcF	QT Interval Corrected Using Fridericia's Formula
QTL	Quality Tolerance Limit
RBC	Red Blood Cell
RNAseq	RNA Sequencing
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
RRMM	Relapsed/Refractory Multiple Myeloma
RMDOR	Restricted Mean Duration of Response
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sBCMA	Soluble B-Cell Maturation Antigen
SC	Subcutaneous/Subcutaneously
sCR	Stringent Complete Response
SD	Stable Disease
SJS	Stevens-Johnson Syndrome
SoA	Schedule Of Activities
SoC	Standard Of Care
SOI	Start Of Infusion
SPEP	Serum Protein Electrophoresis
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEN	Toxic Epidermal Necrolysis
TLS	Tumor Lysis Syndrome
TNFRSF17	Tumor Necrosis Factor Receptor Super Family Member 17
TNFSF	Tumor Necrosis Factor Super Family
TTBR	Time To Best Response

TTP	Time To Disease Progression
TTP/HUS	Thrombotic Thrombocytopenic
TTR	Time To Response
ULN	Upper Limit Of Normal
UPEP	Urine Protein Electrophoresis
US	United States
USPI	United States Prescribing Information
Vd	Bortezomib Plus Dexamethasone
VGPR	Very Good Partial Response
VZIG	Varicella Zoster Immune Globulin
WBC	White Blood Cell
WOCBP	Woman Of Childbearing Potential

Trademark Information

Trademarks of the GSK group of companies
NONE

Trademarks not owned by the GSK group of companies
EAST
MedDRA
POMALYST
VELCADE

Term	**Definition**
Adverse Drug Reaction	An adverse event where a causal relationship between a medicinal product and the adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. a. In the context of a clinical trial, an ADR can be serious or non-serious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). b. For marketed products, ADRs are subject to expedited reporting within the country where they are authorized
Auxiliary Medicinal Product (AxMP) a) Authorised AxMP b) Unauthorized AxMP	Medicinal products used in the context of a clinical trial but not as investigational medicinal products, such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess end-points in a clinical trial. Auxiliary medicinal products should not include concomitant medications, that is medications unrelated to the clinical trial and not relevant for the design of the clinical trial. a. Medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product. 1. Safety reporting with regard to auxiliary medicinal products shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC.

Term	Definition
	b. Medicinal product not authorized in accordance with Regulation (EC) No 726/2004 1. Safety reporting for unauthorised auxiliary medicinal products will follow the same processes and procedures as SUSAR safety reporting
Blinding:	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. In an open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned.
Caregiver	A 'caregiver' is someone who – lives in the close surroundings of a participant and has a continuous caring role or – has substantial periods of contact with a participant and is engaged in their daily health care (e.g., a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home). In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol-specified procedures.
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Co-administered (concomitant) products	A product given to clinical trial participants as required in the protocol as part of their standard care for a condition which is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.
Combination product	Combination product comprises any combination of – drug – device – biological product Each drug, device and biological product included in a combination product is a constituent part.
Comparator	Any product used as a reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).

Term	Definition
Decentralized Trial Platform	A digital engagement technology allowing for the remote delivery and access to trials for participants, sites, and sponsors.
Direct-from-Participant Shipments	Home pickup of collected biological specimens, or pickup and return of unused/partially used/expired trial materials for return to investigator site.
Direct-to-Participant Shipments	Shipping of Investigational Product, lab kits, devices, etc., to the participant's residence under secure and controlled conditions.
eDiary	Electronically registered patient data and automated data entries on, for example, a handheld mobile device, tablet or computer.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
Home Healthcare Services	Deployment of mobile health care professional(s) (nurses or phlebotomists) to perform study activities remotely.
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.
Investigational product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions
Legally acceptable representative	An individual, judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study. The terms legal representative or legally authorized representative are used in some settings.
Medicinal products used to assess end-points	A product given to the participant in a Clinical Trial as a tool to assess a relevant clinical trial endpoint; it is not being tested or used as a reference in the clinical trial.
Participant number	A unique identification number assigned to each participant who consents to participate in the study.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical

Term	Definition
	study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
Pharmacogenomics	The ICH E15 Guidance for Industry defines pharmacogenomics as the "Study of variation of DNA and RNA characteristics as related to drug or treatment response." Pharmacogenetics, a subset of pharmacogenomics, is "the study of variations in DNA sequence as related to drug response." Pharmacogenomic biomarkers include germline (host) DNA and RNA as well as somatic changes (e.g., mutations) that occur in cells or tissues. Pharmacogenomic biomarkers are not limited to human samples but include samples from viruses and infectious agents as well as animal samples. The term pharmacogenomic experiment includes both the generation of new genetic or genomic (DNA and/or RNA) data with subsequent analysis as well as the analysis of existing genetic or genomic data to understand drug or treatment response (PK, safety, efficacy or effectiveness, mode of action). Proteomic and metabolomic biomarker research is not pharmacogenomics.
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
Primary Completion Date	The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. Whether the clinical study ended according to the protocol or was terminated does not affect this date. For clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcome measures.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Remote visit	This term refers to the visit conducted in the place other than the study site.
Self-contained study	Study with objectives not linked to the data of another study.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Standard of Care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or

Term	Definition
	international consensus; there is no regulatory significance to this term. 1. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries
Study intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant. Note: "Study intervention" and "study treatment" are used interchangeably unless otherwise specified.
Study completion date	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Subcohort	A group of participants for whom specific study procedures are planned as compared to other participants or a group of participants who share a common characteristic (e.g., ages, vaccination schedule, etc.) at the time of enrollment.
SUSAR	Suspected Unexpected Serious Adverse Reaction; in a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., Investigator's Brochure for an unapproved investigational medicinal product). All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting.
Telemedicine	The use of electronic information and telecommunications technologies (both video-based and audio-only) to facilitate remote health care delivery, participant and professional health-related education, public health and health administration.
Virtual visit	This term refers to study visits conducted using multimedia or technological platforms.

10.15. Appendix 15: Protocol Amendment History

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

Summary of Previous Amendments

Amendment 03 23 Feb 2023

Overall Rationale for the Amendment 3:

- This protocol amendment changes the primary analysis of response-based efficacy endpoints (with the exception of Progression-Free Survival On Subsequent Line Of Therapy [PFS2]) from being based on a proprietary algorithm-derived confirmed response and dates per IMWG [Kumar, 2016] criteria to being based on Independent Review Committee (IRC) assessed response and dates per IMWG criteria. PFS2 will continue to be analysed based on investigator assessment.
- Timing of primary Progression-Free Survival (PFS) analysis revised: the primary PFS analysis will be conducted after observing approximately 139 PFS events and a minimum of 6 months follow-up, in the randomized participants contributing to the analysis.
- Duration of Response (DoR) moved from secondary to key secondary endpoint and will be tested following PFS and prior to MRD negativity; included in hierarchical testing strategy at time of Primary PFS analysis; endpoint definition revised to include all participants regardless of response status and primary analysis method revised to compare restricted mean DoR (RMDOR) and align with endpoint definition.
- Revised Overall Survival (OS) as another key secondary endpoint (moved from secondary) per regulatory request; included in hierarchical testing strategy at time of Primary PFS analysis.
- Additional details of the sample size re-estimation and IA for harm boundary crossing probabilities have been provided
- Addition of Post Analysis Continued Treatment (PACT) to allow eligible participants to receive study treatment after final analysis DCO.
- Revised EoS definition as “the end of the safety follow-up following the last participant last dose i.e. the completion of the PACT phase”.
- Revised PRO-CTCAE endpoint definition: maximum post-baseline PRO-CTCAE score for each item attribute. Added details of analysis. To align with the planned analyses performed across the program.
- Additional actions to reduce lost to follow-up to help limit the amount and impact of missing data.
- Removed total monoclonal antibody (total mAb) from secondary and exploratory endpoints.

- Removed collection and analysis of circulating plasma cell-free DNA (cfDNA).
- Defined the countries included in the North East Asia region subgroup.
- Additional changes were incorporated which align with program revisions and/or updates.
- Administrative updates to add clarification and/or remove discrepancies

All changes are listed in table below

Section # and Name	Description of Change	Brief Rationale
Headers, cover page, and Protocol Amendment Summary of Changes Table	Headers and cover page were updated with new document number; Protocol Amendment Summary of Changes Table section was created and populated to include details and rationale for this amendment	Editorial changes to align with the GSK's standard protocol template
Throughout	Administrative updates to add clarification and/or remove discrepancies	Editorial changes were made for accuracy, clarity, conformity, flow, and typographical error corrections
Throughout	Removal of proprietary algorithm-derived confirmed response and instead, primary efficacy analyses for response-based endpoints will be based on IRC assessment (with the exception of PFS2 which continues to be based on investigator assessment in line with the data collection for second progression)	To address FDA comments at protocol amendment 2
Section 1.1 Synopsis Section 4.1 Overall Design Section 9.3.1 Primary Endpoint Section 9.5.1 Efficacy Analyses Section 9.6.2 Sequence of Interim and Other Planned Analyses	The primary PFS analysis will be conducted after observing approximately 139 PFS events and a minimum of 6 months follow-up, in the randomized participants contributing to the analysis. Revised from requiring approximately 139 PFS events only.	To ensure adequate follow-up for the study population and specifically, for participants with one prior line of therapy
Section 1.1 Synopsis Section 3 Objectives and Endpoints Section 9 Statistical Considerations (Section 9.1, 9.2, 9.3 and 9.5.1).	Revised DoR as another key secondary endpoint (moved from secondary); updated testing hierarchy; changed DoR definition to include all participants regardless of response status (not just based on responder) and updated primary analysis method for DoR to be based on a comparison of the restricted mean DoR (RMDOR) between the treatment arms. Analyses of DoR among responders retained as supplementary analyses. Inclusion of DoR as key secondary above MRD Negativity changes section numbering: 9.1.2 and 9.1.3 become 9.1.3 and 9.1.4, respectively. 9.3.2, 9.3.3 and 9.3.4 become 9.3.3, 9.3.4 and 9.3.5, respectively.	To enable an ITT analysis using all participants (responders and non-responders) with increased sensitivity and to account for the expected difference in the proportion of responders between the treatment arms so that valid statistical comparisons can be made.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 3 Objectives and Endpoints Section 9 Statistical Considerations	Revised overall survival (OS) as another key secondary endpoint (moved from secondary endpoint); updated testing hierarchy Addition of sections 9.1.4 Key Secondary Overall Survival Endpoint (to define the hypothesis test) and 9.3.4 Key Secondary Endpoint Overall Survival. Revised Section 9.2 to include OS in the hierarchical testing and clarify sequence/timing of testing. Section 9.5.1 moved details of the OS analyses to key secondary and clarified timing of primary OS analyses to align with the planned hypothesis testing	To address FDA comments at protocol amendment 2
Section 1.1 Synopsis Section 1.3 Schedule of Activities Section 4.1 Overall Design Section 4.4 EOS Definition Section 6.8 Continued Access to Study Intervention after the End of the Study Section 8.3.1 Time Period and Frequency for Collecting AE and SAE	Addition of an option for post analysis continued treatment (PACT) to allow eligible participants to continue study treatment Revised End of Study definition Addition subSection 6.8.1 Continued Access to Study Intervention After Final Analysis Data Cut-off prior to EOS Added instructions of the scope and the time period of data collection and reporting during the PACT phase	To allow continued access to belantamab mafodotin and other study drugs in eligible participants and guidance on data collection and reporting
Section 1.1 Synopsis Section 3 Objectives and Endpoints Section 8.5 Pharmacokinetics Section 9.5.1 Efficacy Analyses Section 9.5.3 PK Analyses	Removed total mAb from secondary and exploratory endpoints, and relevent sections in pharmacokinetics	Total mAb concentrations are highly correlated with ADC concentrations which are already being collected
Section 8.6 Belantamab Mafodotin Immunogenicity	Deleted analysis of belantamab mafodotin plasma concentration for ADA samples Added statement on ADA sample collection	Drug concentration is not needed for interpretation of ADA data due to the high drug tolerance of the immunogenicity assays. To allow reducing and termination of ADA sample collection when clinical data of immunogenicity within and cross studies are deemed sufficient.
Section 1.1 Synopsis Section 3 Objectives and Endpoints Section 9.5.2 Safety Analyses	Revised PRO-CTCAE endpoint definition: maximum post-baseline PRO-CTCAE score for each item attribute Added details of secondary endpoint analysis of PRO-CTCAE data	To align with the planned analyses performed across the program. Intended analysis has not changed but endpoint wording revised to align with the intent.

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Schema	Follow-up for OS from every 3 months to every 12 weeks (Figure 1)	To align with the description in SoA
Section 1.3 Schedule of Activities Section 8 Study assessments and procedure Section 8.9.3 Circulating Plasma Cell-Free DNA Analysis Section 9.5.1 Efficacy Analyses	Removed sample collection of circulating plasma cell-free DNA (cfDNA) (Table 1 and Table 2) Removed analysis of cfDNA (Section 8 Table 24, Section 8.9.3 and in Table 33 in Section 9.5.1)	In line with program level changes
Section 1.3 Schedule of Activities Section 8.2.6. Ophthalmic Assessments	Clarify the instruction and frequency of ocular examinations after the 6th dose of belantamab mafodotin (Table 1, footnote 3, and Section 8.2.6.1)	Clarification
Section 1.3 Schedule of Activities Table 1 and Table 2	Added Footnote 26 for GSK for collecting survival data outside the protocol window	Clarification
Section 1.3 Schedule of Activities Table 3	Reorganized header in Table 3,	Clarification
	Added optional EMD tissue sample collection at PD in footnote 14 (Table 1 and Table 2)	Clarification
	Added ±1 month window for follow-up MRD testing in Table 3 footnote f	Clarification
Section 5.1 Inclusion Criteria	Clarification of lenalidomide exposure requirement in inclusion criteria #5	Clarification
	Clarification of footnote 1 in Table 6	Clarification
Section 5.2 Exclusion Criteria	Clarification of exclusion criteria #3	Clarification
Section 5.2 Exclusion Criteria Table 7 Section 10.10 Country Specific Requirements	Additional requirements for Japan Hepatitis B participants	Clarification
Section 6.1.3.2 Corneal Supportive Care Guidelines Section 8.2.6.2 Treatment Arm B	Added ±4 weeks window for on study ocular assessment in Arm B	Clarification
Section 6.1.5 Bortezomib	Updated the reconstituted concentration of bortezomib for intravenous administration (1 mg/mL) instead of subcutaneous administration; Addition of SC injection site per institutional guidance and alternative route of administration	Clarification
Section 6.5.1 Permitted Concomitant Therapies	Allowing concomitant treatment or prophylaxis using monoclonal antibodies for serious conditions unrelated to MM, such as COVID	To align with program language

Section # and Name	Description of Change	Brief Rationale
Section 6.7.1 Guidance on Dose Reductions in Treatment Arm A	Dose modification for creatinine and ACR updated (Table 13)	To align with CTCAE
	Clarify Belantamab mafodotin dose modification for other treatment-related toxicity is described in Table 13 and Table 14	Clarification
Section 7.1 Discountinuation of Study Intervention	Additional instructions of discontinuation of study intervention and PD confirmation	Clarification
Section 7.2 Participant Withdrawal from the study	Additional instructions on withdrawal from study treatment and from the study	To help limit the amount and impact of missing data
Section 7.3 Lost to Follow-up	Added follow-up data collection by third party or from public sources	To help limit the amount and impact of missing data
Section 8.3.7 Disease-Related Events and/or Disease-related Outcomes Not Qualifying as SAE	Removed	In line with program level changes
Section 8.9 Biomarkers	Removed Table 31 Removed Dose 1 D4 and later time points in Table 32 (only collect at screening, C1D1 and EoT)	In line with program level changes
Section 9.1.3 Key secondary MRD negativity endpoint	Changed definition of the null hypothesis from H0: P1=P0 to H0: P1≤P0.	For consistency with the primary when reflecting a one-sided test. No change to planned analysis.
Section 9.3.5 Sample Size Re-Estimation	Added further details of sample size re-estimation	Clarification
Section 9.4 Populations for Analyses	Clarified how to identify the actual treatment arm assignment in the safety population definition (no changes to intended analyses). Separate PK populations are considered for the PK analysis of belantamab mafodotin and pomalidomide, due to differences in data collection. Also added requirement for measurable samples.	Clarification. Separate PK populations are considered due to differences in data collection and for consistency across the program, ensuring sufficient evaluable data is available for analysis.
Section 9.5.1 Efficacy Analyses	Defined the countries included in the North East Asia region consisting of Japan, China, and Republic of Korea Clarified that the same pre-specified pooling strategy as used for the log-rank test will be applied for the cox proportional hazards model used in the supportive PFS analysis – these analyses are expected to align. 95% confidence intervals for the difference (and the implied derivation of the difference between treatment arms) will not be produced for MRD negativity.	Health authority request to clarify definition of NEA pooled analysis based on ICH E17 guidelines Clarification For alignment with the use of the stratified Cochran Mantel Haenszel test and consistency across the program.

Section # and Name	Description of Change	Brief Rationale
Section 9.6 Interim Analyses	Table 35 revised to add clarification (footnotes included and obsolete text related to efficacy boundaries and efficacy boundary crossing probabilities which are not relevant for the IA for harm have been removed) and corresponding text in Section 9.6 updated to clarify that boundaries will be revised based on the observed events at the time of interim analysis for harm. Addition of Table 36 provides a summary of boundary crossing probabilities for harm under a range of underlying true hazard ratios.	Clarification To address FDA comments at protocol amendment 2
Section 9.6.1 Independent Data Monitoring Committee Section 9.6.2 Sequence of Interim and Other Planned Analyses	Addition of descriptive efficacy summaries which may be included alongside safety data for IDMC safety reviews.	Updated to allow safety findings to be put into context with respect to benefit:risk.
Section 9.6.2 Sequence of Interim and Other Planned Analyses	Table of Details of Planned Aalyses revised. More details provided in places where clarification required. Corrected inconsistencies (Primary PFS analysis at approximately 29 months under H1, descriptive OS analyses at 2L analysis will be for all participants not not based on safety population). Reference to Final analysis instead of EOS/Final analysis to avoid confusion due to updated End of Study definition in Section 4.4.	Corrected inconsistencies and added clairfications
Section 10.1.11 Third Parties and Sub-contractors Section 3 Objectives and Endpoints	Addition of Section 10.1.11 listing all vendors used in primary and secondary endpoints. Added a footnote at the end of Section 3	For transparency
Section 10.1.5 Committee Structure	Added purpose and scope of the independent-review committee (IRC)	To align with the implementation of IRC
Section 10.2.1 Definition of AE	Clarify event NOT meeting the AE definition: The disease/disorder being studied or expected progression, , signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.	Clarification
Section 10.4 Liver Safety	In a liver event, blood sample for pharmacokinetic (PK) and sBCMA in the follow-up assessment only apply to participants on Arm A, Blood sample for pomalidomide PK to be obtained within 48 hours of last pomalidomide dose within 48 hours	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 10.9 Appendix 9	Intent of analysis remains unchanged. Separated the planned sensitivity analysis scenarios and censoring rules as 4 separate sensitivity analyses; associated minor changes for clarity. Footnotes updated to align with the appropriate superscripts in the table. Adequate baseline footnote included. Footnote associated with proprietary-algorithm removed.	Clarification To align with planned analyses across the program. Analysis update to be based on IRC-assessment. Proprietary-algorithm no longer used.
Section 10.10 Country Specific Requirements	Added contraceptives methods which are NOT approved in Japan to update country specific requirement.	Clarification

Amendment 02 12 Jul 2022

Overall Rationale for the Amendment: Amendment 02 is a global amendment to include:

- Reduced the total number of participants to be randomized in the study while required number of events, study power, hazard ratio and type 1 error remains the same;
- Updated and clarified key secondary endpoint definition of minimal residual disease (MRD) negativity rate to address Food and Drug Administration (FDA) comments at amendment 01;
- Updated efficacy analyses and addition of a section of sequence of interim and other planned analyses for clarification;
- Updated sections of pharmacokinetics and pharmacodynamics in humans; benefit and risk assessment to align with the changes made in current belantamab mafodotin Investigator Brochure (IB);
- Updated sample collection requirements to reduce testing burden for sites and patients;
- Addition of country-specific requirements of enrolment and sample testing;
- Refined permitted concomitant local therapy for unrelated malignancies and the scope of anti-myeloma therapy in prohibited medications
- Additional changes were incorporated which align with program revisions and/or updates as listed in table below.

Section # and Name	Description of Change	Brief Rationale
Headers, cover page, and Protocol Amendment Summary of Changes Table	Headers and cover page were updated with new document number; Protocol Amendment Summary of Changes Table section was created and populated to include details and rationale for this amendment	Editorial changes to align with the GlaxoSmithKline's (GSK's) standard protocol template
Throughout	Administrative updates to add clarification and/or remove discrepancies	Editorial changes were made for accuracy, clarity, conformity, flow, and typographical error corrections
	Replaced 'anti-cancer therapy' with 'anti-myeloma therapy'	To align with program-wide updates
Section 1.1 Synopsis	Revised the number of participants and removed global enrollment cap on North East Asian (NEA) region, allows continuation of enrollment in regional cohorts after global enrollment completed	Revised based on reduced sample size and to support regional recruitment expectations
Section 1.2 Study Schema	Updated Figure 1	To reflect on reduced number of participants
Section 1.3 Schedule of Activities	Addition of instruction to participants with a history of Hepatitis B or C (footnote 11 in Table 1 and Table 2)	To reflect the procedures indicated in Table 4 and Table 5
	Replace 'imaging for extramedullary disease will be collected and stored by a central vendor' to 'Digital copies of all scans must be maintained at Investigator sites as source document' (footnote 14 in Table 1 and Table 2)	Central vendor for imaging is not applicable in this study, in line with program level requirements
	Update of ocular surface disease index (OSDI) collection frequency (footnote 23 in Table 1 and Table 2)	To clarify OSDI collection frequency matched in both arms
	Changed language in Bone Marrow Assessments for Biomarkers from "BM Biopsy and/or Aspirate for BCMA Expression and Biomarker Research" to "BM Biopsy or Aspirate for BCMA Expression and Biomarker Research"	Biomarkers does not need both a BM biopsy and BM aspirate
	Removed circulating plasma cell-free DNA (cfDNA) collections at MRD assessment time points (Table 1 and Table 2)	Removed cfDNA collections at MRD assessment time points to reduce testing burden for sites and patients

Section # and Name	Description of Change	Brief Rationale
	Removed additional bone marrow collection for biomarker research at MRD assessments, at very good partial response (VGPR) or better confirmation of complete response (CR), stringent complete response (sCR), at suspected progressive diseases (PD). Clarified the language in footnote that biopsy is the preferred sample type for biomarker research when medically feasible and consistent with institutional practice, but bone marrow aspirate is acceptable if biopsy is not obtainable (Table 3, footnote g and h)	Biomarkers only requesting bone marrow sample at screening and optional sample at PD. Reflects change in biomarker collections throughout program
Section 2.3.3 Pharmacokinetics and Pharmacodynamics in Humans	Updated with results from ongoing DREAMM studies	Updated and added newly available information in the current IB
Section 2.3.4 Study 209418 Belantamab mafodotin in combination with pomalidomide and dexamethasone	Updated with study results	Added available information in this study
Section 2.4 Benefit:Risk Assessment	Update of Risk Assessment table to reflect current information from the belantamab mafodotin program	Updated based on emerging data from belantamab mafodotin program in the current IB
Section 3. Objectives and Endpoints	MRD negativity rate will be as assessed in participants with CR or better using derived confirmed response according to International Myeloma Working Group (IMWG) criteria	To address FDA comments at protocol amendment 1, updated and clarified key secondary endpoint definition of MRD negativity rate
	Updated language in Exploratory Biomarker Endpoint: Clarified tumor and blood-based biomarkers • Changed “DNA, RNA and protein” to “DNA, RNA and/or protein” • Changed “clinical response” to “Response to belantamab mafodotin”	Provided Flexibility as not all deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein assays may be performed “Tissue” not required Language change to use samples for broader analysis
Section 4.1 Overall Design	Addition of requirement by local regulatory agencies on country-specific enrollment	To support recruitment expectations in these regions
Section 6.5 Concomitant Therapy	Addition of permitted concomitant therapies while on study (section 6.5.1 permitted concomitant therapies) Clarify prohibited anti-myeloma therapies while on study (section 6.5.2 prohibited concomitant therapies)	Define the allowance of local therapy for unrelated malignancies Define scope of myeloma therapy

Section # and Name	Description of Change	Brief Rationale
Section 6.7 Dose Reductions due to Toxicity	Table 15: consolidated footnote to reduce redundancy. Addition of criteria to re-baseline best-corrected visual acuity (BCVA) if participant has cataract surgery during the study	To support accurate assessment of belantamab mafodotin-associated change in BCVA
Section 8.Study Assessments and Procedures	Table 24 List of Clinical Laboratory Assessments Added an option regarding testing for Total carbon dioxide (CO_2) or carbon dioxide combining power (CO_2CP) Updated note for hepatitis B virus-deoxyribonucleic acid (HBV-DNA) testing Updated BM biopsy/aspirate collection requirements.	To allow flexibility based on local country practices regarding testing for Total CO_2 or CO_2CP To align with program language
Section 8.1.2 Minimal Residual Disease Assessment and PET/CT Imaging	Addition of clonoSEQ and the sensitivity threshold for MRD assay	To address FDA comments at protocol amendment 1
Section 8.5 Pharmacokinetics Section 8.9 Biomarkers	Clarify pharmacokinetic (PK) and accompanying soluble B cell maturation antigen (sBCMA) sample collection may be terminated when sufficient data have been collected	To reduce testing burden for sites and patients
Section 8.6 Belantamab Mafodotin Immunogenicity	Clarify anti-drug antibody (ADA) sample collection may be terminated when sufficient data have been collected	To reduce testing burden for sites and patients
Section 8.9 Biomarkers	Consolidated Biomarker section	Removed extraneous text and redundant description of biomarkers assessed
Section 8.9.1 Soluble B-Cell Maturation Antigen	Removed sBCMA collection at MRD assessment for biomarkers (Table 29, Table 30, Table 31, Table 32)	Reflects change in biomarker collections throughout program
Section 8.9.2 Tumor-Related Biomarkers Section 8.9.4 RNA Transcriptome Research	Removed specific paragraphs for RNA expression research of a subset of RNA species (was in Section 8.9.5) and added language inclusive of potential RNA research in sub-section 8.9.2 and Section 8.9.4	To consolidate and simplify description
Section 8.9.3 Circulating Plasma Cell-Free DNA Analysis	Removed extraneous text and clarified exploratory analysis	To clarify the description

Section # and Name	Description of Change	Brief Rationale
Section 9.3 Sample Size Determination	Reduced total number of participants to be randomized in the study, from 450 to approximately 300	Based on observed recruitment rates and total progression-free survival (PFS) events projection, additional participants would not be needed to reach the required number of total events for the primary PFS analysis. Study assumptions including power, hazard ratio (HR) and type 1 error are maintained with reduced sample size.
Section 9.3.2 Key Secondary Endpoint Minimal Residual Disease Negativity Rate	Revision of power for MRD negativity rate from 99% to at least 88%	Revised based on reduced sample size
Section 9.5.1 Efficacy Analyses	Updated key secondary endpoint definition of MRD negativity rate. Added sensitivity analysis using investigator response. Additional supplementary analyses will be conducted using both derived and investigator response, separately, based on participants with VGPR or better (Table 33). Updated definition of duration of response (DoR): replaced “death due to PD” with “death due to any cause”.	To address FDA comments at protocol amendment 1
Section 9.5.1 Efficacy Analyses	Second line (2L) participants PFS subgroup analysis added	A large proportion of 2L participants were enrolled towards the end of the recruitment period. This ensures that the PFS subgroup analysis will have sufficient follow-up of the 2L participants.
Section 9.6 Interim Analyses	Added Section 9.6.2 Sequence of Interim and Other Planned Analyses (Table 37)	To clarify the planned analyses, the order in which they occur, what data will be included and what objectives/endpoints addressed.
Appendix 2 – 10.2.5 Reporting of Serious Adverse Events to GlaxoSmithKline or Designee	Removal of the requirement for investigators to enter serious adverse event (SAE) causality in electronic case report form (eCRF) within 72 hours	In line with program level requirements
Appendix 9 - 10.9 Progression-Free Survival Event and Censoring Rules	Corrected errors in the definition of extended time without adequate assessment	To align with the schedule of assessments and align with program updates to consider a 7 day window for delayed assessments within the programming logic only.

Section # and Name	Description of Change	Brief Rationale
Appendix 10 - 10.10 Country Specific Requirements	In China, SAEs will be collected from signing of the informed consent form (ICF) and NOT from the start of treatment; the following samples will not be collected: bone marrow biopsy sample for B-cell maturation antigen (BCMA) immunohistochemistry (IHC), BM aspirate for exploratory endpoints, cfDNA and pharmacogenetic samples MRD sample collection and assessment are subject to regulatory approval	Updated according to local country regulatory requirement
Appendix 12-10.12 Home Healthcare and Telemedicine Approaches	Cardiac monitoring test (electrocardiogram) removed from home healthcare (General) visit	In line with cardiac monitoring requirements across belantamab mafodotin program, based on emerging safety data

Amendment 01: 20-APR-2021

Overall Rationale for the Amendment: Amendment 01 is a global amendment to include Keratopathy Visual Acuity (KVA) scale and modified dose modifications based on KVA scale; update stratification strategy and Hep B+, and Hep C+ participants in order to align with the latest regulatory (US FDA) guidance. Additional changes were incorporated which align with program revisions and/or updates as listed in table below.

Section # and Name	Description of Change	Brief Rationale
Headers, cover page, and Protocol Amendment Summary of Changes Table	Headers and cover page were updated with new document number; Protocol Amendment Summary of Changes Table section was created and populated to include details and rationale for this amendment	Editorial changes to align with the GSK's standard protocol template
Throughout	Administrative updates to add clarification and/or remove discrepancies	Editorial changes were made for accuracy, clarity, conformity, flow, and typographical error corrections
Section 1.2 Study Schema	Corrected schema for Cycle 1 Arm A from 2.5 mg/kg IV q4w to state 2.5 mg/kg IV Stratification strategy was updated to include prior anti-CD38 treatment (yes or no)	To clarify as the 2.5 mg/kg IV dose is only once in Cycle 1 and not every 4 weeks. Based on emerging data from investigator sponsored study (MCRN 007/Study 209418) with B-Pd.

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities/ Table 1 Treatment Arm A – Belantamab Mafodotin in Combination with Pomalidomide and Dexamethasone (B-Pd), Table 2 Treatment Arm B – Pomalidomide Plus Bortezomib and Dexamethasone (PVd) Section 8.1.2. Minimal Residual Disease Assessment and PET/CT Imaging	Extended timepoint for MRD negativity confirmation by PET/CT from 28 to 42 days Simplified MRD collection language to align with the program wide guidance	To align with GSK program wide guidance allowing flexibility in the timelines.
Section 1.3. Schedule of Activities/ Table 1 Treatment Arm A – Belantamab Mafodotin in Combination with Pomalidomide and Dexamethasone (B-Pd), Table 2 Treatment Arm B – Pomalidomide Plus Bortezomib and Dexamethasone (PVd) Section 8.2.7. Pregnancy Testing (WOCBP Only)	Pregnancy testing following belantamab mafodotin discontinuation must be repeated at least 70 days after last dose Use of contraceptive for Arm A WOCBP was updated from further 8 months to further 3 months	Clarification
Section 1.3. Schedule of Activities/ Table 2 Treatment Arm B – Pomalidomide Plus Bortezomib and Dexamethasone (PVd)	Clarified that select disease evaluations occurring at Cycles 1-8/Day 1 are for Cycle 1 Day 1, only if disease evaluation at Screening visit was not done Clarified that pregnancy prevention counseling should occur at Screening Clarified that sBCMA biomarker sampling should occur at Screening	Error corrections
Section 1.3. Schedule of Activities/ Table 2 Treatment Arm B – Pomalidomide Plus Bortezomib and Dexamethasone (PVd) Section 6.1.3.2. Corneal Supportive Care Guidelines Section 8.2.6.2. Treatment Arm B: PVd	Removed ocular examination requirement at PFS and OS Follow-Up Visits Clarified that On Treatment ocular examinations should occur every 6, not every 3 months, and as clinically indicated	Per GSK program-wide guidance, the frequency of ocular assessments should occur every 6 months and at the end of treatment, and not required at PFS and OS visits for Arm B.

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities	Added Table 3 for BM Aspirate and Biopsy collection Added Table 4 for additional procedures for participants with a history of Hepatitis B Added Table 5 for additional procedures for participants with a history of Hepatitis C	To clarify BM sample collection To align with the latest regulatory guidance
Section 2 Introduction; Section 2.2.1 Clinical Management of Multiple Myeloma; Section 4.3.2 Pomalidomide use Section 4.3.3 Bortezomib dose	Figure 2 was updated to align with the mechanism of action in the investigator brochure Removed the year from the references to USPI/SmPC of Pomalyst/ pomalidomide and Velcade /bortezomib	Alignment with the recent investigator brochure To avoid discrepancies as the most recent information is widely available
Section 2.3.1 Studies with Belantamab Mafodotin Section 2.3.2 Safety Section 2.3.3 Pharmacokinetics and Pharmacodynamics in Humans	Aligned with new data from the recent belantamab mafodotin Investigator's brochure	Updated based on the recent investigator brochure
Section 2.4.1 Summary of Risk Assessment for the Combination Therapy of B-Pd (Arm A) and PVd (Arm B)	Removal of the risk of potential for cardiotoxicity related to inflammatory response. Revisions to wording of risks for thrombocytopenia, Keratopathy, IRR, pulmonary pneumonitis, nephrotoxicity, other laboratory abnormalities, immunosuppression, fertility and data acquisition Risks related to approved multiple myeloma treatments viz. pomalidomide and bortezomib are removed	Based on a comprehensive review of the data from studies BMA117159 and 205678, the risks are considered discharged. To align with current program level wording based on additional data from DREAMM-2/205678 study and in alignment with Investigator brochure update. For the simplification as updated data are available outside of the protocol

Section # and Name	Description of Change	Brief Rationale
Section 3 Objectives and Endpoints (corresponding change in Section 1.1 Synopsis)	Revision of the HRQoL endpoint to include change from baseline in HRQoL as measured by EORTC QLQ-MY20, in addition to EORTC IL52 and to clarify the EORTC QLQ-MY20 applies to participants enrolled under Protocol Amendment 1 Revision of Endpoint to exploratory Objective of Exploring the relationship between biologic characteristics and response	To maintain program-wide consistency To clarify and encompass all exploratory biomarkers and to maintain program-wide consistency
Section 4.3.1 Belantamab Mafodotin Dose	Dosing rationale for dose reduction for management of corneal toxicities was added	Clarification
Section 5.1 Inclusion Criterion (contraception criterion 10)	Typographical correction, that the length of contraceptive use post -pomalidomide treatment for women of childbearing potential in Arm B is 6 months and not 5 months	Error correction/to align with Section 8.2.7 where this information is correctly provided
Section 5.2 Exclusion Criteria 16 and 17	Updated exclusion criteria for HIV+, Hep B+, and Hep C+ participants	To align with the latest regulatory guidance
Section 5.2 Exclusion Criteria (ongoing Grade 2 peripheral neuropathy criterion 20)	Ongoing Grade 2 peripheral neuropathy with pain within 14 days prior to randomization or ≥ Grade 3 peripheral neuropathy	To align with clinical practice to allow Grade 2 (without pain) or less.
Section 5.2 Exclusion Criteria (criterion 21)	Added 'arterial' to include the history of venous thromboembolism	Clarification
Section 6.1.1 Treatment Arm A Dosing Schedule	Figure 3 was updated to show dosing of belantamab mafodotin Cycle 1 and Cycle 2+	Clarification
Section 6.1.3.2 Corneal Supportive Care Guidelines Section 6.7.1. Guidance on Dose Reductions in Treatment Arm A (B-Pd)/Table 15 Dose Modification Guidelines for Belantamab Mafodotin Treatment-Related Corneal Events Based on KVA Scale Section 7.1.3. Corneal Event Stopping Criteria	Corneal events associated with belantamab mafodotin, will be graded using the modified KVA scale, replacing NCI-CTCAE v5.0 for corneal toxicities	KVA scale has been developed following feedback from Regulatory Authorities for grading treatment related corneal events, taking into consideration findings from both corneal examinations and visual acuity changes

Section # and Name	Description of Change	Brief Rationale
Section 6.5.2 Prohibited Concomitant Therapies	Addition of the language for participants receiving anti-HIV and anti-microbials	Clarification
Section 6.6.2 Guidance on Dose Delays for Treatment Arm B (PVd)	Table 11, item #3 Delay in only dexamethasone, actions for dexamethasone were inadvertently incorrect. These were corrected to align with the planned dosing regimen	Correction
Section 6.7.1 Guidance on Dose Reductions in Treatment Arm A (B-Pd)	Inclusion of a step-down dose levels for belantamab mafodotin following onset of corneal AEs: Dose level -1 of belantamab mafodotin 1.9 mg/kg q8w Dose level -2 as 1.4 mg/kg q8w	Dose reduction of belantamab mafodotin to manage treatment related corneal toxicities.
Section 7.1.2 QTc Stopping Criteria	The section was removed.	Discharged risk
Section 8 Study Assessments and Procedures/Table 24 List of Clinical Laboratory Assessments	Removed blood type assessment, INR, BUN, bone marrow biopsy. The footnotes were revised to be in the order, as it appears in the table	The tests should be performed as clinically indicated, but not required for the study. Correction
Section 8.2.8 Management of Hepatitis participants	Added section to clarify management of Hepatitis B+ participants	To align with the latest regulatory guidance
Section 8.4 Treatment of Overdose	The overdose for belantamab mafodotin was defined as more than 10% above the calculated dose	Clarification
Section 8.5.1 Belantamab Mafodotin Pharmacokinetic Sample Collection	Added a statement, “All PK, sBCMA, and anti-drug antibody (ADA) samples once collected (regardless of dosing) will be analyzed if the sample date and time have been recorded.”	To accurately reflect study conduct
Section 8.9.1 Soluble B-Cell Maturation Antigen/Table 31Treatment Arm A sBCMA Blood Collection Schedule (Enhanced sBCMA Cohort) (Approximately 100 Participants)	Added the qualifier “approximately” regarding the number of sBCMA samples to be collected	To accurately reflect study conduct
Section 8.10 Patient-Reported Outcomes	Edits were made to align with EORTC QLQ-MY20 changes	Clarification
Section 8.11 Non-protocol Specified Healthcare Resource Utilization	Updated the language	To align with the GSK protocol template

Section # and Name	Description of Change	Brief Rationale
Section 9.2 Multiple Comparisons and Multiplicity	Added details for the final primary analysis	Clarification
Section 9.5.1 Efficacy Analyses	Added strategy for pre-specified pooling of strata	To align with the change with stratification strategy.
Section 10.3.2 Contraception Guidance	Removed oral contraception as a combined hormonal contraception in Section 10.3.2	Aligned with pomalidomide labelling (EU SmPC), where oral contraceptive pills are not permitted due to increased risk of venous thromboembolism in patients with multiple myeloma receiving Pd; per protocol addendum DEU01
Section 10.4 Appendix 4: Liver Safety: Required Actions, Follow-up Assessments, and Study Treatment Rechallenge Guidelines	Added requirement for a blood sample collection for sBCMA analysis as a follow-up assessment after a liver stopping event, along with the PK sample collection	sBCMA sample should be collected alongside the PK sample in the case of a liver stopping event
Section 10.9 Appendix 9: Prophylactic Interventions for Corneal Toxicity Corneal Event Grading for Belantamab Mafodotin Treatment-Related Corneal Events (Treatment Arm A)	The contents moved to Section 6.1.3. 3 and Appendix 9 was removed.	Clarification
Section 10.10 Appendix 10: Country Specific Requirements	An additional inclusion criterion for participants in Israel regarding prior multiple myeloma treatment: Participants must have prior treatment with daratumumab, if available, cannot get access to daratumumab for any reason, or cannot tolerate daratumumab	Due to local guidelines in Israel for multiple myeloma treatment, additional consideration is to be given for prior exposure to daratumumab for participants there (per protocol addendum ISR01)
Section 10.12 Appendix 12: Home Healthcare and Telemedicine Approaches (new)	Added a new appendix to allow for home healthcare and telemedicine approaches	To allow flexibility in study conduct
Section 10.13 Appendix 13: Data Management/Monitoring (new)	Added a new appendix	To allow flexibility in study conduct

Abbreviations: ADA=Antidrug Antibody; B-Pd=Belantamab Mafodotin In Combination With Pomalidomide And Dexamethasone; INR=International Normalized Ratio; KVA=Keratopathy Visual Acuity; MRD=Minimal Residual Disease; NCI-CTCAE=National Cancer Institute Common Terminology Criteria For Adverse Events; OS=Overall Survival; Pd=Pomalidomide In Combination With Dexamethasone; PET/CT=Positron Emission Tomography/Computed Tomography; PFS=Progression-Free Survival; PK=Pharmacokinetic; PVd=Pomalidomide In Combination With Bortezomib And Dexamethasone; sBCMA-Soluble B Cell Maturation Antigen; WOCBP=Women of Childbearing Potential.

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