TITLE PAGE

Protocol Title: DREAMM 7: A Multicenter, Open-Label, Randomized Phase III Study to Evaluate the Efficacy and Safety of the Combination of Belantamab Mafodotin, Bortezomib, and Dexamethasone (B-Vd) Compared with the Combination of Daratumumab, Bortezomib and Dexamethasone (D-Vd) in Participants with Relapsed/Refractory Multiple Myeloma

Protocol Number: 207503 / Amendment 6

Compound Number: GSK2857916

Brief Title: Phase III study of belantamab mafodotin, bortezomib, and dexamethasone (B-Vd) versus daratumumab, bortezomib, and dexamethasone (D-Vd) in participants with relapsed/refractory multiple myeloma

Study Phase: Phase 3

Acronym: DREAMM 7

Sponsor Name and Legal Registered Address:

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

Regulatory Agency Identifying Number(s):

Registry	ID
IND number	119333
EudraCT number	2018-003993-29

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

Sponsor Signatory:

Sumita Roy-Ghanta, MD
Clinical Development Lead

Approval Date: 20 Sep 2023

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Number**
Amendment 6	20 Sep 2023	TMF-15691281
Amendment 5	19 Dec 2022	TMF-15039862
Amendment 4	15 Jul 2022	TMF-14626992
Amendment 3	15 Jul 2021	TMF-13879371
Amendment 2	16 Dec 2020	TMF-7925758
Amendment 1	16 Jul 2020	2018N372572_01
Original Protocol	13 Dec 2019	2018N372572_00

Amendment 6 (20 Sep 2023)

Where this Protocol Amendment applies:

Protocol Amendment 6 applies to all participants in all countries and all sites.

Overall Rationale for the current amendment:

This protocol has been amended to update the number of PFS events required to trigger the primary PFS analysis and to include an interim analysis for PFS at [redacted] information fraction. The updates allow for a longer duration of follow up and increasing OS data maturity at the time of Primary PFS analysis. The addition of an interim analysis allows the opportunity to test for efficacy as well.

This amendment has also been updated to incorporate an additional sensitivity analysis for conventional DoR using investigator-assess response in the statistical analysis section, an update of the terminology from Reporting and Analysis Plan" (RAP) to "Statistical Analysis Plan" (SAP), and a modified multiplicity strategy as well as changes to the targeted overall survival hazard ratio assumption within the sample size determination section. Additional details regarding planned OS interim analyses and OS sample size assumptions have been included.

An update to urine immunofixation requirements in the schedule of activities has been made. Additional administrative changes have been made including correction of an administrative numbering error in the inclusion and exclusion criteria and clarification of data collection for overall survival.

List of main changes in the protocol and their rationale:

Section # and title	**Description of change**	**Brief rationale**
Throughout the document	Reporting and analysis Plan (RAP) updated to Statistical Analysis Plan (SAP) Updated Investigator Brochure version Minor typographical corrections	In alignment with GSK naming and style conventions

Section # and title	Description of change	Brief rationale
Section 1.3 Schedule of Activities	Clarification on survival data collection in Table 1 and Table 2	Added clarity on the overall survival data collection
Section 1.3 Schedule of Activities	Added wording to indicate urine immunofixation must be performed each time M-protein is not quantifiable by UPEP (0 mg/24 hr) AND SPEP (0 g/dL)	A urine immunofixation result is required with a serum immunofixation result for sCR, CR and VGPR response, as per IMWG 2016 criteria. It is not required alone.
Section 2.3.1 Summary of Risk Assessment for Belantamab Mafodotin (Treatment Arm A), Daratumumab (Treatment Arm B), and Bor/Dex (Treatment Arms A and B)	Updates to potential overlapping toxicities and the risks related to belantamab mafodotin.	To provide the most up to date information in alignment with IB v11.
Section 3 Objectives and Endpoints and Section 9.5.1 Efficacy Analyses	OS bullet moved up.	Moved up for consistency with other DREAMM-7 study documents.
Section 4.2 Scientific Rationale for Study Design	Addition of interim analysis.	The addition of an interim analysis allows the opportunity to test for efficacy prior to the primary analysis.
Section 5.1 Inclusion Criteria	Numbering of the last 2 inclusion criterion has been changed from 1 and 2 to 10 and 11 to continue numbering from the previously listed inclusion criteria.	To correct a numbering error.
Section 5.2 Exclusion Criteria	Numbering has been changed to begin from 1, instead of continuing on from inclusion crtieria numbering.	To correct a numbering error.
Section 7.1 Discontinuation of Study Intervention	Clarification on survival data collection.	Added clarity on the overall survival data collection
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 Section 9.3.
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	Update to the number of PFS events needed for the Primary PFS Analysis from [redacted]	To align with the addition of an interim analysis for efficacy.
Section 9.3 Sample Size Determination	Primary Endpoint PFS: changed wording of “progression” to “progression or death”.	Added clarity onto the definition of progression-free survival within the sentence.

Section # and title	Description of change	Brief rationale
Section 9.3 Sample Size Determination	Subsections for key secondary endpoints removed.	To permit a longer follow up, increase OS data maturity at the time of Primary PFS analysis/IA2 and account for PFS interim analysis for efficacy (IA1). Subsections for key secondary endpoints provided no additional value.
Section 9.5.1 Efficacy Analyses	Added sentence defining an additional sensitivity analysis that may be performed.	Additional statistical analysis that may be performed depending on IRC concordance.
Section 9.5.1 Efficacy Analyses	Removed reference to significance level for testing and added clarification of p-values and confidence intervals to be produced.	Multiplicity strategy is defined in Section 9.2 and will be clarified in the SAP.
Section 9.6.1 Periodic IDMC Safety Reviews and CPMS Early Access	Section restructured and multiple interim analyses considered for IDMC review.	Addition of interim analyses for efficacy.
Section 9.6.1 Periodic IDMC Safety Reviews and CPMS Early Access	Added clarification that potential delegate(s) 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.	To allow for sufficient time to prepare and conduct planned analyses.
Section 9.6.2 Interim Analysis	Interim analyses for efficacy included. Tables of Stopping Boundaries for Interim Analysis for PFS Efficacy added. Additional OS analyses considered.	Interim analyses added to allow the opportunity to test for efficacy early. If requested, additional OS analyses may be required.
Section 9.6.4 Final Analysis	Interim analyses for efficacy included. Primary PFS analysis/IA2 and final analysis events and timing modified.	Interim analyses added to allow the opportunity to test for efficacy early. Primary PFS analysis/IA2 and final analysis events and timing modified to permit a longer follow up and increase OS data maturity.
Section 10.1.11 Third parties and Sub-Contractors	Alliance Pharma has been changed to Resolian Bioanalytics (name change only)	Alliance Pharma Inc. is now doing business as Resolian Bioanalytics
Section 10.14 Appendix 14: Abbreviations and Trademarks	Updated abbreviations list	Inclusion of IA and SAP; removal of RAP

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

DREAMM 7: A Multicenter, Open-Label, Randomized Phase III Study to Evaluate the Efficacy and Safety of the Combination of Belantamab Mafodotin, Bortezomib, and Dexamethasone (B-Vd) Compared with the Combination of Daratumumab, Bortezomib and Dexamethasone (D-Vd) in Participants with Relapsed/Refractory Multiple Myeloma

Short Title:

Phase III study of belantamab mafodotin, bortezomib, and dexamethasone (B-Vd) versus daratumumab, bortezomib, and dexamethasone (D-Vd) in participants with relapsed/refractory multiple myeloma

Rationale:

In relapsed or refractory multiple myeloma (RRMM), combination therapies utilizing agents with differing modes of action have dramatically improved outcomes. Combining active agents with bortezomib/dexamethasone (bor/dex) treatment can yield improved patient outcomes with acceptable toxicity profiles, establishing new global standard of care (SoC) regimens. The approval of the anti-CD38 antibody daratumumab has demonstrated that the addition of a targeted monoclonal antibody, with activity as a monotherapy, to bor/dex can result in significant improvements in progression-free survival (PFS) in patients with RRMM, and the combination of daratumumab with bor/dex is currently a widely accepted SoC for MM patients who have received at least 1 prior line of therapy.

Belantamab mafodotin (GSK2857916) has demonstrated strong single-agent activity in RRMM in the First-Time-in-Human (FTIH) study BMA117159. As of 31 August 2018, the Overall Response Rate (ORR) in 35 participants treated at the recommended Phase 2 dose of 3.4 mg/kg was 60.0% (95% CI: 42.1, 76.1) and the median PFS was 12.0 months (95% CI: 3.1, NR) in a heavily pre-treated population (57% ≥5 prior lines of therapy). In participants refractory to both immunomodulators and proteasome inhibitors (n=32/35), the ORR was 56% (95% CI: 37.7, 73.6).

In Study BMA117159, the maximum clinical benefit (ORR) was observed at the 3.4 mg/kg dose level, but a significant number of participants required dose delays and dose reductions to manage adverse events. In phase II Study 205678, belantamab mafodotin was further evaluated as monotherapy in RRMM patients at the dose of 2.5 mg/kg and 3.4 mg/kg Q3W; both dose levels, 2.5 and 3.4 mg/kg, have a positive benefit/risk profile. Overall, there were no new safety signals identified in the 205678 study, and the profile of adverse events was similar to the experience in DREAMM-1 for both arms. The dose of 2.5 mg/kg appears to have a lower incidence of adverse events and less frequent dose delays and reductions, and it results in similar efficacy with 3.4 mg/kg dose as measured by ORR. The dose of 2.5 mg/kg Q3W has been further

evaluated in combination with bortezomib and dexamethasone in Study 207497 and based on the safety evaluation, this dose has been selected for this study.

It is hypothesized that the combination of belantamab mafodotin and bor/dex will lead to greater patient benefit, as measured by progression-free survival (PFS), compared to the SoC combination of daratumumab and bor/dex. While there are some potential overlaps in the pattern of identified toxicities between belantamab mafodotin and bor/dex (primarily hematologic), they are expected to be manageable.

Primary and Secondary Objectives and Endpoints:

Objectives	Endpoints[1]
Primary	
The primary objective of this study is to compare the efficacy of belantamab mafodotin in combination with bortezomib and dexamethasone (bor/dex) with that of daratumumab in combination with bor/dex in participants with RRMM	• Progression-Free Survival (PFS), defined as the time from the date of randomization until the earliest date of documented disease progression or death due to any cause
Key Secondary	
To compare the efficacy of belantamab mafodotin in combination with bor/dex with that of daratumumab in combination with bor/dex in participants with RRMM	• Overall Survival (OS), defined as the time from the date of randomization until 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 • Minimal Residual Disease (MRD) negativity rate, defined as the percentage of participants who are MRD negative by next-generation sequencing (NGS)
Secondary	
To further assess the efficacy of belantamab mafodotin in combination with bor/dex with that of daratumumab in combination with bor/dex in terms of other efficacy outcomes in participants with RRMM	• Complete Response Rate (CRR), defined as the percentage of participants with a confirmed complete response (CR) or better (i.e., CR, stringent complete response (sCR)) • Overall Response Rate (ORR), defined as the percentage of participants with a confirmed partial response (PR) or better (i.e., PR, VGPR, CR, sCR) • Clinical Benefit Rate (CBR), defined as the percentage of participants with a confirmed minimal response (MR) or better per International Myeloma Working Group (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 confirmed PR or better

Objectives	Endpoints[1]
	• Time to Progression (TTP), defined as the time from the date of randomization until the earliest date of documented PD or death due to PD • PFS2, defined as time from randomization to disease progression 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 belantamab mafodotin when administered in combination with bor/dex	• Incidence of adverse events (AEs) and changes in laboratory parameters • Ocular findings on ophthalmic exam
To further describe the exposure to belantamab mafodotin when administered in combination with bor/dex	• Plasma concentrations of belantamab mafodotin, and cys-mcMMAF
To assess anti-drug antibodies (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 bor/dex	• Maximum post-baseline PRO-CTCAE score for each item attribute
To evaluate and compare changes in symptoms and health-related quality of life (HRQOL)	• Change from baseline in HRQOL as measured by EORTC QLQ-C30 and EORTC IL52 (disease symptoms domain from the EORTC QLQ-MY20)

1. All categories of disease response (sCR, CR, VGPR, PR, SD, PD) used in the calculation of study endpoints will be determined by an IRC using IMWG 2016 criteria.

Overall Design:

This is a multicenter Phase III, randomized, open-label study evaluating the efficacy and safety of the combination of belantamab mafodotin and bor/dex versus with the combination of daratumumab and bor/dex in participants with RRMM.

Disclosure Statement:

This is a randomized, parallel group treatment study with 2 arms and no blinding.

Number of Participants:

Approximately 600 participants will be screened to achieve about 478 participants randomized in a 1:1 ratio between the 2 study arms. There will be a CCI global enrollment cap on North East Asia Countries. In these countries, the respective regulatory authorities require a sufficient number of their country populations to be included in marketing authorizations.

Intervention Groups and Duration:

Following screening, participants will be stratified based on the number of prior lines of therapy, prior treatment with bortezomib and revised international staging system (R-ISS, see Appendix 13) at screening, and centrally randomized in a 1:1 ratio to either arm. No more than CCI of participants with 2 or more prior lines of treatment will be enrolled. No cross-over will be allowed.

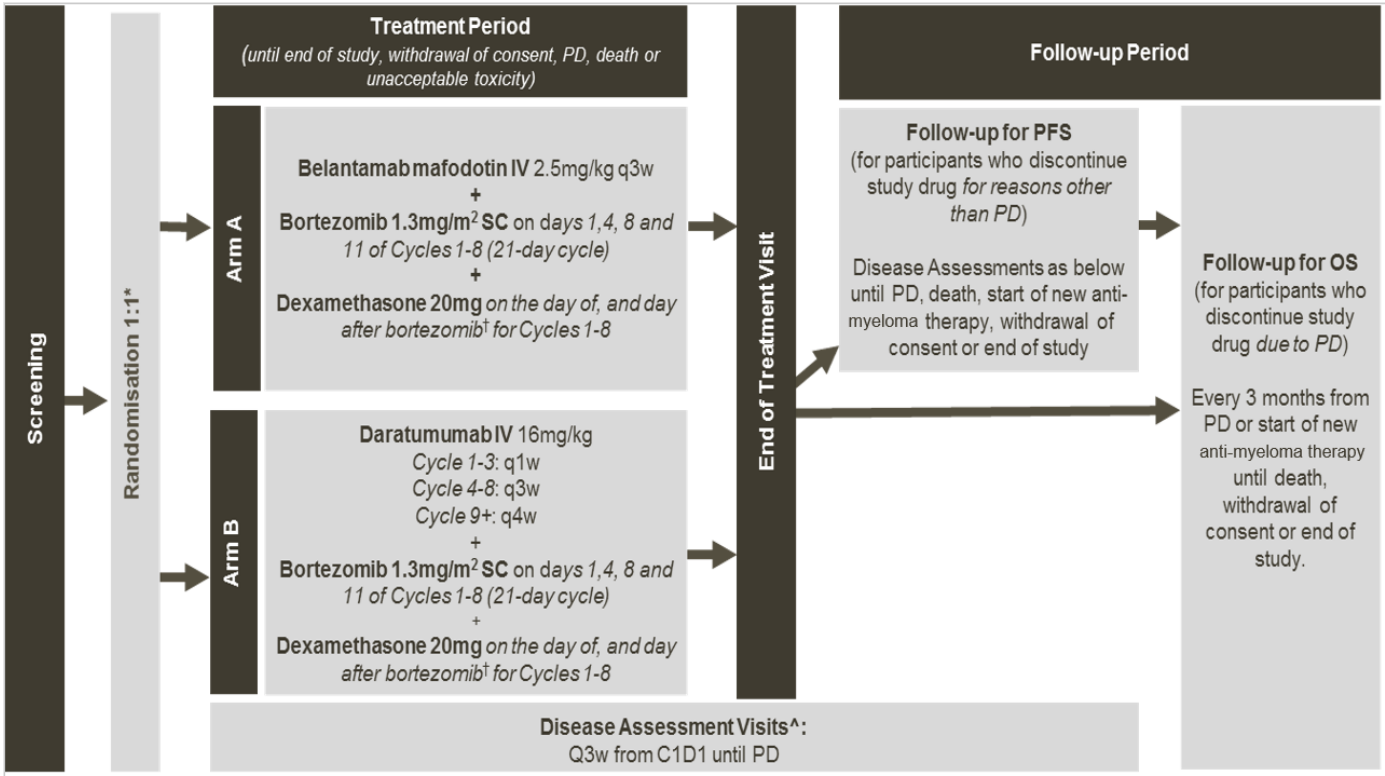
Treatment Arm A: Belantamab mafodotin 2.5 mg/kg (IV) Q3W to progression. Cycles 1 through 8: bortezomib 1.3 mg/m^2 (SC) on Days 1, 4, 8, and 11 of every 21-day cycle; and dexamethasone 20 mg (IV or PO) on the day of and the day after bortezomib treatment.

Treatment Arm B: Daratumumab 16 mg/kg (IV) weekly for Cycles 1 through 3 (Weeks 1-9; 21-day cycles, total of 9 doses), on Day 1 of Cycles 4 through 8 (Weeks 10 – 24; 21-day cycles, total of 5 doses), and then every 4 weeks from Cycle 9 (Week 25) onwards until progression (28-day cycles). For Cycles 1 through 8: bortezomib 1.3 mg/m^2 (SC) on Days 1, 4, 8, and 11 of every 21-day cycle; and dexamethasone 20 mg (IV or PO, but IV prior to first daratumumab dose) on the day of and the day after bortezomib treatment.

Treatment will continue in both arms until progressive disease, death, unacceptable toxicity, withdrawal of consent, or end of study, whichever occurs first. Dose delays or reductions may be required following potential drug-associated toxicities.

Data Monitoring/Other Committee: Yes, refer to Section 10.1.5.

1.2. Schema



* Stratification: Prior lines of treatment (1 vs 2/3 vs ≥4), R-ISS (I vs II/III), Prior bortezomib (yes vs no).

† Reduce starting dose of dexamethasone to 10 mg for participants older than 75 years of age, who have a body-mass index of less than 18.5, who had previous unacceptable side effects associated with glucocorticoid therapy, or who are unable to tolerate the starting dose (For guidance on further dose modification, see Table 15, Section 6.6.4).

PD = Progressive Disease; C1D1 = Cycle 1 Day 1; IV = intravenous; SC = subcutaneous; Q1W = once weekly; Q3W = once every 3 weeks; Q4W = once every 4 weeks; PFS = Progression-free Survival; OS = Overall Survival.

1.3. Schedule of Activities (SoA)

Table 1 Schedule of Activities – Treatment Arm A (Belantamab Mafodotin/Bortezomib/Dexamethasone)

- **Screening assessments do not need to be repeated on C1D1 if conducted within 72 hours of C1D1 dosing, unless otherwise specified**.
- The 28-day Screening period is initiated upon signature of the informed consent form (Day 1). The full 28 days can be taken to determine the eligibility of the participants. Participants can be randomized during or upon completion of the 28 days i.e. the day after the Screening period has ended. Study treatment (C1D1) should be initiated within 72 hours after randomization.
- 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 Q3W. 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 and PK where applicable.
- **End of Treatment (EOT**) visit will occur within 30 days from the last cycle, or prior to initiation of new anti-myeloma therapy (whichever occurs first). AEs and SAEs will be collected up to at least 70 days after the last dose of belantamab mafodotin, either via phone or a follow up visit. Participants who have ocular symptoms at EOT will be followed up for ocular exams and OSDI questionnaire as described in Section 8.2.6. After discontinuation of study treatment, the participant should continue disease assessments as per the SoA. Every effort should be made to confirm disease progression per the IMWG criteria prior to initiating a new anti-myeloma therapy.
- **PFS follow-up**: 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 until:
    - Disease progression according to IMWG criteria (then move to Survival follow-up)
    - New anti-myeloma therapy is initiated (then move to Survival follow-up)
    - Death
    - Withdrawal of consent
    - Loss to follow-up
    - End of study
- **Survival follow-up**: Participants will be followed for survival and subsequent anti-myeloma therapy (PFS2) by chart review, phone call, or any form of communication every 12 weeks (14-day window) from the last Q3W assessment visit until death, withdrawal of consent, lost to follow-up or end of the study, whichever comes first. Participant does not need to come in for visit unless they are being followed for treatment-related changes in vision that are present at the EoT. Record the participant's survival status and whether subsequent treatment for disease was given.
- GSK may request that updated survival data be collected on all treated/randomized participants outside the protocol window noted in the Schedule of Assessments. 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 publicly available death registers will be used for participants withdrawn from study or lost to follow-up prior to death.
- For details on Home Healthcare and Telemedicine Approaches, please refer to Appendix 15.

Schedule of Activities – Treatment Arm A (Belantamab Mafodotin/Bortezomib/Dexamethasone)												
Procedure		**Treatment Period (±3 days)**								**Follow up**		
Cycle / Visit	**Screening (-28days)**	**C1**	**C2-8**	**C1-8**	**C1-8**	**C1-8**	**C9 +**	**Fixed Visits Q3W (Starting at Week 4)**	**End of Treatment (EOT)**	**PFS Follow-up Visit Q3W (±3 days)**	**OS Follow-up Visit Q12W (±14 days)**	
Day		**D1**		**D4**	**D8**	**D11**	**D1**					
Informed Consent[1,2]	X											
Baseline Demographics	X											
Medical/Disease History, and Characteristics	X											
Body Weight	X	X	X				X		X			
Height	X											
Safety												
Physical Exam[3]	X	X	X				X		X	X		
ECOG Performance Status	X		X				X		X	X		
Ocular Exam[4]	X		X[4] (see footnote)				X[4] (see footnote)	X[4] (see footnote)	X	X[4]	X[4]	
Vital Signs[5] (BP, Heart rate, Body Temp)	X	X	X	If clinically indicated			X		X			
12-Lead ECG[6]	X											
Adverse Events/SAEs		Adverse events and SAEs will be collected throughout the study until at least 70 days after the last dose of belantamab mafodotin. SAEs related to study participation or related to belantamab mafodotin are collected from time of consent until end of study. See Section 8.3.1.										
Concomitant Medications	Concomitant medications will be collected, as reported by the participant or through participant medical record review.											
Survival Follow-up Phone call[7]												X
Laboratory Assessments[8]												
Hematology[9,10]	X	X	X	X	X	X	X	X[1]	X	X		
Clinical Chemistry[9, 10]	X	X	X	X	X	X	X	X[1]	X	X		
HbA1c	As clinically indicated											
eGFR[11]	X	X						X[1]	X			

Schedule of Activities – Treatment Arm A (Belantamab Mafodotin/Bortezomib/Dexamethasone)											
Procedure		**Treatment Period (±3 days)**								**Follow up**	
Cycle / Visit	**Screening (-28days)**	**C1**	**C2-8**	**C1-8**	**C1-8**	**C1-8**	**C9 +**	**Fixed Visits Q3W (Starting at Week 4)**	**End of Treatment (EOT)**	**PFS Follow-up Visit Q3W (±3 days)**	**OS Follow-up Visit Q12W (±14 days)**
Day		**D1**		**D4**	**D8**	**D11**	**D1**				
Urine dipstick for protein OR Spot Urine (Albumin/Creatinine ratio[12])	X	X						X[1]	X		
HbsAg, HbcAb, Hep C Ab, Hep C RNA[13]	X										
Indirect antiglobulin test (Indirect Coombs test)	X										
Blood type and screen	X										
Pregnancy Test for WOCBP[14]	X	X	X				X		X	X[13]	X[13] (phone call only)
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 sample collection (serum/urine) **before** institution of any new anti-myeloma therapy and preferably within 14 days of the date of the initial assessment showing unconfirmed disease progression. This may be performed at the EOT visit.											
β2 Microglobulin	X										
SPEP (Serum Protein Electrophoresis)	X							X[1]	X	X	
UPEP (Urine Protein Electrophoresis) (on 24-hour collected urine)	X							X[1]	X	X	
Serum M Protein Calculation	X							X[1]	X	X	
Serum Kappa Lambda Free LC, FLC Ratio	X							X[1]	X	X	
Serum Immunofixation	X		Serum immunofixation must be performed each time that M-protein is not quantifiable by SPEP (0g/dL)								
Urine Immunofixation	X										

Schedule of Activities – Treatment Arm A (Belantamab Mafodotin/Bortezomib/Dexamethasone)											
Procedure		**Treatment Period (±3 days)**								**Follow up**	
Cycle / Visit	**Screening (-28days)**	**C1**	**C2-8**	**C1-8**	**C1-8**	**C1-8**	**C9 +**	**Fixed Visits Q3W (Starting at Week 4)**	**End of Treatment (EOT)**	**PFS Follow-up Visit Q3W (±3 days)**	**OS Follow-up Visit Q12W (±14 days)**
Day		**D1**		**D4**	**D8**	**D11**	**D1**				
			Urine immunofixation must be performed each time that M-protein is not quantifiable by UPEP (0 mg/24 hr) AND SPEP (0 g/dL)								
Calcium Corrected for Albumin (serum)	X							X[1]	X	X	
IgG, IgM, IgA	X							X[1]	X	X	
IgD/IgE[15]	X							X[1]	X	X	
Imaging for Extramedullary Disease[16]	X							X[1, 16] (Q12W)	X	X (Q12W)	
PET-CT upon achieving MRD negativity by NGS								To be performed ONCE after achieving MRD negativity by NGS, within 42 days (6 weeks) of testing negative			
Skeletal Survey[17]	X	As clinically indicated									
Response Assessment by IMWG[18]								X[1]	X	X	

Schedule of Activities – Treatment Arm A (Belantamab Mafodotin/Bortezomib/Dexamethasone)											
Procedure		**Treatment Period (±3 days)**								**Follow up**	
Cycle / Visit	**Screening (-28days)**	**C1**	**C2-8**	**C1-8**	**C1-8**	**C1-8**	**C9 +**	**Fixed Visits Q3W (Starting at Week 4)**	**End of Treatment (EOT)**	**PFS Follow-up Visit Q3W (±3 days)**	**OS Follow-up Visit Q12W (±14 days)**
Day		**D1**		**D4**	**D8**	**D11**	**D1**				
Bone Marrow Assessments[19]											
BM Biopsy and 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 Aspirate/Biopsy for Disease Assessments											
BM Aspirate for MRD Testing											
BM Biopsy to Confirm sCR by IHC											
Optional BM and/or Tissue Sample at PD for BCMA Expression and Biomarker Research [2]											
Treatments Administered											
Belantamab mafodotin[20]		X	X				X				
Bortezomib[21]		X	X	X	X	X					
Dexamethasone		Days 1, 2, 4, 5, 8, 9, 11 and 12 of each 21-Day cycle for Cycles 1 through 8. Dose modifications will follow guidance in Section 6.6.									
Supportive Medication		Supportive medication to be provided for each agent as per institutional guidelines, see Section 6.5.									
Dispense/Return Medication Diary[22]		X	X				X		X		

Schedule of Activities – Treatment Arm A (Belantamab Mafodotin/Bortezomib/Dexamethasone)											
Procedure		**Treatment Period (±3 days)**								**Follow up**	
Cycle / Visit	**Screening (-28days)**	**C1**	**C2-8**	**C1-8**	**C1-8**	**C1-8**	**C9 +**	**Fixed Visits Q3W (Starting at Week 4)**	**End of Treatment (EOT)**	**PFS Follow-up Visit Q3W (±3 days)**	**OS Follow-up Visit Q12W (±14 days)**
Day		**D1**		**D4**	**D8**	**D11**	**D1**				
Ocular Supportive Care for Belantamab Mafodotin											
Preservative-free Artificial Tears		4 to 8 times daily in each eye. Daily beginning on Cycle 1 Day 1 until EOT. Allow 5-10 min between administration of artificial tears and steroid eye drops, if administered together. 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		May apply to both eyes for as long as tolerated up to 4 hours									
Health Outcomes											
PRO-CTCAE[23]		X						X	X		
EORTC QLQ-C30[23]		X						X	X	X	X[23]
EORTC IL52[23]		X						X	X	X	X[23]
EQ-5D-3L		X						X (Q6W)	X	X	X[23]
PGIS		X						X (Q6W)	X	X	
PGIC		X						X (Q6W)	X	X	
FACT-GP5[23]		X						X	X	X	
OSDI[24]		X						X (Q6W)	X	X	X
Healthcare Resource Utilization		X						X[1]			
Pharmacokinetics and ADA											
Pharmacokinetics[25]		X (See Table 20 and Table 21)					X (See Table 20 and Table 21)		X		
ADA[25]		X (See Section 8.6)					X (See Section 8.6)		X		
Biomarkers[19]											
Soluble BCMA[25, 26]	X	See Section 8.9.1, Table 22 and Table 23									
Plasma cfDNA		X (predose)	At every MRD assessment and EOT. For enhanced PK cohort collect also Q12W after C1D1 until EOT								

Schedule of Activities – Treatment Arm A (Belantamab Mafodotin/Bortezomib/Dexamethasone)											
Procedure		**Treatment Period (±3 days)**								**Follow up**	
Cycle / Visit	**Screening (-28days)**	**C1**	**C2-8**	**C1-8**	**C1-8**	**C1-8**	**C9 +**	**Fixed Visits Q3W (Starting at Week 4)**	**End of Treatment (EOT)**	**PFS Follow-up Visit Q3W (±3 days)**	**OS Follow-up Visit Q12W (±14 days)**
Day		**D1**		**D4**	**D8**	**D11**	**D1**				
Genetics											
Optional Genetic Sample[2]		X									

ADA = Anti-drug antibody; BM= Bone marrow; BCMA= B-cell maturation antigen; C1D1 = Cycle 1 Day 1, etc.; cfDNA = Circulating free DNA; CR = Complete response; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eGFR = Estimated glomerular filtration rate; EOI = End of Infusion; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module; EORTC IL 52 = European Organization for Research and Treatment of Cancer Item Library 52; FISH = Fluorescence in-situ hybridization; EOT = End of Treatment; FLC = Free light chain; FSH = Follicle-stimulating hormone; IHC = Immunohistochemistry; IMWG = International Myeloma Working Group; IP = Investigational Product; IV = Intravenous; MRD = Minimal residual disease; OS = Overall Survival; OSDI = Ocular Surface Disease Index; NGS = Next-generation sequencing; PD = Progressive disease; PGIC= Patient Global Impression of Change; PGIS= Patient Global Impression of Severity; PK = Pharmacokinetics; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events; SAE = Serious adverse event; sCR = Stringent Complete Response; SPD = Sum of the Products of the maximal perpendicular Diameters; SRM = Study Reference Manual; VGPR= Very Good Partial Response; WOCBP = Women of childbearing potential.

1. To be performed regardless of dosing.
2. Informed consent 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 lost, damaged, or of insufficient quality to perform the analysis.
3. Physical exam must be within 72 hours prior to the first dose of study drugs to be administered in that cycle.
4. C1D1 ocular exam does not need to be repeated if performed within 28 days of screening exam. Participants will be assessed by a qualified eye care specialist (Appendix 10) at screening/baseline and then Q3W prior to dosing up to the sixth dose of belantamab mafodotin (assessment window of up to 5 days prior to dosing, but all effort should be made to schedule as close to belantamab mafodotin dosing as possible). If there are no significant ocular examinations findings, patient's symptoms or vision changes at or prior to the time of the sixth dose exam, participants may have their ophthalmologic exams decreased to once every 3 months. If a participant subsequently develops vision changes or other ocular symptoms, the participant should be promptly evaluated by a qualified eye care specialist. In case of persistent ophthalmic exam findings, newly developed ocular symptoms or vision changes at the sixth dose exam, the participants will have further ophthalmologic exams, at least every cycle until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by the qualified eye care specialist. See Section 8.2.6 for full details of ocular exam procedures. Participants who have treatment-related ocular AEs present at the end of treatment will continue to be followed by qualified eye care specialist at least every 3 months, for up to 12 months or until resolution (to Grade 1 or baseline), whichever comes first.

5. For belantamab mafodotin: C1D1 vital signs must be assessed within 30 mins prior to Start of Infusion (SOI), 15 mins after SOI (±10 min), within 15 min after End of Infusion (EOI), and at 1 hour (±10 min) after EOI. On subsequent dosing days, vital signs must be assessed at pre-dose (within 30 mins prior to SOI) and within 15 min after EOI, and as clinically indicated. On days where vital sign time points align with blood sampling time points, vital signs should be assessed prior to blood samples being drawn.
   Vital signs should be assessed for bortezomib as clinically indicated. See Section 8.2.3 for full details of vital signs.
6. Single ECG.
7. 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.
8. All laboratory tests with values considered clinically significantly abnormal during participation in the study or at least 70 days after the last dose of study treatment should be repeated until the values return to normal or baseline. See Table 19 for list of comprehensive list of lab tests that must be collected for all participants
9. Hematology and clinical chemistry must be repeated if not within 72 hours prior to first dose of study drugs to be administered in Cycle 1. For Cycles 2 to 8, haematology and chemistry must be repeated, if not within 24 hours prior to each dose of study drugs. Starting at Cycle 9, hematology and chemistry must be repeated if not within 24 hours prior to each dose of belantamab mafodotin. On Day 1 of any planned cycle, Absolute Neutrophil Count (ANC) must be ≥1.0×10^9/L to administer treatment. Results must be evaluated prior to treatment administration.
10. Hematology, chemistry and vital signs (as clinically indicated) must be repeated if not within 24 hours prior to each dose of bortezomib, except for C1D1 as the tests are done within 72 hours prior to the first dose.
11. As calculated by Modified Diet in Renal Disease (MDRD) formula (Appendix 7).
12. Urine dipstick for protein may be used to assess for presence of urine protein. Urine dipstick should be performed at a local lab. Albumin/creatinine ratio needs to be done in any participant with urine dipstick protein result of ≥1+ (at screening visit), or ≥2+ (during study treatment), or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab. If local testing is not available, then central testing will be performed (first void). Spot Urine (albumin/creatinine) testing does not need to be repeated on i) C1D1 if conducted within 7 days of C1D1 dosing (in case of screening assessment), and
    ii) D1 of subsequent cycles if conducted within 5 days of D1 dosing of a given cycle (C2 onwards).
    Results must be received prior to dosing.
13. Hepatitis C RNA testing will be done to determine a participant's eligibility if Hep C Ab is positive. This will be performed at a local lab, or if not available then at a central lab. Results must be received prior to dosing. For additional procedures during Screening and upon enrollment for participants who have a history of Hepatitis B and/or Hepatitis C, please refer to Table 4 and Table 5, respectively.
14. Perform only on women of childbearing potential (WOCBP). A serum pregnancy test must be performed at screening; if the test is completed within 72 hours prior to the first dose of belantamab mafodotin, this assessment does not have to be repeated on C1D1. For questionable cases, follicle-stimulating hormone (FSH) and estradiol should be performed at local lab to determine childbearing potential. WOCBP must have a negative highly sensitive serum pregnancy test within 72 hours of dosing on C1D1. Subsequent pregnancy tests on dosing days may be either serum or urine. Final pregnancy test (serum or urine) must be performed in WOCBP at the EOT Visit and repeated at least 70 days after last dose. Follow up pregnancy assessment by telephone (for WOCBP only) should be performed 4 months after the last dose of belantamab mafodotin or 7 months after the last dose of bortezomib, whichever is longest.
15. Only in participants with IgD/IgE myeloma
16. Imaging is only required for participants with known extramedullary disease or if there is a suspected appearance of a new lesion. Screening assessments may be performed up to 30 days prior to C1D1. Subsequent imaging should be performed Q12W (±7 days) and then if clinically indicated by either CT, MRI, or PET-CT per local guidance. Needs to be performed by the same method throughout the study as was done at baseline. Selected target lesion needs to be measured and followed over time. Plasmacytoma measurements should be taken from the CT portion of the PET-CT, or MRI scans, or dedicated CT scans where applicable. For participants with only skin involvement, skin lesions should be

measured with a ruler. Measurement of tumor size will be determined by the SPD of measured lesions.
Participants undergoing PET-CT should have all blood samples taken before the PET-CT is performed.
For participants with PD due to extramedullary disease, confirmatory scans are not required. The laboratory parameters do not need to be repeated if the extramedullary disease is the only site of progression. If the last radiographic assessment occurred ≥8 weeks prior to the 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.
Digital copies of all scans must be maintained at Investigator site as source document.

17. Survey results within 30 days prior to C1D1 date are acceptable. Imaging of bones for lytic lesions should be performed by a method aligned with institutional guidance (i.e., X-ray, CT or MRI). At later Cycles, repeat as clinically indicated, or if worsening clinical symptoms suggest PD. Needs to be performed by the same method throughout the study as was done at baseline.
18. Response to treatment will be assessed, based on laboratory tests and imaging (if applicable), using the International Myeloma Working Group (IMWG) criteria [Kumar, 2016].
19. All biomarker and BM samples (biopsy and aspirate), once collected, will be analyzed if the sample date and time have been recorded.
20. Belantamab mafodotin administration: belantamab mafodotin 2.5 mg/kg, Q3W will be administered as an IV infusion (see Pharmacy Manual for details), followed by a 1-hour observation period. A window of ±3 days is acceptable for administration of belantamab mafodotin after C1D1. At least 21 days should elapse between consecutive doses of belantamab mafodotin. Please refer to Section 6.6.1 for instructions on dose delays.
21. If a bortezomib dose was delayed, subsequent doses should be adjusted to account for delay as all bortezomib doses must be at least 72 hours/3 calendar days apart. Doses that need to be withheld are skipped and will not be made up later in the cycle. Individual doses within a cycle have a ±1-day window.
22. Participant diary will be used to keep a record of self-administered dexamethasone.
23. PRO-CTCAE, EORTC QLQ-C30, FACT-GP5, and EORTC IL52 should be collected Q3W, prior to any treatment administration on C1D1 and all subsequent visits. EQ-5D-3L, PGIC, and PGIS should be administered Q6W on treatment. EORTC QLQ-C30, EORTC IL52 and EQ-5D should be collected at 3, 6 and 12 months during OS follow up (can be collected by phones using interviewer administration).
24. OSDI should be collected at C1D1, then Q3W up to the 6th DOSE of belantamab mafodotin, then Q6W onward until EOT. In addition, all participants will complete the OSDI at the EOT visit. Participants with no treatment-related ocular AEs per CTCAE v5.0 for corneal events at the EOT ocular assessment will have no further OSDI collection. Participants with treatment-related ocular AEs per CTCAE v5.0 for corneal events at the EOT ocular assessment will have OSDI collected Q12W until resolution (to Grade 1 or baseline) OR for up to 12 months, whichever is sooner.
25. PK, PK-associated sBCMA and ADA sample collection is relative to dose of belantamab mafodotin, which is independent of cycle number to account for the possibility that belantamab mafodotin may be held whilst other agents continue. ADA samples are collected pre-dose only. All PK, sBCMA, and ADA samples, once collected (regardless of dosing), will be analysed if the sample date and time have been recorded.
26. See Section 8.9.1, Table 22 and Table 23 for sBCMA schedules. Also, sBCMA should be collected at screening, and when there is a PK-associated sBCMA sample collection in which case only the PK sample needs to be collected (only 1 sample needed). Likewise, collect sBCMA at the end of treatment.

Table 2 Schedule of Activities - Treatment Arm B (Daratumumab/Bortezomib/Dexamethasone)

- **Screening assessments do not need to be repeated on C1D1 if conducted within 72 hours of C1D1 dosing, unless otherwise specified.**
- The 28-day Screening period is initiated upon signature of the informed consent form (Day 1). The full 28 days can be taken to determine the eligibility of the participants. Participants can be randomized during or upon completion of the 28 days i.e. the day after the Screening period has ended. Study treatment (C1D1) should be initiated within 72 hours after randomization.
- 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 Q3W. 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 and PK where applicable.
- **End of Treatment (EOT)** visit will occur within 30 days from the last cycle, or prior to initiation of new anti-myeloma therapy (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. Participants who have ocular symptoms at EOT will be followed up for ocular exams and OSDI questionnaire as described in Section 8.2.6. After discontinuation of study treatment, the participant should continue disease assessments as per the SoA. Every effort should be made to confirm disease progression per the IMWG criteria prior to initiating a new anti-myeloma therapy.
- **PFS follow-up**: 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 until:
  - Disease progression according to IMWG criteria (move to Survival follow-up)
  - New anti-myeloma therapy is initiated (move to Survival follow-up)
  - Death
  - Withdrawal of consent
  - Loss to follow-up
  - End of study
- **Survival follow-up**: Participants will be followed for survival and subsequent anti-myeloma therapy (PFS2) by chart review, phone call, or any form of communication every 12 weeks (14-day window) from the last q3w assessment visit until death, withdrawal of consent, lost to follow-up or end of the study, whichever comes first. Participant does not need to come in for visit unless they are being followed for treatment-related changes in vision that are present at the EOT. Record the participant's survival status and whether subsequent treatment for disease was given.
- GSK may request that updated survival data be collected on all treated/randomized participants outside the protocol window noted in the Schedule of Assessments. 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 publicly available death registers will be used for participants withdrawn from study or lost to follow-up prior to death.
- For details on Home Healthcare and Telemedicine Approaches, please refer to Appendix 15.

Schedule of Activities - Treatment Arm B: Daratumumab/Bortezomib/Dexamethasone

Procedure	Screening (-28 days)	Treatment Period (±3 days for Q3W visits)									End of Treatment (EOT)	Follow up	
Cycle /Visit		C1-3 (Dara)	C1 (Bor)	C2-8 (Bor)	C4-8 (Dara)	C1-8 (Bor)	C1-8 (Bor)	C1-8 (Bor)	C9 +	Fixed Visits Q3W (Starting at Week 4)		PFS Follow-up Visit Q3W (±3 days)	OS Follow-up Visit Q12W (±14 days)
Day		D1, D8, D15	D1			D4	D8	D11	D1				
Informed Consent[1, 2]	X												
Baseline Demographics	X												
Medical/Disease History and Characteristics	X												
Body Weight	X		X	X					X		X		
Height	X												
Safety													
Physical Exam[3]	X	X (D1 only)	X	X	X				X		X	X	
ECOG Performance Status	X	X (D1 only)	X	X	X				X		X	X	
Ocular Exam[4]	X	X[4] (see footnote)			X[4] (see footnote)				X[4] (see footnote)	X[4] (see footnote)	X	X[4]	X[4]
Vital Signs (BP, Heart rate, Body Temp)[5]	X	X	X	X	X	If clinically indicated			X		X		
12-Lead ECG[6]	X												
Adverse Events/SAEs		Adverse events and SAEs will be collected throughout the study until at least 70 days after the last dose. SAEs related to study participation are collected from time of consent until end of study. See Section 8.3.1.											
Concomitant Medications	Concomitant medications will be collected, as reported by the participant or through participant medical record review.												
Survival Follow-up Phone call[7]													X
Laboratory Assessments[8]													
Hematology[9,10]	X	X	X	X	X	X	X	X	X	X[1]	X	X	
Clinical Chemistry[9,10]	X	X	X	X	X	X	X	X	X	X[1]	X	X	
HbA1c	As clinically indicated												
eGFR[11]	X		X							X[1]	X		
Urine dipstick OR Spot Urine (Albumin/Creatinine ratio[12])	X		X							X[1]	X		

Schedule of Activities - Treatment Arm B: Daratumumab/Bortezomib/Dexamethasone

Procedure	Screening (-28 days)	Treatment Period (±3 days for Q3W visits)									End of Treatment (EOT)	Follow up	
Cycle /Visit		C1-3 (Dara)	C1 (Bor)	C2-8 (Bor)	C4-8 (Dara)	C1-8 (Bor)	C1-8 (Bor)	C1-8 (Bor)	C9 +	Fixed Visits Q3W (Starting at Week 4)		PFS Follow-up Visit Q3W (±3 days)	OS Follow-up Visit Q12W (±14 days)
Day		D1, D8, D15	D1			D4	D8	D11	D1				
HbsAg, HbcAb, Hep C Ab, Hep C RNA[13]	X												
Indirect antiglobulin test (Indirect Coombs test)	X												
Blood type and screen	X												
Daratumumab-specific immunofixation assay[14]		X[15]								X[15]	X	X	
Pregnancy Test for WOCBP[16]	X		X	X					X		X	X[16]	X[16]
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 sample collection (serum/urine) before institution of any new anti-myeloma therapy and preferably within 14 days of the date of the initial assessment showing unconfirmed disease progression. This may be performed at the EOT visit.													
β2 Microglobulin	X												
SPEP (Serum Protein Electrophoresis)	X									X[1]	X	X	
UPEP (Urine Protein Electrophoresis) (on 24-hour collected urine)	X									X[1]	X	X	
Serum M Protein Calculation	X									X[1]	X	X	
Serum Kappa Lambda Free LC, FLC Ratio	X									X[1]	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 hr) AND SPEP (0 g/dL)									
Calcium Corrected for Albumin (serum)	X									X[1]	X	X	
IgG, IgM, IgA	X									X[1]	X	X	
IgD/IgE[17]	X									X[1]	X	X	
Imaging for Extramedullary Disease[18]	X									X[1, 18] (Q12W)	X	X (Q12W)	

Schedule of Activities - Treatment Arm B: Daratumumab/Bortezomib/Dexamethasone

Procedure	Screening (-28 days)	Treatment Period (±3 days for Q3W visits)									End of Treatment (EOT)	Follow up	
Cycle /Visit		C1-3 (Dara)	C1 (Bor)	C2-8 (Bor)	C4-8 (Dara)	C1-8 (Bor)	C1-8 (Bor)	C1-8 (Bor)	C9 +	Fixed Visits Q3W (Starting at Week 4)		PFS Follow-up Visit Q3W (±3 days)	OS Follow-up Visit Q12W (±14 days)
Day		D1, D8, D15	D1			D4	D8	D11	D1				
PET-CT upon achieving MRD negativity by NGS										To be performed ONCE after achieving MRD negativity by NGS, within 42 days (6 weeks) of testing negative			
Skeletal Survey[19]	X			As clinically indicated									
Response Assessment by IMWG[20]										X[1]	X	X	
Bone Marrow Assessments[21]													
BM Biopsy and 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 Aspirate/Biopsy for Disease Assessments													
BM Aspirate for MRD Testing													
BM Biopsy to Confirm sCR by IHC													
Optional BM and/or Tissue Sample at PD for BCMA Expression and Biomarker Research [2]													
Treatments Administered													
Daratumumab[22]		X			X				X (Q4W)				
Bortezomib[23]			X	X		X	X	X					
Dexamethasone		Days 1, 2, 4, 5, 8, 9, 11 and 12 of each 21-Day cycle for Cycles 1 through 8. Dose modifications will follow guidance in Section 6.6.											
Supportive Medication	Supportive medication to be provided for each agent as per institutional guidelines, see Section 6.5.												
Dispense/Return Medication Diary[24]			X	X					X		X		

Schedule of Activities - Treatment Arm B: Daratumumab/Bortezomib/Dexamethasone

Procedure	Screening (-28 days)	Treatment Period (±3 days for Q3W visits)									End of Treatment (EOT)	Follow up	
Cycle /Visit		C1-3 (Dara)	C1 (Bor)	C2-8 (Bor)	C4-8 (Dara)	C1-8 (Bor)	C1-8 (Bor)	C1-8 (Bor)	C9 +	Fixed Visits Q3W (Starting at Week 4)		PFS Follow-up Visit Q3W (±3 days)	OS Follow-up Visit Q12W (±14 days)
Day		D1, D8, D15	D1			D4	D8	D11	D1				
Health Outcomes													
PRO-CTCAE[25]			X							X	X		
EORTC QLQ-C30[25]			X							X	X	X	X[25]
EORTC IL52[25]			X							X	X	X	X[25]
EQ-5D-3L			X							X (Q6W)	X	X	X[25]
PGIS			X							X (Q6W)	X	X	
PGIC			X							X (Q6W)	X	X	
FACT-GP5[25]			X							X	X	X	
OSDI[26]			X							X (Q12W)	X		
Healthcare Resource Utilization			X							X[1]			
Biomarkers[21]													
Soluble BCMA[27]	X		See Table 24 in Section 8.9.1										
Plasma cfDNA			X (pre-dose)	At every MRD assessment timepoint							X		
Genetics													
Optional Genetic Sample[2]			X										

ADA = Anti-drug antibody; BM= Bone marrow; BCMA= B-cell maturation antigen; C1D1 = Cycle 1 Day 1, etc.; cfDNA = Circulating free DNA; CR = Complete response; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eGFR = Estimated glomerular filtration rate; EOI = End of Infusion; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module; EORTC IL52 = European Organization for Research and Treatment of Cancer Item Library 52; FISH = Fluorescence-in-situ hybridization; EOT = End of Treatment; FLC = Free light chain; FSH = Follicle-stimulating hormone; IHC = Immunohistochemistry; IMWG = International Myeloma Working Group; IP = Investigational product; MRD = Minimal residual disease; OS = Overall Survival; OSDI = Ocular Surface Disease Index; NGS = Next-generation sequencing; PD = Progressive disease; PGIC= Patient Global Impression of Change; PGIS= Patient Global Impression of Severity; PK = Pharmacokinetics; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events; SAE = Serious adverse event; sCR = Stringent Complete Response; VGPR= Very Good Partial Response; WOCBP = Women of childbearing potential.

1. To be performed regardless of dosing.
2. Informed consent 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 assessment prior to signing consent need not be repeated if done within the

appropriate screening window. Separate consent required for optional samples. For optional sample, 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 lost, damaged, or of insufficient quality to perform the analysis.

3. Physical exam must be within 72 hours prior to the first dose of study drugs to be administered in that cycle.
4. C1D1 ocular exam does not need to be repeated if performed within 28 days of screening exam. Ocular exam may be performed up to 5 days prior to dosing. On treatment ocular exams to be performed at Cycle 6 and then decreased to every 6 months (±4 week window) until and including eye exam at end of treatment. If a participant subsequently develops vision changes or other ocular symptoms, the participant should be promptly evaluated by a qualified eye care specialist. In case of persistent ophthalmic exam findings, newly developed ocular symptoms or vision changes, the participants will have further ophthalmologic exams, at least every cycle until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by the qualified eye care specialist (Appendix 10). Participants who have treatment-related ocular AEs present at the end of treatment will continue to be followed by qualified eye care specialist at least every 3 months, for up to 12 months or until resolution (to Grade 1 or baseline), whichever comes first. See Section 8.2.6.2 for full details of ocular exam procedures.
5. On days where vital sign time points align with blood sampling time points, vital signs should be assessed prior to blood samples being drawn. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated. Vital signs should be assessed for bortezomib as clinically indicated. Blood pressure and heart rate are to be measured at the following time points at the time of first daratumumab administration:
   - Within 30 min prior to Start of Infusion (SOI)
   - At 30 mins, 2 hours, and 3 hours 30 min after SOI (±10 mins);
   - Within 15 min of End of Infusion (EOI)
   - 30 min, 1 hour, and 2 hours after EOI (±10 mins)

   On Cycle 1 Day 1, if daratumumab administration is split and given over Day 1 and Day 2, vital signs are to be measured on both Day 1 and Day 2 as per above time points. For all other daratumumab infusions, blood pressure will be measured within 30 min prior to SOI and within 15 min after EOI, and as clinically indicated. See Section 8.2.3.2 for full details of vital signs.
6. Single ECG.
7. 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.
8. All laboratory tests with values considered clinically significantly abnormal during participation in the study or 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 19 for a comprehensive list of lab tests that must be collected for all participants.
9. Hematology and chemical chemistry must be repeated if not within 72 hours prior to first dose of study drugs to be administered in Cycle 1. Hematology and clinical chemistry are to be performed every cycle up to 72 hours prior to every daratumumab administration. Results must be evaluated prior to treatment administration. Refer to Table 19 for a comprehensive list of lab tests that must be collected for all participants.
10. Hematology, clinical chemistry and vital signs (as clinically indicated) must be repeated if not within 24 hours prior to each dose of bortezomib, except for C1D1 as the tests are done within 72 hours prior to the first dose. When bortezomib administration coincides with and Daratumumab administration, hematology, clinical chemistry, and vital signs (as clinically indicated) will be performed within 24 hours prior to dosing.
11. As calculated by Modified Diet in Renal Disease (MDRD) formula (Appendix 7).
12. Urine dipstick for protein may be used to assess for presence of urine protein. Urine dipstick should be performed at a local lab. Albumin/creatinine ratio needs to be done in any participant with Urine dipstick protein result of ≥1+ (at screening visit), or ≥2+ (during study treatment), or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab. If local testing is not available, then central testing will be performed (first void). In case of Screening assessment, Spot Urine (albumin/creatinine) testing does not need to be repeated on C1D1 if conducted within 7 days of C1D1 dosing. Results must be received prior to dosing.

13. Hepatitis C RNA testing will be done to determine a participant's eligibility if Hep C Ab is positive. This will be performed at a local lab, or if not available then at a central lab. Results must be received prior to dosing. For additional procedures during Screening and upon enrollment for participants who have a history of Hepatitis B and/or Hepatitis C, please refer to Table 4 and Table 5, respectively.
14. Participants with IgG kappa myeloma and disease response of CR with suspected PD, or disease response of VGPR with suspected CR, are required to undergo central testing with a daratumumab-specific immunofixation assay to confirm PD or CR/sCR.
15. First sample to be collected only on Day 1 of Cycle 1, prior to dosing; subsequent samples will be collected at each fixed visit Q3W starting at Week 4.
16. Perform only on women of childbearing potential (WOCBP). A serum pregnancy test must be performed at screening; if the test is completed within 72 hours prior to the first dose of daratumumab, this assessment does not have to be repeated on C1D1. For questionable cases, follicle-stimulating hormone (FSH) and estradiol should be performed at local lab to determine childbearing potential. WOCBP must have a negative highly sensitive serum pregnancy test within 72 hours of dosing on C1D1. Subsequent pregnancy tests on dosing days may be either serum or urine. Final pregnancy test (serum or urine) must be performed in WOCBP at the EOT Visit and repeated at least 70 days after last dose). Follow up pregnancy assessment by telephone (for WOCBP only) should be performed 7 months after the last dose of bortezomib or 3 months from the last dose of daratumumab, whichever is longest.
17. Only in participants with IgD/IgE myeloma
18. Imaging is only required for participants with known extramedullary disease or if there is a suspected appearance of a new lesion. Screening assessments may be performed up to 30 days prior to C1D1. Subsequent imaging should be performed at Q12W(±7 days) and then if clinically indicated by either CT, MRI, or PET-CT per local guidance. Needs to be performed by the same method throughout the study as was done at baseline. Selected target lesion needs to be measured and followed over time. Plasmacytoma measurements should be taken from the CT portion of the PET-CT, or MRI scans, or dedicated CT scans where applicable. For participants with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD of measured lesions.
    Participants undergoing PET-CT should have all blood samples taken before the PET-CT is performed.
    For participants with PD due to extramedullary disease, confirmatory scans are not required. The laboratory parameters do not need to be repeated if the extramedullary disease is the only site of progression. If the last radiographic assessment occurred ≥8 weeks prior to the 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.
    Digital copies of all scans must be maintained at Investigator site as source document.
19. Survey results within 30 days prior to C1D1 date are acceptable. Imaging of bones for lytic lesions should be performed by a method aligned with institutional guidance (i.e., X-ray, CT or MRI). At later Cycles, repeat as clinically indicated, or if worsening clinical symptoms suggest PD. Needs to be performed by the same method throughout the study as was done at baseline.
20. Response to treatment will be assessed, based on laboratory tests and imaging (if applicable), using the International Myeloma Working Group (IMWG) criteria [Kumar, 2016]
21. All biomarker and BM samples (biopsy and aspirate), once collected, will be analyzed if the sample date and time have been recorded.
22. Daratumumab 16 mg/kg IV. Corticosteroid should be administered prior to daratumumab infusion unless prior intolerance. On days when daratumumab coincides with dexamethasone, dexamethasone is sufficient as the pre-infusion corticosteroid. On days when daratumumab does not coincide with dexamethasone an additional pre-infusion corticosteroid should be given. The Week 1 dose of daratumumab ONLY may be administered as a single infusion or a split infusion over 2 days, according to the local/regional label and institutional guidelines (for details see Section 6.1.4).
23. If a bortezomib dose was delayed, subsequent doses should be adjusted to account for delay as all bortezomib doses must be at least 72 hours/3 calendar days apart. Doses that need to be withheld are skipped and will not be made up later in the cycle. Individual doses within a cycle have a ±1-day window.
24. Participant diary will be used to keep a record of self-administered dexamethasone.

25. PRO-CTCAE, EORTC QLQ-C30, FACT-GP5, and EORTC IL52 should be collected Q3W, prior to any treatment administration on C1D1 and all subsequent visits. EQ-5D-3L, PGIC, and PGIS should be administered Q6W on treatment. EORTC QLQ-C30, EORTC IL52 and EQ-5D should be collected at 3, 6 and 12 months during OS follow up (can be collected by phones using interviewer administration).
26. OSDI should be collected at C1D1, then Q3W up to the 6th cycle, then Q12W onward until EOT. In addition, all participants will complete the OSDI at the EOT visit.
27. See Section 8.9.1, Table 24 for sBCMA collection schedule. sBCMA should be collected at screening and at the end of treatment.

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

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

BCMA = B-cell maturation antigen; BM = bone marrow; CR = complete response; FISH = fluorescence in situ hybridization; MRD = minimal residual disease; PD = progressive disease; 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 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 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. **FISH results are required prior to randomization**.
f. Minimal residual disease (MRD) testing to be performed at Screening and at the time of first achieving VGPR or better (i.e. achieving CR without prior VGPR). Thereafter, MRD testing must be repeated every 6 months ($\pm$1 month) from the time of last sample collection until PD. In case of deepening of response from VGPR to suspected CR, MRD testing must be performed at the time of achieving suspected CR and repeated every 6 months from the time of last sample collection until PD.
g. BM core biopsy and aspirate samples to be collected at Screening for BCMA expression and biomarker research. BM biopsy is the preferred sample for these exploratory analyses. Every effort should be made to collect a BM biopsy for this test, however, if for any reason BM biopsy is not obtainable, then an aspirate must be collected for BCMA expression and biomarker research. Any remaining biopsy and/or aspirate sample will be used for biomarker research (which may include immune cell characterization and/or profiling and/or DNA/RNA analyses).
h. Optional BM core biopsy and/or aspirate and/or tissue sample (if from extramedullary tumor) for BCMA expression and biomarker research may be collected at PD to evaluate mechanisms of response/resistance. Separate consent required for this optional sample at PD.

Table 4 Hepatitis B (HBV) SoA – Additional Procedures

Note: The procedures listed in this table apply ONLY to participants in screening and who have been enrolled and who have a history of Hepatitis B; all procedures must be done as needed **in addition** to the required procedures for all participants detailed in Table 1 and Table 2

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 study treatment and subsequently every 3 months, or if LFT elevations requiring increased monitoring or stopping criteria occur, 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 study treatment, continues through to completion of treatment and should not be stopped unless advised by local hepatology or virology services.
HBV-DNA testing	X[2]	X[2]	X[2]	
Prevention of HBV reactivation	X[3]	X[3]	X[3]	

HBsAg = Hepatitis B surface antigen; HBV = Hepatitis B; LFT = liver function test

Table 5 Hepatitis C (HCV) SoA – Additional Procedures

Note: The procedures listed in this table apply ONLY to participants in screening and who have been enrolled and who have a history of Hepatitis C; all procedures must be done as needed in addition to the required procedures for all participants detailed in Table 1 and Table 2.

HCV Study Assessments	During Screening / Prior to starting treatment	During Treatment	Post Treatment	Notes
HCV-RNA testing	X[1]	X[1]		1. HCV- RNA testing prior to the start of study treatment and subsequently every 3 months, or if LFT elevations requiring increased monitoring or stopping criteria occurs, or for any clinical suspicion of hepatitis reactivation. 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. HCV 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

2. INTRODUCTION

2.1. Study Rationale

Multiple myeloma (MM) is an incurable malignancy and accounts for 1% of all cancers and for 10% of all hematologic malignancies. Worldwide, approximately 139,000 new cases are diagnosed annually [Cowan, 2018], and an estimated 30,770 new cases and 12,770 deaths will occur in the U.S. in 2018 [Siegel, 2019]. Despite significant advances, current novel therapies and hematopoietic stem cell transplant (HSCT) cannot achieve cure, and most MM participants will die of disease progression or complications of myeloma. Thus, new treatments are urgently needed.

B-cell maturation antigen (BCMA) is a target present on mature B cells and on tumour cells in patients with MM [Tai, 2015; Tai, 2006]. Belantamab mafodotin is an antibody-drug conjugate (ADC) consisting of a humanized anti-BCMA monoclonal antibody (mAb) that is conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF) with a maleimidocaproyl linker (cysteine maleimidocaproyl MMAF [cys-mcMMAF]; also, known as SGD-1362).

Belantamab mafodotin binds to BCMA and kills MM cells via a multi-modal mechanism including delivery of cytotoxic, cys-mcMMAF to BCMA-expressing MM cells, thereby inducing apoptosis, enhancing antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, and inducing immunogenic cell death (Figure 1) [Tai, 2014; Montes De Oca, 2019]. Exposure of dendritic cells to tumour cells undergoing immunogenic cell death is expected to result in a tumour antigen-specific T-cell response, enhancing the immunogenic response against MM.

Of the 4 proposed MoA for belantamab mafodotin, the ADC and ADCC MoAs have been linked to efficacy in non-clinical models: in vitro and in vivo against multiple myeloma cell lines, and ex vivo against primary patient myeloma samples. Inhibition of BCMA signalling has been demonstrated biochemically; however, functional effects on myeloma cells have not been demonstrated. ICD markers on cells are induced by belantamab mafodotin both in vivo and in vitro. In vivo, induction of ICD correlates with an adaptive immune response and long-term tumour regression in immune-competent murine allograft models. These different mechanisms may enable belantamab mafodotin to deliver anti-tumour activities targeting both dividing and nondividing tumour cells and associate the cell kill with an adaptive immune response. These MoA characteristics clearly differentiate belantamab mafodotin from existing approved treatments. Several assets targeting BCMA by different mechanisms are in clinical development for MM, including BCMA CAR-T cells and BCMA bispecific antibodies. However, none of the currently approved therapies for MM have the same MoAs as belantamab mafodotin.

Despite new medicines in a relapsed refractory population providing clinical benefit, multiple myeloma is not currently curable and an unmet need still remains. Belantamab mafodotin has shown strong single-agent activity in the first time in human (FTIH) study (BMA117159). Among the 35 participants receiving belantamab mafodotin at 3.4 mg/kg IV, Q3W, with a median of 5 prior therapies, the ORR was 60% (95% CI: 42.1%, 76.1%); the median PFS was 12.0 months (95% CI: 3.1, -NE months) and the duration of

response, not previously estimable at the interim analyses, was estimated at 14.3 months [Trudel, 2019]. Due to novel MoAs, it is possible that belantamab mafodotin may be able to overcome resistance to existing therapies.

In Study BMA117159, the maximum clinical benefit (ORR) was observed at the 3.4 mg/kg dose level, but a significant number of participants required dose delays and dose reductions to manage adverse events. In phase II Study 205678, belantamab mafodotin was further evaluated as monotherapy in RRMM patients at the dose of 2.5 mg/kg and 3.4 mg/kg Q3W and based on benefit/risk assessment, a dose of 2.5 mg/kg Q3W has been proposed as the monotherapy dose. This dose of 2.5 mg/kg Q3W has been further evaluated in combination with bortezomib and dexamethasone in Study 207497 and based on the safety evaluation, this dose has been selected for this study.

The efficacy for belantamab mafodotin monotherapy is reviewed in the Investigator's Brochure (IB) (see Section 2.2.4) [GSK document No. RPS-CLIN-051778].

Given this previous experience, the combination of belantamab mafodotin with other therapies with different MoA is an attractive option to explore for patients with MM who have relapsed or become refractory to standard of care (SoC). The combination with other agents may result in additive, or potentially synergistic effects which could translate into deep and long-lasting responses.

It is hypothesized that the combination of belantamab mafodotin and bor/dex will lead to greater patient benefit, as measured by progression-free survival (PFS), compared to the SoC combination of daratumumab and bor/dex. While there are some potential overlaps in the pattern of identified toxicities between belantamab mafodotin and bor/dex (primarily hematologic), they are expected to be manageable.

2.2. Background

2.2.1. Current Treatment of Multiple Myeloma

Most, if not all patients treated with myeloma regimens inevitably relapse, with a median overall survival (OS) of about 5 years [Robinson, 2014; Hou, 2017; Palumbo, 2015]. Each relapse requires salvage therapy, and the duration of response (DoR) to each subsequent line of salvage therapy typically decreases. For example, in a retrospective chart review of patients who become refractory to bortezomib and IMIDs, the median OS time was disappointingly short (~ 9 months), with 7% achieving VGPR, 24% achieving partial response (PR), and 10% with stable disease after retreatment [Kumar, 2012]. While the main treatment goal for RRMM is usually the preservation of organ function, control of the disease, and maintaining quality of life, the depth of response is also considered a predictor of durability of response and patient survival [Lonial, 2014].

While combining agents with existing SoC therapies might be a straightforward approach, an alternative strategy to achieving deep responses is to evaluate combinations of agents that have preclinical evidence or scientific rationale for enhancing the clinical benefit of belantamab mafodotin.

2.2.2. Role of B-Cell Maturation Antigen in Multiple Myeloma.

BCMA, also designated as tumour necrosis factor receptor superfamily member 17 (TNFRSF17) is expressed on the surface of normal and malignant B lymphocytes at later stages of differentiation as they mature [Novak, 2004]. Ligands targeting BCMA such as B-cell activating factor of the tumour necrosis factor family (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]. Soluble BCMA (sBCMA) is present in the serum of MM patients, and its levels have been postulated to correlate with tumour burden, response to therapy and OS [Robinson, 2014; Sanchez, 2012]. Mice deficient for BCMA are viable, have normal B-cell development, and exhibit normal humoral responses [Belnoue, 2008; Jiang, 2011; 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 makes it a very good target for a therapeutic antibody with direct cell killing activity and expected to have limited off target effects [Tai, 2015].

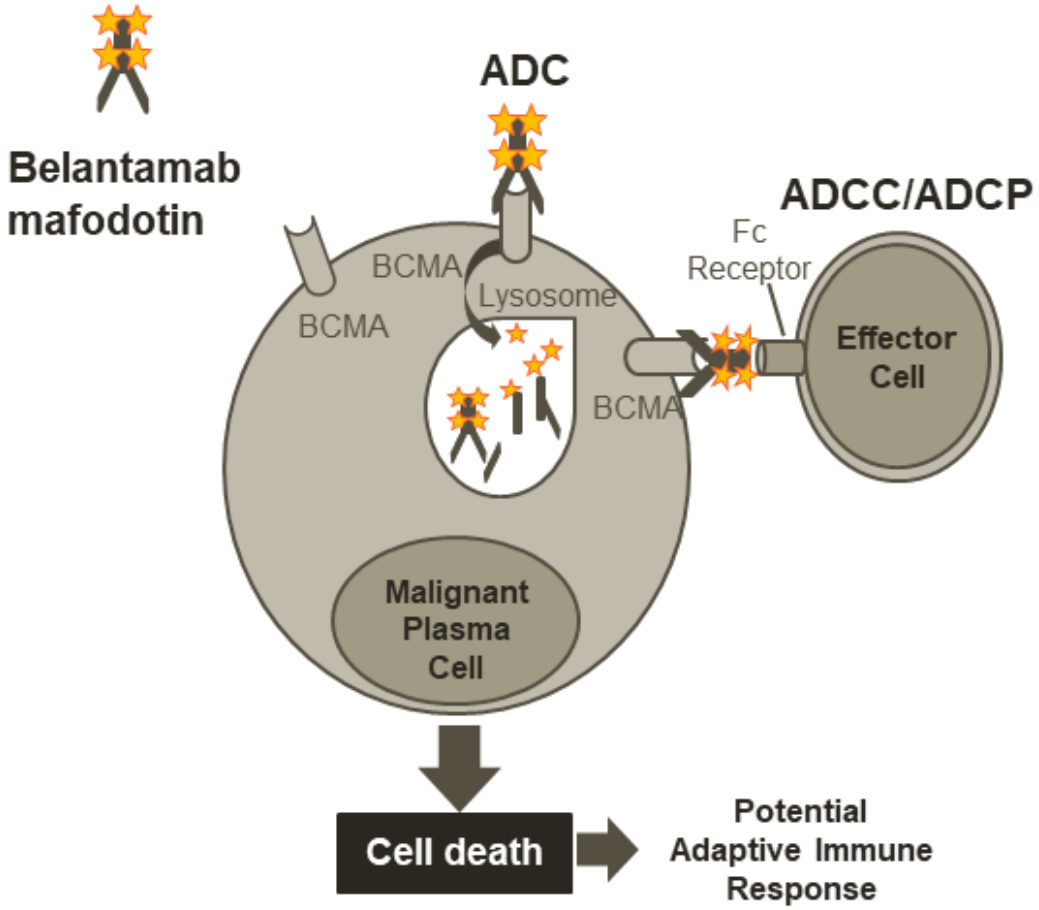
BCMA has been validated as a therapeutic target in MM in preclinical studies [Tai, 2014] and more recently in the clinic, where impressive results were demonstrated with BCMA-targeted Chimeric Antigen T cell therapy (CAR-T) [Pont, 2019], and belantamab mafodotin as single agent [GSK document No. RPS-CLIN-051778; Trudel, 2018; Trudel, 2019].

2.2.3. Antibody-Drug Conjugate Belantamab Mafodotin

Belantamab mafodotin is a humanized (IgG1) ADC which binds specifically to BCMA with different mechanisms of action as detailed in the IB [GSK document No. RPS-CLIN-051778].

Of the 4 proposed MoAs for belantamab mafodotin, the ADC and ADCC MoAs have been linked to efficacy in non-clinical models: in vitro and in vivo against multiple myeloma cell lines, and ex vivo against primary patient myeloma samples. These different mechanisms may enable belantamab mafodotin to deliver anti-tumour activities targeting both dividing and nondividing tumour cells and associate the cell kill with an adaptive immune response; these MoA characteristics clearly differentiate belantamab mafodotin from existing approved treatments. All patients with MM express various levels of BCMA on the surface of the tumour cells, making them potentially responsive to treatment with belantamab mafodotin [Darce, 2007].

Figure 1 Mechanism of Action of Belantamab Mafodotin



ADCC/ADCP=antibody-dependent cell-mediated cytotoxicity/antibody-dependent cellular phagocytosis

2.2.4. Clinical Experience with Belantamab Mafodotin

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

FTIH study BMA117159/DREAMM-1

In the FTIH DREAMM-1 study, which consisted of a dose escalation phase (Part 1, n=38) and a dose expansion phase (Part 2, n=35), as of the primary analysis cut-off date of 31 August 2018, a total of 73 participants with RRMM received at least 1 dose of belantamab mafodotin [GSK document No. RPS-CLIN-051778; Trudel, 2019].

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

Phase II study 205678/DREAMM-2

DREAMM-2 is a Phase II, randomized, 2-arm open-label study evaluating the efficacy and safety of belantamab mafodotin monotherapy (Blenrep), given at 2.5 mg/kg or 3.4 mg/kg IV once every 3 weeks in adult patients with relapsed or refractory multiple myeloma. Study participants had previously received 3 or more prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and were refractory to an immunomodulatory agent and a proteasome inhibitor. A total of 196 participants were treated in the 2 dose cohorts, 97 in the 2.5 mg/kg cohort and 99 in the 3.4 mg/kg cohort. In the primary analysis, the ORR assessed by an independent review committee was 31% (97.5% CI: 20.8, 42.6) in the 2.5 mg/kg cohort and 34% (97.5% CI: 23.9, 46.0) in the 3.4 mg/kg cohort.

The final analysis of the study (Data Cut-off Date: 31 March 2022) confirmed the efficacy and safety results of the primary analysis. 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. More than half of responders (58% and 69%) had a response of VGPR or better. The median duration of response was 12.5 months (95% CI: 4.2,19.3) in the 2.5 mg/kg cohort and 6.2 months (95% CI: 4.8,18.7) at 3.4 mg/kg cohort. The median PFS was 2.8 months (95% CI: 1.6, 3.6) and 3.9 months (95% CI: 2.0, 5.8), respectively. The median OS was 15.3 months (95% CI: 9.9, 18.9) in the 2.5 mg/kg cohort and 14.0 months (95% CI: 10.0, 18.1) in the 3.4 mg/kg cohort.

Key safety data of the DREAMM-2 study include the following (data for 2.5 mg/kg cohort are presented first, followed by the 3.4 mg/kg cohort): Serious adverse events (SAE) occurred in 45% and 54% of participants, of which 15% and 21% were related to study treatment. SAE in >3% of participants in either cohort included pneumonia (7% and 14%), pyrexia (7% and 5%), and hypercalcemia (4% and none). Fatal SAEs related to study treatment occurred in 1% and 2% of participants, including sepsis (1%), cardiac arrest (1%), and lung infection (1%). Grade 3 or 4 AEs related to study treatment were reported in 58% and 64% of the participants. The most common treatment-related Grade ≥2 AEs reported were keratopathy (59% and 64%), thrombocytopenia (14% and 27%), vision blurred (13% and 18%), infusion related reaction (13% and 5%), anemia (6% and 10%), and neutropenia (4% and 10%). The most common AEs (≥25%) were keratopathy, thrombocytopenia, anemia, nausea, vision blurred, and pyrexia. Infusion-related reactions of any Grade occurred in 21% and 16% of participants, including Grade 3 in 3% and 1%.

Permanent discontinuation due to AEs occurred in 12% of participants in both cohorts of which 9% and 5% were considered treatment related. Keratopathy (3% each in both cohorts) was the most frequent AEs resulting in permanent discontinuation. Dose interruptions due to an AE occurred in 54% and 62% of participants. Dose reductions due to an AE occurred in 36% and 44% of participants. AEs which required a dose reduction in >3% of patients included keratopathy (28% and 30%) and thrombocytopenia (4% and 11%). The most common Grade 3 or 4 (≥10%) laboratory abnormalities were decreases of lymphocytes, platelet count, haemoglobin, neutrophils, and leukocytes, and increases in gamma-glutamyl transferase values.

2.2.4.1. Pharmacokinetics and Pharmacodynamics in Humans

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

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

Belantamab mafodotin pharmacokinetics were well described by a linear, 2-compartment population model, with a time-varying decrease in clearance in a population pharmacokinetic analysis. At Cycle 1, belantamab mafodotin had a systemic clearance of 0.92 L/day, steady-state volume of distribution of 10.8 L, and an elimination half-life of 12 days in participants with RRMM in Study 205678. Over time, clearance was reduced by 28%, resulting in an elimination half-life of 14 days. The time to 50% change in clearance was approximately 50 days.

No clinically significant differences in the pharmacokinetics of belantamab mafodotin or cys-mcMMAF were observed based on age (34 to 89 years), sex, race (African American/Black and White), body weight (42 to 130 kg), mild or moderate renal impairment (eGFR ≥ 30 ml/min/1.73m2) or mild hepatic impairment (NCI-ODWG classification). Higher serum levels of β_2-microglobulin, IgG, and soluble BCMA (sBCMA) and lower levels of albumin are associated with more advanced multiple myeloma or a higher multiple myeloma disease burden. Higher baseline IgG and sBCMA levels, and lower baseline albumin levels were associated with higher belantamab mafodotin clearance leading to lower average and trough concentrations (Ctau) of belantamab mafodotin. Higher baseline IgG and sBCMA levels were associated with higher cys-mcMMAF central volume of distribution leading to lower cys-mcMMAF Cmax.

In nonclinical studies, cys-mcMMAF had limited metabolic clearance. In vitro data suggested that belantamab mafodotin and cys-mcMMAF are unlikely to perpetrate a drug-drug interaction or to be a victim of a drug-drug interaction with inhibitors or

inducers of cytochromes (CYP) P450. Cys-mcMMAF was an in vitro substrate of organic anion transporting polypeptides (OATP)1B1 and OATP1B3, multidrug resistance associated proteins (MRP)1, MRP2, and MRP3, a borderline substrate of bile salt export pump (BSEP), and a possible substrate of P-glycoprotein (P-gp). Following the administration of belantamab mafodotin to participants with RRMM, only intact cys-mcMMAF was detected in pooled human urine, with no evidence of other MMAF-related urinary metabolites.

Free sBCMA levels were measured in Study BMA117159 and Study 205678. All participants exhibited reductions in free sBCMA concentration at end of infusion compared to baseline at Cycle 1, with a return to near-baseline level by 7 days after dosing, reflecting binding of belantamab mafodotin to sBCMA. CCI [redacted]

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

Additional information related to belantamab mafodotin clinical PK, PD, and exposure-response relationships can be found in the IB [GSK document No. RPS-CLIN-051778].

2.3. Benefit/Risk Assessment

2.3.1. Summary of Risk Assessment for Belantamab Mafodotin (Treatment Arm A), Daratumumab (Treatment Arm B), and Bor/Dex (Treatment Arms A and B)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential Overlapping Toxicities of Belantamab mafodotin/Bortezomib/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. **Bortezomib:** Associated with thrombocytopenia that follows a cyclical pattern with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of subsequent cycle.	Routine monitoring of hematologic panels as outlined in the SoA. Supportive therapy per local medical practice (e.g., platelet transfusion, growth factors). Recommendations for dose reduction and treatment discontinuation criteria are detailed in Section 6.6 and Section 7.
Pneumonitis	**Belantamab mafodotin:** Nonclinical safety experiments have demonstrated the presence of progressive microscopic changes in the lungs (prominent alveolar macrophages associated with eosinophilic material; mixed perivascular inflammation) in rats, at all doses tested. Cases of pneumonitis, including fatal events, have been observed with belantamab mafodotin although a causal association has not been established. **Bortezomib:** Acute Respiratory Distress Syndrome and acute diffuse infiltrative pulmonary disease of unknown etiology, such as pneumonitis, interstitial pneumonia, and lung infiltration have been reported rarely in patients receiving bortezomib. Some of these events have been fatal. There have been reports of pulmonary hypertension associated with bortezomib administration in the absence of left heart failure or significant pulmonary disease.	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, further diagnostic tests and management should be performed and further treatment with belantamab mafodotin delayed (refer to Section 6). An overall benefit/risk assessment should be considered for the participant prior to continuing belantamab mafodotin treatment. Further diagnostic tests and management will be implemented immediately in cases of suspected pneumonitis as described in Section 6.6.1 in Table 10. In the event of new or worsening cardiopulmonary symptoms, consider interrupting bortezomib until a prompt and comprehensive diagnostic evaluation is conducted.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Increased Infections due to immunosuppression or neutropenia	**Belantamab mafodotin:** In nonclinical studies, belantamab mafodotin has been associated with decrease in immunoglobulins in monkeys, at all doses. An increase in immunoglobulins was seen in rats (rats are not an antigen specific species for belantamab mafodotin). Immunosuppression is frequently associated with an increased risk of infection. Serious and non-serious infections have been reported in belantamab mafodotin studies, including respiratory infections, pneumonia, and sepsis. Neutropenic events, including febrile neutropenia have been observed with belantamab mafodotin. **Bortezomib:** Cases of herpes zoster reactivation and infection have been reported in patients receiving bortezomib. Associated with neutropenia that follows a cyclical pattern with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of subsequent cycle **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.	Participants with an active infection are excluded. Monitoring for infections and immediate treatment of immunosupression according to standard practice. 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. Participants on bortezomib will receive antiviral prophylaxis (*e.g.* acyclovir or other antiviral agent) according to institutional guidelines. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immune globulin may be indicated. Dose modification guidelines are provided in Section 6.
Keratopathy (changes to the corneal epithelium, potentially resulting in vision changes)	**Belantamab mafodotin:** Changes in corneal epithelium on ocular examination have been frequently observed with belantamab mafodotin and was most commonly associated with keratopathy (changes in the corneal epithelium upon examination), dry eyes, photophobia, blurred vision and changes in visual acuity. Participants with a history of dry eye were more prone to develop changes in the corneal epithelium. Based on available follow-up data, vision returned to, or near baseline in most cases.	Active monitoring of the corneal epithelium and visual acuity as outlined in the SoA. Evaluation and management by an eye care professional. Recommendations for dose delays / reductions and treatment stopping guidance are provided in Section 7.1.3 and Table 11

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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.	
Risks Related to Belantamab Mafodotin (not listed under potential overlapping toxicity)		
Infusion-related Reactions (IRR)	IRRs were reported in participants treated with belantamab mafodotin. Most IRRs were Grade 1 to 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 7.1.4.
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 chronic study. The renal changes were dose-dependent and reversible. Severe tubular degeneration/regeneration and marked glomerulonephritis as a result of immune complex disease associated with ADA led to the early euthanasia of 1 monkey following 5 weekly doses of 10 mg/kg. Increase albumin/creatinine ratio (albuminuria) has been reported in participants receiving belantamab mafodotin not indicative of disease progression, 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 criteria for increased serum creatinine and urinary albumin/creatinine ratio are provided in Section 7.
Risks Related to Daratumumab		
IRR	Severe and/or serious infusion reactions, including anaphylactic reactions.	Premedicate with antihistamines, antipyretics and corticosteroids as detailed in Section 6.1.4.1. and monitor participants during infusion. Interrupt daratumumab infusion for reactions of any severity and institute medical management as needed.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Recommendations for dose delays / reductions and treatment stopping guidance are provided in Section 7.1.4. Post-medicate patients with corticosteroid according to the guidance laid out in Section 6.1.4.1.
Interference with Serological Testing	Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (Indirect Coombs test), which may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. Determination of ABO and Rh blood type not impacted.	Participants receiving daratumumab will be typed and screened prior to daratumumab administration.
Thrombocytopenia/ Neutropenia	Daratumumab may increase neutropenia and thrombocytopenia induced by background therapy.	Hematologic panels will be routinely assessed as outlined in the SoA.
Viral Infections, Especially Herpes Zoster	Cases of herpes zoster infection have been reported in patients receiving daratumumab.	Patients assigned to Treatment Arm B will receive antiviral prophylaxis (for example acyclovir or other according to institutional guidelines) from C1D1 until 3 months after the completion of daratumumab treatment.
Risks Related to Bortezomib (not listed under potential overlapping toxicity with belantamab mafodotin)		
Allergic Reactions	Bortezomib is contraindicated for patients with hypersensitivity to bortezomib, boron, or mannitol, including anaphylactic reactions.	Participants with known hypersensitivity reactions to bortezomib, boron, or mannitol are not allowed on study. Bortezomib will be discontinued if such reactions are confirmed.
Peripheral Neuropathy	Bortezomib treatment causes a peripheral neuropathy that is predominantly sensory; however, cases of severe sensory and motor peripheral neuropathy have been reported.	Participants with ≥Grade 2 peripheral neuropathy at Screening excluded from study participation. Monitor for symptoms of neuropathy. Dose will be adjusted accordingly. Bortezomib administered subcutaneously to reduce risk of peripheral neuropathy.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hypotension	Incidence of hypotension (postural, orthostatic, and hypotension not otherwise specified [NOS]) was 8%.	Participants with a history of syncope, or receiving medications associated with hypotension, or dehydrated will be closely monitored. Adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics will follow the institutional guidelines.
Posterior Reversible Encephalopathy Syndrome (PRES)	PRES; formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has occurred in patients receiving bortezomib.	Discontinue bortezomib if PRES occurs. The safety of reinitiating bortezomib therapy in patients previously experiencing PRES is not known.
Gastrointestinal Toxicity	Treatment with bortezomib can cause nausea, diarrhea, constipation, and vomiting sometimes requiring use of antiemetic and antidiarrheal medications; ileus can occur.	Maintain adequate hydration; fluid and electrolyte replacement should be administered to prevent dehydration. Interrupt bortezomib for severe symptoms.
Hepatotoxicity	Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include hepatitis, increases in liver enzymes, and hyperbilirubinemia.	Only participants with well-preserved liver function per the inclusion/exclusion criteria will be allowed on study. Participants with chronic Hepatitis B and C excluded. Liver function tests will be monitored per SOA. Liver stopping criteria outlined in Section 7.1.2.
Tumor Lysis Syndrome (TLS)	TLS has been reported with bortezomib therapy.	Participants at risk for TLS (*e.g.* high tumor burden) will be monitored and appropriate precautions instituted per local practice.
Thrombotic Microangiopathy	Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/haemolytic uremic syndrome (TTP/HUS), have been reported in patients receiving bortezomib.	Monitor for clinical signs and symptoms potentially related to thrombotic microangiopathy. If suspected, stop bortezomib and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting bortezomib.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential for cardiotoxicity related to an inflammatory response	Acute development or exacerbation of congestive heart failure and new onset of decreased LVEF have occurred during bortezomib therapy, including reports in patients with no risk factors for decreased LVEF.	Participants with significant cardiac risk factors will be excluded from the study participation. Monitoring of cardiac parameters as clinically indicated. Treatment as medically indicated.
Seizures	Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.	Participants with a history of seizures or epilepsy, will be closely monitored. In the event of new onset or worsening seizures, consider interrupting bortezomib until a prompt and comprehensive diagnostic evaluation is conducted.
Progressive Multifocal Leukoencephalopathy (PML)	Very rare cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with bortezomib. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their first dose of bortezomib.	Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PML is suspected, patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue bortezomib if PML is diagnosed.
Risks Related to Dexamethasone (not listed under overlapping toxicity with belantamab mafodotin)		
Vaccination	Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.	Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted. Immunizations with live/ live-attenuated vaccines are not allowed in the study.
Allergic or Hypersensitivity Reactions	Contraindicated in patients who are hypersensitive to any components of this product. Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy.	Enrollment of participants with known hypersensitivity reactions to any component of the formulation is prohibited.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Endocrine	Hypothalamic-pituitary adrenal axis suppression with the potential for corticosteroid insufficiency after withdrawal of treatment.	Avoid rapid withdrawal of corticosteroids if used at high doses for a prolonged period.
Gastrointestinal	Use with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation, or GI bleeding.	Hematologic parameters will be monitored as outlined in the SoA. New cases of anemia should be fully investigated, including the possibility of GI bleeding.
Musculoskeletal	Decreased bone formation and increase bone resorption. Acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with neuromuscular disorders, or in patients receiving neuromuscular blocking drugs.	Ongoing monitoring of AEs.
Neuropsychiatric	Psychic derangements ranging from mild symptoms to severe depression, to frank psychotic manifestations. Existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.	Ongoing monitoring of AEs.
Potential for cardiotoxicity	Average and large doses of corticosteroids can cause elevation of blood pressure, sodium and water retention, and increased excretion of potassium.	Participants with significant cardiovascular risk factors will be excluded from study participation.
Risks from Study Procedures		
Bone Marrow Aspiration/biopsy	Pain, infection, bleeding may occur after the procedure.	Participants will be treated according to institution's practice.
Incidental Findings During Imaging Data Acquisition	During the acquisition of imaging data (*e.g.*, MRI, PET-CT), non-MM disease or drug-related clinical abnormalities could be found by the radiographer performing the exams.	All imaging scans will be reported at the site by a radiographer (non-anonymized) for non-MM disease or drug-related clinical abnormalities.

Refer to the belantamab mafodotin Investigator's Brochure and local/regional prescribing information (where available) for daratumumab, bortezomib and dexamethasone, for further information.

2.3.2. Benefit Assessment

The FTIH study BMA117159, as of 31 August 2018, indicated that belantamab mafodotin monotherapy administered at 3.4 mg/kg is active in patients with RRMM (n=35), with an ORR of 60.0% (95% CI: 42.1, 76.1) and a median PFS was 12.0 months (95% CI: 3.1, NR) in a heavily pre-treated population (57% ≥5 prior lines of therapy) [Trudel, 2018; Trudel, 2019].

In the ongoing Phase II study 205678/DREAMM 2, the 2 single agent doses (2.5 mg/kg and 3.4 mg/kg) are being studied via a 2-arm, randomized design in participants who have failed at least 3 prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and who are refractory to an IMiD and a PI. Both dose levels, 2.5 and 3.4 mg/kg, have a positive benefit/risk profile. Overall, there were no new safety signals identified in the 205678 study, and the profile of adverse events was similar to the experience in DREAMM-1 for both arms. Primary analysis show both dose levels of belantamab mafodotin (2.5 and 3.4 mg/kg) to have a positive benefit/risk profile. The dose of 2.5 mg/kg appears to have a lower incidence of adverse events and less frequent dose delays and reductions, and it results in similar efficacy with 3.4 mg/kg dose as measured by ORR [Lonial, 2020].

Increased anti-myeloma activity has been demonstrated when additional agents, with individual activity, are given in combination with bortezomib and dexamethasone, including monoclonal antibodies. The combination treatment of a highly active drug, belantamab mafodotin, with bortezomib and dexamethasone is therefore expected to result in increased benefit to MM patients who have relapsed after at least 1 prior line of therapy, with improved patient outcomes as measured by progression-free survival.

The ongoing Phase I/II open-label, dose escalation and expansion study 207497 (DREAMM 6) is evaluating the safety and clinical activity of belantamab mafodotin when given in combination with Lenalidomide/Dexamethasone (Arm A) on a 28-day cycle, or with bortezomib/dexamethasone (Arm B) in participants with RRMM who have received at least 1 prior line of therapy. For Arm B (GSK2857916 with bor/dex), during Part 1 (dose escalation), CCI [redacted] Part 2 (dose expansion) of the study is further evaluating the safety and preliminary clinical activity of both the dose levels (2.5 and 3.4 mg/kg) and up to 2 dosing schedules of belantamab mafodotin (administered as SINGLE dose on Day 1 of each cycle, and administered as 2 equal divided doses a week apart on Day 1 and Day 8 of each cycle) with bor/dex. CCI [redacted]
For the current study Phase III study 207503, the dose of 2.5 mg/kg of belantamab mafodotin has been selected.

2.3.3. Overall Benefit: Risk Conclusion

Considering the observed clinical activity of belantamab mafodotin as a single agent in participants with RRMM, and the observed safety profile in mono- and combination therapy, it is reasonable to assume that the combination of belantamab mafodotin with bor/dex may offer additional benefit to patients with RRMM, by improving progression-free survival. Although there is the potential for overlapping toxicities, it is anticipated that belantamab mafodotin/bor/dex treatment will have an acceptable risk/benefit profile, with manageable toxicities. Considering the measures taken to minimize risk to participants, the potential risks associated with belantamab mafodotin in combination with bor/dex are justified by the anticipated benefits that may be afforded to participants with MM.

3. OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**[1]
Primary	
The primary objective of this study is to compare the efficacy of belantamab mafodotin in combination with bortezomib and dexamethasone (bor/dex) with that of daratumumab in combination with bor/dex in participants with RRMM	• Progression-Free Survival (PFS), defined as the time from the date of randomization until the earliest date of documented disease progression or death due to any cause
Key Secondary	
To compare the efficacy of belantamab mafodotin in combination with bor/dex with that of daratumumab in combination with bor/dex in participants with RRMM	• Overall Survival (OS), defined as the time from the date of randomization until 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 • Minimal Residual Disease (MRD) negativity rate, defined as the percentage of participants who are MRD negative by next-generation sequencing (NGS)
Secondary	
To further assess the efficacy of belantamab mafodotin in combination with bor/dex with that of daratumumab in combination with bor/dex in terms of other efficacy outcomes in participants with RRMM	• Complete Response Rate (CRR), defined as the percentage of participants with a confirmed complete response (CR) or better (i.e., CR, sCR) • Overall Response Rate (ORR), defined as the percentage of participants with a confirmed partial response (PR) or better (i.e., PR, VGPR, CR, sCR) • Clinical Benefit Rate (CBR), defined as the percentage of participants with a confirmed minimal response (MR) or better 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 confirmed PR or better • Time to Progression (TTP), defined as the time from the date of randomization until the earliest date of documented PD or death due to PD • PFS2, defined as time from randomization to disease progression 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

Objectives	**Endpoints**[1]
To evaluate the safety and tolerability of belantamab mafodotin when administered in combination with bor/dex	• Incidence of adverse events (AEs) and changes in laboratory parameters • Ocular findings on ophthalmic exam
To further describe the exposure to belantamab mafodotin when administered in combination with bor/dex	• Plasma concentrations of belantamab mafodotin, and cys-mcMMAF
To assess anti-drug antibodies (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 bor/dex	• Maximum post-baseline PRO-CTCAE score for each item attribute
To evaluate and compare changes in symptoms and health-related quality of life (HRQOL)	• Change from baseline in HRQOL as measured by EORTC QLQ-C30 and EORTC IL52 (disease symptoms domain from the EORTC QLQ-MY20)
Exploratory	
To further assess the efficacy of belantamab mafodotin in combination with bor/dex with that of daratumumab in combination with bor/dex in terms of additional efficacy outcomes in participants with RRMM	• 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 • VGPR rate, defined as the percentage of participants with a confirmed Very Good Partial Response (VGPR) or better (i.e., VGPR, CR, sCR) • Sustained MRD negativity rate: defined as the percentage of participants with MRD negativity confirmed by NGS minimum of one year apart, per IMWG criteria
To further evaluate the safety and tolerability of belantamab mafodotin when administered in combination with bor/dex	• Changes in safety assessments, including vital signs
To evaluate self-reported ocular symptomatic adverse effects of belantamab mafodotin in combination with bor/dex	• 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	• Change from baseline in EQ-5D-3L • Change from baseline in PGIS and change in PGIC over time
To further evaluate the impact of side effects on QOL	• Change from baseline in FACT-GP5

Objectives	**Endpoints**[1]
To assess imaging plus MRD-negativity rate	• Imaging plus MRD-negativity rate, defined as the percentage of participants who are MRD negative by NGS and who have no evidence of disease on PET-CT
To evaluate and compare healthcare resource utilization (HCRU)	• Number of office/outpatient/hospital clinic visits by specialty • 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]) • Use of supportive care medication
To further describe the pharmacokinetic of belantamab mafodotin when administered in combination with bor/dex	• Derived pharmacokinetic parameter values of belantamab mafodotin, and cys-mcMMAF, as data permit
To explore the exposure-response relationship between belantamab mafodotin exposure and clinical endpoints in participants treated with belantamab mafodotin in combination with bor/dex	• Belantamab mafodotin exposure (e.g., concentration, Cmax, or AUC) vs. efficacy and safety endpoints (e.g., PFS, ORR, CRR, corneal events)
Explore the relationship between clinical response and biologic characteristics including, but not limited to, BCMA expression on tumor cells and sBCMA concentrations	• Assess various biomarkers at baseline and on-treatment, by tumor and blood-based analysis of DNA, RNA, and protein including but not limited to evaluating baseline BCMA expression and/or immune status in tumor tissue and in the tumor microenvironment and/or serum soluble BCMA levels, and their relationship to clinical response

1. All categories of disease response (sCR, CR, VGPR, PR, SD, PD) used in the calculation of study endpoints will be determined by an IRC using IMWG 2016 criteria.

ADA = anti-drug antibodies; AE = adverse event; BCMA = B-cell maturation antigen; bor/dex = bortezomib/dexamethasone; CBR = Clinical Benefit Rate; CRR = complete response rate; DNA = deoxyribonucleic acid; DoR = duration of response; EORTC QLQ C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30 item Core module; EORTC IL52 = European Organisation for Research and Treatment of Cancer Item Library 52; HCRU = health care resource utilization; HRQoL = health-related quality of life; IMWG = International Myeloma Working Group; MRD = minimal residual disease; NGS = Next-generation sequencing; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; PRO-CTCAE = Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QOL = quality of life; RRMM = relapsed/refractory multiple myeloma; TTR = time to response; TTBR = time to best response; TTP = time to progression; VGPR = very good partial response.

4. STUDY DESIGN

4.1. Overall Design

- This is a multicenter Phase III, randomized, open-label study evaluating the efficacy and safety of the combination of belantamab mafodotin and bor/dex compared with the standard of care combination of daratumumab and bor/dex in participants with RRMM (Section 6.1).

- 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 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 (yes vs no), and the Revised International Staging System (R-ISS I vs II/III), and centrally randomized in a 1:1 ratio to either arm, as described in Section 6.1. No more than 50% of participants with 2 or more prior lines of treatment will be enrolled. No cross-over will be allowed.

- During the Treatment period, safety and disease assessments will be performed regularly according to the Schedule of Activities (Section 1.3) for each arm. Treatment will continue in both arms until progressive disease (PD), death, unacceptable toxicity, withdrawal of consent or end of study, whichever occurs first. Dose interruptions or reductions may be required to address potential drug-associated toxicities (see Section 6.6)

- For participants who discontinue study treatment for reasons other than PD, disease evaluations will continue to be performed every 3 weeks (±3 days) until confirmed PD (documented), death, start of a new anti-myeloma treatment, withdrawal of consent, loss to follow-up or end of the study (as defined in Section 4.4), whichever occurs first. In case of PD, participants will be followed to ascertain subsequent anti-myeloma therapy, progression on the subsequent line of therapy (PFS2), and survival status Q12W (±14 days) until withdrawal of consent, loss to follow-up, death or the end of the study.

- GSK may request that updated survival data be collected on all treated/randomized participants outside the protocol window noted in the Schedule of Assessments. 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.

4.2. Scientific Rationale for Study Design

Since their introduction, proteasome inhibitors (PIs) have led to substantial improvements in outcomes in MM [Kumar, 2014; Kumar, 2008; Richardson, 2007]. Bortezomib is the most frequently used PI approved for the treatment of MM [Velcade USPI, 2021; Velcade SmPC, 2020]. Bortezomib is administered in combination with dexamethasone as this combination has been shown to improve ORRs in MM [Dimopoulos, 2015; Kropff, 2005]. Studies have demonstrated that adding a third agent to bor/dex leads to improved patient outcomes, with acceptable safety profiles [Palumbo, 2016; Reeder, 2009; Richardson, 2010]. European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines recommend triplet combination regimens for induction therapy for fit patients with MM eligible for autologous stem cell transplant (ASCT), and triplet combinations are increasingly also preferred for RRMM [Moreau, 2017; NCCN, 2018].

The addition of the anti-CD38 monoclonal antibody daratumumab to bor/dex has demonstrated significant clinical benefit in patients with RRMM. The combination of daratumumab and bor/dex resulted in a 68% reduction in the risk of disease progression or death (PFS 16.7 vs 7.1 months, HR 0.31, 95% CI: 0.24, 0.39, p<0.001) and a 21% increase in ORR (84% vs. 63%, p<0.001) when compared to bor/dex alone [Spencer, 2018]. The addition of daratumumab to bor/dex was associated with a manageable safety profile, with increased rates of neutropenia and thrombocytopenia, and 45% of patients had infusion-related reactions [Palumbo, 2016]. Combination therapy with daratumumab/bor/dex is approved for the treatment of patients with RRMM and at least 1 prior line of therapy [see Darzalex USPI, 2019; Darzalex SmPC, 2020] and is a SoC regimen in RRMM, and hence an appropriate comparator [Moreau, 2017; NCCN, 2018].

Belantamab mafodotin has demonstrated strong single-agent activity in RRMM in a FTIH study, with an ORR of 60.0% (95% CI: 42.1, 76.1) and a median PFS of 12.0 months (95% CI: 3.1, NR) in a heavily pre-treated population (57% ≥5 prior lines of therapy) [Trudel, 2018; Trudel, 2019]. Belantamab mafodotin activity in monotherapy compares favorably to similar experience with daratumumab monotherapy, where an ORR of 29% (95% CI: 20.8, 38.9) and median PFS of 4.0 months (95% CI: 2.8, 5.6) were observed in a population with a median of 5 prior lines of therapy [Lonial, 2016].

In relapsed or refractory multiple myeloma (RRMM), doublet or triplet regimens utilizing agents with differing modes of action have dramatically improved outcomes, and are now the preferred options at first or subsequent relapses [Moreau, 2017; NCCN, 2018]. As described above, multiple studies have demonstrated that adding a third agent, including daratumumab, to bor/dex leads to improved patient outcomes with acceptable toxicity profiles [Palumbo, 2016; Reeder, 2009; Richardson, 2010].

Nonclinical data with belantamab mafodotin suggest CCI [redacted] It is therefore hypothesized that the combination of belantamab mafodotin and bor/dex will lead to greater patient benefit, as measured by progression-free survival (PFS), compared to the SoC combination of daratumumab and bor/dex. While there are some potential overlaps

in the pattern of identified toxicities between belantamab mafodotin and bor/dex (primarily hematologic), they are expected to be manageable.

The 2-arm design of this study will enable a comparison of the efficacy and safety of belantamab mafodotin/bor/dex vs daratumumab/bor/dex in RRMM. The primary endpoint is PFS, defined as the time from the date of randomization until the earliest date of documented disease progression, determined by a blinded IRC, or death, whichever occurs first. Studies have shown a strong correlation between improvements in PFS and resultant OS benefits in myeloma, including RRMM [Dimopoulos, 2017; 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. PFS as a primary endpoint has supported registration of several therapies for MM including the recent regulatory approvals of carfilzomib and daratumumab combination regimens in a similar patient population [Kyprolis SmPC, 2018; Darzalex USPI, 2019; Darzalex SmPC, 2020].

This study will evaluate a comprehensive panel of secondary endpoints (Section 3) including MRD negativity by NGS (key secondary), response rates, and OS (key secondary, defined as the time from the date of randomization until the date of death due to any cause).

An IRC consisting of experts within the field will determine disease response to ensure consistent and correct application of the IMWG criteria. In order to be able to determine disease response, IRC members will receive Central Laboratory disease assessment results as well as Electronic Case Report Form (eCRF) data, and Local Laboratory results where available.

An IDMC consisting of at least 2 physicians and 1 statistician, as defined in the IDMC Charter, will review data from the interim analysis. An interim analysis is planned based on CCI [redacted], allowing for early stopping due to efficacy. In addition, safety data will be reviewed periodically starting from when CCI [redacted], and then every CCI [redacted] or as requested by the IDMC thereafter. *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.

4.3. Justification for Dose

4.3.1. Belantamab Mafodotin Dose

The belantamab mafodotin monotherapy dose in RRMM has been chosen to be 2.5 mg/kg when administered on a Q3W schedule. This is based on the results from Study 205678 that evaluated 2 doses of belantamab mafodotin (2.5 mg/kg and 3.4 mg/kg) administered Q3W until disease progression in participants who have failed at least 3 prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and who are refractory to an IMiD and a proteasome inhibitor (n=218). Belantamab mafodotin monotherapy has generally been well tolerated, with manageable toxicities [Lonial, 2020]. The most frequent AEs (≥30% of participants) were corneal exam findings, cough, increased AST, thrombocytopenia/decreased platelet count, nausea, anemia, diarrhea, pyrexia, and chills (Section 2.2.4).

Belantamab mafodotin dose of 2.5 mg/kg Q3W is currently being evaluated in combination with bortezomib and dexamethasone in Study 207497 in RRMM participants who have failed at least 1 prior line of therapy. CCI [redacted] this combination dose has been shown to have an acceptable safety profile, with an adverse event profile consistent with each of the adverse event profiles for bortezomib, dexamethasone, and belantamab mafodotin monotherapy.

The pharmacokinetics of belantamab mafodotin were evaluated in combination with bortezomib and dexamethasone. CCI [redacted].

Based on this information, a dose of 2.5 mg/kg of belantamab mafodotin in combination with bortezomib and dexamethasone is planned for this study.

4.3.2. Daratumumab Dose

Daratumumab is an anti-CD38 monoclonal antibody approved in the US, EU and a number of other countries worldwide for the treatment of RRMM as both a mono- and combination therapy [Darzalex USPI, 2019; Darzalex SmPC, 2020].

Daratumumab will be administered at the approved dose for treatment as a combination therapy with bor/dex (refer to the most recently approved country-specific IV daratumumab label). For participants assigned to Treatment Arm B, daratumumab will be administered as an IV infusion at a dose of 16 mg/kg weekly for Cycles 1-3 (Weeks 1-9), then once every 3 weeks (Q3W) on Day 1 of Cycles 4-8 (Weeks 10-24), and every 4 weeks thereafter (C9+, Week 25 onwards). For the first daratumumab dosing in Week 1 only, in accordance with the local/regional label and institutional guidance and to facilitate administration, the single infusion on Day 1 may be split over 2 days (see Section 6.1.4 for details). Each participant's dose will be calculated based on the participant's weight to the nearest kilogram. For each daratumumab infusion, participants will receive pre-infusion and post-infusion medications to reduce the risk of infusion-related reactions as specified in Section 6.1.4.1.

4.3.3. Bortezomib Dose

Bortezomib is a proteasome inhibitor approved for use in patients with MM. In both treatment arms, bortezomib will be administered at the approved dose regimen for use in combination with dexamethasone, according to the most recently approved country-specific bortezomib label . This is also the approved regimen for use in combination therapy with daratumumab/bor/dex (refer to the most recently approved country-specific IV daratumumab label).

Bortezomib will be administered at 1.3 mg/m^2 SC on Days 1, 4, 8, and 11 of every 21-day cycle for a total of 8 cycles, according to the most recently approved country-specific bortezomib label.

At least 72 hours/3 calendar days 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 bortezomib, according to the most recently approved country-specific bortezomib label.

Dexamethasone will be administered at 20 mg, orally or IV, on Days 1, 2, 4, 5, 8, 9, 11, and 12 of every 21-day cycle for the first 8 cycles.

Starting dose of dexamethasone may be reduced to 10 mg for participants older than 75 years of age, who have a body-mass index of less than 18.5, who had previous unacceptable side effects associated with glucocorticoid therapy, or who are unable to tolerate the starting dose (For guidance on further dose modification, see Table 15 in Section 6.6.4).

Dexamethasone should be taken at the same time of the day and may be taken at home. Bortezomib plus dexamethasone will be administered according to institutional instructions.

4.4. End of Study Definition

A participant is considered to have completed the study if he or she is followed until death or the end of study.

End of study is defined as 5 years from Last Participant First Visit (LSFV), or when all participants have died, withdrawn consent, or have been lost to follow-up, whichever occurs first. At this time no further participant data will be collected.

5. STUDY POPULATION

The study will enroll adult participants with RRMM who have been previously treated with 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. Full criteria are included below.

5.1. Inclusion Criteria

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

1. Capable of giving signed informed consent as described in 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).
3. Confirmed diagnosis of multiple myeloma as defined by the IMWG criteria [Rajkumar, 2014].
4. Previously treated with at least 1 prior line of MM therapy, and must have documented disease progression during or after their most recent therapy. **Note:** induction + ASCT + maintenance is 1 line of therapy
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (Section 10.6).
6. Participants with a history of autologous SCT are eligible for study participation provided the following eligibility criteria are met:
   a. ASCT was >100 days prior to initiating study treatment, and
   b. No active bacterial, viral, or fungal infection(s) present.
7. Must have at least ONE aspect of measurable disease, defined as one the following:
   a. Urine M-protein excretion ≥200 mg/24h, 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).
8. All prior treatment-related toxicities (defined by National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI-CTCAE] v5.0) must be ≤ Grade 1 at the time of enrollment, except for alopecia.
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	
Absolute neutrophil count (ANC)[a]	≥1.0 × 10^9/L
Hemoglobin	≥8.0 g/dL
Platelets	≥75x10^9/L
Hepatic	
Total bilirubin	≤1.5xULN; (Isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
Alanine aminotransferase (ALT)	≤2.5xULN
Renal	
eGFR[b]	≥30 mL/min/1.73 m^2
Urine dipstick for protein 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)

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.

a. Without growth factor support, blood transfusion or platelet stimulating agents for the past 14 days, excluding erythropoietin.
b. As calculated by Modified Diet in Renal Disease (MDRD) formula (Section 10.7).

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

Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency (Section 10.3) during the intervention period and for 4 months after the last dose of belantamab mafodotin, 3 months from the last dose of daratumumab, and 7 months from the last dose of bortezomib, whichever is longer, and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

WOCBP must have a negative highly sensitive serum pregnancy test within 72 hours of dosing on C1D1.

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

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.

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 until 6 months after the last dose of belantamab mafodotin, and 4 months from the last dose of bortezomib, 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 with a WOCBP (including pregnant females).

5.2. Exclusion Criteria

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

1. Intolerant to daratumumab.
2. Refractory to daratumumab or any other anti-CD38 therapy (defined as progressive disease during treatment with anti-CD38 therapy, or within 60 days of completing that treatment).
3. Intolerant to bortezomib, or refractory to bortezomib (defined as progressive disease during treatment with a bortezomib-containing regimen of 1.3 mg/m^2 twice weekly, or within 60 days of completing that treatment). Note: participants with progressive disease during treatment with a weekly bortezomib regimen are allowed.
4. Ongoing Grade 2 or higher peripheral neuropathy or neuropathic pain.
5. Prior treatment with anti-BCMA therapy.
6. Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study drugs, or treatment with an investigational agent or approved systemic anti-myeloma therapy (including systemic steroids) within 14 days or 5 half-lives of receiving the first dose of study drugs, whichever is shorter.
7. Plasmapheresis within 7 days prior to the first dose of study drug.

8. Has received radiotherapy to a large pelvic area (check with sponsor). Bridging radiotherapy otherwise is allowed. NOTE: Disease assessment should be repeated if RT is done prior to first dose of study drug within screening window.
9. Prior allogenic stem cell transplant. NOTE – Participants who have undergone syngeneic transplant will be allowed, only if no history of GvHD.
10. Any major surgery within 4 weeks prior to the first dose of study drug. Exception allowed for bone stabilizing surgery after consultation with medical monitor.
11. Presence of active renal condition (infection, requirement for dialysis or any other condition that could affect participant's safety). Participants with isolated proteinuria resulting from MM are eligible, provided they fulfil criteria given in Table 6.
12. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions (including lab abnormalities) that could interfere with participant's safety, obtaining informed consent or compliance to the study procedures.
13. Evidence of active mucosal or internal bleeding.
14. Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal 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.
15. Previous or concurrent malignancies other than multiple myeloma, unless the second malignancy has been considered medically stable for at least 2 years. The participant must not be receiving active therapy, other than hormonal therapy for this disease. NOTE: Participants with curatively treated non-melanoma skin cancer are allowed without a 2-year restriction.
16. Evidence of cardiovascular risk including any of the following:
    a. Evidence of current clinically significant untreated arrhythmias, including clinically significant ECG abnormalities including second degree (Mobitz Type II) or third 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 functional classification system (Section 10.8).
    d. Uncontrolled hypertension.
17. Known immediate or delayed hypersensitivity reaction or idiosyncratic reaction to drugs chemically related to belantamab mafodotin, daratumumab, bortezomib, boron or mannitol or any other components of the study treatment.
18. Active infection requiring treatment.
19. Known 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).

20. Patients with Hepatitis B will be excluded unless the following criteria can be met.

Serology	Screening	During Study Treatment
HBcAb+, HbsAg-	• HBV DNA undetectable	• Monitoring per protocol (Table 18) • Antiviral treatment instituted if HBV DNA becomes detectable
HBsAg+ at screen or within 3 months prior to first dose	• HBV DNA undetectable • Highly effective antiviral treatment started at least 4 weeks prior to first dose of study treatment • Baseline imaging per protocol • Participants with cirrhosis are excluded	• Antiviral treatment maintained throughout study treatment • Monitoring and management per protocol (Table 18)

NOTE: presence of Hep B surface antibody (HBsAb) indicating previous vaccination will not exclude a participant.

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

22. Current corneal epithelial disease except for mild punctate keratopathy (Section 10.9).

23. Intolerance or contraindications to anti-viral prophylaxis.

24. Symptomatic amyloidosis, active POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma proliferative disorder, skin changes) or active plasma cell leukaemia at the time of screening.

5.3. Lifestyle Considerations

Contact lenses are prohibited for participants on Treatment Arm A (belantamab mafodotin/bor/dex) while on the study treatment (from first dose to EoT). Contact lens

use may be restarted after EoT after a qualified eye care specialist (Appendix 10) confirms there are no other contraindications. 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 identified as Screen Failures may be rescreened if the failure was based on elements of eligibility that may change, e.g., laboratory test results. Rescreening of a participant more than once requires discussion with the Medical Monitor. 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 7.

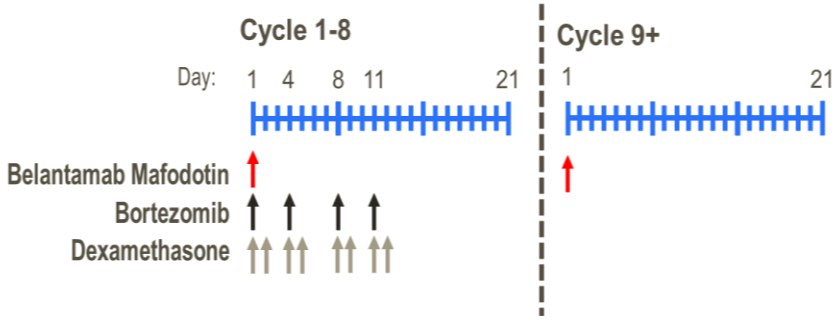
Table 7 Study Treatment

Product name	Belantamab mafodotin	Bortezomib	Daratumumab	Dexamethasone
Dosage form	Lyophilized powder for reconstitution	Lyophilized powder for reconstitution	Concentrate for solution for IV infusion	Tablet/ solution for IV infusion.
Dosage level(s):	2.5 mg/kg	1.3 mg/m^2	16 mg/kg IV (Split dosing (2 x 8 mg/kg IV) is only a possibility in W1)	20 mg oral or IV
Route of Administration	Intravenous infusion – 30 min- 60 min	Subcutaneous	Intravenous	Oral or Intravenous (has to be IV before first dose of daratumumab in Treatment Arm B)
Frequency of Administration	**Single dose:** IV infusion on Day 1 of each 21-day cycle	**Cycle 1 – 8:** Once daily on Days 1, 4, 8 and 11 of each 21-day cycle	**Cycle 1 – 3**: Once weekly of each 21-day cycle (Except split dosing possibility in W1) **Cycle 4 – 8:** Once every 3 weeks on Day 1 of each 21-day cycle **Cycle 9 onward:** Once every 4 weeks on day 1 of each 28-day cycle	**Cycle 1 – 8:** Once daily on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle

6.1.1. Treatment Arm A Dosing Schedule

The dosing schedule for Treatment Arm A (belantamab mafodotin in combination with bor/dex) is depicted in Figure 2.

Figure 2 Summary of Dosing Schedule for Treatment Arm A (Belantamab mafodotin/bor/dex)



Belantamab mafodotin will be administered intravenously (IV) at the recommended combination dose of 2.5 mg/kg on Day 1 (D1) of every 21-day cycle until confirmed PD, unacceptable toxicity, death, withdrawal of consent or study end, whichever occurs first. A window of ±3 days is acceptable for administration belantamab mafodotin after C1D1, but at least 21 days should elapse between consecutive planned doses of belantamab mafodotin. Ocular prophylaxis is required throughout treatment (Section 6.1.3.2).

Bortezomib 1.3 mg/m^2 will be administered subcutaneously (SC) on Days 1, 4, 8, and 11 of every 21-day cycle for a total of 8 cycles. Bortezomib should be administered approximately 1 hour after the belantamab mafodotin infusion is complete, assuming the participant is clinically stable.

Dexamethasone 20 mg (PO or IV) should be administered on the day of and the day after bortezomib treatment. For participants with contraindications or intolerance to this dose, refer to Section 6.6.4. On days where bortezomib and dexamethasone administration coincides with administration of belantamab mafodotin, dexamethasone should be administered PO or IV prior to the infusion of belantamab mafodotin.

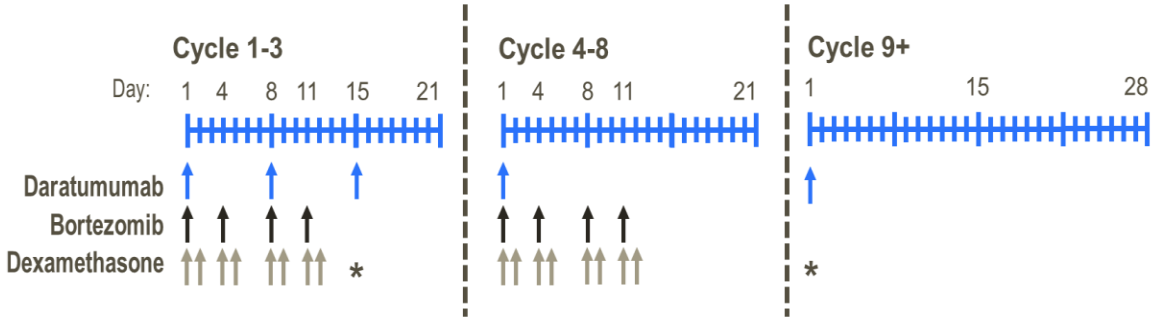
Efficacy assessments will be performed every 3 weeks (±3 days), irrespective of dosing. See Section 6.6 for guidance on dose modification and dose delays.

For details on Home Healthcare and Telemedicine Approaches, please refer to Appendix 15.

6.1.2. Treatment Arm B Dosing Schedule

The dosing schedule for Treatment Arm B (daratumumab in combination with bor/dex) is depicted in Figure 3.

Figure 3 Summary of Dosing Schedule for Treatment Arm B (Daratumumab/bor/dex)



* Corticosteroid is required as pre- and post-medication on the days when daratumumab is administered without bor/dex, as detailed in Section 6.1.4.1.

Daratumumab 16 mg/kg IV will be administered according to the approved label schedule in combination with bor/dex weekly for Cycles 1 through 3 (Weeks 1 to 9) (21-day cycles, total of 9 doses), on Day 1 of Cycles 4 thorough 8 (Weeks 10 to 24) (21-day cycles, total of 5 doses), and then every 4 weeks from Cycle 9 (Week 25) onwards (28-day cycles). For the first dose of daratumumab dosing at Week 1 only, in accordance with the label and institutional guidance and to facilitate administration, the single infusion of daratumumab may be split over 2 days (see Section 6.1.4 and the most recently approved country-specific IV daratumumab label).

Bortezomib 1.3 mg/m^2 will be administered SC on Days 1, 4, 8, and 11 of every 21-day cycle for a total of 8 cycles. Bortezomib should be administered approximately 1 hour after the daratumumab infusion is complete, assuming the participant is clinically stable.

Dexamethasone 20 mg (PO or IV) should be administered on the day of and the day after bortezomib treatment. Administration should be IV prior to the first dose of daratumumab. Starting dose of dexamethasone may be reduced to 10 mg for participants older than 75 years of age, who have a body-mass index of less than 18.5, who had previous unacceptable side effects associated with glucocorticoid therapy, or who are unable to tolerate the starting dose (For guidance on further dose modification, see Table 15, Section 6.6.4). On days where bortezomib and dexamethasone administration coincides with administration of daratumumab, dexamethasone should be administered prior to the IV infusion of daratumumab. Corticosteroids are required as part of pre/post-medication for daratumumab infusions (Section 6.1.4.1).

Efficacy assessments will be performed every 3 weeks (±3 days), irrespective of dosing. See Section 6.6 for guidance on dose modification and dose delays.

For details on Home Healthcare and Telemedicine Approaches, please refer to Appendix 15.

6.1.3. Belantamab Mafodotin

Belantamab mafodotin 2.5 mg/kg (Table 8) will be administered intravenously. See the Pharmacy Manual for further guidance on administration. The dose to be administered is based on actual body weight measurement on C1D1 prior to dosing. For subsequent dosing, if the change in body weight is ≤10% from C1D1 (prior to dosing), the dose does not need to be recalculated. However, if the change of body weight is >10%, the dose should be re-calculated based on the actual body weight at the time of dosing. The dose may be reduced to address toxicity according to protocol guidelines (Section 6.6).

Table 8 Administration of Belantamab Mafodotin

Product name	**Belantamab Mafodotin**
Dosage form	Powder for solution for infusion
Unit dose strength(s)/dose level(s)	100 mg / 2.5 mg/kg
Route/Administration/Duration	Intravenous use (see Pharmacy Manual)
Dosing instructions	Reconstitute belantamab mafodotin for injection, 100 mg with 2.0 mL of sterile water for injection, dilute with saline before use. Dilute belantamab mafodotin in normal 0.9% saline to the appropriate concentration for the dose [See the GSK document No. RPS-CLIN-051778]. Doses of belantamab mafodotin are to be administrated as an IV infusion via an infusion pump. See the Investigator's Brochure for compatible administration materials.

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 IRRs at first or any subsequent infusion with belantamab mafodotin.

On days where belantamab mafodotin administration coincides with bortezomib, dexamethasone may be administered IV or PO prior to belantamab mafodotin administration.

IRRs should be managed by guidelines provided in Section 7.1.4. 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 10.9. See the SoA (Section 1.3) for guidance on required monitoring for corneal toxicity.

Sites are required to establish a close collaboration with a qualified eye care specialist (Appendix 10) who will be responsible for assessing participants on Treatment Arm A, in close communication with GSK Medical Monitor and possibly a GSK ophthalmologist, and managing those who develop corneal toxicity.

Participants on Treatment Arm A will be assessed by a qualified eye care specialist (Appendix 10) at screening/ baseline, and then Q3W prior to dosing up to the sixth dose of belantamab mafodotin (assessment window of up to 5 days prior to dosing, but all effort should be made to schedule as close to belantamab mafodotin dosing as possible), as detailed in the SoA. If there are no significant ocular examinations findings, patient's symptoms or vision changes at or prior to the time of the sixth dose exam, participants may have their ophthalmologic exams decreased to once every 3 months. If a participant subsequently develops vision changes or other ocular symptoms, the participant should be promptly evaluated by a qualified eye care specialist. In case of persistent ophthalmic exam findings, newly developed ocular symptoms or vision changes at the sixth dose exam, the participants will have further ophthalmologic exams, at least every cycle until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by the qualified eye care specialist.

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 the end of treatment will continue to be followed by qualified eye care specialist at least every 3 months for up to 12 months or until resolution (to Grade 1 or baseline), whichever comes first.

Treatment related corneal events are to be graded according to the guidelines of the Keratopathy Visual Acuity (KVA) Scale (Appendix 9, Table 30). Dose modification guidelines and stopping criteria for belantamab mafodotin treatment-related corneal events based on KVA scale are provided in Table 11.

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 includes:

- Prophylactic preservative-free artificial tears must be administered in each eye at least 4-8 times daily, beginning on Cycle 1 Day 1 until the end of belantamab mafodotin treatment.
- At the start of each belantamab mafodotin infusion, participants may apply cooling eye masks to their eyes for as long as tolerated, up to 4 hours.

6.1.4. Daratumumab

Daratumumab 16 mg/kg should be administered as an intravenous infusion after dilution in 0.9% sodium chloride. The dose to be administered is based on actual body weight measurement on C1D1 prior to dosing. For subsequent dosing, if the change in body weight is ≤10% from C1D1 (prior to dosing), the dose does not need to be recalculated. However, if the change of body weight is >10% from C1D1 (prior to dosing), the dose should be re-calculated based on the actual body weight at the time of dosing.

Administer daratumumab intravenously at the infusion rate described in the local label. Consider incremental escalation of the infusion rate only in the absence of infusion reactions.

For the first daratumumab dosing at Week 1 only, in accordance with the local/regional label and institutional guidance and to facilitate administration, the single infusion of 16 mg/kg can be split into 2 infusions of 8 mg/kg administered on consecutive days (Day 1 and Day 2, see Table 2 and Section 6.1.4.1 below). If the Day 2 dose cannot be administered, it will not be made up. See the Pharmacy Manual and the most recently approved country-specific IV daratumumab label.

6.1.4.1. Daratumumab Required Pre/Post-medication

The administration of pre- and post-infusion medications to reduce the risk of IRRs for daratumumab should follow the guidance reported in the most recently approved country-specific IV daratumumab label.

6.1.4.2. Antiviral Prophylaxis

Antiviral prophylaxis is recommended in accordance with local prescribing information in participants being treated with bortezomib or daratumumab.

6.1.4.3. Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the participant's serum. The determination of a participant's ABO and Rh blood type are not impacted [Darzalex USPI, 2019; Darzalex SmPC, 2020].

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a participant has received daratumumab.

As specified in Table 19, participants on Treatment Arm B should undergo blood typing and screening prior to starting daratumumab, and should carry a card with their blood antigen profile with them at all times.

6.1.4.4. Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some participants with IgG kappa myeloma protein [Darzalex USPI, 2019; Darzalex SmPC, 2020].

Participants on Treatment Arm B with IgG Kappa MM are required to undergo further testing with a daratumumab-specific IFE assay (Section 1.3 and Section 8.1.2) in the following settings:

- VGPR with suspected CR
- CR with suspicion of PD (e.g increases in monoclonal protein as measured by SPEP that may or may not yet meet criteria for PD).

6.1.5. Bortezomib

Bortezomib 1.3 mg/m^2 SC will be administered on Days 1, 4, 8, and 11 of every 21-day cycle for a total of 8 cycles. Bortezomib should be administered approximately 1 hour after the belantamab mafodotin or daratumumab infusion is complete, assuming the participant is clinically stable. In participants who experience an IRR during or after belantamab mafodotin or daratumumab administration, the administration of bortezomib will be delayed until the IRR 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 [e.g.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 6.6.3 for more information.

At least 72 hours/3 calendar days should elapse between consecutive doses of bortezomib.

Sites for each injection should be rotated. New injections should be given at least 1 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 contained in package inserts.

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. Drug Interactions

For details on concomitant medications that can alter bortezomib exposure see Section 6.5.2.

6.1.6. Dexamethasone

Dexamethasone 20 mg PO or IV will be given on day of and day after bortezomib administration (Days 1, 2, 4, 5, 8, 9, 11, and 12) of every 21-day cycle for the first 8 cycles. The dexamethasone starting dose may be reduced at PIs discretion as described in Table 15, Section 6.6.4. Dexamethasone should be taken at the same time of the day and may be taken at home when administered PO.

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

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 Study Reference 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 Monitor and/or GSK study contact.

6.3. Measures to Minimize Bias: Randomization and Blinding

Open-label using central randomization via Interactive Response Technology (IRT) system	This is an open-label study; therefore, no blinding of treatment identity is needed for either Treatment Arm A or Treatment Arm B. However, to ensure trial integrity steps will be taken to restrict access to key information while the study is ongoing and prevent data aggregation except for where specified in the protocol. Upon completion of all the required screening assessments, eligible participants will be centrally randomized using a central Interactive Response Technology (IRT) system, RAMOS NG, by the investigator or authorized site staff. RAMOS NG allows study sites to register and randomize participants, and also records stratification information. Randomization list will be done centrally using a randomization schedule generated by the GSK Clinical Statistics Department in RandALL NG, which will assign participants in a 1:1 ratio to Treatment Arm A and Treatment Arm B. Separate randomization lists will be generated for any extension cohorts required.
Stratification	Stratification factors used for the stratified analyses are number of prior lines of therapy (1 vs 2 or 3 vs ≥4), prior bortezomib (yes vs no) and Revised International Staging System (R-ISS I vs II/III). No more than 50% of participants with 2 or more prior lines of treatment will be enrolled. 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.

Belantamab mafodotin and daratumumab 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 case report form (eCRF).

When participants self-administer oral study treatment(s) at home, dosing with dexamethasone 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 eCRF. 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 eCRF.

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. Concomitant medications administered after the EoT should be recorded for SAEs/AESIs as defined in Section 8.3. Any concomitant medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

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

The Medical Monitor should be contacted if there are any questions regarding concomitant 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, antidiarrheals, and analgesics, as appropriate. Concomitant therapy with bisphosphonates is allowed and recommended. See Section 6.1.4.1 for recommended concomitant therapies to be used with daratumumab.

Participants may receive local irradiation for pain or stability control.

Use of approved monoclonal antibody treatments for serious conditions unrelated to multiple myeloma, such as pre-exposure prophylaxis of COVID-19, may be permitted, but needs to be discussed with the GSK Medical Monitor.

While on study, a participant who is diagnosed with an unrelated malignancy that can be addressed by local therapy can remain on study, study treatment may be resumed as per investigator discretion after discussion with the GSK Medical Monitor. 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 are prohibited, with the following exceptions:

- Low dose prednisolone (≤10 mg/day) as substitution in participants with adrenal insufficiency.
- Short course (7 days) of steroids to manage an adverse event.

- Steroids to treat IRRs.
- Inhaled, intranasal, topical and topical ophthalmic steroids.

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

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 proteasome inhibitors). This is inclusive of all medications with activity against multiple myeloma and medications used for other indications that have anti-myeloma properties.
- Investigational agents other than belantamab mafodotin
- Inhibitors of P-gp and Organic Anion Transporting Polypeptide (OATP): Caution should be exercised when belantamab mafodotin is combined with strong inhibitors of P-gp. Strong inhibitors of OATP should be avoided unless considered medically necessary.
- See the SRM for more detailed information and a list of Prohibited Concomitant Medications.

<u>For participants receiving anti-HIV and anti-microbials</u>:

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

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

<u>For participants receiving bortezomib</u>:

- CYP3A4-inhibitors: Closely monitor when giving bortezomib in combination with potent CYP3A4-inhibitors. Co-administration with strong CYP3A4

inhibitors can increase bortezomib exposure by 35%. Monitor participants for signs of bortezomib toxicity and consider a bortezomib dose reduction, if necessary.
- CYP3A4 inducers: Strong CYP3A4 inducers are not recommended in combination with bortezomib. Co-administration with strong CYP3A4 inducers may decrease bortezomib exposure by 45% or more, which may reduce bortezomib efficacy.
- St. John's Wort (*Hypericum perforatum*) may decrease bortezomib exposure unpredictably and should be avoided.
- For further information see the most recently approved country-specific bortezomib label.

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 >42 days, the GSK Medical Monitor should be contacted to discuss the investigator's plan for 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 1 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.

6.6.1. Belantamab Mafodotin

The dose allowed for belantamab mafodotin may be reduced once from the starting dose (Dose Level -1). Participants not able to tolerate Dose Level -1, will permanently discontinue belantamab mafodotin treatment due to unacceptable toxicity (Section 7.1.1). Detailed guidance for belantamab mafodotin dose levels and AE-related dose modifications including dose modification guidelines for belantamab mafodotin treatment-related corneal events based on Keratopathy Visual Acuity (KVA) Scale (Appendix 9, Table 30) are shown in Table 9, Table 10, and Table 11. General guidance for belantamab mafodotin dose modifications and management of drug-related AEs otherwise unspecified is shown in Table 12. The guidance for dose delay is shown in Table 16.

Table 9 Dose Levels Belantamab Mafodotin: Treatment Arm A

Dose Level	**Belantamab Mafodotin Dose**
Starting Dose	2.5 mg/kg IV q21 days
Dose Level -1	1.9 mg/kg IV q21 days

Table 10 Dose Modification Guidelines for Adverse Events Associated with Belantamab Mafodotin

Toxicity	Grade/Symptoms	Recommendations
Serum creatinine Graded according to NCI-CTCAE criteria	Grade 2 >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	• Repeat within 48 hours if elevation cannot be explained by concomitant sepsis, TLS, other severe condition with fever or dehydration. • If confirmed: withhold belantamab mafodotin, initiate treatment and monitoring as clinically indicated, and follow for resolution. • Discuss any further dosing with Medical Monitor
	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 (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:[a] ○ Interrupt treatment with belantamab mafodotin ○ Repeat testing within 4 weeks ○ If spot urine ≤2000 mg/g (224 mg/mmol), may restart belantamab mafodotin with 1 dose level reduction ○ If spot urine remains >2000 mg/g (224 mg/mmol) after 4 weeks, consider permanently discontinuing belantamab mafodotin and provide treatment as clinically indicated and follow for resolution[a].
Urine dipstick for protein	2+	• May continue belantamab mafodotin dosing • Confirm by quantitative assessment using either albumin/creatinine (spot urine from first void) performed at a local lab (or at a central lab if local lab is not available) • If albumin/creatinine ≥2000 mg/g, at the next cycle follow guidance given 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 1 dose level reduction. Consider reverting to previous dose once thrombocytopenia recovered to Grade 2, or less. • With bleeding: withhold the dose, continue treatment after recovery with 1 dose level reduction. • Consider additional supportive treatment (e.g., transfusion), as clinically indicated and per local practice.
	Grade 4	• Withhold the belantamab mafodotin dose. Consider restarting with 1 dose level reduction if recovered to≤ Grade 3, only if there is no active bleeding at time of treatment restart

Toxicity	Grade/Symptoms	Recommendations
		• If thrombocytopenia is considered disease-related, is not accompanied by bleeding, and recovers with transfusion to >25 x10^9/L, continuing treatment with dose reduction may be considered after discussion with the Medical Monitor.
Afebrile neutropenia Graded according to NCI-CTCAE criteria	Grade 3-4 (Defined as ANC <1.0x10^9/L)	• If noted on Day 1 of any cycle, withhold belantamab mafodotin dose. • Resume belantamab mafodotin at pre-held dose once neutropenia recovers to Grade ≤ 2 (ANC ≥ 1.0x10^9/L) on Day 1 of a subsequent cycle. • Prophylactic antibiotics, per physician discretion and local institutional guidance. Consider growth factors. • Local guidance must be followed for hematological monitoring if more conservative than the protocol SoA specifications. • In cases of frequent recurrent neutropenia (ANC <1.0x10^9/L), consider dose reduction of 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 <1.0x10^9/L)	• Withhold belantamab mafodotin and immediately hospitalize participant with appropriate management, per local institutional guidance. • Consider additional supportive treatment per local practice (e.g. growth factors). • Upon recovery, consider dose reduction of belantamab mafodotin, if neutropenia was drug-related.
Infusion Reaction 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 Monitor. Continuation only allowed after recovery to ≤ Grade 1 and with premedication, 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, restart treatment with 1 dose level reduction. • If patient is already at the lowest dose level (1.9 mg/kg), then rechallenge with the same dose must be discussed with the medical monitor
	Grade 3-4	• Permanently discontinue treatment with belantamab mafodotin

a) Medical Monitor may consult GSK's nephrology panel about plans to continue therapy.

Table 11 Dose Modification Guidelines for Belantamab Mafodotin Treatment-Related Corneal Events based on KVA[1] Scale

Grade per KVA scale	Grade 1	Grade 2	Grade 3	Grade 4
Recommended Dosage Modifications[2]	Continue treatment at current dose.	Withhold belantamab mafodotin until improvement in **either** corneal examination findings **or** changes in BCVA to Grade 1 or better and resume at same dose.	Withhold belantamab mafodotin until improvement in **either** corneal examination findings **or** changes in BCVA to Grade 1 or better and resume at reduced dose (1 level)[3] Consider re-escalating after at least 2 ophthalmic assessments post treatment re-initiation, for events that do not worsen after resuming at lower dose and following benefit/risk assessment and discussion with the Sponsor.	Permanently discontinue belantamab mafodotin. Patient may be re-challenged on a case-by-case basis at a reduced dose after improvement and following benefit/risk assessment and discussion between the eye care specialist, the investigator, and the Sponsor.

BCVA = best corrected visual acuity; KVA = Keratopathy Visual Acuity.
1. Refer to Section 10.9, Appendix 9, Table 30 for Keratopathy Visual Acuity Scale for Treatment-related Corneal Events.
2. 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.
3. If already on reduced dose (1.9 mg/kg), participant should resume treatment at that dose.

Table 12 General Dose Modification and Management Guidelines for Drug-Related Adverse Events Not Otherwise Specified

Severity[a]	Management	Follow-up
Grade 1	• Administer symptomatic treatment as appropriate • Continue study drug(s)[b]	• Provide close follow-up to evaluate for increased severity, no dose modification necessary
Grade 2	• Administer symptomatic treatment • Investigate etiology • Consider consulting subspecialist, and/or diagnostic procedure	*Symptoms resolved in ≤7 days:* • Continue after resolution at the current dose *Symptoms ongoing >7 days or worsening*: • Delay study drug[c], or consider at the same dose level • If recovery takes >3 weeks, consult GSK MM • If symptoms continue or worsen to Grade 3-4, see below

Severity[a]	Management	Follow-up
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 MM. **Exceptions**: Participants who develop Grade 3 toxicities which respond to standard treatment and resolve to ≤Grade 1 within 48 hours may continue treatment at scheduled dose
Grade 4	• Provide appropriate medical treatment • Consider consulting subspecialist • Discuss with Sponsor/Medical Monitor	• Interrupt treatment. • Further treatment with belantamab mafodotin only allowed on individual basis if in the discussion with MM it is agreed that benefits outweigh the risks for a given participant

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

6.6.2. Daratumumab

Detailed guidance for daratumumab dose delays is shown in Table 17. No daratumumab dose modifications are permitted, in line with the most recently approved country-specific IV daratumumab label.

The daratumumab dose should be delayed if any of the following criteria are met:

- Grade 4 hematologic toxicity, or Grade 3 or higher thrombocytopenia with bleeding
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea or Grade 3 vomiting that responds to antiemetic treatment
  - Grade 3 diarrhea that responds to antidiarrheal treatment
  - Isolated Grade 3 gamma-glutamyltransferase elevation
  - Grade 3 fatigue or asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab.

Daratumumab dosing should be resumed when the toxicity has resolved to ≤ Grade 2. See Table 17 for guidance on treatment windows.

For guidance on infusion-related reactions see Section 7.1.4.

6.6.3. Bortezomib

Detailed guidance for bortezomib dose reductions and delays is shown in Table 16 and Table 17.

If the decision is made to permanently discontinue bortezomib, but belantamab mafodotin (Arm A) or daratumumab (Arm B) treatment continues, a participant may remain in the trial and continue treatments and assessments as described in the SoA (Section 1.3).

Dose adjustments should be based on the highest grade of toxicity that is attributed to bortezomib. Bortezomib therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological toxicities excluding neuropathy. Once the symptoms of the toxicity have resolved, bortezomib therapy may be reinitiated at a reduced dose per approved labeling [Velcade USPI, 2021], as described in Table 13 and Table 14.

Table 13 Dose Levels for Bortezomib

Dose Level	Bortezomib Dose
Starting Dose	1.3 mg/m^2
Dose Level -1	1.0 mg/m^2
Dose Level -2	0.7 mg/m^2
Dose Level -3	Discontinue bortezomib

Table 14 Dose Modification Guidelines for Hematologic and Other Toxicities Associated with Bortezomib and Dexamethasone Treatment

Toxicity	Grade[a]	Recommendations
Hematological toxicity[b]	Grade ≥ 4	• Withhold bortezomib therapy until symptoms of toxicity have resolved. • 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).
Non-hematological toxicities (excluding peripheral neuropathy)[b]	Grade ≥3	• Withhold bortezomib therapy until symptoms of toxicity have resolved. Then, bortezomib may be reinitiated with a 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 and in Table 5 of the package inserts [Velcade USPI, 2021]
Peripheral neuropathy[c]	Grade 1	• Defined as clinical or diagnostic observations only • Grade 1 Asymptomatic, without pain or loss of function – No action needed • Grade 1 with pain: reduce bortezomib dose to 1 mg/m^2
	Grade 2	• Defined as moderate symptoms; limiting instrumental Activities of Daily Living (ADL)[d] • Grade 2 with no pain: reduce bortezomib dose to 1 mg/m^2 • Grade 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	• Defined as severe symptoms; limiting self-care ADL[e] • Grade 3: 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	• Defined as life-threatening consequences; urgent intervention indicated • Discontinue bortezomib

a. Grading based on NCI-CTCAE v5.0.
b. Criteria and recommendations taken from Section 2.6 and Table 2 of the package inserts [Velcade USPI, 2021].
c. Criteria and Recommendations for Peripheral Neuropathy are taken from Section 2.7 and Table 5 of the package inserts [Velcade USPI, 2021].
d. Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc.
e. Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
d. Data source: Table 2, Table 5 and Section 2.6 of the package inserts [Velcade USPI, 2021].

6.6.4. Dexamethasone

Starting dose of dexamethasone may be reduced to 10 mg for participants older than 75 years of age, who have a body-mass index of less than 18.5, who had previous unacceptable side effects associated with glucocorticoid therapy, or who are unable to tolerate the starting dose (For guidance on further dose modification, see Table 15).

For participants with contraindications to the starting dose regimen of dexamethasone in combination with bortezomib, or who are intolerant to this regimen, the dose of dexamethasone can be reduced to Dose Level -1. If Dose Level -1 is not tolerated, the dexamethasone dose can be reduced to Dose Level -2. If this is also not tolerated, dexamethasone should be discontinued (Table 15).

Table 15 Permitted Dose Reductions for Dexamethasone in Both Arms

Dose Level	≤75 years of age	>75 years of age, BMI ≤ 18.5 Kg/m^2
Starting dose	20 mg	10 mg
Dose level -1	12 mg	6 mg
Dose level -2*	8 mg	4 mg

*Dexamethasone could be reduced further than Dose Level -2 per investigator discretion.

If bortezomib dosing is delayed or discontinued, dexamethasone dosing could continue per investigator discretion and local institutional guidelines.

In Arm B, corticosteroid should be given prior to each daratumumab infusion as described in Section 6.1.4.1.

6.6.5. Guidance on Dose Delays for Treatment Arm A and B

Table 16 and Table 17 provide guidance on dose delays for Treatment Arm A and Treatment Arm B, respectively.

A cycle is defined as a planned dosing period in which any study treatment (belantamab mafodotin (Arm A) or daratumumab (Arm B), and/ or bortezomib, dexamethasone is administered (and can be either 3 weeks or 4 weeks in duration). The start of a cycle is the date the first study treatment agent is administered; a cycle has not started unless a study treatment agent has been administered.

In any dosing delay scenario, Q3W assessments should continue to be carried out as described in the SoA. For treatment delays within the treatment window, subsequent treatment dates will not be adjusted.

In Arm B, if there are dosing delays, the switch to Q4W dosing for daratumumab will be after 14 doses of daratumumab (as per the daratumumab label), or after 8 full or truncated cycles of bortezomib, whichever is soonest.

Table 16 Dose Delays for Treatment Arm A (Cycles 1-8 only)

Scenario	Actions for Belantamab Mafodotin	Actions for bortezomib
1. Delay of only belantamab mafodotin	After Cycle 1, a window of ±3 days is acceptable for belantamab mafodotin dosing. Outside this window, treatment should be given on D1 of the next planned cycle.	Continue bortezomib according to the regimen outlined in the SoA, until completion of 8 full or truncated cycles of bortezomib.
2. Delay of only bortezomib	Continue belantamab mafodotin according to the regimen outlined in the SoA.	Bortezomib should be administered on the planned treatment day. If treatment cannot be administered as planned, when a participant is ready to resume treatment, bortezomib may be re-started at the appropriate point in the planned dosing regimen, e.g., if the participant is unable to receive bortezomib on D1 and D4 of a given cycle, treatment could resume on D8 or D11, and missed D1 and D4 doses will not be made up.
3. Delay of both belantamab mafodotin and bortezomib ≤21 days (Cycles 1-8)	Bortezomib can be resumed at the appropriate point in the cycle, e.g., in Cycles 1-8, if the participant is unable to receive bortezomib on D1 and D4, resume treatment with bortezomib on D8 or D11. Belantamab mafodotin should be administered on D1 of the next planned cycle. Visits and assessments should continue to occur as specified in the SoA until treatment is restarted.	
4. Delay of both belantamab mafodotin and bortezomib >21 days (Cycles 1-8)	Follow the guidance as outlined in Scenario 1 above.	Follow the guidance as outlined in Scenario 2 above.

Table 17 Dose Delays for Treatment Arm B (Cycles 1-8)

Scenario	Actions related to daratumumab	Actions related to bortezomib
1. Delay of only daratumumab	For Cycles 1-3, a window of ±1 day is acceptable for daratumumab dosing. After Cycle 3, a window of ±3 days is acceptable for daratumumab dosing. Outside these windows, treatment should be given on the next planned dosing day. If 8 cycles of bortezomib are administered without all 14 planned doses of daratumumab being administered, participants should move to the Q4W daratumumab dosing regimen.	Continue bortezomib according to the regimen outlined in the SoA. If 8 full or truncated cycles of bortezomib are administered without all 14 planned doses of daratumumab being administered, participants should move to the Q4W daratumumab dosing regimen.
2. Delay of only bortezomib	Continue daratumumab according to the regimen outlined in the SoA.	Bortezomib should be administered on the planned treatment day. If treatment

Scenario	Actions related to daratumumab	Actions related to bortezomib
	Switch to Q4W administration of daratumumab when either 8 full or truncated cycles of bortezomib have been administered OR after 14 doses of daratumumab have been administered, whichever is soonest.	cannot be administered as planned, when a participant is ready to resume treatment, bortezomib may be re-started at the appropriate point in the planned dosing regimen, e.g., if the participant is unable to receive bortezomib on D1 and D4 of a given cycle, treatment could resume on D8 or D11, and missed D1 and D4 doses will not be made up.
3. Delay of both daratumumab and bortezomib ≤21 days (Cycles 1-8)	Bortezomib can be resumed at the appropriate point in that cycle, e.g., in Cycles 1-8, if the participant is unable to receive bortezomib on D1 and D4, resume treatment with bortezomib on D8 or D11. Daratumumab should be administered on the next planned dosing day (e.g., in Cycles 1-3, on either D1, D8 or D15 and in Cycle 4 onwards on D1 of the next cycle). Visits and assessments should continue to occur as specified in the SoA until treatment is restarted.	
4. Delay of both daratumumab and bortezomib >21 days (Cycles 1-8)	Follow the guidance as outlined in Scenario 1 above.	Follow the guidance as outlined in Scenario 2 above.

6.6.6. 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 Monitor is required prior to enrolment into the study for participants with positive titres to Hepatitis B.

- Participants should be monitored according to SoA Table 4.

- Participants who experience clinically significant elevations in liver chemistry should follow liver event monitoring and stopping criteria (Section 7.1.2 and Appendix 4), 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 Monitor should be contacted for any participant who develops detectable HBV DNA levels.**

Table 18 Dose Modification Guideline for Hepatitis B Reactivation

Toxicity	Grade/description of toxicity	Recommendations
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 Medical Monitor must be obtained prior to further dosing of study treatment • Follow liver monitoring/stopping guidelines per protocol for elevation in liver function tests.

6.7. Intervention After the End of the Study

There is no planned intervention following the EOS. The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition.

Participants who have not progressed at the time of the final OS analysis (EOS) may be offered belantamab mafodotin for further treatment until progression or unacceptable toxicity, if considered appropriate based on the study results.

Refer to the SoA for follow-up assessments of participants who are to be followed for disease progression and survival after they permanently discontinue from study treatment.

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:

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

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.

Note: As per IMWG criteria: All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed.

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
- All or part of the study is closed or terminated

If the participant voluntarily discontinues from treatment due to toxicity, the adverse event (AE) will be recorded as the primary reason for permanent discontinuation on the electronic case report form (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 End of Treatment (EOT) follow-up as specified in Table 1 or Table 2.

All participants must be followed for survival, up to the end of study 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. Where permitted, data from publically available death registers will be used for participants withdrawn from study or lost to follow-up prior to death.

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. Where permitted, public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

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.

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:

- Disease progression according to IMWG criteria
- New anti-myeloma therapy is initiated
- 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 the end of study (as described in Section 4.4), whichever occurs first.

7.1.1. Discontinuation of Individual Components of Combination Study Treatment

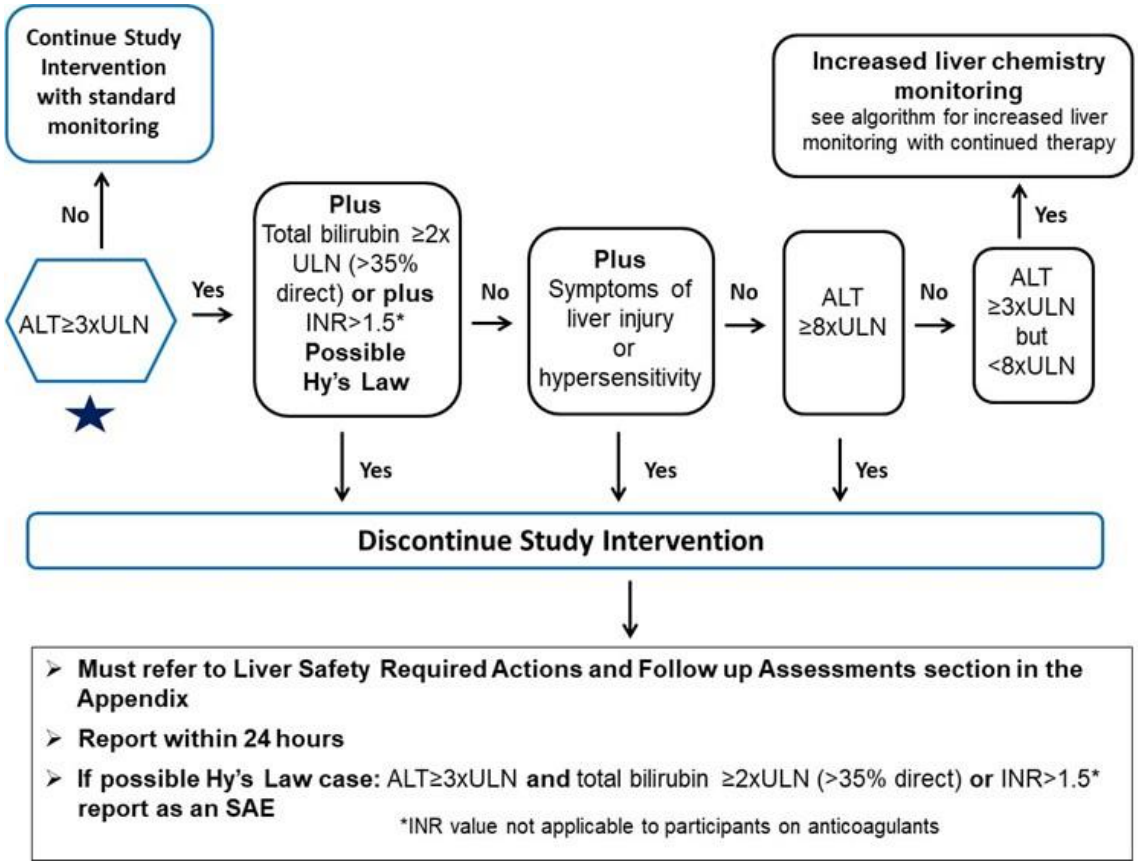
At the discretion of the investigator, participants meeting the stopping criteria for bortezomib and dexamethasone may continue belantamab mafodotin (Arm A) or daratumumab (Arm B) monotherapy until PD, unacceptable toxicity, or death occurs or end of study. Similarly, participants meeting the stopping criteria for belantamab

mafodotin (Arm A) or daratumumab (Arm B) may continue bortezomib and dexamethasone until completion of 8 cycles (after which they should attend an End of Treatment Visit and be followed up according to the SoA), PD, unacceptable toxicity, or death (whichever occurs first). The primary reason for discontinuation of each study treatment must be documented independently in the medical record and on the eCRF.

7.1.2. Liver Chemistry Stopping Criteria

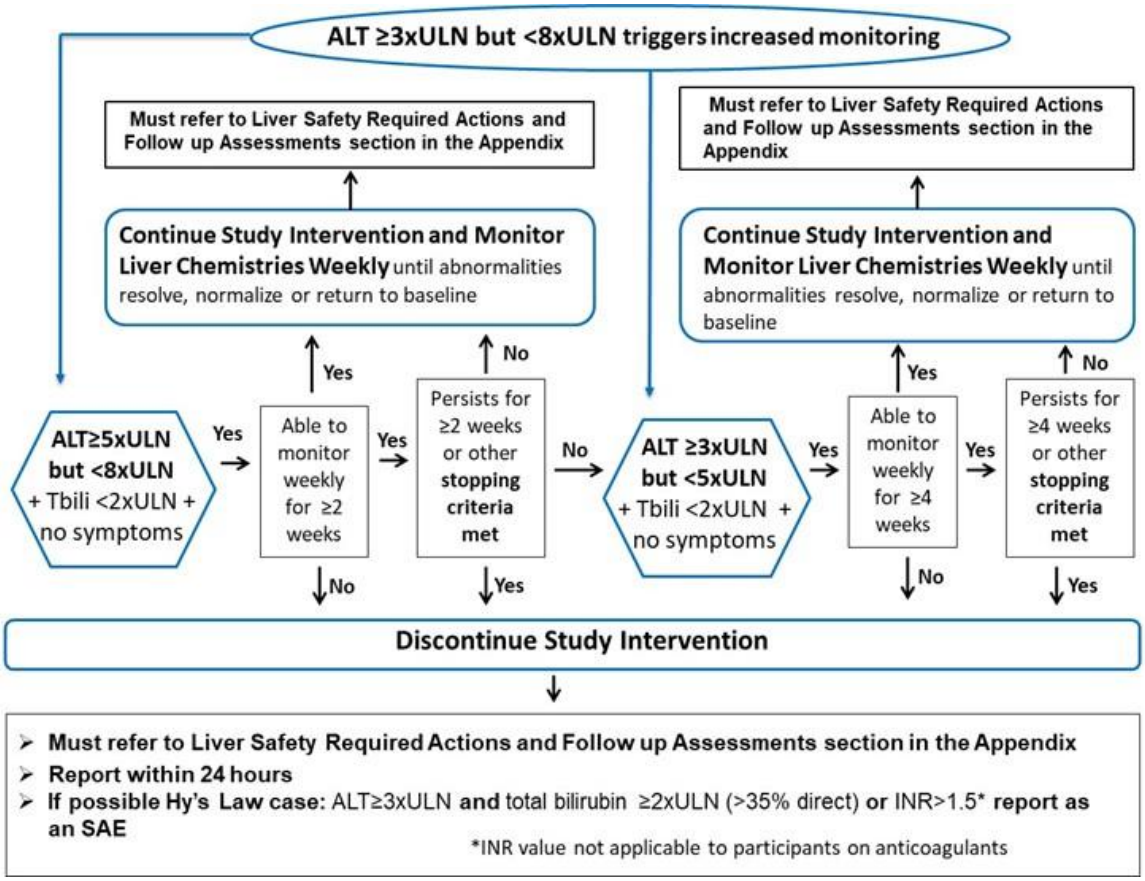
Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology. Discontinuation of study treatment for abnormal liver tests is required when the participant satisfies any of the stopping rules as shown in Figure 4.

Figure 4 Liver Stopping and Monitoring Event Algorithm (ALT ≥ 3xULN)



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 5 Liver Stopping and Monitoring Event Algorithm for ALT ≥ 3xULN but <8xULN



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.

7.1.2.1. 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/Independent Ethics Committee (IRB/IEC) approval is obtained, if required, and
- Separate ICF for study intervention restart/rechallenge is signed by the participant and participant is informed of any associated risks

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

Refer to Section 10.4 and the SRM for full guidance.

7.1.3. Corneal Event Stopping Criteria

Dose modifications and stopping criteria of belantamab mafodotin for treatment-related corneal events (Table 11) should be based on grading of corneal events according to the guidelines of Keratopathy Visual Acuity (KVA) Scale (Section 10.9, Appendix 9, Table 30).

Participants who develop Grade 4 corneal events according to the KVA Scale must be discussed in detail between the treating qualified eye care specialist (Appendix 10), the GSK Medical Monitor 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 (Table 11). If a participant is allowed to continue treatment, the dose of belantamab mafodotin will be reduced by 1 dose level (Section 6.6.1). The decision will be documented in study files, together with individual assessment of risk-benefit.

7.1.4. Infusion-Related Reactions Stopping Criteria

7.1.4.1. Belantamab Mafodotin

Premedication is not required prior to infusion unless deemed medically appropriate by the investigator following evaluation of infusion-related reactions (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.

7.1.4.2. Daratumumab

Pre/post-medication should be given for every daratumumab infusion as described in Section 6.1.4.1.

For infusion reactions of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or permanent discontinuation of study treatment as outlined in the most recently approved country-specific IV daratumumab label and below.

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the participant does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate up to

the maximum rate of 200 mL/hour (refer to Pharmacy Manual and local/regional label [if applicable] for infusion rates).

- Grade 3 (severe): Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the participant does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in the Pharmacy Manual and local/regional label (if applicable) for infusion rates. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion reaction.

- Grade 4 (life threatening): Permanently discontinue daratumumab treatment.

7.1.5. 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 Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons. This is expected to be uncommon.
- At the time of withdrawal from the study, if possible, an End of Treatment Visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the End of Treatment Visit.
- The participant will be permanently discontinued both from the study intervention and from the study at that time. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Withdrawn participants will not be replaced.

7.3. Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 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. Where permitted, public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.10.

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Demographic and baseline assessments will include year of birth, sex, race, and ethnicity.
- Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.1 and Section 5.2.
- Immediate safety concerns must be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, 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 within 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 C1D1 unless otherwise specified.
  - Safety labs completed within 72 hours of first dose do not need to be repeated on C1D1.
  - Pregnancy testing must be completed within 72 hours prior to first dose.

- Imaging must be completed within 30 days prior to first dose.
- On-study Q3W assessments have a ±3-day window.
- After C1D1, on-study ocular exams should be performed within 5 days prior to dosing.
- Follow-up Visits have a ±3-day window.
- Overall Survival Follow-up Visits have a ±14-day window.

For details on Home Healthcare and Telemedicine Approaches, please refer to Appendix 15.

A list of clinical laboratory tests required during the study is included in Table 19.

Table 19 List of Clinical Laboratory Tests

Hematology[1]			
Platelet count	**Red Blood Cell (RBC) Indices**: MCV, MCH, MCHC	**Automated WBC Differential**: Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils	
RBC count			
White blood cell (WBC) count (absolute)			
Hemoglobin			
Hematocrit			
Clinical Chemistry[1]			
Creatinine	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin
Glucose	Chloride	Alanine aminotransferase (ALT)	Uric acid
Sodium	Total bicarbonate	Gamma glutamyl transferase (GGT)	Albumin
Magnesium	Calcium	Alkaline phosphatase	Total protein
eGFR	Phosphorous	Creatine kinase (CK)	Lactate dehydrogenase (LDH)
Urine[1]			
Urine dipstick[6] for protein OR Spot Urine (from first void) for albumin/creatinine ratio[3]			
Other Laboratory Tests (as indicated in Section 1.3)			
HbA1c[1]; Pregnancy Test (urine or blood)[1]; Follicle-stimulating hormone (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, Hepatitis C RNA test[1,3] (optional), blood type assessment[1], indirect antiglobulin test[1]. Note: Hepatitis C RNA testing is optional but must be done to determine participant eligibility if hepatitis C antibody positive.			
PK and ADA[2]			
Belantamab mafodotin pharmacokinetics (PK) Anti-drug antibodies (ADA) to belantamab mafodotin			
Disease Evaluation Laboratory Tests			
Urine protein electrophoresis (UPEP)[2]	Serum immunofixation[2]	Ca corrected for albumin (serum)[2]	
Serum protein electrophoresis (SPEP)[2]	Urine immunofixation[2]	IgG, IgM, IgA, IgD/IgE[2,4]	

Serum kappa/lambda free light chain (FLC) ratio[2]	24-hour urine collection for M protein[2]	Beta-2 microglobulin[2]	
Biomarker Measurements[2]			
sBCMA (serum), cfDNA (plasma)			
Optional Testing[2,5]			
Pharmacogenomics sample[5]			

1. To be performed at local laboratory.
2. To be performed at central laboratory.
3. If not available locally it can be performed centrally. Spot Urine (albumin/creatinine) testing: i) does not need to be repeated on C1D1 if conducted within 7 days of C1D1 dosing (in case of screening assessment), and ii) does not need to be repeated on D1 of subsequent cycles if conducted within 5 days of D1 dosing of a given cycle (C2 onwards).
4. Only for participants with IgD/E myeloma.
5. Informed consent for optional samples (genetic research) must be obtained before collecting a sample.
6. Urine dipstick for protein should be performed at a local lab (If albumin/creatinine ratio not available locally, then at a central lab). Albumin/Creatinine ratio needs to be done in any patient with urine dipstick protein result of ≥1+ (for screening), and in any patient with ≥2+ (on study) or with positive protein if urine dipstick protein quantification is not available.

8.1. Efficacy Assessments

The primary endpoint of this study is PFS. 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 biopsy) at screening and to confirm CR/sCR. Additional BM testing if CR is achieved: biopsy for immunohistochemistry (IHC) to confirm sCR. BM aspirate for MRD at screening and at MRD assessments (Section 8.1.3).
- PET-CT is required for participants that achieve MRD-negative status, at the time of achieving this status (within 42 days [6 weeks] of the availability of MRD results) (Section 8.1.3).
- Imaging of extramedullary disease (in participants with extramedullary disease) or if a new lesion is suspected for confirmation of progressive 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 Uniform Response Criteria for Multiple Myeloma [Kumar, 2016].

Baseline serum/urine disease assessment will be completed during the Screening period (within 28 days prior to the first dose of study treatment) and baseline imaging within 30 days prior to the first dose of study treatment. On study serum and urine-based assessments (M-protein, FLC, ± immunofixation) will be performed every 3 weeks. Details for the preparation and shipment of samples for central laboratory assessments will be provided in the Lab 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 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 of laboratory parameters must be performed from a different blood collection either on the same day, or 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 the End of Treatment 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 progressive disease 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], as determined by a blinded IRC, as well as by the investigator.

8.1.2. Assessment of CR Where Daratumumab Interference is Suspected

Daratumumab is an IgG kappa monoclonal antibody that can be detected in serum electrophoresis and immunofixation assays. This can have an impact on the detection of CR and/or disease progression in participants who achieve CR/sCR with IgG kappa myeloma. Participants in Arm B with IgG kappa myeloma and suspected PD, or with VGPR and suspected CR, are required to undergo central testing with a daratumumab-specific immunofixation assay to confirm PD or CR/sCR (see Lab Manual for further details).

8.1.3. MRD Assessment and PET-CT Imaging

Targeted next generation sequencing (NGS) will be used to assess minimal residual disease (MRD) status, utilizing a central testing lab. After the initial MRD sample collection during Screening, further MRD testing should first take place when a participant first achieves a confirmed response of VGPR, and every 6 months from the time of last sample collection until disease progression or suspected CR. In case of deepening response from VGPR to suspected CR (e.g. negative immunofixation by serum and urine, disappearance of any soft tissue plasmacytomas if present at Screening, normal FLC ratio for patients whose only measurable parameter at Screening is serum FLC), MRD testing should be performed at the time of achieving suspected CR and repeated every 6 months from the time of last sample collection, until PD. Response evaluation will be performed according to the IMWG Uniform Response Criteria for Multiple Myeloma [Kumar, 2016]. For participants who are MRD negative by NGS (at 10^{-5} sensitivity threshold), a PET-CT will be performed within 42 days (6 weeks) of confirming MRD negativity to assess for absence of disease on imaging.

MRD samples could be analyzed once collected as long as date and time information is collected.

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 exams
- ECOG performance status
- Clinical chemistry, hematology, and other laboratory tests (Table 19)
- Serum beta-human chorionic gonadotropin (β-HCG) pregnancy test for female participants of childbearing potential only
- 12-lead ECG at Screening.
- Patient-Reported Outcome Version of Common Toxicity 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 the Ocular Surface Disease Index (OSDI, [Schiffman, 2000]).

8.2.1. Physical Examinations

At screening, on dosing days, and at EoT Visit a full physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, lungs, cardiovascular, neurological, 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 Eastern Cooperative Oncology Group (ECOG) scale provided in 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 where vital sign time points align with blood sampling time points, vital signs should be assessed prior to blood samples being drawn. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

8.2.3.1. Vital Sign Measurement for Treatment Arm A

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

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

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

Vital signs should be assessed for bortezomib as clinically indicated.

8.2.3.2. Vital Sign Measurement for Treatment Arm B

For Treatment Arm B, vital signs are to be measured at the following time points at the time of first daratumumab administration:

- Within 30 mins prior to Start of Infusion (SOI)
- At 30 mins, 2 hours, and 3 hours 30 mins after the start of the infusion (±10 mins)

- Within 15 mins of EOI
- 30 minutes, 1 hour, and 2 hours after EOI (±10 mins)

On Cycle 1 Day 1, if daratumumab administration is split and given over Day 1 and Day 2, vital signs are to be measured on both Day 1 and Day 2 as per above time points.

For all other daratumumab infusions, blood pressure will be measured within 30 mins prior to SOI and within 15 mins after EOI, and as clinically indicated.

Vital signs should be assessed for bortezomib as clinically indicated.

8.2.4. Electrocardiogram

A 12-lead electrocardiogram (ECG) is obtained at screening as specified in the Schedule of Activities. The ECG machine should automatically calculate the heart rate and measure PR, QRS, QT, and QTc intervals according to Fridericia's formula (QTcF). No further ECGs are required, but if obtained as part of medical care a 12-lead ECG should be performed by qualified personnel at the site after the participant has at least a 5-minute rest.

Triplicate ECG should be performed if during treatment QTcF is >530 msec.

Where triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicate ECGs should be completed in 4 minutes or less.

Whenever vital signs, 12-lead electrocardiograms (ECGs), and blood draws are scheduled for the same nominal time, the 12-lead ECG should be performed first.

8.2.5. Clinical Safety Laboratory Assessments

Clinical laboratory tests to be performed are listed in Table 19. 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 SRM/Clinical Lab Manual.

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

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

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

8.2.6. Ophthalmic Assessments

Study sites must establish a close collaboration with a qualified eye care specialist (Appendix 10) who will be responsible for assessing participants while they are on study and managing participants who develop corneal changes associated with belantamab mafodotin. Management of participants with corneal findings must be performed in close communication with the GSK Medical Monitor and the coordinating eye care specialist.

Participants will be assessed by a qualified eye care specialist (Appendix 10) at screening/baseline in both arms.

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

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

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

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

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

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

8.2.6.1. Treatment Arm A

Participants will be assessed by a qualified eye care specialist at screening/baseline and then Q3W prior to dosing up to the sixth dose of belantamab mafodotin (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 at or prior to the time of the sixth dose exam, participants may have their ophthalmologic exams decreased to once every 3 months.
- If a participant subsequently develops vision changes or other ocular symptoms, the participant should be promptly evaluated by a qualified eye care specialist.
- In case of persistent ophthalmic exam findings, newly developed ocular symptoms or vision changes at the sixth dose exam, the participants will have further ophthalmologic exams, at least every cycle until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by the qualified eye care specialist.

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

Participants with treatment-related ocular AEs at the End of Treatment Visit will be followed by the qualified eye care specialist (Appendix 10) at least every 3 months, for up to 12 months or until resolution (to Grade 1 or baseline), whichever comes first. These examinations are referred to as "follow-up visits".

8.2.6.2. Treatment Arm B

Ocular exam may be performed up to 5 days prior to dosing. On treatment ocular exams to be performed at Cycle 6 and then decreased to every 6 months (±4 week window) until and including eye exam at end of treatment. In case of persistent or newly developed ocular symptoms or vision changes, participants will have further ophthalmologic exams by a qualified eye care specialist (Appendix 10), as clinically indicated, until resolution (to Grade 1 or baseline).

Participants who have treatment-related ocular AEs present at the end of treatment will continue to be followed by qualified eye care specialist at least every 3 months, for up to 12 months or until resolution (to Grade 1 or baseline), whichever comes first.

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

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

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

8.2.8. 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.

Women of child-bearing potential (WOCBP) must have a negative highly sensitive serum pregnancy test within 72 hours of dosing on C1D1. Participants with positive pregnancy test result must be excluded from the study. Participants with negative pregnancy test result must agree to use a highly effective method of contraception (with a failure rate of <1% per year) during the study and for 4 months following the last dose of belantamab mafodotin (Arm A), 3 months from the last dose of daratumumab (Arm B), and 7 months from the last dose of bortezomib whichever is longest.

Subsequent pregnancy testing on dosing days may be either by serum or urine testing. Each pregnancy test must be performed within 72 hours prior to dosing.

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 intervention 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.
- 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 eCRF, not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in 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.

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 AEs/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 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 has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for Suspected Unexpected Serious Adverse Reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAE) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Details of all pregnancies in female participants will be collected after the start of study treatment and for 4 months following the last dose of belantamab mafodotin, or 7 months for bortezomib, whichever is longest.

Details of pregnancies from female partners of male participants will be collected after the start of study treatment and for 6 months following the last dose of belantamab mafodotin or 4 months for bortezomib, whichever is longest.

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

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

8.3.6. Cardiovascular and Death Events

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

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

The CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific Cardiovascular section of the eCRF within 1 week of receipt of a CV event data query prompting its completion.

Death due to the disease under study is to be recorded on the Death eCRF.

8.3.7. Adverse Events of Special Interest

Adverse events of special interest (AESI) for belantamab mafodotin are corneal events, thrombocytopenia and infusion-related reactions. Severity of all AESIs will be graded using National Cancer Institute-Common Toxicity Criteria for Adverse Events (CTCAE, v5.0). Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in Section 6.6. Dose modifications for belantamab mafodotin corneal events (Table 11) will be based on grading of corneal events according to the guidelines of Keratopathy Visual Acuity (KVA) Scale (Appendix 9, Table 30).

8.4. Treatment of Overdose

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

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

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

There is no known specific antidote for 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 USPI, 2021; Velcade SmPC, 2020].

There is no known specific antidote for daratumumab overdose. In the event of an overdose, the participant should be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment should be instituted immediately [Darzalex USPI, 2019; Darzalex SmPC, 2020].

An overdose or prolonged use of dexamethasone may exaggerate glucocorticoid adverse effects. Treatment should be symptomatic and supportive with the dosage of dexamethasone being reduced or slowly withdrawn where possible.

For further information, see the SRM for package inserts.

8.5. Pharmacokinetics

8.5.1. Belantamab Mafodotin Blood Sample Collection for Pharmacokinetics

In Treatment Arm A, blood samples for PK analysis of belantamab mafodotin (ADC with or without total monoclonal antibody) and cys-mcMMAF will be collected at the time points indicated in the SoA, Table 20, and Table 21. 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.

The first approximately 20% of participants in Treatment Arm A, as well as all participants from North East Asia receiving belantamab mafodotin, will undergo additional belantamab mafodotin PK sampling (Enhanced PK Cohort) according to the schedule in Table 20. For all remaining participants on Treatment Arm A, the samples

will be collected as per the Standard PK Collection schedule in Table 21. For further details, see the SRM.

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

Soluble BCMA (sBCMA) samples should be collected at all PK time points (according to either the standard or enhanced schedule, see Section 8.9.1, Table 22 and Table 23). All PK, sBCMA, and ADA samples, once collected (regardless of dosing), will be analysed 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 20 PK Schedule for Enhanced PK Collection (Treatment Arm A Only)

Dose/Day[1]	Timing	Comments
Dose1 Day1	Pre-dose	Within 30 min prior to Start of Infusion (SOI)
	End of Infusion (EOI)	Within 30 min after EOI
	2 hours after SOI	2 hours (±15 min) after C1D1 SOI
Dose 1 Day 1/Dose 1 Day2	24 hours after SOI on C1D1	24h (±2h) hours after Dose 1 SOI
Dose 1 Day 4	Prior to bortezomib administration	72h (±24h) hours after C1D1 SOI. If this coincided with a bortezomib administration day, PK sample should be taken prior to bortezomib administration.
Dose 1 Day 8 to Day15	1 sample on any one study day between C1D8 and C1D15	Any time between D8 and D15. If this coincided with a bortezomib administration day, PK sample should be taken prior to bortezomib administration.
Dose 2 Day 1	Pre-dose	Collect within 30 min prior to SOI If Cycle 2 belantamab mafodotin dose is delayed, 1 PK sample must be taken at Dose1 Day 22.
	EOI	Within 30 min after EOI
4th and 6th Belantamab Mafodotin dose	Pre-dose AND EOI	Within 30 min prior to SOI Within 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; for treatment beyond Dose 12, pre-dose samples will be collected every 6 doses (Dose 18, Dose 24, Dose 30 and so on, until the last sample at EOT).

Note: C = Cycle; D = Day; SOI = Start of Infusion; EOI = End of Infusion; h = hour; sBCMA = soluble BCMA; EOT = End of Treatment.

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 Vd continues.

Participants on Treatment Arm A not requested to undergo Enhanced PK sampling should follow the schedule for Standard PK assessments as laid out in Table 21.

Table 21 PK Schedule for Standard PK Collection (Treatment Arm A Only)

Dose/Day[1]	Timing	Comments
Dose 1 Day 1	Pre-dose	To be collected within 30 min prior to SOI
	EOI	Within 30 min after EOI
Dose 1 Day 1/Dose 1 Day2	24 hours after SOI on C1D1	24 (±2 hours) hours after Dose 1 SOI
Dose 2 Day 1	Pre-dose	Collect within 30 min prior to SOI. If Cycle 2 belantamab mafodotin dose is delayed, 1 PK sample must be taken at Dose 1 Day 22.
	EOI	Within 30 min after EOI
4th, and 6th belantamab mafodotin dose	Pre-dose and EOI	Within 30 min prior to SOI and after EOI (0-30 min)
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; for treatment beyond Dose 12, pre-dose samples will be collected every 6 doses (Dose 18, Dose 24, Dose 30 and so on, until the last PK sample at EOT).

Note: C = Cycle; D = Day; SOI = Start of Infusion; EOI = End of Infusion; h = hour; sBCMA = soluble BCMA; EOT = End of Treatment.

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 Vd continues.

8.5.2. Belantamab Mafodotin PK Sample Analysis

Plasma analysis will be performed under the control of GSK, the details of which will be included in the Lab Manual. Concentrations of belantamab mafodotin (ADC with or without total monoclonal antibody) and cys-mcMMAF will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the Lab Manual).

Once the plasma has been analyzed for belantamab mafodotin (ADC with or without total monoclonal antibody)) and cys-mcMMAF, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate GSK protocol.

8.5.3. Daratumumab and Bortezomib

No PK sampling or analysis is required for bortezomib, dexamethasone, or daratumumab in Arms A and B. For daratumumab, no anti-daratumumab antibody sampling or analysis is required.

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. 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 the belantamab mafodotin. Anti-belantamab mafodotin antibody samples will be disposed 3 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 IEC/IRB 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, bone marrow, and tumor biopsies. Soluble BCMA (sBCMA), BCMA expression in tumor cells, and circulating plasma cell-free DNA (cfDNA) analyses will be performed and the relationship of these biomarkers relative to response to belantamab mafodotin will be assessed. Additionally, any blood, serum, plasma, and bone marrow samples collected during this study may be used to measure novel biomarkers to identify factors associated with the biological and clinical responses to belantamab mafodotin. If relevant, this approach may be extended to include the identification of biomarkers associated with AEs. Unless stated otherwise, these investigations may be performed irrespective of whether a response to belantamab mafodotin is observed. The novel biomarkers may involve DNA analysis, RNA analysis, and/or protein analysis.

Samples will be collected at the time points indicated in the SoA. Biomarker samples, including bone marrows and sBCMA, could be analyzed as long as date and time information is collected.

The sample collection strategy may be adjusted on the basis of emerging data from this study or other studies involving belantamab mafodotin in order to ensure optimal evaluation of any potential biomarkers. If biomarkers potentially predictive of response or associated with AEs are identified, samples may be used for the development of validated assays and/or diagnostic tests. Additionally, novel biomarkers may also be incorporated, as data warrant. These analyses may include but not be limited to:

CCI

8.9.1. Soluble BCMA

The BCMA receptor undergoes gamma-secretase mediated cleavage, leading to release of the BCMA extracellular domain as soluble BCMA (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 (according to either the standard or enhanced schedules). See Table 22 and Table 23 below.

sBCMA samples will also be taken in Arm B, as described in Table 24 below.

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

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

Table 22 Treatment Arm A sBCMA Blood Collection (Enhanced PK Cohort)

Dose/Day[1]	Timing	Comments
Screening	Screening	Anytime during screening
Dose1 Day1[1]	Pre-dose	Within 30 min prior to Start of Infusion (SOI)
	End of Infusion (EOI)	Within 30 min after EOI
	2 hours after SOI	2 hours (±15 min) after C1D1 SOI
Dose 1 Day 1/Dose 1 Day2[1]	24 hours after SOI on C1D1	24h (±2h) hours after Dose 1 SOI
Dose 1 Day 4[1]	Prior to bortezomib administration	72h (±24h) hours after C1D1 SOI. If this coincided with a bortezomib administration day, sample should be taken prior to bortezomib administration
Dose 1 Day 8 to Day15[1]	1 sample on any one study day between C1D8 and C1D15	Any time between D8 and D15. If this coincided with a bortezomib administration day, sample should be taken prior to bortezomib administration
Dose 2 Day 1[1]	Pre-dose	Collect within 30 min prior to SOI If Cycle 2 belantamab mafodotin dose is delayed, 1 sample must be taken at Dose1 Day 22
	EOI	Within 30 min after EOI
4th and 6th Belantamab Mafodotin dose[1]	Pre-dose AND EOI	Within 30 min prior to SOI Within 30 min after EOI
9th and 12th Belantamab Mafodotin dose[1]	Pre-dose	Within 30 min prior to SOI
Every 6 subsequent doses[1]	Pre-dose	Within 30 min prior to SOI; for treatment beyond Dose 12, pre-dose samples will be collected every 6 doses (Dose 18, Dose 24, Dose 30 and so on, until the last sample at EOT)
EOT	EOT visit	Anytime

C = Cycle; D = Day; SOI = Start of Infusion; EOI = End of Infusion; h = hour; sBCMA = soluble BCMA; EOT = End of Treatment.

1. This PD 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 Vd continues.

Table 23 Treatment Arm A sBCMA Blood Collection (Standard PK Cohort)

Dose/Day[1]	Timing	Comments
Screening	Screening	Anytime during screening
Dose 1 Day 1[1]	Pre-dose	Within 30 min prior to SOI
	EOI	Within 30 min after EOI
Dose 1 Day 1/Dose 1 Day2[1]	24 hours after SOI on C1D1	24 (±2 hours) hours after Dose 1 SOI
Dose 2 Day 1[1]	Pre-dose	Collect within 30 min prior to SOI. If Cycle 2 belantamab mafodotin dose is delayed, 1 sample must be taken at Dose 1 Day 22
	EOI	Within 30 min after EOI
4th and 6th belantamab mafodotin dose[1]	Pre-dose AND EOI	Within 30 min prior to SOI Within 30 min after EOI
9th and 12th belantamab mafodotin dose[1]	Pre-dose	Within 30 min prior to SOI
Every 6 subsequent doses[1]	Pre-dose	Within 30 min prior to SOI; for treatment beyond Dose 12, pre-dose samples will be collected every 6 doses (Dose 18, Dose 24, Dose 30 and so on, until the last PD sample at EOT)
EOT	EOT visit	Anytime

Note: C = Cycle; D = Day; SOI = Start of Infusion; EOI = End of Infusion; h = hour; sBCMA = soluble BCMA; EOT = End of Treatment.

1 This PD 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 Vd continues.

Table 24 Treatment Arm B sBCMA Blood Collection

Dose/Day[1]	Timing	Comments
Screening	Screening	Anytime during screening
Dose1 Day1[1]	Pre-dose	Within 30 min prior to Start of Infusion (SOI)
	End of Infusion (EOI)	Within 30 min after EOI
Dose 1 Day 4[1]	Prior to bortezomib administration	72h (±24h) hours after C1D1 SOI. If this coincided with a bortezomib administration day, sample should be taken prior to bortezomib administration
Dose 1 Day 8 to Day15[1]	1 sample on any one study day between C1D8 and C1D15	Anytime between D8 and D15. If this coincided with a bortezomib administration day, sample should be taken prior to bortezomib administration
EOT	EOT visit	Anytime

C = Cycle; D = Day; SOI = Start of Infusion; EOI = End of Infusion; h = hour; sBCMA = soluble BCMA; EOT = End of Treatment

1. This PD sample is tied to the DOSE of daratumumab. This may not correspond to the CYCLE of treatment e.g., in the event that daratumumab is held whilst Vd continues. On Cycle 1 Day 1 first daratumumab dosing only, if daratumumab administration is split and given over Day 1 and Day 2, then the sBCMA sample will need to be collected within 30 min after EOI on Day 2 only.

8.9.2. Tumor-related Biomarkers

While BCMA expression is present in all multiple myeloma cells, there is some cell by cell variability and also differences in membranous and cytosolic localization patterns. Therefore, it is important to determine if there is any association between the expression

levels of BCMA on multiple myeloma cells and clinical responses. Bone marrow samples will be collected during this study at the time points indicated in the SoA.

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

BCMA expression analysis to be performed preferably on a bone marrow biopsy sample, any remaining aspirate and/or biopsy sample will be used for biomarker research (which may include immune cell characterization and/or profiling and/or DNA/RNA analyses).

8.9.3. Circulating Cell-Free DNA (cfDNA) Analysis

Tumor specific circulating nucleic acid levels detected in plasma or serum have been found to correlate with increasing tumor burden and decline following therapy. cfDNA in cancer patients can harbor many genetic alterations (mutations, microsatellite alterations, aberrant methylation), which are generally consistent with the tumor. Tumor-specific circulating cfDNA has the potential to be a useful biomarker of therapeutic response as well as offer a less invasive blood-based technique for identifying and selecting patients for certain treatments. Given this promise, cfDNA will be explored to determine if mutations can be identified and correlate to response or resistance to treatment. This analysis may also explore correlating increasing cfDNA levels with increasing tumour burden.

8.10. Health-Related Quality of Life

Five health-related quality-of-life (HRQoL) assessments will be performed in this study. The questionnaires will be administered to participants in different regions based on the availability of translated versions. More details about all participant questionnaires can be found in the SRM.

All participants will complete the self-administered version of the PRO questionnaires unless their vision prevents them from being able to complete the questionnaire on their own. Participants who are not able to complete the questionnaire on their own and require assistance should use an interviewer-administered format. If the interviewer-administered format is used, it should be read to the participant's verbatim, and participant responses should be recorded directly without any interpretation. For any additional assessments conducted via telephone (either during participation in the Treatment period or during Follow-up), the interviewer-administered format should be used. 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.

8.10.1. 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/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. European Organization for Research and Treatment of Cancer Item Library 52 (disease symptoms domain from the EORTC Quality of Life Questionnaire 20-item Multiple Myeloma module (EORTC QLQ-MY20)

The EORTC QLQ-MY20 is a supplement to the QLQ-C30 instrument used in patients with multiple myeloma [Aaronson, 1993; Cocks, 2007]. Only the Disease Symptoms domain of the QLQ-MY20 will be administered, which includes bone aches or pain, back pain, hip pain, arm or shoulder pain, chest pain, and pain increasing with activity. The disease symptom domain of the EORTC QLQ-MY20 will be referred to as the EORTC IL52. As with the QLQ-C30, QLQ-MY20 domain scores are averaged and transformed linearly to a score ranging from 0–100. A high score for Disease Symptoms represents a high level of symptomatology or problems [Proskorovsky, 2014].

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

The EQ-5D-3L is a standardised 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 1 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.

8.10.4. 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 it 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.

8.10.5. 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].

8.11. Visual Function Questionnaires

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 Schedule of Activities.

8.12. Non-protocol Specified Health Care Resource Utilization

Non-protocol specified Healthcare Resource Utilization (HRU) will be assessed in this study and reported by participants to study staff at each visit. Parameters to be measured include:

- Number of office/outpatient/hospital clinic visits by specialty.
- Number of emergency room/urgent care facility visits.
- Number and duration of in-patient 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

Primary PFS endpoint

The following primary efficacy hypothesis will be tested, comparing the distribution of PFS between the 2 treatment groups:

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

where, θ is the PFS HR (belantamab mafodotin/bor/dex vs. daratumumab/bor/dex arm).

Key secondary Overall Survival endpoint

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

$$H_0: \theta_1 \geq 1 \qquad VS. \qquad H_1: \theta_1 < 1$$

where, θ_1 is the OS HR (belantamab mafodotin/bor/dex vs. daratumumab/bor/dex arm).

Key secondary Duration of Response endpoint

The following key secondary hypotheses may 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 the belantamab mafodotin/bor/dex arm and μ_0 is the RMDOR for the daratumumab/bor/dex arm.

Key secondary Minimal Residual Disease Negativity Endpoint

A key secondary objective of the study is to compare the proportion of participants with MRD negativity, as assessed by NGS with a 10^{-5} sensitivity between the 2 treatment groups. The following statistical hypotheses 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 (daratumumab/bor/dex)

P_1 = proportion of participants with MRD negativity Arm A (belantamab mafodotin/bor/dex).

9.2. Multiple Comparisons and Multiplicity

The objective of the study to compare the efficacy of Treatment A versus Treatment B 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 9.6.4. The study will provide multiplicity control for multiple hypotheses as well as interim analyses (planned interim analyses are defined in Section 9.6.2). 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 family 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.

The primary PFS endpoint will be evaluated at an interim analysis (IA1) and at a primary PFS analysis / Interim Analysis 2 (IA2). The PFS analysis is based on using a Lan-DeMets (O'Brien-Fleming) alpha spending function to define an efficacy boundary [Lan, 1983] CCI [redacted] The amount of alpha allocated to the interim and primary PFS analyses is given in Table 28. The efficacy boundaries 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; IA1, Primary PFS analysis/IA2, IA3 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 Statistical Analysis Plan (SAP).

9.3. Sample Size Determination

Primary Endpoint: PFS

Based on data from the CASTOR study, the median PFS in Treatment Arm B is expected to be approximately 16.7 months [Spencer, 2018]. It is expected that treatment with belantamab mafodotin in combination with bor/dex will lead to a CCI [redacted]

The primary PFS analysis will be conducted after observing approximately CCI PFS events. With CCI events, the study has a power of CCI [redacted] This calculation assumes participants are randomized to the two treatment arms in a 1:1 randomization ratio. Assuming that a total of 478 participants will be randomized in a 1:1 ratio to Arm A or Arm B and a uniform enrollment rate of CCI participants per month, enrollment will continue for approximately 16 months. It is estimated that the targeted CCI PFS events will be observed approximately CCI months from the time when the first participant is randomized under H_1, assuming an annual dropout rate of CCI These calculations were conducted using East 6.4.

There will be a CCI global enrollment cap on North East Asia Countries. 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, as required by local regulatory bodies, have been reached. Additional participants that are enrolled in separate cohorts will not be included in the analysis portion of the study planned for the marketing application, which is based on approximately CCI events. However, these additional participants will be included in country-specific supplemental analyses, requested by the applicable regulatory authorities concerned, as detailed in the country-specific SAP.

9.4. Populations for Analyses

For purposes of 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 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 criteria below will be included:
	• Have received at least 1 line of prior therapy
	• With measurable disease at baseline
	• Randomized and received at least 1 dose of planned study treatment
	  ○ Patient randomized to the belantamab mafodotin arm that received daratumumab will be excluded and vice versa
	  ○ Patient randomized but never treated will be excluded

Safety	All randomized participants who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic	The Pharmacokinetic Population will consist of those participants in the Safety Population from whom at least 1 PK sample has been obtained and analyzed. This population will be the primary population for PK analyses.

9.5. Statistical Analyses

9.5.1. Efficacy Analyses

Analysis of efficacy endpoints will be based on assessments determined by an IRC with the ITT population unless otherwise specified. Sensitivity analyses will be based on investigator-assessed responses. The analytical methods planned for each endpoint are described in Table 25.

Stratification factors used for the stratified analyses include number of prior lines of therapy (1 vs 2/3 vs ≥4), prior bortezomib (yes vs no) and the revised International Staging System at screening (R-ISS I vs II/III).

Appropriate subgroup analyses may be performed if data permits, e.g., the primary endpoint PFS may be analyzed by age (<65 years, ≥65 years), gender (Female, Male), ethnicity (Hispanic, non-Hispanic) and race groups (American Indian or Alaskan Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Mixed Race), region (North America, Europe, North East Asia, etc.), prior anti-cancer therapy and other baseline characteristics.

Table 25 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, determined by an IRC, according to IMWG criteria [Kumar, 2016], or death due to any cause. Determination of dates for PFS event and dates for censoring is described in Section 10.11. Final PFS (primary efficacy) analysis will be conducted at the time of observing approximately CCI PFS events. 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 2 treatment arms using log-rank test stratified by randomization factors used for randomization. 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 randomization factors with treatment arm as the sole explanatory variable. If the proportional hazard assumption does not hold, Restricted Mean Survival Time (RMST) may be conducted in addition as appropriate. Sensitivity analyses will be conducted using alternative PFS censoring rules as described in Section 10.11 and using investigator-assessed responses and dates. Subgroup PFS analysis by randomization factors will be conducted at PFS analysis.
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 of last contact or last known alive. OS analysis will be conducted at planned analyses using similar approach as for the PFS analysis (i.e. Kaplan-Meier estimates, stratified log-rank test, Cox proportional hazards model stratified by randomization factors, and examination of non-proportional hazards effect).

Endpoint	Statistical Analysis Methods
	The hypothesis testing and boundary crossing decision of the key secondary endpoint OS will be based on ITT population. Analyses of OS may also be performed based on mITT population. The analyses will only include Kaplan-Meier estimates, Cox proportional hazards model stratified by randomization factors. Details are provided in the SAP. Subgroup OS analysis by randomization factors will be conducted at primary PFS analysis based on ITT population. Details are provided in the SAP. **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 determined by an IRC according to IMWG criteria [Kumar, 2016]. DoR will be analyzed based on the restricted mean DoR (RMDOR) using a non-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. 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. The hypothesis testing of the key secondary endpoint DoR will be based on the ITT populations. Subgroup DoR analyses by randomization factors may be conducted at primary PFS analysis based on ITT population. Details are provided in the SAP. 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) as determined by an IRC, according to 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]. An additional analysis may be conducted for conventional DoR using investigator-assessed responses. **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 two-sided 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 three randomization factors: number of prior lines of therapy, prior bortezomib use, and R-ISS stage. A one-sided p-value will be produced. 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.

Endpoint	Statistical Analysis Methods
Secondary/Exploratory	The following secondary analyses will be conducted: **CRR**, defined as the percentage of participants with a confirmed CR or better (i.e., CR, and sCR) as determined by an IRC, according to 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. CRR will also be compared between treatment arms using the Cochran Mantel Haenszel test stratified by randomization factors. The exact 95% CI for the difference will be calculated. Sensitivity analysis will be conducted using investigator-assessed responses. **ORR**, defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR, and sCR) as determined by an IRC, according to 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 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. ORR will also be compared between treatment arms using the Cochran Mantel Haenszel test stratified by randomization factors. The exact 95% CI for the difference will be calculated. **CBR**, defined as the percentage of participants with a confirmed minimal response (MR) or better as determined by an IRC, according to IMWG criteria [Kumar, 2016]. The number and percentage of participants with MR or better as the Best Overall Response (BOR) will be summarized by treatment arm. The corresponding exact 95% CI for CBR 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. CBR will also be compared between treatment arms using the Cochran Mantel Haenszel test stratified by randomization factors. The exact 95% CI for the difference will be calculated. Sensitivity analysis will be conducted using investigator-assessed responses. **VGPR rate**, defined as the percentage of participants with a confirmed Very Good Partial Response (VGPR) or better (i.e., VGPR, CR, sCR), as determined by an IRC, according to IMWG criteria [Kumar, 2016]. The number and percentage of participants with VGPR or better as the Best Overall Response (BOR) will be summarized by treatment arm. The corresponding exact 95% CI for VGPR rate 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. VGPR rate will also be compared between treatment arms using the Cochran Mantel Haenszel test stratified by randomization factors. The exact 95% CI for the difference will be calculated. Sensitivity analysis will be conducted using investigator-assessed responses. **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) as determined by an IRC, according to IMWG criteria [Kumar, 2016].

Endpoint	Statistical Analysis Methods
	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 as determined by an IRC, according to 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 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. Analysis for PFS2 will use investigator-assessed responses. **TTBR**, defined as the interval of time between the date of randomization and the earliest date of achieving best response among participants who achieve a response (i.e., confirmed PR or better) as determined by an IRC, according to IMWG criteria [Kumar, 2016]. **Sustained MRD negativity rate**, defined as Sustained MRD Negativity rate: defined as the percentage of participants with MRD negativity confirmed by NGS minimum of one year apart, per IMWG criteria. **Imaging plus MRD negativity,** defined as the percentage of participants who are MRD negative by NGS and who have no evidence of disease on PET-CT.

9.5.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Table 26 Statistical Analytical Methods: Safety

Endpoint	Statistical Analysis Methods
Secondary	**Adverse Events**: All adverse events, whether serious or non-serious, will be reported from the start of treatment until at least 70 days after the last dose of study treatment, 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, Version 5.0. For AE reporting, the verbatim term used in the eCRF by investigators to identify adverse events will be coded using the latest version of MedDRA coding dictionary [NCI, 2010]. Adverse events will be summarized by frequency and proportion of total participants, by system organ class and preferred term. Separate summaries will be given for all AEs, common (>5%) AEs, treatment-related AEs, SAEs, and AEs leading to dose delays and discontinuation of study treatment and AEs of special interest. Adverse events, if listed in the NCI-CTCAE (Version 5.0) 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.

Endpoint	Statistical Analysis Methods
	• 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.
Exploratory	**Other Safety Measures**: Data for vital signs and ophthalmic examination findings will be summarized. For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages. Details will be provided in the SAP.

9.5.3. Pharmacokinetic Analyses

Concentration-Time Data: Linear and semi-logarithmic individual concentration-time profiles and median profiles (when appropriate) may be plotted for belantamab mafodotin (ADC and total mAb, if available) and cys-mcMMAF. Concentrations of belantamab mafodotin (ADC and total mAb, if available) 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 current population pharmacokinetic model at the time of the analysis to generate post hoc pharmacokinetic parameter estimates for the individual participants in Arm A of Study 207503. Results may be reported separately. Concentration-time data from the participants with enhanced PK schedule may also be analyzed using standard non-compartmental approach.

9.5.4. Pharmacokinetic/PD Analyses

If deemed appropriate and if data permit, exposure-response relationships between belantamab mafodotin exposure (e.g., dose, dose intensity, concentration, Cmax, or AUC) and clinical activity and/or toxicity (e.g., response, corneal event) 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 statistical analysis plan or in a separate statistical analysis plan (e.g. biomarker clinical study plan). The population PK analysis and pharmacodynamic analyses may be presented separately from the main clinical study report (CSR).

9.6. Planned Analyses

9.6.1. Periodic IDMC Safety Reviews and CPMS Early Access

Safety data will be reviewed periodically starting from when CCI [redacted], and then every CCI [redacted] or as requested by the IDMC thereafter. IDMC will review efficacy and safety data at the interim analysis.

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 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.

9.6.2. Interim Analyses

Three interim analyses (IAs) are planned for the study, including an interim analysis at the time of Primary PFS analysis (Table 27). Additional descriptive analyses of OS may be performed without alpha-adjustment, only if requested by health authorities.

Table 27 Summary of Planned Interim Analyses

Analysis	Purpose	Timing
Interim Analysis 1 (IA1)	Efficacy	CCI [redacted]
Primary PFS Analysis / Interim Analysis 2 (IA2)	Efficacy. This will also be the planned primary analysis of PFS.	
Interim Analysis 3 (IA3)	Efficacy	

An interim analysis (IA1) is planned at the time of approximately CCI [redacted] targeted PFS events CCI [redacted] information fraction) have been observed. The interim analysis will allow for stopping early for efficacy. All participants are expected to have been enrolled at the time of the interim analysis. The Lan-DeMets (O'Brien-Fleming) alpha spending function will be used to define the efficacy boundary based on the actual observed number of PFS events.

Boundary crossing probabilities for each of the planned PFS analyses for efficacy based on the targeted CCI PFS events are provided in Table 28. The boundaries will be revised based on the observed number of PFS events at the time of analysis.

If PFS demonstrates statistical significance at IA1 (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.

Table 28 Stopping Boundaries for PFS Interim and Primary Analyses

Information fraction	N of events	Cum. α Spent	Efficacy Boundary (p-value)	Efficacy Boundary (HR)	Incremental Boundary Crossing Probabilities	
					Under H0	Under H1
CCI [redacted]						

Details of further and any future analyses for key secondary endpoints will be outlined within the SAP.

9.6.3. Final Analysis

The final OS analysis will occur 5 years from Last Participant First Visit (LSFV), or when all participants have died, withdrawn consent, or have been lost to follow-up, whichever occurs first. For participants still on active treatment at the time of final OS analysis (End of Study) please refer to Section 6.7.

9.6.4. Sequence of Interim and Other Planned Analyses

All planned analyses are listing in Table 29 below.

Table 29 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 CCI [redacted], and then every CCI	Key safety (AEs, SAEs, AESIs, deaths, ocular, exposure, dose modifications, laboratory parameters), descriptive efficacy	All data available at the time of the data cut

Analysis	Reason/impact	Timing	Endpoints included	Data to be used
		CCI or as requested by the IDMC thereafter.	summaries (e.g. response rates, counts of PFS/OS events, if requested) and study population summaries.	
Interim Analysis 1 (IA1)	Efficacy	CCI	Minimally, key safety, study population and PFS. Additional analyses may be performed to support decision making if requested by IDMC. CCI	All data available at the time of the data cut
Primary PFS analysis / Interim Analysis 2 (IA2)	Efficacy. This will also be the planned primary analysis of PFS.		All endpoints CCI CCI	All data available at the time of the data cut
Interim Analysis 3 (IA3)	Efficacy		CCI	All data available at the time of the data cut

Analysis	Reason/impact	Timing	Endpoints included	Data to be used
Final analysis	To ensure OS data is more mature and provide updated efficacy and safety	CCI [redacted]		All data

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require 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.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- 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 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.
- 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.

10.1.5. Committees Structure

Safety Review Team (SRT)

A safety review team (SRT) is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.

Independent Data Monitoring Committee (IDMC)

- 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 analysis and periodic safety reviews. Details of the interim analyses are included in Section 9.6.2. Details of safety reviews are included in Section 9.6.1.
- 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.

Independent Review Committee (IRC)

An IRC, (BioClinica. Inc a Clario company) 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. Further details on the IRC process will be defined in the IRC charter. Results from the IRC will not be provided to the investigator sites.

10.1.6. 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.

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

10.1.8. Data Quality Assurance

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

- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Additional information regarding remote data management and monitoring are provided in Section 10.16, Appendix 16.

10.1.9. Source Documents

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

10.1.10. Study and Site Closure

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

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

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

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

10.1.11. Third Parties and Sub-contractors

Third Party/Sub-Contractor	Service Provided	Endpoint/Analysis/Oversight
CCI	Central Laboratory Results	Primary endpoint
	PK analysis (cys-MMAF), anti-drug antibodies (ADA), sBCMA	Secondary endpoint
	PK analysis (total mAb & ADC)	Secondary endpoint
	PK analysis (CYS-mcMMAF, ADC, Total mAb), sBCMA, and anti-drug antibodies (ADA)	Secondary endpoint
	Statistical data analysis (IDMC, Primary and Final Analysis)	Data Analysis
	Statistical Data Analysis (IDMC)	Data Analysis
	Electronic Clinical Outcomes Assessment (eCOA) services	Secondary endpoint
	Independent Review Committee (IRC)	Primary endpoint
	Minimal Residual Disease (MRD) Analysis	Key Secondary Endpoint
	Feasibility, Monitoring, Regulatory, Investigator Recruitment (Greece, Czech Republic, Israel)	Country Oversight
	Lost to Follow-up Patient Search	Key Secondary Endpoint

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

10.2.1. Definition of AE

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

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

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

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

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 <u>and</u> impaired liver function defined as:

- ALT ≥3 x ULN and total bilirubin* ≥2 x ULN (>35% direct), **or**
- ALT ≥3 x ULN and INR** >1.5

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥3 x ULN and total bilirubin ≥2 x ULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

h. Refer to Section 10.4.1 for liver chemistry follow-up procedures.

10.2.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the eCRF 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 AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- 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 eCRF 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 ADL*.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.

- Grade 5: Death related to AE.

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the 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 eCRF.

- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.2.5. Reporting of SAEs to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAEs 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.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF

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

10.3. 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.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea confirmation with more than 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 one of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.3.2. Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY
Highly Effective Methods[b] That Have Low User Dependency:
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner – *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
Highly Effective Methods[b] That Are User Dependent:
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
• Sexual abstinence – *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

10.3.3. 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, whichever is longest, by telephone 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), 3 months from the last dose of daratumumab (Arm B) or 7 months from the last dose of bortezomib, whichever is longest.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.

- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study 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

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

Required Actions, Monitoring and Follow up Assessments	
Actions	**Follow Up Assessments**
• **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**) **MONITORING:** **If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver 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 <2xULN and INR ≤1.5):** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend • Blood sample for pharmacokinetic (PK) analysis and a blood sample for sBCMA, obtained within 70 days after last dose of belantamab mafodotin[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH), gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on 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 ≥3xULN AND total bilirubin ≥2xULN or INR >1.5** obtain the following in addition to the assessments listed above:

RESTART/RECHALLENGE • **Restart/rechallenge is allowed per protocol but do not resume study intervention unless GSK approval is granted;** If restart/rechallenge is **not granted**, permanently discontinue study intervention and continue participant in the study for any protocol specified follow up assessments. Refer to Restart/Rechallenge guidelines in Section 10.4.1.	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins) • Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week. (e.g., where the participant has been resident in the clinical unit throughout) • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease; complete Liver Imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance: o In patients when serology raises the possibility of autoimmune hepatitis (AIH) o In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In patients with acute or chronic atypical presentation: • If liver biopsy conducted complete liver biopsy form.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥ 3xULN **and total** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** total bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; 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 [Le Gal, 2005].
5. PK sample may not be required for participants in Treatment Arm B receiving daratumumab/bor/dex. Record the date/time of the PK/sBCMA blood sample draw and the date/time of the last dose of study intervention 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.

Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** total bilirubin <2xULN or INR ≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** total bilirubin <2xULN or INR ≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study intervention • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin and INR) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN (total bilirubin <2xULN and INR ≤1.5), continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN and INR ≤1.5, monitor participants twice monthly until liver chemistries resolve or return to within baseline.

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 Re-Challenge Guidelines

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

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

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

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 rate across all drugs in prospective studies [Andrade, 2009]**. Clinical outcomes vary by drug, with nearly 50% fatality with halothane re-administered within

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

Risk factors for a fatal drug rechallenge outcome include:

- Hypersensitivity with initial liver injury (e.g., fever, rash, eosinophilia) [Andrade, 2009]
- Jaundice or bilirubin >2 x 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 preclinical liability (e.g., reactive metabolites; mitochondrial impairment) [Hunt, 2010]

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 PI 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 must be obtained.

If the rechallenge is approved by GSK in writing:

- The participant must be provided with a clear description of the possible benefits and risks of study 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 Medical Governance 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 Monitor, 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, 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:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (*e.g.*, biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3 x ULN).
- Possible study treatment-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 will apply.
- There is no evidence of alcoholic hepatitis.
- IRB/IEC approval of study treatment restart must be obtained, as required.
- **If restart of study intervention 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 restart of 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 Monitor, and IRB/IEC must be informed of the participant's outcome following study treatment restart.
- GSK to be notified of any adverse events, 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 IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to belantamab mafodotin or multiple myeloma and related diseases. They may also be used to develop tests/assays (including diagnostic tests) related to belantamab mafodotin or study interventions of this drug class, and multiple myeloma. Genetic research may consist of the analysis of 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 clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on belantamab mafodotin (or study interventions of this class) or multiple myeloma continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

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.

Source: Oken, 1982.

10.7. Appendix 7: Modified Diet in Renal Disease (MDRD) Formula

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

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

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

The 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: Corneal Event Grading and Prophylactic Interventions for Corneal Toxicity (Treatment Arm A)

Dose modifications of belantamab mafodotin for treatment-related corneal events should be based on grading of corneal events according to the guidelines of Keratopathy Visual Acuity (KVA) Scale as provided in Table 30:

Table 30 Keratopathy Visual Acuity (KVA) Scale for Treatment-related Corneal Events:

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

*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.

[a] Mild superficial keratopathy = mild superficial punctate keratopathy (documented worsening from baseline), **with or without** symptoms.

[b] Moderate superficial keratopathy = any/ or a combination of: moderate superficial punctate keratopathy, patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity.

[c] Severe superficial keratopathy = any/ or a combination of: severe superficial punctate keratopathy, diffuse microcyst-like deposits involving the central cornea, sub-epithelial haze (central), or a new central stromal opacity.

[d] Corneal epithelial defect such as corneal ulcers. Corneal ulcer by definition means an epithelial defect with underlying stromal infiltration.

[e] Changes in visual acuity due to treatment-related corneal findings.

- For participants who have BCVA worse than 20/20 in either eye at baseline, dose modification for that eye will be determined by the worsening of vision from baseline only (not by absolute BCVA at the visits).
- If a participant has a baseline BCVA of 20/200 or worse in an eye, then belantamab mafodotin-related changes in vision in the other eye will drive the dose modification. If a participant has baseline BCVA of 20/200 or worse in both the eyes, then the decision to delay or reduce belantamab mafodotin dose will be based on PI's assessment of benefit vs. risk based on corneal exam findings following a discussion with the qualified eye care specialist.

BCVA- best corrected visual acuity

See Table 11 for dose modification guidelines and stopping criteria for belantamab mafodotin treatment-related corneal events based on the KVA scale.

Prophylactic interventions for corneal toxicity associated with belantamab mafodotin is provided in Table 31.

Table 31 Prophylactic Measures for Corneal Toxicity Associated with Belantamab Mafodotin

Prophylactic Measure[a]	Dose and Administration	Timing
Preservative-free artificial tears	Administer in each eye at least 4 to 8 times daily	Administer daily beginning on Cycle 1 Day 1 until EOT. Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops (if administered together)
Cooling eye mask	May apply cooling eye mask to both eyes for approximately 1 hour or as much as tolerated by the participant	During belantamab mafodotin infusion administration in the first hour for up to 4 hours, as tolerated

a. Dose modifications and treatment for corneal 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 decrease ocular side effects.

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

A qualified eye care specialist (Appendix 10) consult is required for all participants who develop signs or symptoms of corneal events or require steroid eye drops for more than 7 days.

10.10. Appendix 10: 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 patients, which includes routine check-ups, treatment and ongoing management of visual disease. Qualified eye care specialists, including optometrist, will also be able to communicate with patients on the effect of belantamab mafodotin on eye.

Specifically, qualified eye care specialists must be able to:

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

10.11. Appendix 11: Progression-Free Survival Event and Censoring Rules

Situation	**Date of Event (Progression/Death) or Censored**	**Event (Progression/Death) or Censored**
No adequate 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 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[2]	Date of assessment of progression	Event
Progression documented between scheduled visits and Progression documented without extended loss-to-follow-up time[2]	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[3]	Censored
No adequate post-baseline assessment before start of new anti-myeloma therapy	Randomization	Censored
With adequate post-baseline assessment and new anti-myeloma treatment started (prior to documented disease progression)[4]	Date of last 'adequate' assessment of response[3] (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 or progression after missing 2 or more scheduled assessments[2]	Date of randomization if no post-baseline assessments, or date of last 'adequate' assessment of response[3] (prior to missed assessments): since disease	Censored (S3) Event

Situation	Date of Event (Progression/Death) or Censored	Event (Progression/Death) or Censored
	assessment is every 3 weeks, a window of 49 days (6 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 49 days, PFS will be censored at the last adequate disease assessment prior to PD/death. (S3) Date of death or progression	
(S4) Treatment discontinuation due to clinical PD 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.

Notes:
(S1) (S2) (S3) (S4) Rules to be applied For PFS Sensitivity Analysis.
Event or censored are based on confirmed responses.

Footnotes:
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. Extended loss-to-follow-up time = 6 weeks + 7 day window = 49 day window; Without extended loss-to-follow-up time is defined as: <= 49 days; after an extended loss-to-follow-up time is defined as: >49 days.
3. An adequate assessment is defined as an assessment where the response is sCR, CR, PR, VGPR, MR, or SD.
4. If PD and new anti-myeloma therapy occur on the same day, assume the progression was documented first; e.g., outcome is progression and the date is the date of the assessment of progression.

10.12. Appendix 12: Country Specific Requirements

Inclusion / Exclusion Criteria:

- In Republic of Korea, a participant must be over 19 years of age inclusive, at the time of signing the informed consent.
- In France a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category

Adverse Events:

- For all studies conducted in China, SAEs will be collected from signing of the ICF and NOT from the start of treatment.
- For Japan, GFR = $175 \times (\text{Scr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (0.808 \text{ if Japanese})$

Genetics:

For participants from China, any description in connection with collection and using of Human Genetic Resources in this protocol shall be subject to the approval of Human Genetics Resources Administration of China (HGRAC).

10.13. Appendix 13: Revised International Staging System for Multiple Myeloma

Prognostic Factor	Criteria
ISS Stage	
I	Serum β2-microglobulin <3.5 mg/L, serum albumin ≥3.5 g/dL
II	Not ISS Stage I or III
III	Serum β2-microglobulin ≥5.5 mg/L
CA by iFISH	
High Risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard Risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH ≥ the upper limit of normal
R-ISS Stage (A new model for risk stratification for MM)	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS Stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

Abbreviations: CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System

Source: Palumbo, 2015b

10.14. Appendix 14: Abbreviations and Trademarks

Abbreviations

ABO	Blood grouping system
ADA	Anti-drug antibodies
ADC	Antibody-drug conjugate
ADCC	Antibody-dependent cellular cytotoxicity
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AMD	Age-related macular degeneration
ANC	Absolute neutrophil count
ART	Anti-retroviral therapy
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
BAL	Bronchoalveolar lavage
BCMA	B-cell maturation antigen
BCVA	Best corrected visual acuity
BM	Bone marrow
BMI	Body mass index
BOR	Best Overall Response
BOR	Bortezomib
Bor/Dex	Bortezomib/Dexamethasone
BSA	Body surface area
CAR-T	Chimeric antigen T-cell therapy
CBR	Clinical Benefit Rate
cfDNA	Circulating plasma cell-free DNA
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
Cmax	Maximum plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CR	Complete Response
CRAB	Myeloma-related syndrome characterized calcium elevation, renal failure, anemia, and bone lesions
CRF	Case Report Form
CRR	Complete Response Rate
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
CYP	Cytochrome P

Cys-mcMMAF	Cysteine maleimidocaproyl MMAF
DILI	Drug-induced liver injury
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of Response
DREAMM	Driving Excellence in Approaches to Multiple Myeloma
DVT	Deep vein thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOI	End of infusion
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of Treatment
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FISH	Fluorescence-in-situ hybridization
FLC	Free light chain
FSH	Follicle-stimulating hormone
FTIH	First-Time-in-Human
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
HbcAb	Hepatitis B core antibody
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCRU	Health care resource utilization
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
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 Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1

IHC	Immunohistochemistry
IMiD	Immunomodulatory drugs
IMWG	International Myeloma Working Group
INR	International normalization ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	Infusion-related reaction
IRT	Interactive Response Technology
ISS	International Staging System
ITT	Intention-to-treat
IV	Intravenous
KVA	Keratopathy Visual Acuity
LDH	Lactate dehydrogenase
LEN	Lenalidomide
LSFV	Last Subject First Visit
LVEF	Left ventricular ejection fraction
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MM	Multiple myeloma
MMAF	Monomethyl auristatin-F
MoA	Mechanism of action
MR	Minimal Response
MRD	Minimal Residual Disease
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next-generation sequencing
NOS	Not otherwise specified
NYHA	New York Heart Association
OATP	Organic anion transporting polypeptides
ORR	Overall Response Rate
OS	Overall Survival
OSDI	Ocular Surface Disease Index
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free Survival
PFS2	Progression-free Survival on Subsequent Line of Therapy
PFT	Pulmonary function tests
P-gp	P-glycoprotein
PGIC	Patient global impression of change

PGIS	Patient global impression of severity
PI	Proteasome inhibitors
PK	Pharmacokinetic(s)
PO	Per os (oral)
POEMS	Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasmaproliferative disorder, skin changes
PR	Partial Response
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient-reported outcome
PTS	Platform Technologies and Science
QD	Once daily
QID	Four times daily
QLQ	Quality of life questionnaire
QoL	Quality of life
QT	Q and T waves in ECG
QTc	Corrected QT interval
QTcF	Fridericia's formula
R-ISS	Revised International Staging System
RBC	Red blood cell
RMDOR	Restricted mean duration of response
RMST	Restricted mean survival time
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
RPLS	Reversible posterior leukoencephalopathy syndrome
RRMM	Relapsed/Refractory multiple myeloma
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sBCMA	Soluble BCMA
SC	Subcutaneous
sCR	Stringent Complete Response
SCT	Stem cell transplant
SD	Standard deviation of the mean
SDV/SDR	Source Data Verification/Source Document Review
SoA	Schedule of activities
SoC	Standard of care
SOI	Start of Infusion
SPD	Sum of the products of the maximal perpendicular diameters of measured lesions
SPEP	Serum protein electrophoresis
SRM	Study Reference Manual
SRT	Safety Review Team
t1/2	Serum half-life
TLS	Tumor lysis syndrome
tmax	Time to maximum plasma concentration
TNF	Tumor necrosis factor
TTBR	Time to Best Response

TTP	Time to Disease Progression
TTR	Time to Response
UK	United Kingdom
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
USPI	United States Product Information
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
Blenrep

Trademarks not owned by the GSK group of companies
Darzalex
Kyprolis
MedDRA
RandALL NG
Velcade

10.15. Appendix 15: Home Healthcare and Telemedicine Approaches

Home Healthcare (General Visit)

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

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

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

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

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

Home Healthcare (Ophthalmologic Exam)

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

care specialist clinic. Activities that may be done as part of in-home eye exams must follow the schedule provided in the SoA (Section 1.3) and include:

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

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

Telemedicine

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

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

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

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

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

Remote Patient Reported Outcomes (PRO) Administration

Where applicable country and local regulations and infrastructure allow, remote PRO administration may be permitted. Remote PRO administration is defined administration of protocol PROs by a qualified third party over the telephone. The remote PRO Administrator will use the versions of the PROs designed for verbal administration. The

remote PRO Administrator will have access to the electronic PRO portal for the study and input participant responses as the interview is being conducted.

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

10.16. Appendix 16: Data Management/Monitoring

Source Data Verification/Source Document Review (SDV/SDR)
During periods in which on-site monitoring is not permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution and in accordance to with local law and regulatory guidance documents.
Remote SDV/SDR will be proposed to study sites to meet a patient and/or critical data quality need, e.g., to assess patient safety or to ensure data integrity. The study specific monitoring plan will be updated in accordance with remote monitoring practices adopted for the country/study. The subject informed consent will be updated in line with local regulations to permit remote monitoring practices. In case of remote SDV/SDR, GSK will work with the site to ensure subject privacy.

eCRF/CRF Final or Interim Sign off Process:
The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study patient is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 and 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.

10.17. Appendix 17: Protocol Amendment History

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

Amendment 5: 19 Dec 2022

Where this Protocol Amendment applies:

Protocol Amendment 5 applies to all participants in all countries and all sites.

Overall Rationale for the current amendment:

This protocol has been amended to remove the interim analysis for futility and superiority that was planned at CCI information. Enrollment was completed for the Intent-To-Treat population in June 2021 and safety data is continuing to be reviewed periodically with the Independent Data Monitoring Committee (IDMC) every CCI. The IDMC has not noted any new/significant safety signals for the study to date.

The protocol has also been amended to introduce an Independent Review Committee (IRC) and to document that the analysis of efficacy endpoints will be based on assessments determined by an IRC instead of derived confirmed response based on an algorithm. In addition, Duration of Response and Overall Survival, which were secondary endpoints for the study, have now been classified as key secondary endpoints. Additional changes have been incorporated to align with program-level and protocol template updates.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Section 1.3 Schedule of Activities (SoA)	Table 1: Edit to footnote 4 on when participants may have their ophthalmologic exams decreased to once every 3 months to add “or prior to” the time of the sixth dose exam.	For clarification.
	Table 1 and Table 2: Added footnote 7 on collection of OS data.	To ensure data integrity for the OS endpoint.
	Table 2: Added ocular exam to be performed at Fixed Visits. Edit to footnote 4 on timing of ocular exams.	For clarification.
	Table 3: Edit to footnote f to add a ±1 month window for follow-up MRD testing.	For clarification.
Section 2.2.4 Clinical Experience with Belantamab Mafodotin	Updated with results from the final analysis for Study 205678 (DREAMM-2).	To provide the most up to date information.

Section # and title	Description of change	Brief rationale
Section 2.3.1 Summary of Risk Assessment for Belantamab Mafodotin (Treatment Arm A), Daratumumab (Treatment Arm B), and Bor/Dex (Treatment Arms A and B)	Updates to potential overlapping toxicities and the risks related to belantamab mafodotin.	To provide the most up to date information.
Section 3 Objectives and Endpoints	The efficacy endpoint of OS has been changed from a secondary endpoint to a key secondary endpoint.	To enable formal statistical testing.
Section 3 Objectives and Endpoints	The efficacy endpoint of DoR has been changed from a secondary endpoint to a key secondary endpoint; 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.	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 3 Objectives and Endpoints	Deleted “total monoclonal antibody” from the exposure and pharmacokinetic endpoints.	Based on adequacy of understanding of exposure-response relationship from previous belantamab mafodotin studies.
Section 3 Objectives and Endpoints	Updated wording of PRO-CTCAE endpoint.	To align with the wording of this endpoint in the program.
Section 3 Objectives and Endpoints	Footnote number 1 added to clarify that all disease response categories will be determined by an IRC.	For clarification.
Section 4.1 Overall Design	Added information on collection of survival data outside of the protocol window noted in the SoA.	To ensure data integrity for the OS endpoint.
Section 4.2 Scientific Rationale for Study Design	Added paragraph on data that will be used by the IRC to determine disease response. Deleted text on interim analysis from final paragraph.	For clarification. To align with the removal of the interim analysis.
Section 6.1.3.2 Corneal Supportive Care Guidelines and Section 8.2.6.1 Treatment Arm A	Edit to text on when participants may have their ophthalmologic exams decreased to once every 3 months to add “or prior to” the time of the sixth dose exam.	For clarification.
Section 6.5.1 Permitted Concomitant Therapies	Added that use of approved monoclonal antibody treatments for serious conditions unrelated to multiple myeloma must be discussed with the GSK Medical Monitor.	To enable participants to receive monoclonal antibody treatments for serious conditions unrelated to MM during the study
Section 6.6.1 Belantamab Mafodotin	Updates to the dose modification guidance for AEs associated with belantamab mafodotin based on serum creatinine and albumin/creatinine ratios.	To align with program-level update.

Section # and title	Description of change	Brief rationale
Section 7.1 Discontinuation of Study Intervention	Added information on follow-up for survival to the end of study regardless of whether the participant has discontinued study intervention. Added information on modified follow-up if the participant does not agree to continue in-person visits.	To ensure data integrity for the OS endpoint.
Section 7.3 Lost to Follow Up	Added information on the collection of vital status of randomized participants.	To ensure data integrity for the OS endpoint.
Section 8.1.1 Response Evaluation	An IRC has been added to assess efficacy endpoints. Derivation of response via a proprietary algorithm has been deleted.	To address health authority feedback received on another study in the program that the algorithm is not validated and therefore cannot be used as the primary analysis of efficacy endpoints.
Section 8 Study Assessments and Procedures Table 19 and Section 8.2.5 Clinical Safety Laboratory Assessments	Removed request for participants with elevations of LDH, CK and/or AST to have samples tested centrally for CK and LDH isoenzyme levels if possible.	Potential for Other Laboratory Abnormalities removed with risk table update.
Section 8.2.6.2 Treatment Arm B	Edit to wording on timing of ocular exams to add a ±4 week window for 6 monthly eye exams.	For clarification.
Section 8.5.1 Belantamab Mafodotin Blood Sample Collection for Pharmacokinetics and Section 8.5.2 Belantamab Mafodotin PK Sample Analysis	Updated to make analysis of total antibody optional.	Based on adequacy of understanding of PK and exposure-response relationship from previous belantamab mafodotin studies PK sampling for each ADA sample is not needed due to the drug tolerance of the immunogenicity assays.
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 immunogeniticity within and cross studies are deemed sufficient.
Section 9.1 Statistical Hypotheses	Statistical hypotheses that will be tested for DoR and OS have been added.	To support addition of DoR and OS as key secondary endpoints.
Section 9.2 Multiple Comparisons and Multiplicity	Deleted text on the interim analysis. Updates to the hierarchical testing procedure to add DoR and OS as key secondary endpoints.	To align with the removal of the interim analysis. To support addition of DoR and OS as key secondary endpoints.
Section 9.3 Sample Size Determination	Updates to the power calculation and target PFS events based on the removal of the interim analysis. Added information on sample size determination for DoR and OS as key secondary endpoints.	To align with the removal of the interim analysis. To support addition of DoR and OS as key secondary endpoints.

Section # and title	Description of change	Brief rationale
Section 9.4.1 Efficacy Analyses	Analysis of efficacy endpoints will be based on IRC-assessed response instead of derived response. Addition of statistical analysis methods for DoR and OS as key secondary endpoints. Addition of statistical analysis methods for imaging plus MRD negativity.	To align with addition of an IRC. To support addition of DoR and OS as key secondary endpoints. Had been missed inadvertanely in previous versions of the protocol.
Section 9.4.3 Pharmacokinetic Analyses	Updated to make analysis of total antibody optional.	Based on adequacy of understanding of PK and exposure-response relationship from previous belantamab mafodotin studies.
Section 9.5 Interim Analyses	Deleted text on the interim analysis for futility and superiority. Changed section heading to “Planned Analyses” and created sub-headings.	To align with the removal of the interim analysis and clarification on the planned analyses.
Section 10.1.4 Data Protection	Addition of text around protection of personal data of the investigator and site staff, responsibilities of the parties related to data protection, and information technology systems used to collect, process and store study-related data.	To align with updates to the protocol template on data protection.
Section 10.1.5 Committees Structure	Addition of information on the IRC.	To align with addition of an IRC.
Section 10.11 Appendix 11: Progression-Free Survival Event and Censoring Rule	Update to table and footnotes.	For clarification of PFS censoring rules.
Section 10.1.11 Appendix 1: Regulatory, Ethical, and Study Oversight Consideration	Addition of Section 10.1.11 listing all third parties and sub-contractors used in the study.	For transparency.

Amendment 4: 15 Jul 2022

Where this Protocol Amendment applies:

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

Overall Rationale for the Amendment 04:

This protocol has been amended to update the statistical analyses to include Clinical Benefit Rate (CBR) as a secondary endpoint and Sustained MRD negativity rate as an exploratory endpoint. The Key Secondary Endpoint of MRD Negativity has been clarified to state that the analysis will conducted in participants with CR or better, and a sensitivity analysis will be conducted in patients with a best overall response of VGPR. The definition for MRD negativity has been updated to state that participants in the ITT population without MRD assessment will be treated as non-negative MRD.These updates clarify how endpoints will be analyzed and will allow for further assessment of clinical activity and characterization of efficacy.

In addition, the term "anti-cancer therapy" has been updated to state "anti-myeloma therapy" in the Prohibited Concomitant Therapies section and where relevant throughout the protocol document. This clarifies the intent that "anti-cancer therapy" should be specifically limited to therapies directed against multiple myeloma and those therapies that have anti-myeloma properties."

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
Section 1.1 Synopsis	Updated to include - Clinical Benefit Rate (CBR) as a Secondary Endpoint. The definition for Duration of Response (DoR) has been updated to include death due to any cause.	CBR is an additional method of assessment of clinical activity to further characterize efficacy. The definition for DoR has been updated to be consistent with regulatory guidance regarding the endpoint.
Section 1.3 Schedule of Activities, Table 1 and Table 2	Updated to clarify the requirements for PFS follow-up as well as timing of Serum and Urine Immunofixation testing.	Update improves readability and removes ambiguity when specifying the protocol requirements for PFS follow-up and immunofixation testing.
Section 2.3.1.Summary of Risk Assessment for Belantamab Mafodotin (Treatment Arm A), Daratumumab (Treatment Arm B), and Bor/Dex (Treatment Arms A and B)	The Risk Assessment table been amended to be consistent with clarifications and updates made in the most current version of the belantamab mafodotin Investigator Brochure (v10.0).	To align protocol language with the updates in the most current version of the belantamab mafodotin Investigator Brochure (v10.0).
Section 3 Objectives and Endpoints	Updated to include Secondary endpoint of Clinical Benefit Rate (CBR) and Exploratory Endpoint of Sustained MRD negativity rate. The definition for Duration of Response (DoR) has been updated to include death due to any cause.	CBR is an additional method of assessment of clinical activity to further characterize efficacy. MRD is recognized as a dynamic indicator that requires consistent monitoring before MRD utility is fully defined, and sustained MRD negativity is a significant prognostic factor. The definition for DoR has been updated to be consistent with regulatory guidance regarding the endpoint.
Section 6.1.4.4 Interference with Serum Protein Electrophoresis and Immunofixation Tests	Updated to clarify the requirements for performing daratumumab-IFE assay	Update improves readability when specifying the protocol requirements for performing assay.
Section 6.5.1 Permitted Concomitant Therapies	Updated to include text regarding therapy for unrelated malignancies.	Clarification that patients with an unrelated second malignancy may remain on study if the malignancy may be addressed by localized therapy.
Section 6.5.2 Prohibited Concomitant Therapies	Updated to specify "anti-myeloma therapy" in place of "anti-cancer therapy".	Clarification that prohibited therapy is specific to therapy for multiple myeloma.
Section 6.6 Dose Modification and Delay	Updated to specify that Medical Monitor should be contacted prior to restarting therapy for patients with dose delays/interruptions longer than 42 days.	Provide specific guidance that sites should contact the Medical Monitor prior to restarting therapy following significant dosing delays in order to protect patient safety and study integrity.

Section # and Name	Description of Change	Brief Rationale
Section 6.6.5 Guidance on Dose Delays for Treatment Arm A and B	Updated to further clarify the definition of a cycle of study treatment.	Clarification provides explicit guidance on what is considered to be the start of a cycle and that if no therapy is given.
Section 6.7 Intervention After the End of the Study	This section has been updated to clarify that no further interventions will occur after the End of Study (final OS analysis).	Clarification provides an explicit statement regarding interventions following the End of Study (final OS analysis).
Section 7.1 Discontinuation of Study Intervention	Updated to require that the Medical Monitor be contacted to review disease assessments and confirm disease progression prior to participant discontinuation for Progressive Disease.	Provide guidance that sites should contact the Medical Monitor to confirm that suspected Progressive Disease meets IMWG criteria in order to prevent patients from being prematurely discontinued from study treatment in the instance that the reason for discontinuation is specifically limited to disease progression.
Section 8.1.3 MRD Assessment and PET-CT Imaging	Updated to clarify the timing for initial and subsequent MRD testing.	Clarification provides more detail in specifying the timing of initial MRD testing and when to perform subsequent testing.
Section 8.5.1 Belantamab Mafodotin Blood Sample Collection for Pharmacokinetics	Added clarification that PK and accompanying sBCMA sample collection may be terminated when sufficient data have been collected.	Clarification informs sites that PK collection may be terminated when sufficient data has been collected, thus reducing the burden on study participants and study sites.
Section 8.9.1 Soluble BCMA	Updated to remove requirement for sBCMA sample collection independent from PK samples and dosing at fixed timepoints.	Biomarker sample collection will not be required at additional timepoints beyond those for PK and dosing at fixed timepoints as these samples are no longer needed to characterize sBCMA activity.
Section 9.4.1 Efficacy Analyses, Table 25	Updated to include Secondary endpoint of Clinical Benefit Rate (CBR) and Exploratory Endpoints of Sustained MRD negativity rate, Time To Best Response (TTBR) and VGPR rate. The definition for Duration of Response (DoR) has been updated to include death due to any cause. The definition for MRD negativity rate has been updated as well.	CBR is an additional method of assessment of clinical activity to further characterize efficacy. MRD is recognized as a dynamic indicator that requires consistent monitoring before MRD utility is fully defined, and sustained MRD negativity is a significant prognostic factor. TTBR and VGPR rate were already included in Section 3.3 Objectives and have been added in Section 9.4.1 for consistency.
Section 9.6 Final Analyses	Section 9.6 has been added to clarify the timing of the final OS analyses and that this analyses will coincide with the End of Study.	The addional text provides specific detail around the timing of the final OS analysis and confirms it will coincide with the End of Study.

Amendment 3: 15 Jul 2021

Where this Protocol Amendment applies:

Protocol Amendment 3 applies to all participants in all countries and all sites.

Overall Rationale for the Amendment 03:

The protocol has been amended to remove the first of two interim analyses that were planned for the 207503 study. The first interim analysis is based on CCI of progression-free survival (PFS) events, allowing for early stopping due to harm (inferior efficacy), and the second interim analysis is based on CCI of PFS events, allowing for early stopping due to futility or efficacy. In addition, safety data is being reviewed periodically starting from when CCI and then every CCI CCI or as requested by the Independent Data Monitoring Committee (IDMC) thereafter. The first interim analysis was removed as the trial has accrued faster than anticipated and completed enrolment well in advance of the estimated date for the first interim analysis.

Safety data will continue to be reviewed periodically every CCI and the interim analysis based on CCI of PFS events will be performed as planned.

Additional changes were incorporated which align with program revisions and/or updates as listed in table below.

Original Section/Table/Figure	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Updated Footnote 15 in the Arm A Schedule of Activities to specify imaging should be retained at the clinical study site.	Imaging should be retained at the clinical study site to be available if needed for analysis rather than being stored at a central vendor.
	Updated Footnote 17 in the Arm B Schedule of Activities to specify imaging should be retained at the clinical study site.	Imaging should be retained at the clinical study site to be available if needed for analysis rather than being stored at a central vendor.
Section 2.2.4.2 Pharmacokinetics and Pharmacodynamics in Humans	Background information has been amended to be consistent with clarifications and updates made in the most current version of the Investigator Brochure (v9.0).	To align language with the most current version of the Investigator Brochure (v9.0).
Section 4.2 Scientific Rationale for Study Design	Text has been updated to specify a single interim analysis will be performed.	Interim analysis for harm (inferior efficacy), based on CCI of PFS events has been removed due to faster than anticipated accrual and completion of enrolment well in advance of the estimated date for the first interim analysis.

Original Section/Table/Figure	Description of Change	Brief Rationale
Section 6.6.5 Guidance on Dose Delays for Treatment Arm A and B, Table 16, Table 17	Text in Row 3 of Table 16 & 17 has been updated from "…bortezomib >21 days" to "…bortezomib ≤21 days" Text in Row 4 of Tables 16 & 17 has been updated from "…bortezomib <21 days" to "…bortezomib >21 days"	This change corrects a typographical error in Table 16 and 17.
Section 9.1.1 Multiple Comparisons and Multiplicity	Text has been updated to specify a single interim analysis will be performed. References to the interim analysis for harm (inferior efficacy) have been removed.	Interim analysis for harm (inferior efficacy), based on CCI of PFS events has been removed due to faster than anticipated accrual and completion of enrolment well in advance of the estimated date for the first interim analysis.
Section 9.2 Sample Size Determination	The number of PFS events needed to trigger Primary Endpoint analysis has been updated from CCI The reference to the software package used for calculation of the Key Secondary Endpoint: Minimal Residual Disease (MRD) Negativity has been updated from East 6.4 to PASS 2019, v19.0.1	The required number of PFS events to trigger Primary Endpoint analysis has been recalculated as a result of the removal of the first interim analysis. The software package used for the calculation of the Stopping Boundaries for the Key Secondary Endpoint: MRD Negativity has been updated to allow for a more precise estimate.
Section 9.4.1 Efficacy Analyses, Table 25	The number of PFS events needed to trigger Primary Endpoint analysis has been updated from CCI.	The required number of PFS events has been recalculated as a result of removing the first interim analysis.
Section 9.5 Interim Analyses, Table 27, Table 28	Text has been updated to specify a single interim analysis will be performed. References to the interim analysis for harm (inferior efficacy) have been removed. The number of PFS events needed to trigger the interim analysis for futility and superiority has been updated from CCI The Stopping Boundaries for PFS Interim Analyses (Table 28) have been recalculated.	Interim analysis for harm (inferior efficacy), based on CCI of PFS events has been removed due to faster than anticipated accrual and completion of enrolment well in advance of the estimated date for the first interim analysis. The required number of PFS events to trigger Primary Endpoint analysis has been recalculated as a result of the removal of the first interim analysis.
Section 9.5 Interim Analyses Table 29	The Stopping Boundaries for MRD Negativity (Table 29) have been recalculated.	The software package used for the calculation of the Stopping Boundaries for the Key Secondary Endpoint: MRD Negativity has been updated to allow for a more precise estimate.

Original Section/Table/Figure	Description of Change	Brief Rationale
Section 10.2.5 Reporting of SAEs to GSK	The follow text has been removed: The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to investigative product/study participation (causality) within 72 hours of SAE entry into the eCRF.	This requirement is no longer in effect. The need for Principal Investigators to document in the electronic case report form (eCRF) that they have reviewed the adverse event/serious adverse event and provide an assessment of causality is not required as they still must document this assessment in the medical record as per the wording in Section 10.2.4.

Amendment 2: 16 Dec 2020

Overall Rationale for the Amendment 02:

The protocol has been amended to update exclusion criteria for HIV+, Hep B+, and Hep C+ participants in order to align with the latest regulatory (US FDA) guidance, to provide clarification to the administration of supportive infusion medications for daratumumab, and to clarify conditions regarding study intervention restart or rechallenge after liver stopping criteria are met.

Additional changes were incorporated which align with program revisions and/or updates as listed in table below.

Original Section/Table/Figure	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Clarified language on Screening period (both Arms)	To clarify language
	Clarified language for collection of AEs and SAEs (Arm B)	To clarify language
	Added clarifying language for analysis of biomarker and BM samples to be done if date and time have been recorded	To clarify language
	Updated Table 2 (Arm B) footnote 5 vital signs based on edits in Section 8.2.3.2	To clarify language
	Added Table 3 for BM Aspirate and Biopsy collection	To clarify BM sample collection
	Added Table 4 for additional procedures for participants with a history of Hepatitis B	To align with the latest regulatory guidance
	Added Table 5 for additional procedures for participants with a history of Hepatitis C	To align with the latest regulatory guidance
	Removed triplicate ECG at Screening in case of QTcF prolongation (both Arms)	To align with deletion of QTc stopping criteria (previous Section 7.1.3) as per belantamab mafodotin program-wide Cardiac Safety Panel recommendations

Original Section/Table/Figure	Description of Change	Brief Rationale
Section 3 Objectives and Endpoints	Added the exploratory objective of assessment of imaging plus MRD negativity rate	To maintain program-wide consistency
Section 4.3.2. Daratumumab Dose, Section 4.3.3. Bortezomib Dose, Section 4.3.4. Dexamethasone Dose, Section 6.1.2. Treatment Arm B Dosing Schedule, Section 6.1.4.1. Daratumumab Required Pre/Post-medication, Section 6.5.2. Prohibited Concomitant Therapies, Section 6.6.2. Daratumumab, Section 7.1.4.2. Daratumumab	Replaced references to USPI/SmPC of Darzalex and Velcade with reference to the most recently approved country-specific label	To avoid discrepancies between USPI/SmPc and country-specific labels
Section 5.2 Exclusion Criteria	Updated exclusion criteria for HIV+, Hep B+, and Hep C+ participants	To align with the latest regulatory guidance
Section 6.1.1. Treatment Arm A Dosing Schedule - Dexamethasone"	Added clarifying language for days of co-administration of treatments	To correct a typographical error
Section 6.1.3 Belantamab Mafodotin and Section 6.1.4 Daratumumab	Added clarifying language for body weight at baseline and dose calculations in case of body weight changes	To clarify dose calculations
Section 6.1.4.1 Daratumumab Required Pre/Post-medication	Replaced existing language with reference to daratumumab label	To clarify pre- and post-infusion medications for daratumumab administration based on the label guidance
Section 6.5.2 Prohibited Concomitant Medications	Added language for participants receiving anti-HIV and anti-microbials:	To align with the latest regulatory guidance
Section 6.6.4 Dexamethasone	Clarified language for dose reduction if Dose Level -1 is not tolerated	To clarify the dose modification for dexamethasone
Section 6.6.6 Management of Hepatitis B+ participants	Added section to clarify management of Hepatitis B+ participants	To align with the latest regulatory guidance
Section 7.1.2.1 Study Intervention Restart or Rechallenge after Liver Stopping Criteria Are Met	Clarified that IRB/IEC approval is obtained if required	To align with GSK liver monitoring requirements
Section 7.1.3 QTc Stopping Criteria	Removed section	To align with belantamab mafodotin program-wide Cardiac Safety Panel recommendations
Section 8.1 Efficacy Assessments and Section 8.1.3 MRD Assessment and PET-CT Imaging	Extended timepoint for MRD negativity confirmation by PET-CT from 21 days to 42 Days	To align with GSK program
Section 8.2.3.2 Vital Sign Measurement for Treatment Arm B	Added clarifying language for measurements in case of daratumumab split dosing	To clarify language
Section 8.9.1 Soluble BCMA Table 20	Added clarifying language in table footnote for sBCMA sample collection in case daratumumab administration on C1D1 is split over Day 1 and Day 2	To clarify collection of sBCMA sample

Original Section/Table/Figure	Description of Change	Brief Rationale
Section 9.4.3 Pharmacokinetic Analyses	Updated text by using a more precise language around the Population PK model	To clarify the Population PK model to be used in the analysis
Section 10.4.1 Liver Safety Drug Restart or Re-Challenge Guidelines	Clarified that IRB/IEC approval is obtained if required	To align with GSK liver monitoring requirements
Section 10.9 Appendix 9: Corneal Event Grading and Prophylactic Interventions for Corneal Toxicity (Treatment Arm A)	Clarified definition of corneal ulcer and definition of superficial keratopathy	To align with GSK program
Section 10.16 Appendix 16 Data Management/Monitoring	Added new Appendix on remote Data Management/Monitoring	To allow flexibility in study conduct
Throughout document	Minor editorial and document formatting revisions	Minor revisions without change to content, therefore have not been specifically delineated

Amendment 01: 16 Jul 2020

Overall Rationale for the Amendment:

The protocol has been amended based on regulatory agency comments. Additional changes were incorporated to align with program-wide revisions and/or updates. In addition, based upon feedback from regulatory agencies, a new Keratopathy Visual Acuity (KVA) scale has been introduced in this amendment for grading of treatment-related corneal events. Furthermore, dose modification guidelines and stopping criteria for belantamab mafodotin for treatment-related corneal events have been aligned with the guidelines of the new KVA Scale.

Protocol Amendment 1 includes the following:

Original Section/Table/Figure	Description of Change	Brief Rationale
Section 1.1 Primary and Secondary Objectives and Endpoints	Added the row for the Key Secondary Objective/Endpoint: Minimal Residual Disease (MRD) negativity rate. This was previously a secondary endpoint	Differentiate the Key Secondary Objective/endpoint from other Secondary Objectives/endpoints based on regulatory agency feedback
Section 1.3 Schedule of Activities (SoA) Table 1 and Table 2	Added a new text related to Home Healthcare and Telemedicine Approaches	To allow flexibility in study conduct
Section 1.3 Schedule of Activities (SoA) – Arm A and ARM B	Bone Marrow sample for BCMA expression; added required biopsy in addition to aspirate collection for biomarker research. Replaced aspirate clot by aspirate.	Change in sample type due to observed assay failure secondary to hemodilution in bone marrow aspirate clots. BCMA IHC is validated in bone marrow biopsy samples
Section 1.3 Schedule of Activities (SoA) – Arm A and ARM B	• Ocular Exam: updated language and footnote number • Adverse Events/SAEs: updated the language • Added Urine dipstick for protein	Ocular exam language updated based on regulatory agency feedback for Arm A. Ocular exam updated for Arm B per program-wide language. Administrative changes were made as described.

Original Section/Table/Figure	Description of Change	Brief Rationale
	• Imaging for Extramedullary Disease: updated schedule requirement • Bone Marrow Assessments: updated language for optional samples • Updated footnotes 11,13, 15, 21 and 22	
Section 1.3. SoA (Arm B).	Added requirement to undergo central testing with a daratumumab-specific immunofixation assay to confirm PD or CR/sCR	To be consistent with the assessment of CR where daratumumab Interference is suspected (Section 8.1.2)
Section 2.1 Study Rationale	Update text regarding the mechanism of action of belantamab mafodotin	To clarify the mechanism of action of belantamab mafodotin
Section 2.2.3 Figure 1	The figure of Mechanism of Action has been updated	To clarify the mechanism of action of belantamab mafodotin
Section 2.3.1 Summary of Risk Assessment for Belantamab Mafodotin (Treatment Arm A), Daratumumab (Treatment Arm B), and Bor/Dex (Treatment Arms A and B)	Inserted Seizures and Progressive multifocal leukoencephalopathy (PML) description	Updated to comply with bortezomib label
Section 2.2.4 Clinical Experience with Belantamab Mafodotin	Added Section: 2.2.4.1. Safety and Section 2.2.4.2. Pharmacokinetics and Pharmacodynamics in Humans. Updated the existing text regarding safety and efficacy.	To reflect latest clinical and safety information included in the new IB Version 8.
Section 2.2.4.2 Clinical Pharmacokinetics	Updated the section number and title to Section 2.2.4.2. “Pharmacokinetics and Pharmacodynamics in Humans” Updated text regarding the pharmacokinetics and pharmacodynamics of belantamab mafodotin	To reflect latest clinical and safety information included in the new IB Version 8.
Section 3 Objective and Endpoints	Added the row for the Key Secondary Objective : Minimal Residual Disease (MRD) negativity rate. This was previously included as a secondary objective Deleted the exploratory objective of assessment of imaging plus MRD negativity rate	Differentiate the Key Secondary Objective from other Secondary Objectives To maintain program-wide consistency
Section 5.1 Inclusion Criteria	Updated the IC 4 as: “Previously treated with at least 1 prior line of MM therapy, and	IC4 updated in acknowledgement of the fact that progressive disease during or after most recent therapy prior to

Original Section/Table/Figure	Description of Change	Brief Rationale
	must have documented disease progression during or after their most recent therapy. **Note**: induction + ASCT + maintenance is 1 line of therapy" Updated language IC #10	enrolment might not be fully according to IMWG criteria. Routine clinical practice may not collect sufficient information about disease status to confirm disease progression treatment lines prior to study entry using formal IMWG criteria. Clinical assessment of disease progression by the investigator will be utilized. On-study disease response will still be assessed according to IMWG criteria. Added the time for the use of contraceptives post-last dose for patients having received daratumumab. Updated time of contraceptive use related to belantamab mafodotin.
Section 5.1 Inclusion Criteria Table 3 - Adequate Organ System Function Based on Safety Assessments	Added Urine dipstick for protein test Updated language	To add an optional method to screen for urine protein
Section 5.3 Lifestyle Considerations	Clarified language regarding the use of contact lenses. Moved the sentence about administration of live/ live-attenuated vaccine to Prohibited Concomitant Medication.	The text was moved to a more appropriate section
Section 6.1.1 Treatment Arm A Dosing Schedule	Added new text related to Home Healthcare and Telemedicine Approaches	To allow flexibility in study conduct
Section 6.1.2 Treatment Arm B Dosing Schedule	Added new text related to Home Healthcare and Telemedicine Approaches	To allow flexibility in study conduct
Section 6.1.2. Daratumumab	Specified the number of weeks corresponding to the cycle number during the treatment with daratumumab	To clarify the dosing schedules
Section 6.1.6 Dexamethasone	Updated language	To clarify dose modification
Section 6.5.2 Prohibited Concomitant Therapies	Added administration of live/ live-attenuated vaccine text. See the change for Section 5.3 above.	To enhance patients' safety, the period for prohibited use of live/live-attenuated vaccines has been extended
Section 6.6.1 Belantamab Mafodotin – Table 6 Dose Modifications	Urine dipstick for protein test has been added. (New Table 7)	Urine dipstick added as an optional method to screen for urine protein
Section 6.6.1 Belantamab mafodotin Dose Modification	Added a new table- Table 9- General Dose Modification and Management Guidelines for Drug-Related Adverse Events Not Otherwise Specified	To further clarify dose modification for adverse events associated with belantamab mafodotin

Original Section/Table/Figure	Description of Change	Brief Rationale
Section 6.6.1. Belantamab mafodotin dose modification for Corneal AEs	A table that provided guidelines for treatment-related corneal events that was originally in Appendix 9 was moved to Section 6.6.1 in the amendment. This table in Section 6.6.1 has been replaced by a new table (Table 8) that provides updated guidelines for treatment-related corneal events based on Keratopathy Visual Acuity Scale for grading corneal events that is now in Appendix 9 as a new table (Table 26). The new Appendix 10 lists the required qualifications of eye care specialists who will assess corneal AEs.	To move key dose modification into a more appropriate section and improve clarity of qualifications of eye care specialists. The dose modification guidelines for belantamab mafodotin treatment-related corneal events have been updated for additional clarity and these are based on a new Keratopathy Visual Acuity Scale for treatment-related corneal events (in Appendix 9) that takes in consideration both corneal examination findings as well as visual acuity changes to grade the corneal toxicities.
Section 6.6.4 Dexamethasone	Added a new table – Table 12- to provide guidelines for permitted dose reductions for Dexamethasone in both treatment Arms	To clarify dose modification for dexamethasone
Section 7.1.2. Liver Chemistry Stopping Criteria	Updates to GSK liver safety algorithm	To align with GSK liver monitoring requirements.
Section 7.1.2.1 Study Intervention Restart or Rechallenge after Liver Stopping Criteria Are Met	Updates to GSK liver safety algorithm	To align with GSK liver monitoring requirements.
Section 8 Study Assessment and Procedures	Added new text related to Home Healthcare and Telemedicine Approaches	To allow flexibility in study conduct
Section 8 Study Assessment and Procedure – Table 11	• Urine dipstick for protein has been added - (Now Table 15) • Bone Marrow Aspiration / Biopsy section has been updated	To allow sites to use urine dipstick testing as a first pass for urine protein monitoring at screening. To clarify the distinction between mandatory and optional BM tests for biomarker analysis
Section 8.2.6.1 Treatment Arm A	Updated ocular assessment schedule	To clarify ocular assessment for participants treated with belantamab mafodotin based on regulatory agency feedback.
Section 8.2.6.2 Treatment Arm B	Updated ocular assessment schedule	To clarify ocular assessment for participants treated with daratumumab.
Section 8.2.8 Pregnancy Testing (WOCBP only)	Language has been updated to add the duration of required contraception for patients receiving daratumumab. Updated time of contraceptive use related to belantamab mafodotin	Ensure clarity of requirements To reflect latest clinical and safety information included in the new IB Version 8

Original Section/Table/Figure	Description of Change	Brief Rationale
Section 8.3.5 Pregnancy	Updated time of contraceptive use related to belantamab mafodotin	To reflect latest clinical and safety information included in the new IB Version 8
Section 8.4 Overdose	Dose holding guidance updated in setting of overdose. Monitor closely for AEs/SAEs and laboratory abnormalities until: (a) belantamab mafodotin can no longer be detected systemically (at least 3 months); (b) Monitor closely for AEs, SAEs, and laboratory abnormalities until resolution. Provided guidance re. timing of obtaining an additional PK and serum sBCMA sample in the event of an overdose.	New PK data supports revised guidance.
Section 8.9.2 Tumor related biomarkers	Language updated	Clarified which sampling for biomarker analysis is optional.
Section 9.2 Sample Size Determination	Added description of sample size justification for MRD negativity	Description of sample size and power is provided since MRD Negativity is a key secondary endpoint that will be formally tested
Section 9.4.1 Table 17	Stats analysis methods table updated to include the new key secondary endpoint of MRD Negativity (Now Table 21)	Added details of how MRD will be analysed and described in the study report.
Section 9.1.1. Multiplicity	New subsection added to address multiplicity of analysis issues.	Description of sample size and power is provided since MRD Negativity is a key secondary endpoint that will be formally tested
Section 9.5 Table 19 Summary of Planned Interim Analyses Table 20 Stopping Boundaries for Interim Analyses	• (Now Table 23 and Table 24) • Updates were made to the planned interim analysis and stopping boundaries due to changing the information fraction for the second PFS analysis to a higher fraction to provide more mature efficacy data. • Due to the inclusion of the new key secondary endpoint of MRD Negativity in the testing hierarchy procedure at the second PFS interim analysis, stopping boundaries were added	Following the regulatory agency comments, the second PFS interim analysis that was to be performed at CCI information has been changed to occur at CCI information fraction. A summary description of the stopping rules for MRD negativity at the second PFS interim analysis is needed for the protocol

Original Section/Table/Figure	Description of Change	Brief Rationale
Section 10.4 Liver safety (Appendix 4)	• INR follow-up analysis now applies to ALL countries and not just Japan. • Blood sample for PK analysis and for sBCMA now to be obtained within 70 days, and not 45 days, after last dose of belantamab mafodotin. • Updates made to the GSK liver safety algorithm	. Revised per GSK standard for liver safety Follow-up lengthened based on new pk data Revised per GSK standard for liver safety
Section 10.9 Appendix 9: Corneal Event Grading and Prophylactic Interventions for Corneal Toxicity (Treatment Arm A)	Appendix title modified to "Corneal Event Grading and Prophylactic Interventions for Corneal Toxicity (Treatment Arm A)". A new Keratopathy Visual Acuity (KVA) Scale for treatment-related corneal events (new Table 26) has been added that provides guidance for grading treatment-related corneal events.	This updated grading scale (KVA scale) for treatment-related corneal events takes in consideration both corneal examination findings as well as visual acuity changes to grade the corneal toxicities.
Section 10.10 Eye care specialist's qualifications and requirements	Added a new Appendix 10: Eye care specialist's qualifications and requirements	To clarify the qualifications and expectations for eye care specialist responsible for eye exams
Section 10.12 Country specific requirements	GFR formula included for Japan	To be consistent with GSK standard
Section 10.16 Home Healthcare and Telemedicine Approaches	Added a new Appendix to allow Home Healthcare and Telemedicine Approaches	To allow flexibility in study conduct

11. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365-376.

Ali SA, Shi V, Maric I, et al. T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma. Blood. 2016;128(13): 1688-1700.

Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. Stat Med. 1998 May 30;17(10):1103-1120.

Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst. 2014;106(9).

Bellucci, R, Alyea, EP, Chiaretti, S, et al. Graft-versus-tumor response in patients with multiple myeloma is associated with antibody response to BCMA, a plasma-cell membrane receptor. Blood. 2005;105(10):3945-3950.

Belnoue, E, Pihlgren, M, McGaha, TL, et al. APRIL is critical for plasmablast survival in the bone marrow and poorly expressed by early-life bone marrow stromal cells. Blood. 2008;111(5):2755-2764.

Bretz F, Maurer W, Brannath W, et al. A graphical approach to sequentially rejective multiple test procedures. Statistics in medicine. 2009;28(4):586-604.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982;38(1):29-41.

Cartier S, Zhang B, Rosen VM, et al. Relationship between treatment effects on progression-free survival and overall survival in multiple myeloma: a systematic review and meta-analysis of published clinical trial data. Oncol Res Treat. 2015;38(3):88-94.

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A,et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. Journal of Clinical Oncology, 1993;11(3): 570-579.

Cocks K, Cohen D, Wisløff F, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-MY20) in assessing the quality of life of patients with multiple myeloma. Eur J Cancer. 2007 Jul;43(11):1670-1678.

Cowan AJ, Allen C, Barac A, et al. Global burden of multiple myeloma: a systematic analysis for the global burden of disease study 2016. JAMA Oncol. 2018 Sep 1;4(9):1221-1227.

Darce JR, Arendt BK, Wu X, et al. Regulated expression of BAFF-binding receptors during human B cell differentiation. J Immunol. 2007;179(11):7276-7286.

Darzalex SmPC (2019). https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf (Last visited: 4 Dec 2019).

Darzalex USPI (2019). https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761036s024lbl.pdf (Last visited: 4 Dec 2019).

Dimopoulos M, Sonneveld P, Nahi H, et al. Progression-free survival as a surrogate endpoint for overall survival in patients with relapsed or refractory multiple myeloma. Value Health. 2017;20(9): A408.

Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): A randomized, phase 3, open-label, multicenter study. Lancet Oncol. 2016; 17(1):27-38.

Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;375(14):1319-1331.

Dimopoulos MA, Orlowski RZ, Facon T, et al. Retrospective matched-pairs analysis of bortezomib plus dexamethasone versus bortezomib monotherapy in relapsed multiple myeloma. Hematologica. 2015;100:100-106.

Dimopoulos MA, Oriol A, Nahi H, et al. Overall survival with daratumumab, lenalidomide, and dexamethasone in previously treated multiple myeloma (POLLUX): A randomized, open-label, phase III trial J Clin Oncol 2023;41:8:1590-1599.

Donaghy H. Effects of antibody, drug and linker on the preclinical and clinical toxicities of antibody-drug conjugates. MAbs. 2016;8(4):659–671. doi:10.1080/19420862.2016.1156829

Dougherty BE, Nichols JJ, Nichols KK. Rasch analysis of the Ocular Surface Disease Index (OSDI). Invest Ophthalmol Vis Sci. 2011 ;52(12): 8630-8635.

Eaton JS, Miller PE, Mannis MJ, et al. Ocular adverse events associated with antibody-drug conjugates in human clinical trials. J Ocul Pharmacol Ther. 2015;31(10):589-604.

FDA, 2009, Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. Services, UDoHaH. Rockville, MD.

FDA, 2020, Guidance for Industry. Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment. Docket Number: FDA-2018-D-3090.

GSK2857916 Investigator's Brochure. GSK document No. RPS-CLIN-051778. Effective 12 May 2023.

Guy W (ed). ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration, 1976.

Hou H-A, Tang C-H, Liu H-Y, Qiu H. Real world treatment patterns and survival in patients with multiple myeloma in Taiwan. Blood. 2017;130:5434.

Huang B, Tian L. Utilizing restricted mean duration of response for efficacy evaluation of cancer treatments. Pharm Stat. 2022 Sep;21(5):865-878. doi: 10.1002/pst.2198. Epub 2022 Feb 21. PMID: 35191170.

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.

Jiang C, Loo WM, Greenley EJ, et al. B cell maturation antigen deficiency exacerbates lymphoproliferation and autoimmunity in murine lupus. J Immunol. 2011 ;186(11): 6136-6147.

Kropff MH, Bisping G, Wenning D, Berdel WE, Kienast J. Bortezomib in combination with dexamethasone for relapsed multiple myeloma. Leuk Res. 2005 May;29(5):587-90.

Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-346.

Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia. 2014;28(5):1122-1128.

Kumar SK, Lee, JH, Lahuerta, JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. Leukemia. 2012;26(1):149-157.

Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111(5):2516-2520.

Kyprolis SmPC. (2018). https://www.ema.europa.eu/documents/product-information/kyprolis-epar-product-information_en.pdf (Last visited: 16 Nov 2018).

Kyprolis USPI. (2019). https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/kyprolis/kyprolis_pi.pdf (Last visited: 15 May 2019).

Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70:659-663.

Langat DL, Wheaton DA, Platt JS, Sifers T, Hunt JS. Signaling pathways for B cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL) in human placenta. Am J Pathol. 2008;172(5):1303–1311. doi:10.2353/ajpath.2008.071139

Laurent SA, Hoffmann FS, Kuhn PH, et al. Gamma-secretase directly sheds the survival receptor BCMA from plasma cells. Nat Commun. 2015 ;6 :7333.

Li X, Wulfsohn MS, Koch GG. Considerations on testing secondary endpoints in group sequential design. Statistics in Biopharmaceutical Research. 2017 Oct 2;9(4):333-7.

Lonial S, Anderson KC. Association of response endpoints with survival outcomes in multiple myeloma. Leukemia. 2014;28(2):258-268.

Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. N Engl J Med 2015;373(7):621-631.

Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomized, phase 2 trial. Lancet. 2016 Apr 9;387(10027):1551-1560.

Lonial S, Lee HC, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomized, open-label, phase 2 study. Lancet Oncol. 2020:21:207-21.

Montes De Oca R, Bhattacharya S, Vitali N, et al. The anti-BCMA antibody-drug conjugate GSK2857916 drives immunogenic cell death and immune-mediated anti-tumour responses, and in combination with an OX40 agonist potentiates in vivo activity. HemaSphere. 2019;1: 231.

Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomized, phase 3, non-inferiority study. Lancet Oncol. 2011 May 1;12(5):431-440.

Moreau P, San Miguel J, Sonneveld P, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals Oncol. 2017; 0:1-11.

Moreau P, Touzeau C. Multiple myeloma: From front-line to relapsed therapies. American Society of Clinical Oncology Educational Book 35. http://meetinglibrary.asco.org/record/104109/edbook#fulltext, American Society of Clinical Oncology. 2015:504-511.

Moreaux J, Legouffe E, Jourdan E, et al. BAFF and APRIL protect myeloma cells from apoptosis induced by interleukin 6 deprivation and dexamethasone. Blood. 2004;103(8):3148-3157.

NCCN (National Comprehensive Cancer Network) Multiple myeloma guidelines. 2018. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf (Accessed 3 Sept 2018).

NCI. NCI Common Terminology Criteria for Adverse Events, Version 5 (2010) https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf (Accessed 3 Sept 2018).

New York Heart Association (1994). The Criteria Committee of the New York Heart Association (NYHA). Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th Ed. Boston, MA:253-256.

Novak AJ, Darce JR, Arendt BK, et al. Expression of BCMA, TACI, and BAFF-R in multiple myeloma: a mechanism for growth and survival. Blood. 2004;103(2):689-694.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655.

Palumbo A, Avet-Loiseau H, Olivia S, et al. Revised International Staging System for Multiple Myeloma: A Report from the International Myeloma Working Group. Clin Oncol 2015b 33:2863-2869.

Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med. 2016;375(8):754-766.

Palumbo A, Gay F. How to treat elderly patients with multiple myeloma: combination of therapy or sequencing. ASH Education Program Book. 2009 Jan 1;2009(1):566-77.

Palumbo A, Offidani M, Pégourie B, et al. Elotuzumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma: 2-year follow-up. Blood. 2015 126:510.

Pont MJ, Hill T, Cole G, Abbott J, Kelliher J, Salter A, et al. γ-secretase inhibition increases efficacy of BCMA-specific chimeric antigen receptor T cells in multiple myeloma. Blood. 2019; Doi: 10.1182/blood.2019000050.

Proskorovsky I, Lewis P, Williams CD, et al. Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. Health Qual Life Outcomes. 2014 Mar 11;12:35.

Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538-548.

Rajkumar SV, Kumar S. Multiple myeloma: diagnosis and treatment. In Mayo Clinic Proceedings 2016 Jan 1 (Vol. 91, No. 1, pp. 101-119). Elsevier.

Rajkumar SV. Updated Diagnostic Criteria and staging system for multiple myeloma. Am Soc Clin Oncol Educ Book. 2016;35:e418-423.

Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. Leukemia. 2009 Jul;23(7):1337.

Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med. 2003;348(26):2609-2617.

Richardson PG, Barlogie B, Berenson J, et al. Extended follow-up of a phase II trial in relapsed, refractory multiple myeloma: final time-to-event results from the SUMMIT trial. Cancer. 2006;106(6):1316-1319.

Richardson PG, Hideshima T, Mitsiades C, et al. The emerging role of novel therapies for the treatment of relapsed myeloma. J Natl Compr Canc Netw. 2007;5(2):149-162.

Richardson PG, Rocafiguera AO, Beksac M, et al. Pomalidomide (POM), bortezomib, and low-dose dexamethasone (PVd) vs bortezomib and low-dose dexamethasone (Vd) in lenalidomide (LEN)-exposed patients (pts) with relapsed or refractory multiple myeloma (RRMM): Phase 3 OPTIMISMM trial. 2018; Abstract #8001; 2018 ASCO Annual Meeting, Chicago.

Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005 Jun 16;352(24):2487-98.

Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood. 2010 Aug 5;116(5):679-686.

Robinson D, Kaura S, Keily D, Hussein MA, Impact of novel treatments on mutiple myeloma survival. Blood. 2014;124:566.

Sanchez E, Li M, Kitto A, et al. Serum B-cell maturation antigen is elevated in multiple myeloma and correlates with disease status and survival. Br J Hematol. 2012;158(6):727-738.

Schiffman RM, Christianson MD, Jacobsen G, et al. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol. 2000;118(5):615-621.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019; 69:7-34.

Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. J Clin Oncol. 2012 Aug 20;30(24):2946-2955.

Sonneveld P, Chanan-Khan A, Weisel K,et. al. Overall survival with daratumumab, bortezomib, and dexamethasone in previously treated multiple myeloma (CASTOR): a randomized, open-label, phase III trial. J Clin Oncol. 2023;41(8):1600-1609.

Spencer A, Lentzsch S, Weisel K, et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. Haematologica. 2018; 103: 2079-87.

Stewart K, Siegel D, Ludwig H, et al. Overall survival (OS) of patients with relapsed/refractory multiple myeloma (RRMM) treated with carfilzomib, lenalidomide,

and dexamethasone (KRd) versus lenalidomide and dexamethasone (Rd): final analysis from the randomized Phase 3 Aspire Trial. Blood 2017;130 (Supplement 1):743.

Tai YT, Anderson KC. Targeting B-cell maturation antigen in multiple myeloma. Immunotherapy. 2015;7(11):1187-1199.

Tai YT, Li XF, Breitkreutz I, et al. Role of B-cell-activating factor in adhesion and growth of human multiple myeloma cells in the bone marrow microenvironment. Cancer Res. 2006 ;66(13):6675-6682.

Tai YT, Mayes PA, Acharya C, et al. Novel anti–B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. Blood. 2014 May 15;123(20):3128-3138.

Trudel S, Lendvai N, Popat R, et al. Antibody-drug conjugate, GSK2857916, in relapsed/refractory multiple myeloma: an update on safety and efficacy from dose expansion phase I study. Blood Cancer J. 2019 Mar 20;9(4):37.

Trudel S, Lendvai N, Popat R, et al. Deep and durable responses in patients (Pts) with relapsed/refractory multiple myeloma (MM) treated with monotherapy GSK2857916, an antibody drug conjugate against B-cell maturation antigen (BCMA): preliminary results from part 2 of study BMA117159. Blood. 2017;130(Suppl 1):741.

Trudel S, Lendvai N, Popat R, et al. Targeting B-cell maturation antigen with GSK2857916 antibody–drug conjugate in relapsed or refractory multiple myeloma (BMA117159): a dose escalation and expansion phase 1 trial. Lancet Oncol. 2018 Dec;19(12):1641-1653.

Varfolomeev E, Kischkel F, Martin F, et al. APRIL-deficient mice have normal immune system development. Mol Cell Biol. 2004;24(3):997-1006.

Velcade SmPC (2020). https://www.ema.europa.eu/en/documents/product-information/velcade-epar-product-information_en.pdf (Last visited: 4 Dec 2019).

Velcade USPI (2021). https://www.velcade.com/files/pdfs/VELCADE_PRESCRIBING_INFORMATION.pdf (Last visited: 22 Jun 2022).

West CD, Boyd E (2000). Nomogram for Body Surface Area Calculation, modified from data of E. Boyd by C.D. West. Nelson textbook of pediatrics (16th ed.). Behrman, RE, Kliegman, RM and Jenson, HB. Philadelphia, W.B. Saunders.

Signature Page for 207503 TMF-16739525 v2.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 20-Sep-2023 15:38:46 GMT+0000

Signature Page for TMF-16739525 v2.0