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Protocol Title: A Phase I/II, Open-label, Dose Escalation and Expansion Study to Evaluate Safety, Tolerability, and Clinical Activity of the Antibody-Drug Conjugate GSK2857916 Administered in Combination with Lenalidomide Plus Dexamethasone (Arm A), or Bortezomib Plus Dexamethasone (Arm B) in Participants with Relapsed/Refractory Multiple Myeloma – (DREAMM 6)

Protocol Number: 207497 / Amendment 04

Compound Number: GSK2857916

Brief Title: Phase I/II study of the Antibody-Drug Conjugate GSK2857916 Administered in Combination with Lenalidomide Plus Dexamethasone (Arm A), or Bortezomib Plus Dexamethasone (Arm B) in Participants with Relapsed/Refractory Multiple Myeloma

Study Phase: Phase 1/Phase 2

Acronym: DREAMM 6

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 4	*30 Jun 2022*	*TMF-14624358*
Amendment 3	*13-Jul-2020*	*2017N330850_04*
Amendment 2	*26-Apr-2019*	*2017N330850_03*
Amendment 1 (Republished)	*14-May-2018*	*2017N330850_02*
Amendment 1	*07-May-2018*	*2017N330850_01*
Original Protocol	*28-Feb-2018*	*2017N330850_00*

Amendment 04: 30 Jun 2022

Overall Rationale for the Amendment:

This protocol has been amended to update the end of study definition and to include continued access to study intervention (Post Analysis Continued Treatment [PACT]) after final analysis.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1 Synopsis	Added additional content to implement post analysis continued treatment (PACT) phase and clarification of end of study definition	To allow continued treatment of study participants who continue to derive clinical benefit post the final analysis
Section 3 Schedule of Activities	Added additional content to clarify visit schedule for PACT phase	To allow continued treatment of study participants who continue to derive clinical benefit post final analysis
Section 4.3.1 Risk Assessment	Updated the summary of risk assessment table for the Combination Therapy of Belantamab Mafodotin with Len/Dex (Arm A) and Belantamab Mafodotin with Bor/Dex (Arm B)	Changes made as per the latest IB
Section 5 Objectives and Endpoints	Included additional exploratory objectives	To match plans for final statistical analysis
Section 6.1 Overall Design	Updated the language of the overall design section to differentiate between the end of data collection and the end of study timepoints	To allow continued treatment of study participants who continue to derive clinical benefit post final analysis

Section # and Name	Description of Change	Brief Rationale
Section 6.3 Participant Study Completion, Study Analysis and End of Study	Updated the language of study analysis section to combine the primary and final analysis	Support deliverables for final CSR and to implement PACT
Section 6.4 End of Study Definition	Added additional content to implement PACT phase and end of study	To allow continued treatment of study participants who continue to derive clinical benefit post final analysis
Section 8.1.4 Pharmaceutical Presentations	Added additional content to dosage form of belantamab mafodotin as a lyophilized powder	To allow continued treatment of study participants who continue to derive clinical benefit post final analysis
Section 8.1.5 Preparation of Doses	Added additional content to preparation of belantamab mafodotin in lyophilized form	To allow continued treatment of study participants who continue to derive clinical benefit post final analysis
Section 8.8 Treatment After the End of the Study	Clarification around treatment following end of the study	To allow continued treatment of study participants who continue to derive clinical benefit post final analysis
Section 8.9 Continued Access to Study Intervention after Final Data Cut	New section to align with implementation of PACT phase	To allow continued treatment of study participants who continue to derive clinical benefit post final analysis
Section 10.2.1 Time Period and Frequency for Collecting AE and SAE Information	Included additional content to align with implementation of PACT phase	To allow continued treatment of study participants who continue to derive clinical benefit post final analysis
Section 12.4.9 Final Analysis	Updated the language of study analysis section to combine the primary and final analysis	Support deliverables for final CSR and to implement PACT

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1. SYNOPSIS

Protocol Title: A Phase I/II, Open-label, Dose Escalation and Expansion Study to Evaluate Safety, Tolerability, and Clinical Activity of the Antibody-Drug Conjugate GSK2857916 Administered in Combination with Lenalidomide Plus Dexamethasone (Treatment Arm A), or Bortezomib Plus Dexamethasone (Treatment Arm B) in Participants with Relapsed or Refractory Multiple Myeloma – **DREAMM 6.**

Short Title: Dose Escalation/Dose Expansion Study of GSK2857916 Administered with Lenalidomide Plus Dexamethasone (Arm A), or Bortezomib Plus Dexamethasone (Arm B) in Participants with RRMM.

Brief Rationale

Belantamab mafodotin is a humanized IgG1 antibody drug conjugate (ADC) which binds specifically to B-cell maturation antigen (BCMA) (Figure 3) [Tai, 2014; Montes De Oca, 2019]. Upon binding to the cell surface, belantamab mafodotin is rapidly internalized and active drug (cysteine monomethyl auristatin F [cys-mcMMAF]) is released inside the cell. Belantamab mafodotin has been produced in an afucosylated form to generate an enhanced ADCC/ADCP response upon binding to FcγRIIIa receptors on the surface of human effector cells. Importantly, BCMA expression is maintained at the cell surface over time following belantamab mafodotin binding and internalization due to rapid BCMA receptor recycling and/or new protein synthesis.

We hypothesize that the combination of belantamab mafodotin with standard of care (SoC) therapies (lenalidomide/dexamethasone [Len/Dex] or bortezomib/dexamethasone [Bor/Dex]) may potentially result in additive or enhanced effects and could potentially translate into deeper and longer responses for relapsed/refractory multiple myeloma (RRMM) participants treated with either Len/Dex or Bor/Dex alone. While there are some potential overlaps in the pattern of identified toxicities (primarily hematologic), they are expected to be manageable. Given the single agent activity of belantamab mafodotin in RRMM, the combination therapy with these agents remains an attractive option to explore for RRMM.

This study will evaluate the safety and tolerability profile of belantamab mafodotin when administered in combination with approved SoC regimens of either Len/Dex (Arm A) or Bor/Dex (Arm B) in participants with RRMM, i.e., those who have relapsed or who are refractory to at least 1 line of approved therapy. Part 1 of the study is a dose escalation phase to evaluate the safety and tolerability of up to 3 dose levels and up to 2 dosing schedules of belantamab mafodotin in combination with the two SoC regimens. Part 2 will further evaluate the safety and preliminary clinical activity of belantamab mafodotin at selected dose levels and alternate dosing schedules in combination with Len/Dex or Bor/Dex.

Overall Objectives and Endpoints

The primary and secondary objectives, along with the corresponding endpoints for study 207497 are listed below.

Objectives	Endpoints
Primary	
Dose Escalation Determine safety, tolerability of belantamab mafodotin in combination with either Len/Dex (Arm A) or Bor/Dex (Arm B) to establish a recommended dose range and schedule to evaluate in Dose Expansion for participants with RRMM	Number (%) of participants with dose-limiting toxicities (DLTs). Number (%) of participants with adverse events (AEs), changes in clinical signs and laboratory parameters.
Dose Escalation and Expansion[a] Select the dose(s) and dosing schedule for further investigation based on safety and tolerability of belantamab mafodotin in combination with either Len/Dex (Arm A) or Bor/Dex (Arm B) for participants with RRMM	A comprehensive determination based on safety and serious adverse events (SAEs)/AEs.
Dose Expansion To determine preliminary clinical activity of belantamab mafodotin in combination with either Len/Dex (Arm A) or Bor/Dex (Arm B) for participants with RRMM	A specific determination based on ORR defined as percentage (%) of participants achieving ≥PR as defined by the IMWG Uniform Response Criteria for MM [Kumar, 2016].
Secondary **Dose Escalation and Expansion**	
To evaluate the pharmacokinetics profile of belantamab mafodotin when administered in combination with Len/Dex (Arm A) or Bor/Dex (Arm B) in participants with RRMM	Belantamab mafodotin PK parameters, as data permit
To evaluate the pharmacokinetics profile of lenalidomide when administered in combination with belantamab mafodotin and dexamethasone	Lenalidomide PK parameters, as data permit in Cycle 1
To evaluate the pharmacokinetics profile of bortezomib when administered in combination with belantamab mafodotin and dexamethasone	Bortezomib PK parameters, as data permit in Cycle 1
To assess anti-drug antibodies (ADAs) against belantamab mafodotin	Incidence and titers of ADAs against belantamab mafodotin pre-dose in Cycle 1 and selected subsequent cycles
To evaluate the effect and tolerability of belantamab mafodotin in combination with Len/Dex (Arm A) or Bor/Dex (Arm B) on	Changes from baseline in symptoms and related impacts as measured by OSDI, NEI-VFQ-25 and PRO CTCAE

Objectives	Endpoints
symptomatic adverse events in participants with RRMM	
To further characterize safety of belantamab mafodotin administered in combination with Len/Dex (Arm A) or Bor/Dex (Arm B) in participants with RRMM	Incidence of AEs, including SAEs and AEs of special interest (corneal events, thrombocytopenia and infusion related reactions). Ocular findings on ophthalmic exam
To evaluate the effect of belantamab mafodotin in combination with Len/Dex (Arm A) or Bor/Dex (Arm B) on health-related quality of life in participants with RRMM	Changes from baseline in health-related quality of life as measured by the EORTC QLQ-C30 and QLQ-MY20

a. Data from the both the Escalation and Expansion cohorts will be used to evaluate this composite endpoint.

Overall Study Design

This is a Phase I/II, open-label, dose escalation and expansion study to select the dose and dosing schedule of belantamab mafodotin when given in combination with Len/Dex (Arm A) on a 28-day cycle, or with Bor/Dex (Arm B) on a 21-day cycle, and to evaluate safety and clinical activity of the combination treatments in participants with RRMM. The study will consist of two parts.

Part 1 is a dose escalation phase to evaluate the safety and tolerability of belantamab mafodotin in combination with two SoC regimens: Arm A – belantamab mafodotin with Len/Dex, and Arm B – belantamab mafodotin with Bor/Dex.

Part 2 is a dose expansion phase to further evaluate the safety and clinical activity of belantamab mafodotin in combination with Len/Dex (Arm A) and Bor/Dex (Arm B).

The overall study design is summarized in Schematic of Study Structure figures (Figure 1 and Figure 2).

Dosing Schedules

SINGLE Dosing Schedule (both Arm A and Arm B): belantamab mafodotin will be administered as a SINGLE full dose on Day 1 of each 28-day (Arm A) or 21-day (Arm B) cycle.

SPLIT Dosing Schedule (both Arm A and Arm B): belantamab mafodotin will be split into two equal halves and each half dose will be administered on Day 1 and Day 8 of each 28-day (Arm A) or 21-day (Arm B) cycle.

In **protocol amendment 3**, the following new schedules are being introduced to evaluate the safety and clinical activity of belantamab mafodotin with Len/Dex (Arm A) or Bor/ Dex (Arm B):

Arm A only:

- **STRETCH** Dosing Schedule: A STRETCH dosing schedule for the 1.9 mg/kg dose level might be considered for Arm A if emerging data suggests that this schedule may further optimize the tolerability or offers an improved benefit/risk profile. In STRETCH schedule, belantamab mafodotin will be administered on Day 1 of alternate 28-day cycles with any 2 consecutive planned belantamab mafodotin doses at least 56 (±3) days apart. The treatment cycle duration will remain at 28 days (4 weeks).

Arm B only:

- **STRETCH** Dosing Schedule: belantamab mafodotin will be administered on Day 1 of alternate cycles with any two consecutive planned doses at least 42 (±3) days apart. The treatment cycle duration will remain at 21 days (3 weeks).
- **Step-Down (S/D) STRETCH** Dosing Schedule: belantamab mafodotin will be administered as a full 2.5 mg/kg dose on Day 1 of Cycle 1 followed by subsequent planned doses of 1.9 mg/kg S/D dose starting on Day 1 of alternate 21-day cycles (C3, C5, C7, and so on) with any two consecutive planned doses at least 42 (±3) days apart. The treatment cycle duration will remain at 21 days (3 weeks).

Number of Participants

Overall, it is estimated that approximately 152 treated participants will be enrolled in this two-part study; approximately 27 participants in Part 1 and approximately 125 participants in Part 2.

- Part 1 (dose escalation phase): Up to 27 DLT-evaluable participants with RRMM (approximately 14 participants in Arm A and approximately 13 participants in Arm B) will be evaluated.
- Part 2 (dose expansion phase): Approximately 125 participants with RRMM (approximately 31 participants in Arm A and approximately 94 participants in Arm B will be evaluated to further assess the safety and preliminary clinical activity of the combination treatments.

At the time of Amendment 3 more participants have been added to Part 1 (both Arm A and Arm B) for the study due to non-DLT evaluable participants and the requirement for an additional replacement participant to assure an adequate assessment of DLTs. Two participants were added to Part 2 (Arm A and Arm B) as a replacement for participants who either received an incorrect dose or failed to complete a full cycle.

Arm A – Belantamab mafodotin in combination with Len/Dex

Part 1: Dose Escalation

The modified Toxicity Probability Interval (mTPI) design [Ji, 2010] will be used to guide dose escalation in Part 1 with a slight modification (Figure 1). Up to 2 dose levels of belantamab mafodotin (1.9 mg/kg [dose level -1]; 2.5 mg/kg [dose level 1] and alternative dosing schedules are planned to be evaluated in combination with the fixed dose of the Len/Dex treatments. Based on emerging data from Arm A, the first dose investigated in Protocol Amendment 2 was 1.9 mg/kg (Dose Level -1). The design assumes the true underlying toxicity rate for maximum tolerated dose (MTD) of belantamab mafodotin falls within the range from 25% to 35% and centers at 30%. Cohorts will be recruited in blocks of 3 participants. Participants will be treated in a staggered approach with at least 1 day between each participant's first dose of belantamab mafodotin to minimize the risk of inadvertently exceeding the MTD in multiple participants.

Up to 2 dose levels of belantamab mafodotin will be evaluated starting with 1.9 mg/kg. Data from at least 3 DLT-evaluable participants are required before a decision is made to escalate to the next dose level.

Part 2: Dose Expansion

Data from at least 3 DLT-evaluable participants are not required for enrollment of more participants at the same dose level in Part 2.

Once Part 2 expansion is open for each dosing schedule, up to 12 participants will be enrolled in each cohort, unless enrollment is stopped based on emerging data.

Since the implementation of amendment 2, Part 1 has been completed and Part 2 has since been enrolling participants to further evaluate the safety profile and to evaluate the preliminary clinical activity of belantamab mafodotin in combination with Len/Dex at the 2.5 mg/kg dose level with 2 dosing schedules (2.5 mg/kg SINGLE and 2.5 mg/kg SPLIT).

In Amendment 3, in Part 2, an alternate dosing schedule of STRETCH (Q8W) dosing may be explored for the 1.9 mg/kg dose level if emerging data (from either this study or across the program) suggests that this schedule may further optimize the tolerability or offers an improved benefit/risk profile. To enable this, a potential extended dosing schedule has been introduced via amendment 3, where belantamab mafodotin at 1.9 mg/kg will be administered once every 8 weeks (STRETCH) and will be evaluated dependent on emerging data. The cycle duration will remain 28 days/4 weeks. Up to 12 participants will be enrolled in this new cohort.

Safety data from all enrolled participants will be closely monitored while the study is ongoing. The observed number of participants permanently discontinuing study treatment within the first two cycles due to AEs related to belantamab mafodotin will be compared against defined safety stopping rules. Enrollment may stop for a given dose level/dosing schedule if the safety stopping rules are met.

Arm B – Belantamab mafodotin in combination with Bor/Dex

Part 1: Dose Escalation

A mTPI design will be implemented [Ji, 2010] to guide dose escalation in Part 1 (Figure 2). Up to 2 dose levels of belantamab mafodotin (2.5 mg/kg [dose level 1]; 3.4 mg/kg [dose level 1]; 1.9 mg/kg [dose level +1]), starting with 2.5 mg/kg, are planned to be evaluated in combination with a fixed dose of Bor/Dex. Cohorts will be recruited in blocks of 3 participants. Participants will be entered in a staggered approach with at least 1 day between each participant's first dose of belantamab mafodotin to minimize the risk of inadvertently exceeding the MTD in multiple participants. A maximum of 6 participants will be assigned to each dose.

Evaluation of the available safety data over the first cycle of treatment for each participant enrolled in that dose level is required from at least 3 participants before a decision is made to enroll additional participants at the same or the subsequent dose level.

Part 2: Dose Expansion

Part 2 is a dose expansion phase to further evaluate the safety and clinical activity of belantamab mafodotin in combination with Bor/Dex.

Since the implementation of amendment 2, Part 2 has been enrolling in multiple expansion cohorts to further evaluate the safety profile and to evaluate the preliminary clinical activity of belantamab mafodotin in combination with Bor/Dex at 2 dose levels and alternate dosing schedules (2.5 mg/kg SPLIT, 2.5 mg/kg SINGLE, 3.4 mg/kg SPLIT, 3.4 mg/kg SINGLE). Enrollment of each cohort was conducted in blocks of 3 participants until 12 participants each at 2.5 mg/kg SPLIT, 2.5 mg/kg SINGLE, 3.4 mg/kg SPLIT and up to 9 participants at 3.4 mg/kg SINGLE were enrolled.

In Amendment 3, four new cohorts are being introduced (1.9 mg/kg SINGLE, 2.5 mg/kg STRETCH, S/D STRETCH and 1.9 mg/kg STRETCH). Enrollment for each cohort will be conducted in blocks of 3 participants until up to 12 participants are enrolled in each of the 4 new dosing cohorts.

Safety data from all enrolled participants will be closely monitored while the study is ongoing. The observed number of participants permanently discontinuing study treatment within the first two cycles due to AEs related to belantamab mafodotin will be compared against defined safety stopping rules. Enrollment may stop for a given dose level and higher dose level(s) if the safety stopping rules are met.

Treatment Groups and Treatment Duration

Arm A – Belantamab mafodotin in combination with Len/Dex

In Arm A, belantamab mafodotin is given in up to 2 dose levels and up to 3 dosing schedules in combination with Len/Dex on a 28-day cycle (Table 1).

Table 1 Arm A Dosing Regimens

Arm A	Part	Dose Level	Cohort	Dose of Belantamab Mafodotin	Schedule of Belantamab Mafodotin	SoA	Len/Dex treatment
28-day Cycle	1	**-1**	1.9 mg/kg SINGLE	1.9 mg/kg IV	Day 1 of every 28-day cycle	Table 5	Lenalidomide 25mg PO QD, D1-D21; Dexamethasone 20mg PO or IV on D1, 8, 15, 22
	2		*1.9 mg/kg STRETCH*		*Day 1 of alternate 28-day cycles (i.e. C1, C3, C5, C7 and so on)*		
	1 and 2	**1**	2.5 mg/kg SINGLE	2.5 mg/kg IV	Day 1	Table 5	
			2.5 mg/kg SPLIT	1.25 mg/kg IV	Day 1 and Day 8	Table 6	

For SINGLE dosing schedule, belantamab mafodotin will be administered FIRST (prior to Len/Dex) as a single full dose on Day 1 (D1) of every 28-day cycle as a 30-60 min infusion, followed by a 1 to 2 h rest period.

- 2.5 mg/kg SINGLE dosing schedule will administer a 2.5 mg/kg dose on Day 1 of each 28-day cycle
- 1.9 mg/kg SINGLE dosing schedule will administer a 1.9 mg/kg dose on Day 1 of each 28-day cycle

For SPLIT dosing schedule, belantamab mafodotin will be administered FIRST (prior to Len/Dex) in the clinic in two equal divided doses - one on Day 1 and the other on Day 8 of each 28-day cycle as a 30-60 min infusion, followed by a 1 to 2 h rest period.

- 2.5 mg/kg SPLIT dosing schedule will administer a 1.25 mg/kg dose on Day 1 and a 1.25 mg/kg dose on Day 8 of each 28-day cycle

For STRETCH dosing schedule, belantamab mafodotin will be administered FIRST (prior to Len/Dex) as a single dose on Day 1 of every alternate 28-day cycle as a 30-60 min infusion, followed by 1 to 2 h rest period. If a planned dose of belantamab mafodotin was held/missed for any reason, the next dose can be administered at Day 1 of the next planned 28-day cycle, as long as the interval between 2 consecutive doses is at least 56 (±3) days.

- 1.9 mg/kg STRETCH will administer a 1.9 mg/kg dose administered on Day 1 of every alternate 28-day cycles (C1, C3, C5, C7 and so on.)

Lenalidomide will be administered as 25 mg PO daily on Days 1-21 of each 28-day cycle in participants with estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2. The dose of lenalidomide will be reduced to 10 mg daily on Days 1 to 21 of each 28-day cycle in participants with eGFR 40-60 mL/min/1.73 m^2.

Dexamethasone will be given 40 mg weekly PO or IV on Day 1, 8, 15 and 22 of each cycle. For participants >75 years of age, with body mass index (BMI) <18.5 kg/m^2, the dose of dexamethasone can be reduced to 20 mg at the discretion of the investigator.

On days when only lenalidomide and dexamethasone are taken at home, they should be taken in the morning approximately at the same time each day. On lenalidomide and belantamab mafodotin co-administration days, lenalidomide should be administered **after** administration of belantamab mafodotin. On days when lenalidomide pharmacokinetic (PK) samples will be collected, participants will be required to take their morning dose in the clinic. For Cycle 1, the 24 h post-dose lenalidomide PK sample must be collected before lenalidomide dosing on Cycle 1 Day 2.

Participants who are assigned to Arm A may continue combination treatment until the occurrence of progressive disease (PD), intolerable AEs, consent withdrawal, death, or end of study. In case of intolerable AEs related to Len/Dex in combination, the participant may be allowed to continue on belantamab mafodotin monotherapy.

Arm B – Belantamab mafodotin in combination with Bor/Dex

In Arm B, belantamab mafodotin is given up to 3 dose levels and up to 4 dosing schedules in combination with Bor/Dex on a 21-day cycle (Table 2).

Table 2 Arm B Dosing Regimens

Arm B	Part	Dose Level	Cohort	Dose of Belantamab Mafodotin	Schedule of Belantamab Mafodotin	SoA	Bor/Dex treatment (Cycle 1-8)
21-day Cycle	1 and 2	1	2.5 mg/kg SINGLE	2.5 mg/kg IV	Day 1	Table 7	Bortezomib 1.3mg/m^2 SC or IV on D1, D4, D8, D11; Dexamethasone 20mg PO or IV on D1, D2, D4, D5, D8, D9, D11, D12)
	2		2.5 mg/kg SPLIT	1.25 mg/kg IV	Day 1, Day 8	Table 8	
	1 and 2	2	3.4 mg/kg SINGLE	3.4 mg/kg IV	Day 1	Table 7	
	2		3.4 mg/kg SPLIT	1.7 mg/kg IV	Day 1, Day 8	Table 8	
	2		2.5 mg/kg STRETCH	2.5 mg/kg IV	Day 1 in every alternate cycle (i.e. C1, C3, C5, C7 and so on)	Table 9	
	2		S/D STRETCH	Cycle 1: 2.5 mg/kg IV Cycle 3+: 1.9 mg/kg IV	Day 1 in every alternate cycle	Table 9	
	2		1.9 mg/kg SINGLE	1.9 mg/kg IV	Day 1	Table 7	
	2		1.9 mg/kg STRETCH	1.9 mg/kg IV	Day 1 in every alternate cycle	Table 9	

For SINGLE dosing schedule, belantamab mafodotin will be administered FIRST (prior to Bor/Dex) as a single full dose on Day 1 (D1) of every 21-day cycle as a 30-60 min infusion, followed by 1 to 2 h rest period.

- 3.4 mg/kg SINGLE dosing schedule will administer a 3.4 mg/kg dose on Day 1 of each 21-day cycle
- 2.5 mg/kg SINGLE dosing schedule will administer a 2.5 mg/kg dose on Day 1 of each 21-day cycle
- 1.9 mg/kg SINGLE dosing schedule will administer a 1.9 mg/kg dose on Day 1 of each 21-day cycle

For SPLIT dosing schedule, belantamab mafodotin will be administered FIRST (prior to Bor/Dex) in the clinic in two equal divided doses - one on Day 1 and the other on Day 8 of each 21-day cycle as a 30-60 min infusion, followed by a 1 to 2 h rest period.

- 3.4 mg/kg SPLIT dosing schedule will administer a 1.7 mg/kg dose on Day 1 and a 1.7 mg/kg dose on Day 8 of each 21-day cycle
- 2.5 mg/kg SPLIT dosing schedule will administer a 1.25 mg/kg dose on Day 1 and a 1.25 mg/kg dose on Day 8 of each 21-day cycle

For STRETCH dosing schedule, belantamab mafodotin will be administered FIRST (prior to Bor/Dex) as a single dose on Day 1 of every alternate 21-day cycle as a 30-60 min infusion, followed by 1 to 2 h rest period. If a planned dose of belantamab mafodotin was held/missed for any reason, the next dose can be administered at Day 1 of the next planned 21-day cycle, as long as the interval between 2 consecutive doses is at least 42 (±3) days.

- 2.5 mg/kg STRETCH will administer a 2.5 mg/kg dose on Day 1 of every alternate 21-day cycles (C1, C3, C5, C7 and so on)
- 1.9 mg/kg STRETCH will administer a 1.9 mg/kg dose administered on Day 1 of every alternate 21-day cycles (C1, C3, C5, C7 and so on)

For Step-Down (S/D) STRETCH dosing schedule, belantamab mafodotin will be administered FIRST (prior to Bor/Dex) as a 2.5 mg/kg dose on Day 1 of Cycle 1 followed by subsequent planned doses of 1.9 mg/kg starting on Day 1 of alternate 21-day cycles (C3, C5, C7, and so on), as a 30-60 min infusion, followed by 1 to 2 h rest period.

Bortezomib will be administered at 1.3 mg/m^2 SC or IV (depending on participants' and institutional preference) on Days 1, 4, 8, and 11 of every 21-day cycle for a total of up to 8 cycles. The administration of bortezomib will be after belantamab mafodotin administration, approximately after 1 h and after assuring that participant is clinically stable.

Dexamethasone will be administered at 20 mg PO or IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of every 21-day cycle. Dexamethasone dose may be reduced at the investigator's discretion for participants >75 years of age with BMI <18.5 kg/m^2. Dexamethasone will be given for a total of up to 8 cycles.

Participants completing 8 cycles of combination therapy will continue treatment with belantamab mafodotin as monotherapy until PD, intolerable AEs, consent withdrawal, death, or end of study. In case of intolerable AEs related to Bor/Dex in combination, the participant may be allowed to continue on belantamab mafodotin monotherapy.

Study Population

The study will enroll adult participants with RRMM, who have undergone stem cell transplant (SCT), or are considered transplant ineligible, and who have been previously treated with at least 1 prior line of therapy, and who have documented evidence of disease progression during or after their most recent therapy.

Inclusion Criteria

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

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. Male or female, 18 years or older (at the time consent is obtained).
3. Have confirmed diagnosis of Multiple Myeloma as defined by the International Myeloma Working Group (IMWG) criteria [Rajkumar, 2016].
4. Eastern Cooperative Oncology Group (ECOG) performance status:
   - For Arm A only: 0 to 1
   - For Arm B only: 0 to 2
5. Have undergone autologous SCT, or are considered transplant ineligible
6. Have been previously treated with at least 1 prior line of MM therapy and must have documented disease progression during or after their most recent therapy.
7. Must have at least ONE aspect of measurable disease, defined as one of the following:
   a. Urine M-protein excretion ≥200 mg/24 h, or
   b. Serum M-protein concentration ≥0.5 g/dL (≥5.0 g/L), or
   c. Serum free light chain (FLC) assay: involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum free light chain ratio (<0.26 or >1.65).
8. Participants with a history of autologous SCT are eligible for study participation provided the following eligibility criteria are met:
   a. Autologous SCT was >100 days prior to study enrollment
   b. No active bacterial, viral, or fungal infection(s) present
   c. Participant meets the remainder of the eligibility criteria outlined in this protocol
9. All prior treatment-related toxicities (defined by National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE, Version 4.03, 2010) must be Grade ≤1 at the time of enrollment, except for alopecia. Patients with Grade 2 neuropathy can be enrolled into Len/Dex treatment arm, but not into Bor/Dex treatment arm.

10. Adequate organ system functions as defined by the laboratory assessments listed in the table below (Adequate Organ System Function based on Safety Assessments).

Adequate Organ System Function based on Safety Assessments

Organ System and Laboratory Tests	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)[a]	≥1.5 × 10^9/L
Hemoglobin	≥8.0 g/dL
Platelets	≥75 × 10^9/L
Hepatic	
Total bilirubin	≤1.5 × ULN; (Isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
Alanine aminotransferase (ALT)	≤2.5 × ULN
Renal	
eGFR[b]	≥40 mL/min/1.73 m^2
Spot urine (albumin/creatinine ratio from spot urine)	≤500 mg/g (56 mg/mmol)
Cardiac	
Left Ventricular Ejection Fraction (LVEF) by ECHO	≥40%

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

a. Without growth factor support for the past 14 days, excluding erythropoietin
b. As calculated by Modified Diet in Renal Disease (MDRD) formula

11. 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 one of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP)

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency during the intervention period and for **4 months** after the last dose of belantamab mafodotin 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.

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

Additional Inclusion Criteria for WOCBP Participants Assigned to Arm A

Due to lenalidomide being a thalidomide analogue with risk for embryo-fetal toxicity and prescribed under a pregnancy prevention/controlled distribution program, WOCBP participants will be eligible if they commit either to abstain continuously from heterosexual sexual intercourse or to use **two methods** of reliable birth control (one method that is highly effective), beginning 4 weeks prior to initiating treatment with lenalidomide, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of lenalidomide treatment. Thereafter, WOCBP participants must use a contraceptive method that is highly effective (with a failure rate of <1% per year) for a **further 3 months**, and agree not to donate eggs (ova, oocytes) for the purpose of reproduction during this period.

Two negative pregnancy tests must be obtained prior to initiating lenalidomide therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing lenalidomide therapy.

Additional Inclusion Criteria for WOCBP Participants Assigned to Arm B

WOCBP assigned to Arm B must have a negative highly sensitive serum pregnancy test within 72 hours of dosing on C1D1 and agree to use effective contraception during the study and for **4 months** after the last dose of belantamab mafodotin or 7 months from the last dose of bortezomib, whichever is longer.

12. 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:

- Arm A: from the time of first dose of study until **6 months** after the last dose of belantamab mafodotin or 4 weeks from last dose of lenalidomide, whichever is longer, to allow for clearance of any altered sperm.
- Arm B: from the time of first dose of study until **6 months** after the last dose of belantamab mafodotin or 4 months from the last dose of bortezomib, whichever is the longer, to allow for clearance of any altered sperm.

Refrain from donating sperm and either:

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

OR

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

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

If the female partner of the male participant is pregnant at the time of enrollment, or becomes pregnant during the trial, the male participant must agree to remain abstinent (if it is consistent with their preferred and usual lifestyle) or use a male condom.

Exclusion Criteria

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

1. Systemic anti-myeloma therapy (including systemic steroids) within ≤14 days, or plasmapheresis within 7 days prior to the first dose of study drug.
2. Use of an investigational drug within 14 days or five half-lives (whichever is longer) preceding the first dose of study drug.
3. Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study drugs.
4. Prior allogenic stem cell transplant.

   Note: Participants who have undergone syngeneic transplant will be allowed only if they have no history and no currently active, graft versus host disease (GvHD)
5. Evidence of active mucosal or internal bleeding.
6. Any major surgery within the last four weeks.
7. 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 fulfill criteria given in table of Adequate Organ System Function based on Safety Assessments.
8. 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.
9. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, or otherwise stable chronic liver disease per investigator's assessment).
10. Participants with invasive malignancies other than multiple myeloma are excluded, unless the second malignancy has been considered medically stable for at least 2 years. The participant must not be receiving active therapy, other than hormonal therapy for this disease.

    Note: Participants with curatively treated non-melanoma skin cancer are allowed without a 2-year restriction
11. Evidence of cardiovascular risk including any of the following:

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

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

c. Class III or IV heart failure as defined by the New York Heart Association functional classification system.

d. Uncontrolled hypertension.

12. Known immediate or delayed hypersensitivity reaction or idiosyncratic reaction to drugs chemically related to belantamab mafodotin, or any of the components of the study treatment.
13. Pregnant or lactating female.
14. Active infection requiring treatment.
15. Known HIV infection.
16. Presence of hepatitis B surface antigen (HBsAg), or hepatitis B core antibody (HBcAb at Screening or within 3 months prior to first dose of study treatment)
17. Positive hepatitis C antibody test result or positive hepatitis C RNA test result at Screening or within 3 months prior to first dose of study treatment.

    Note: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained. Hepatitis RNA testing is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing
18. Current corneal disease except for mild punctate keratopathy.

    Note: Participants with mild punctate keratopathy are allowed.

Additional Exclusion Criteria for Participants Assigned to Arm A (belantamab mafodotin plus Len/Dex)

19. Participants unable to tolerate antithrombotic prophylaxis must be excluded.
20. Discontinuation of prior treatment with lenalidomide due to intolerable adverse events.

Additional Exclusion Criteria for Participants Assigned to Arm B (belantamab mafodotin plus Bor/Dex)

21. Unacceptable adverse effects from previous bortezomib treatment.
22. Ongoing Grade 2 or higher peripheral neuropathy or neuropathic pain from previous bortezomib treatment.
23. Intolerance or contraindications to anti-viral prophylaxis.

Lifestyle Restrictions

The following lifestyle restrictions apply while the participants are in the study:

- Contact lenses are prohibited while on the study treatment (from first dosing to the end of study treatment). Contact lens use may be restarted after the end of study treatment and a consultation with a qualified eye care specialist confirms there are no other contraindications.
  Use of bandage contact lenses is permitted during study treatment as directed by a qualified eye care specialist.

- Participants must not donate blood while receiving study treatment; participants in Arm A must not donate blood for 28 days following discontinuation of lenalidomide.

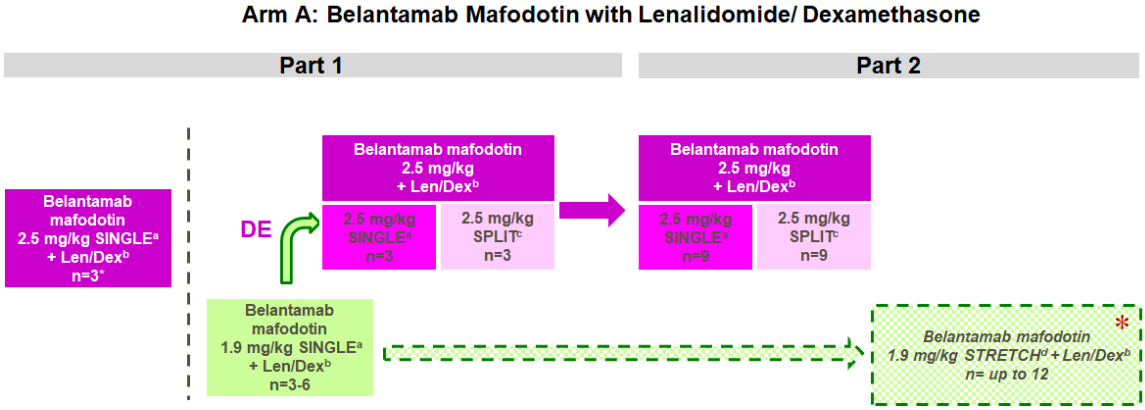
- Intraocular pressure may become elevated with dexamethasone treatment in some individuals. Intraocular pressure should be monitored.

Final Analysis and End of Study Definitions:

Participants in all arms will be treated until confirmed PD, death, start of a new anticancer treatment, withdrawal of consent, or end of the study, whichever occurs first. Following 12 months post last subject first dose, the final analysis will occur and the study will move into the post analysis continued treatment (PACT) phase. At that time, the collection of new data for all recruited participants who no longer receive study treatment will stop entirely and the clinical trial database will be closed. Those participants still benefiting from study drug in the opinion of their treating physician may continue to receive study drug (s). In case the participant meets stopping criteria for belantamab mafodotin, the participant will discontinue all treatment and will continue to be monitored as per standard of care at the participant's particular study site. SAEs, AEs leading to treatment discontinuation, overdose, pregnancy cases, and pre-specified ocular data will be reported directly to GSK. The end of study is defined when the last patient had their last visit (last subject last dose plus 70 days SAE reporting period).

2. STUDY SCHEMA

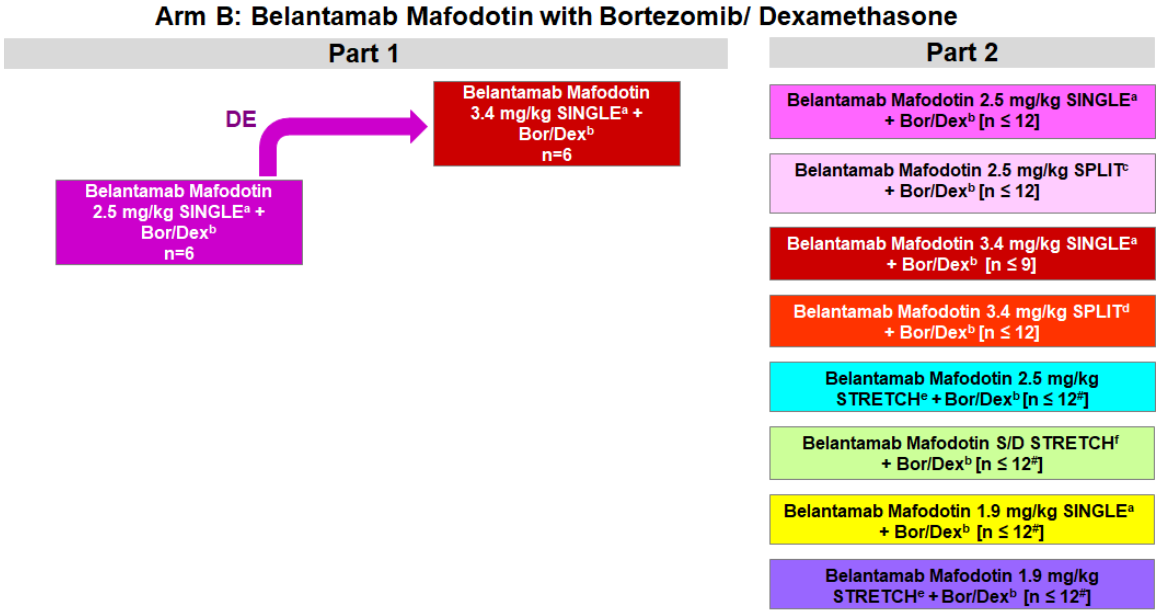
Figure 1 Schematic of Study Structure for Arm A (Belantamab Mafodotin with Len/Dex)



a. Belantamab mafodotin (GSK2857916) SINGLE = full assigned dose of belantamab mafodotin administered on Day 1 of any 28-day cycle.
b. Lenalidomide (25 mg on Days 1-21) + Dexamethasone (40 mg on Days 1, 8, 15, and 22) of any 28-day cycle.
c. Belantamab mafodotin 2.5 mg/kg SPLIT= 1.25 mg/kg on Day 1 and 1.25 mg/kg on Day 8 of any 28-day cycle.
d. **Belantamab mafodotin **1.9 mg/kg STRETCH** = belantamab mafodotin 1.9 mg/kg dose administered on Day 1 of alternate 28-day cycles i.e. Q8W (C1, C3, C5, C7 and so on)*- this cohort may be evaluated if emerging data suggests that this schedule may further optimize the tolerability or offers an improved benefit/risk profile.

All participants will be operated under Amendment 03.
Note: Combination therapy continued until PD, death, intolerable toxicity, consent withdrawn. Cohorts followed up for CCI and CCI
DE=Dose Escalation decision

Figure 2 Schematic of Study Structure for Arm B (Belantamab Mafodotin with Bor/Dex)



a. Belantamab mafodotin (GSK2857916) **SINGLE** = full assigned dose of belantamab mafodotin (1.9 mg/kg, 2.5 mg/kg or 3.4 mg/kg) administered on Day 1 of any 21-day cycle.
b. Bortezomib (1.3 mg/m^2 on Days 1, 4, 8, and 11) + Dexamethasone (20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12) of any 21-day cycle.
c. Belantamab mafodotin 2.5 mg/kg **SPLIT**= 1.25 mg/kg on Day 1 and 1.25 mg/kg on Day 8 of any 21-day cycle.
d. Belantamab mafodotin 3.4 mg/kg **SPLIT**= 1.7 mg/kg on Day 1 and 1.7 mg/kg on Day 8 of any 21-day cycle.
e. Belantamab mafodotin **STRETCH**= belantamab mafodotin 1.9 mg/kg or 2.5 mg/kg dose administered on Day 1 of alternate 21-day cycles i.e. Q6W (C1, C3, C5, C7 and so on).
f. Belantamab mafodotin **Step-Down (S/D) STRETCH** = belantamab mafodotin 2.5 mg/kg dose at C1D1 followed by 1.9 mg/kg step-down dose on Day 1 of alternate 21-day cycles C3 onwards (C3, C5, C7, and so on).

All participants will be operated under Amendment 03.
#New cohorts in Amendment 3.
Note: Combination therapy continued for up to 8 combination cycles; belantamab mafodotin further continued until PD, death, intolerable toxicity, consent withdrawn. Cohorts followed up for CCI and CCI
DE=Dose Escalation decision; CCI ; PD=Progressive Disease; CCI ;
S/D=Step-down.

3. SCHEDULE OF ACTIVITIES

The two treatment arms use different cycle lengths to accommodate the approved standard of care (SoC) regimens for lenalidomide plus dexamethasone (Len/Dex; Arm A, 28-day cycle) and bortezomib plus dexamethasone (Bor/Dex; Arm B, 21-day cycle) in combination with belantamab mafodotin.

The different schedule of activities (SoA) tables are identified (Table 3):

Table 3 List of Schedule of Activities Tables

Study Phase	Arm	Dosing schedule	Table
Screening	All	All	Table 4
On-Treatment	Arm A	SINGLE[a] and STRETCH[b]	Table 5
		SPLIT[c]	Table 6
On-Treatment	Arm B	SINGLE[a]	Table 7
		SPLIT[c]	Table 8
		STRETCH[b] and S/D STRETCH[d]	Table 9
End of Treatment	All	All	Table 10

a. **SINGLE** Dosing Schedule: belantamab mafodotin will be administered as a SINGLE full dose on Day 1 of each 28-day (Arm A) or 21-day (Arm B) cycle.
b. **STRETCH** Dosing Schedule: belantamab mafodotin will be administered as a SINGLE full dose on Day 1 of every **alternate** 28-day (Arm A) or 21-day (Arm B) cycle. In Arm A, Len/Dex will continue to be administered every 28-day cycle as per SoC. In Arm B, Bor/Dex will continue to be administered every cycle for the first 8 cycles (21-day cycles) as. per SoC.
c. **SPLIT** Dosing Schedule: belantamab mafodotin will be split into two equal halves and each half dose will be administered on Day 1 and Day 8 of each 28-day (Arm A) or 21-day (Arm B) cycle.
d. **Step-Down (S/D) STRETCH** Dosing Schedule: belantamab mafodotin will be administered as a SINGLE full dose on Day 1 of every **alternate** 28-day (Arm A) or 21-day (Arm B) cycle. The dose of belantamab mafodotin will be 2.5 mg/kg in C1 followed by a step-down dose of 1.9 mg/kg on Day 1 of every **alternate** cycle from C3 onwards (C3, C5, C7 and so on). In Arm A, Len/Dex will continue to be administered every 28-day cycle as per SoC. In Arm B, Bor/Dex will continue to be administered every cycle for the first 8 cycles (21-day cycles) as per SoC.

PACT Phase: All participants who continue to receive study treatment during the PACT phase will be monitored and receive follow-up care in accordance with standard local clinical practice. Assessments will revert to the standard of care at the participant's particular study site and only SAEs, AEs leading to discontinuation of study treatment, overdoses, prespecified ocular data, and pregnancies will be reported directly to the Sponsor via paper forms (see Section 9 and Section 10.2). For participant discontinuing treatment in the PACT phase, no end of treatment visit is required.

Table 4 Schedule of Activities – SCREENING Assessments for Arm A (belantamab mafodotin in combination with lenalidomide plus dexamethasone) and Arm B (belantamab mafodotin in combination with bortezomib plus dexamethasone)

Study Assessments[1]	Screen
Informed Consent	X
Baseline Demographics	X
Medical History, disease history and characteristics	X
ECOG Performance Status	X
Adverse Events/SAEs[2]	X
Concomitant Medications	X
Safety	
Physical Exam	X
Ocular Exam[3]	X
Vital Signs (BP, Heart rate, Body Temperature)	X
Body Weight (BW) and Height	X
Hematology[4]	X
Clinical chemistry[4]	X
HbA1c	X
C-reactive protein (CRP)[4]	X
Urinalysis (dipstick)[4]	X
Estimated Glomerular Filtration Rate (eGFR) by MDRD formula	X
Spot urine for albumin/creatinine ratio[5]	X
HbsAg, HbcAb, and Hepatitis C antibody. Hepatitis C RNA optional[6]	X
Pregnancy Test for WOCBP[7]	X
12-lead ECG[8]	X
ECHO – LVEF[9]	X
Disease Evaluation	
β_2 microglobulin	X
SPEP (Serum Protein Electrophoresis)	X

1. All assessments apply to Part 1 and 2 unless stated otherwise**.** All screening assessments must be performed within 21 days prior to first dose unless otherwise specified. Informed consent form must be signed before any study-specific assessments are performed. Screening Assessments do not need to be repeated on Cycle 1 Day 1 (C1D1), unless otherwise specified.
2. Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures or invasive tests) will be recorded from the time a participant consents to participate in the study through CCI follow-up. See Section 10.2.1 for details.
3. Screening ocular examinations to be performed by a qualified eye care specialist within 21 days prior to first dosing. See Section 10.6.7.1 for list of ophthalmic exam procedures and Appendix 12 for qualifications and requirements of the eye care specialist.
4. Refer to Section 10.6.10 for a comprehensive list of lab tests that must be collected for all participants. If labs are completed within 72 h prior to the first dose, this assessment need not be repeated on C1D1.
5. Albumin/creatinine ratio (Spot urine from first void) will be performed at local lab, if local testing is not available then by central laboratory.
6. Hep C RNA testing is optional but may be done to determine participant eligibility, if Hep C antibody is positive. If Hep C RNA is positive, participant is ineligible. See Section 7 Study Population for details.
7. Perform only in women of child-bearing potential (WOCBP). WOCBP in Arm A: Two negative serum pregnancy tests must be obtained prior to initiating treatment; one may be performed within 14 days of C1D1, but the second must be performed within 24 h of C1D1. WOCBP in Arm B: 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 (as needed in WOCBP only) should be performed at local lab.
8. Single ECG on Screening. All ECGs will be collected centrally (refer to SRM for details).
9. ECHO to be performed locally. Screening ECHO may be performed up to 30 days prior to C1D1.
10. Only in participants with IgD/IgE myeloma.
11. Imaging is only required for participants with extramedullary disease by either CT, MRI, or PET/CT per local guidance. Screening assessment may be performed up to 30 days prior to C1D1. Needs to be performed by the same method throughout the study as was done at baseline (i.e. if CT/PET scan was used as baseline, participant needs to be followed by CT/PET scans). Selected target lesion needs to be measured and followed over time. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For participants with only skin involvement, skin lesions should be

Study Assessments[1]	Screen	Notes (Screening Arm A and Arm B)
Serum Kappa, lambda free LC, FLC ratio	X	measured with a ruler. Measurement of tumor size will be determined by the Sum of the Products of the maximal perpendicular diameters of measured lesions (SPD). 12. Imaging of bones for lytic lesions by method aligned with institutional guidance (X-ray, CT or MRI). Survey results within 30 days prior to C1D1 date are acceptable. 13. BM aspirate/biopsy within 28 days prior to first dose is acceptable. 14. Fluorescence-in-situ hybridization (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 regardless of timeframe, FISH for these translocations does not need to be repeated. FISH results for amp(1q), del(1p) and del(17p13) from samples taken within 60 days prior to first dose are acceptable. If testing cannot be performed at a local lab the samples can be sent to the central lab. 15. CCI [redacted] to be performed by the central lab at the time of first achieving VGPR or better. Thereafter, CCI [redacted] testing should be repeated every 6 months until PD or CR. In case of deepening of response from VGPR to CR, or achieving CR without prior VGPR, CCI [redacted] testing should be performed at the time of achieving suspected CR and repeated every 6 months until PD. Whenever possible, a further BM aspirate sample may be taken at the same time for biomarker analysis. 16. Samples will be submitted to central lab for BCMA analysis, any remaining bone marrow aspirate sample will be used for biomarker research.
Serum Immunofixation	X	
UPEP (Urine Protein Electrophoresis) (on 24 h collected urine)	X	
Urine Immunofixation	X	
Ca corrected for Albumin (Serum)	X	
IgG, IgM, IgA	X	
IgD/IgE[10]	X	
Imaging for extramedullary disease[11]	X	
Skeletal Survey[12]	X	
Bone Marrow Tests		
BM aspirate/biopsy for Disease Assessment[13]	X	
BM for FISH testing[14]	X	
BM for CCI [redacted] testing[15]	X	
BM aspirate for BCMA expression and biomarker research[15,16]	X	

Table 5 Schedule of Activities – On-Study Assessments for Arm A (belantamab mafodotin in combination with lenalidomide plus dexamethasone) [28-Day Cycle] - belantamab mafodotin SINGLE *and STRETCH* Dosing

Study Assessments[1]	SINGLE *and STRETCH Dosing*	*STRETCH Dosing ONLY*	SINGLE *and STRETCH Dosing*		Notes (Arm A belantamab mafodotin SINGLE *and STRETCH* dosing)
	Cycle 1 Day 1[2]	*Cycle 2 Day 1*	Every 28 Days (Starting at Week 5[3] regardless of dosing)	Starting at Cycle 2[4] - SINGLE dosing [*or Starting at Cycle 3- STRETCH dosing]* (Prior to the first dose of any study drugs at the given cycle)	
ECOG Performance Status			X		1. All assessments apply to Part 1 and 2 of the study, unless stated otherwise.
Adverse Events / SAEs[5]	X	X	Ongoing	Ongoing	2. Screening assessments do not need to be repeated on Cycle 1 Day 1 (C1D1), unless otherwise specified.
Concomitant Medications	X	X	Ongoing	Ongoing	3. All assessments starting at week 5 can be performed within 3 days prior to the scheduled date, unless otherwise specified.
Safety					4. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. Physical Exam must be conducted within 72 h prior to 1st dose of study drugs administrated in that cycle. Body weight at C1D1 (prior to dosing) will be used for dose calculation of belantamab mafodotin. Body weight to be measured prior to each dose. If the change of body weight is greater than 10%,
Physical Exam	X	X	X	X[4]	
Ocular Exam[6]		X	X	X	
Vital Signs (BP, Heart rate, Body Temperature)[7]	X	X		X	
Body Weight (BW) and Height	BW only	BW only		BW only	
Hematology[8,9]	X	X	X	X	
Clinical chemistry[8]	X	X	X	X	
HbA1c	As clinically indicated				
C-reactive protein (CRP)[8]		X	X		
Urinalysis (dipstick)[8]	X	X	X		

Study Assessments[1]	**SINGLE *and STRETCH Dosing***	***STRETCH Dosing ONLY***	**SINGLE *and STRETCH Dosing***		**Notes (Arm A belantamab mafodotin SINGLE *and STRETCH* dosing)**
	Cycle 1 Day 1[2]	***Cycle 2 Day 1***	**Every 28 Days (Starting at Week 5**[3] **regardless of dosing)**	**Starting at Cycle 2**[4] **- SINGLE dosing [*or Starting at Cycle 3- STRETCH dosing]*** **(Prior to the first dose of any study drugs at the given cycle)**	
Estimated Glomerular Filtration Rate (eGFR) by MDRD formula	X	X	X		the dose should be re-calculated based on the actual body weight at the time of dosing. 5. All AEs will be assessed for at least 70 days after the last dose regardless of initiation of new anticancer therapy. All related SAEs are to be collected from consent through CC follow-up. For reporting of ocular events see the guidance provided in Appendix 8. 6. Participants will be assessed by a qualified eye care specialist (Appendix 12) on Day 1 of every cycle prior to dosing up to Dose 6 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 the time of Dose 6 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
Spot urine for albumin/creatinine ratio[10]		X	X		
Pregnancy Test for WOCBP[11]	X	X	X	X	
12-lead ECG[12]	X	X		X	
ECHO – LVEF[13]			Every 12 weeks (At weeks 13, 25, 37, 49 etc)		
Disease Evaluation [every 4 weeks (±3 days) even if the cycle is delayed][14]					
SPEP (Serum Protein Electrophoresis)		X	X		
Serum Kappa, lambda free LC, FLC ratio		X	X		
Serum Immunofixation[15]			At time of suspected CR		

Study Assessments[1]	**SINGLE *and STRETCH Dosing***	***STRETCH Dosing ONLY***	**SINGLE *and STRETCH Dosing***		**Notes (Arm A belantamab mafodotin SINGLE *and STRETCH* dosing)**
	Cycle 1 Day 1[2]	***Cycle 2 Day 1***	**Every 28 Days (Starting at Week 5**[3] **regardless of dosing)**	**Starting at Cycle 2**[4] **- SINGLE dosing [*or Starting at Cycle 3- STRETCH dosing]*** **(Prior to the first dose of any study drugs at the given cycle)**	
			then until suspected PD		exam findings, newly developed ocular symptoms or vision changes at Dose 6 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 10.6.7.1 for full details of ocular exam procedures.
UPEP (Urine Protein Electrophoresis) (on 24 h collected urine)		X	X		7. On each belantamab mafodotin dosing day, vital signs must be assessed within 30 min prior to Start of Infusion (SOI), within 15 min after End of Infusion (EOI), and at 1 h (±15 min) after EOI. On days where vital sign assessments align with PK sampling time points, vital signs should be assessed prior to belantamab mafodotin PK samples being drawn.
Urine Immunofixation[15]			At time of suspected CR then until suspected PD		
Ca corrected for Albumin (Serum)		X	X		
IgG, IgM, IgA		X	X		
IgD/IgE[16]		X	X		8. Hematology and clinical chemistry must be repeated if not done within 24 h prior to 1st dose of study drugs administered in that cycle. Refer to Table 27 for comprehensive list of lab tests.
Imaging for extramedullary disease[17]			Week 13, 25, 37, 49 and then if clinically indicated		9. To be performed up to 24 h before D1, D8, D15, D22 in C1 and C2; then up to 24 h before D1, D15 in C3 to C8 and then up to 24 h before D1 of each cycle from C9 onwards, or more
Skeletal Survey[18]		As clinically indicated	As clinically indicated		

Study Assessments[1]	**SINGLE *and STRETCH Dosing***	***STRETCH Dosing ONLY***	**SINGLE *and STRETCH Dosing***		**Notes (Arm A belantamab mafodotin SINGLE *and STRETCH* dosing)**
	Cycle 1 Day 1[2]	***Cycle 2 Day 1***	**Every 28 Days (Starting at Week 5**[3] **regardless of dosing)**	**Starting at Cycle 2**[4] **- SINGLE dosing [*or Starting at Cycle 3- STRETCH dosing]*** **(Prior to the first dose of any study drugs at the given cycle)**	
Whole body PET/CT			Only once at time of achieving CR or sCR (whichever comes first) according to IMWG 2016		frequently, if clinically indicated. On D1 of any planned cycle, Absolute Neutrophil Count (ANC) must be ≥1.0×10^9/L to administer treatment. 10. Albumin/creatinine ratio (Spot urine from first void) every 4 weeks ±3 days (local lab, if not available then central laboratory testing). 11. Perform only in women of childbearing potential. Two negative serum pregnancy tests must be obtained prior to initiating therapy with lenalidomide; one may be performed within 10-14 days of C1D1, but the second must be performed within 24 h of C1D1. After the first dose of belantamab mafodotin, pregnancy test will be done weekly during the first month, then monthly thereafter in females with regular menstrual cycles or every 2 weeks in females with irregular menstrual cycles. Subsequent pregnancy test on dosing days may be either serum or urine test. Each pregnancy test must be performed within 24 h prior to dosing. 12. SINGLE ECG performed pre-infusion on belantamab mafodotin dosing days. On days when belantamab mafodotin
Response assessment by IMWG[19]		X	X		
Bone Marrow Tests					
BM aspirate/biopsy for Disease Assessment[20, 24]			At time of suspected CR or at time of suspected PD (only if PD not evident otherwise)		

Study Assessments[1]	**SINGLE *and STRETCH Dosing***	***STRETCH Dosing ONLY***	**SINGLE *and STRETCH Dosing***		**Notes (Arm A belantamab mafodotin SINGLE *and STRETCH* dosing)**
	Cycle 1 Day 1[2]	***Cycle 2 Day 1***	**Every 28 Days (Starting at Week 5**[3] **regardless of dosing)**	**Starting at Cycle 2**[4] **- SINGLE dosing [*or Starting at Cycle 3- STRETCH dosing]*** **(Prior to the first dose of any study drugs at the given cycle)**	
BM biopsy to confirm sCR by IHC			Upon achieving CR		PK sampling is performed, PK samples should be drawn shortly after ECG. TRIPLICATE ECGs will be performed as described below with SINGLE ECG performed at all other times. All ECGs will be collected centrally (refer to SRM for details). **Belantamab mafodotin Dose 1 (Cycle 1)** Day 1: TRIPLICATE ECGs Pre-infusion (within 30 min prior to SOI), EOI (up to 15 min after EOI), 2 h (±15 min) after SOI and 24 h (±2 h) after SOI. Day 4 (i.e. 72 h after SOI [±24 h]): TRIPLICATE ECG performed before PK sample. **Belantamab mafodotin Dose 2** Day 1: SINGLE ECG pre-infusion **Belantamab mafodotin Dose 3** Day 1: TRIPLICATE ECGs pre-infusion (within 30 min prior to SOI), EOI (up to 15 min after EOI) 13. ECHO will be performed every 12 weeks (±7 days) and locally.
BM aspirate for CCI [redacted] testing[21]			At time of achieving VGPR or better		
Biomarkers					
CCI [redacted]	X			X	
	X		At time of achieving VGPR or better[21]		
Optional					
Optional tissue sample at PD for BCMA expression and biomarker research[24]			X		
Genetic sample[25]	X				

Study Assessments[1]	**SINGLE *and STRETCH Dosing***	***STRETCH Dosing ONLY***	**SINGLE *and STRETCH Dosing***		**Notes (Arm A belantamab mafodotin SINGLE *and STRETCH* dosing)**
	Cycle 1 Day 1[2]	***Cycle 2 Day 1***	**Every 28 Days (Starting at Week 5**[3] **regardless of dosing)**	**Starting at Cycle 2**[4] **- SINGLE dosing [*or Starting at Cycle 3- STRETCH dosing]*** **(Prior to the first dose of any study drugs at the given cycle)**	
					14. Disease evaluation (except imaging and skeletal survey) will continue to be performed, every 4 weeks (±3 days) even if the cycle is delayed. 15. At time of first achieving SPEP or Urine M protein ~0 g/dl (suspected CR) and until suspected PD after CR or stringent Complete Response (sCR). 16. Only in participants with IgD/IgE myeloma. 17. Imaging is only required for participants with known extramedullary disease at week 13, 25, 37, 49 (±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 (i.e. if CT/PET scan was used as baseline, participant needs to be followed by CT/PET scans). Selected target lesion needs to be measured and followed over time. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable.
PK and ADA					
Pharmacokinetic blood sampling for belantamab mafodotin [22,26]	X[26]			X (at selected cycles)[26]	
Pharmacokinetic blood sampling for lenalidomide[27]	X[27]				
Anti-drug antibodies (ADA)[28]	X[28]			X (at selected cycles)[28]	
Treatment					
Premedication if needed[29]	X			X	
Administration of belantamab mafodotin[30]	X			SINGLE Dosing: Day 1 of each 28-day cycle	

Study Assessments[1]	**SINGLE *and STRETCH Dosing***	***STRETCH Dosing ONLY***	**SINGLE *and STRETCH Dosing***		**Notes (Arm A belantamab mafodotin SINGLE *and STRETCH* dosing)**
	Cycle 1 Day 1[2]	***Cycle 2 Day 1***	**Every 28 Days (Starting at Week 5**[3] **regardless of dosing)**	**Starting at Cycle 2**[4] **- SINGLE dosing [*or Starting at Cycle 3- STRETCH dosing]*** **(Prior to the first dose of any study drugs at the given cycle)**	
				1.9 mg/ kg STRETCH: 1.9 mg/kg on Day 1: at least 56 (±3) days between consecutive doses of belantamab mafodotin.	For participants with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the Sum of the Products of the maximal perpendicular diameters of measured lesions (SPD). 18. Imaging of bones for lytic lesions by method aligned with institutional guidance (X-ray, CT or MRI). Survey results within 30 days prior to C1D1 date are acceptable. At later cycles, repeat as clinically indicated, or if worsening clinical symptoms suggest PD, by the same method used as at screening. 19. Response to treatment will be assessed every 4 weeks (±3 days), based on laboratory tests and imaging (if applicable), using IMWG criteria [Kumar, 2016]. 20. Whenever CR is assessed, if possible, a further BM aspirate sample may be taken at the same time for biomarker research. 21. CCI [redacted]) to be performed by the central lab at the time of first achieving VGPR or better. Thereafter, CCI [redacted] should be repeated every 6 months until PD or CR. In case of deepening of response from VGPR
Administration of lenalidomide[31]	X	X		25 or 10 mg PO Days 1-21 of each 28-day cycle	
Administration of dexamethasone[32]	X	X		40 or 20 mg on Days 1, 8, 15, and 22 of each 28-day cycle	
Preservative-free artificial tears[33]	X				
Cooling eye masks[33]	X			X	
Venous Thrombo-Embolism (VTE) prophylaxis[34]	X				

Study Assessments[1]	**SINGLE *and STRETCH Dosing***	***STRETCH Dosing ONLY***	**SINGLE *and STRETCH Dosing***		**Notes (Arm A belantamab mafodotin SINGLE *and STRETCH* dosing)**
	Cycle 1 Day 1[2]	***Cycle 2 Day 1***	**Every 28 Days (Starting at Week 5**[3] **regardless of dosing)**	**Starting at Cycle 2**[4] **- SINGLE dosing [*or Starting at Cycle 3- STRETCH dosing]*** **(Prior to the first dose of any study drugs at the given cycle)**	
Health Outcomes					
EORTC QLQ-C30 AND QLQ-MY20[35]	X		Every 8 weeks starting W9		
PRO-CTCAE[35]	X	X	X		
OSDI and NEI-VFQ-25[35]	X	X	X		

to CR, or achieving CR without prior VGPR, CCI should be performed at the time of achieving suspected CR and repeated every 6 months until PD. Whenever possible, a further BM aspirate sample may be taken at the same time for biomarker research. Additionally, collect blood plasma for CCI analysis.

CCI [redacted]

24. The optional PD tissue sample should contain tumor cells, either BM aspirate clot, or other tissue in case of extramedullary disease. Samples will be submitted to central lab for BCMA analysis, any remaining bone marrow and/or tissue sample will be used for biomarker research.
25. Informed consent for optional sub-studies (e.g. genetic research) must be obtained before collecting a sample. The sample will be collected at the first opportunity after a participant has met all eligibility requirements, before/ on C1D1 prior to infusion. If insufficient DNA was extracted, or the sample was damaged or otherwise could not be

Study Assessments[1]	**SINGLE *and STRETCH Dosing***	***STRETCH Dosing ONLY***	**SINGLE *and STRETCH Dosing***		**Notes (Arm A belantamab mafodotin SINGLE *and STRETCH* dosing)**
	Cycle 1 Day 1[2]	***Cycle 2 Day 1***	**Every 28 Days (Starting at Week 5**[3] **regardless of dosing)**	**Starting at Cycle 2**[4] **- SINGLE dosing [*or Starting at Cycle 3- STRETCH dosing]*** **(Prior to the first dose of any study drugs at the given cycle)**	
					processed, the site may be requested to recollect the genetic sample where applicable 26. PK samples to be taken in all participants for belantamab mafodotin measurement on: **Belantamab mafodotin Dose 1 (Cycle 1)** **Day 1**: at pre-infusion (within 30 min prior to Start of Infusion), End of Infusion (0 to 15 min after EOI), at 2 h (± 15 min) after SOI and at 24 h (± 2 h) after SOI. **Day 4** (i.e., 72 h after SOI [± 24h]), one PK sample to be taken after ECG performed. Day 8 through and including on Day 15: One PK sample to be taken. Day 29 (STRETCH): One PK sample to be taken. **Belantamab mafodotin Dose 2** **Day 1**: at pre- infusion (within 30 min prior to SOI) and EOI (0 to 15 min after EOI). If Dose 2 is delayed, collect one PK sample on this day (Dose 1 Day 29 for SINGLE and Dose 1 Day 57 for STRETCH) regardless of dosing.

Study Assessments[1]	**SINGLE *and STRETCH Dosing***	***STRETCH Dosing ONLY***	**SINGLE *and STRETCH Dosing***		**Notes (Arm A belantamab mafodotin SINGLE *and STRETCH* dosing)**
	Cycle 1 Day 1[2]	***Cycle 2 Day 1***	**Every 28 Days (Starting at Week 5[3] regardless of dosing)**	**Starting at Cycle 2[4] - SINGLE dosing [*or Starting at Cycle 3- STRETCH dosing]*** **(Prior to the first dose of any study drugs at the given cycle)**	
					Belantamab mafodotin Dose 3 **Day 1**: at pre- infusion (within 30 min prior to SOI) and EOI (0 to 15 min after EOI). **Belantamab mafodotin Dose 6** **Day 1**: at pre- infusion (within 30 min prior to SOI) and EOI (0 to 15 min after EOI). **Belantamab mafodotin Dose 9:** **Day 1**: at pre- infusion (within 30 min prior to SOI). **Belantamab mafodotin Dose 12** **Day 1**: at pre-infusion (within 30 min prior to SOI). For treatment beyond belantamab mafodotin Dose 12, pre-infusion samples will be collected every 6th Dose of belantamab mafodotin (Dose 18, Dose 24, Dose 30 and so on, until PD). CCI samples will be collected every time a belantamab mafodotin PK sample is collected. See footnote 22. 27. PK samples for lenalidomide: During C1D1, PK samples will be collected at pre-dose (within 30 min prior to taking drug), 0.5 h (±2 min), 1 h (±5 min), 2 h (±10 min), and 4 h (±15 min) and 24 h (±2 h) after the administration of lenalidomide. **The**

Study Assessments[1]	SINGLE *and STRETCH Dosing*	*STRETCH Dosing ONLY*	SINGLE *and STRETCH Dosing*		Notes (Arm A belantamab mafodotin SINGLE *and STRETCH* dosing)
	Cycle 1 Day 1[2]	*Cycle 2 Day 1*	Every 28 Days (Starting at Week 5[3] regardless of dosing)	Starting at Cycle 2[4] - SINGLE dosing [*or Starting at Cycle 3- STRETCH dosing]* (Prior to the first dose of any study drugs at the given cycle)	
					24 h post-dose must be collected before lenalidomide dosing on C1D2. 28. All ADA samples will be collected prior to each belantamab mafodotin infusion at Dose 1, 2, 3, 6, 9 and 12 (at the same time as the pre-infusion belantamab mafodotin PK samples are taken); for treatment beyond 12 cycles, 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). 29. Premedication should be considered in any participant who experienced an IRR during the first or any subsequent infusions with belantamab mafodotin. 30. Belantamab mafodotin will be administered first as a 30 min to 1 h infusion, followed by 1-2 h rest period. A window of ±3 days is acceptable for administration of study treatment after C1. Please refer to Section 8.2 for dose modification guidance. Note: "SINGLE" Dosing Schedule: belantamab mafodotin will be administered as a SINGLE full dose on Day 1 of each cycle. For example: A "2.5 mg/kg SINGLE" dosing schedule of belantamab mafodotin will administer a 2.5 mg/kg

Study Assessments[1]	SINGLE *and STRETCH Dosing*	*STRETCH Dosing ONLY*	SINGLE *and STRETCH Dosing*		Notes (Arm A belantamab mafodotin SINGLE *and STRETCH* dosing)
	Cycle 1 Day 1[2]	*Cycle 2 Day 1*	Every 28 Days (Starting at Week 5[3] regardless of dosing)	Starting at Cycle 2[4] - SINGLE dosing [*or Starting at Cycle 3- STRETCH dosing]* (Prior to the first dose of any study drugs at the given cycle)	
					dose on D1 of each cycle. *Note: STRETCH Dosing Schedule: belantamab mafodotin will be administered as a full dose on D1 of every alternate 28-day cycle. For example: A 1.9 mg/kg STRETCH will administer a 1.9 mg/kg dose on Day 1 of every alternate 28-day cycle i.e. STRETCH (C1, C3, C5, C7 and so on*). 31. Lenalidomide: 25 mg orally daily on Days 1 - 21 of each cycle in participants with >60 mL/min/1.73 m^2, or reduced to 10 mg daily if the eGFR is 40-60 mL/min/1.73 m^2. [Refer to lenalidomide PI]. Refer to Section 8.2 for dose modification guidance. 32. Dexamethasone: 40 mg weekly, orally on Days 1, 8, 15, 22 of each cycle, Participants who are >75 y with BMI <18.5 kg/m^2, the dose of dexamethasone can be reduced to 20 mg weekly. If intolerance to dexamethasone develops, dexamethasone may be reduced to 20 mg. If 20 mg is not tolerated, the dexamethasone dose can be further reduced or permanently discontinued. Refer to Section 8.2 for dose modification guidance.

Study Assessments[1]	**SINGLE *and STRETCH Dosing***	***STRETCH Dosing ONLY***	**SINGLE *and STRETCH Dosing***		**Notes (Arm A belantamab mafodotin SINGLE *and STRETCH* dosing)**
	Cycle 1 Day 1[2]	***Cycle 2 Day 1***	**Every 28 Days (Starting at Week 5**[3] **regardless of dosing)**	**Starting at Cycle 2**[4] **- SINGLE dosing [*or Starting at Cycle 3- STRETCH dosing]*** **(Prior to the first dose of any study drugs at the given cycle)**	
					On days where only lenalidomide and dexamethasone are taken at home, they should be taken in the morning approximately at the same time each day. On C1D1, lenalidomide should be administered as close as possible to the end of the 1-2 h rest period after administration of belantamab mafodotin and no later than 6 h after the end of the rest period after administration of belantamab mafodotin. On subsequent lenalidomide and belantamab mafodotin co-administration days such as C2D1, C3D1 and thereafter, lenalidomide should be administered after the end of the 1-2 h rest period after administration of belantamab mafodotin. Participant diary will be used to keep record of self-administered oral study treatment(s) at home. 33. Corneal Events Management: - Prophylactic preservative-free artificial tears must be administered in each eye at least 4-8 times daily beginning on C1D1 until end of treatment. In the event of ocular symptoms (e.g., dry eyes), the use of artificial tears may be increased up to every 2 hours as needed.

Study Assessments[1]	**SINGLE *and STRETCH Dosing***	***STRETCH Dosing ONLY***	**SINGLE *and STRETCH Dosing***		**Notes (Arm A belantamab mafodotin SINGLE *and STRETCH* dosing)**
	Cycle 1 Day 1[2]	***Cycle 2 Day 1***	**Every 28 Days (Starting at Week 5**[3] **regardless of dosing)**	**Starting at Cycle 2**[4] **- SINGLE dosing [*or Starting at Cycle 3- STRETCH dosing]*** **(Prior to the first dose of any study drugs at the given cycle)**	
					- At the start of each infusion, participants may apply cooling eye masks for approximately 1 h or as long as tolerated. 34. ASA or LMH or oral anticoagulants according to institutional guidance for the duration of treatment with lenalidomide. 35. EORTC QLQ-C30 AND QLQ-MY20 will be collected every 8 weeks, and PRO-CTCAE, OSDI and NEI-VFQ-25 will be collected every 4 weeks, even if cycle is delayed. Participants who cannot complete the self-administered version should use an Interviewer-Administered format. The interview may be administered over the telephone. If the Interviewer-Administered format is used, it should be read to the participants verbatim, and participant responses should be recorded directly without any interpretation. Refer to SRM for further details.

Table 6 Schedule of Activities – On-Study Assessments for Arm A (belantamab mafodotin in combination with lenalidomide plus dexamethasone) [28-Day Cycle] – belantamab mafodotin SPLIT Dosing Only

Study Assessments[1]	Cycle 1		Every 28 Days (Starting at Week 5[3] regardless of dosing)	Starting at Cycle 2[4] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm A belantamab mafodotin SPLIT dosing only)
	Day 1[2]	Day 8			
ECOG Performance Status			X		1. All assessments apply to Part 1 and 2 of the study unless stated otherwise.
Adverse Events/ SAEs[5]	X		Ongoing	Ongoing	2. Screening assessments do not need to be repeated on Cycle 1 Day 1 (C1D1) unless otherwise specified.
Concomitant Medications	X		Ongoing	Ongoing	3. All assessments starting at week 5 can be performed within 3 days prior to the scheduled date unless otherwise specified.
					4. Assessments scheduled on days of dosing should be conducted prior to drug administration, unless otherwise specified. Physical Exam must be within 72 h prior to 1st dose of study drugs to be administrated in that cycle. Body weight at C1D1 (prior to dosing) will be used for dose calculation of belantamab mafodotin. Body weight to be measured prior to each dose. If the change of body weight is greater than 10%, the dose should be re-calculated based on the actual body weight at the time of dosing.
Safety					5. Treatment-related toxicities will be assessed for at least 70 days after the last dose regardless of initiation of new anticancer therapy. All related SAEs are to be collected from consent through CC follow-up. For reporting of ocular events see the guidance provided in Appendix 8.
Physical Exam	X	X	X	X[4]	6. Participants will be assessed by a qualified eye care specialist (Appendix 12) on Day 1 of every cycle prior to dosing up to Dose 6 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 the time of Dose 6 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
Ocular Exam[6]				X	
Vital Signs (BP, Heart rate, Body Temperature)[7]	X	X		X	
Body Weight (BW) and Height	BW only			BW only	
Hematology[8,9]	X	X	X	X	
Clinical chemistry[8]	X		X	X	
HbA1c	As clinically indicated				
C-reactive protein (CRP)[8]			X		
Urinalysis (dipstick)[8]	X		X		
Estimated Glomerular Filtration Rate (eGFR) by MDRD formula	X		X		
Spot urine for albumin/creatinine ratio[10]			X		
Pregnancy Test for WOCBP[11]	X		X	X	
12-lead ECG[12]	X	X		X	

Study Assessments[1]	Cycle 1		Every 28 Days (Starting at Week 5[3] regardless of dosing)	Starting at Cycle 2[4] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm A belantamab mafodotin SPLIT dosing only)
	Day 1[2]	Day 8			
ECHO – LVEF[13]			Every 12 weeks (At week 13, 25, 37, 49 and so on)		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 Dose 6 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 10.6.7.1 for full details of ocular exam procedures. 7. On each belantamab mafodotin dosing day, vital signs must be assessed within 30 min prior to Start of Infusion (SOI), within 15 min after End of Infusion (EOI), and at 1 h (±15 min) after EOI. On days where vital sign assessments align with PK sampling time points, vital signs should be assessed prior to belantamab mafodotin PK samples being drawn. 8. Hematology and clinical chemistry must be repeated, if not done within 24 h prior to 1st dose of study drugs to be administered in that cycle. Refer to Table 27 for comprehensive list of lab tests. 9. To be performed up to 24 h before D1, D8, D15, D22 in C1 and C2; then up to 24 h before D1, D15 in C3 to C8 and then up to 24 h before Day 1 of each cycle from C9 onwards, or more frequently, if clinically indicated. On D1 of any planned cycle, Absolute Neutrophil Count (ANC) must be ≥1.0×10^9/L to administer treatment. 10. Albumin/creatinine ratio (Spot urine from first void) every 4 weeks ±3 days (local lab, if not available then central laboratory testing). 11. Perform only in women of childbearing potential. Two negative serum pregnancy tests must be obtained prior to initiating therapy with lenalidomide; one may be performed within 10-14 days of C1D1, but the second must be performed within 24 h of C1D1. After the first dose of belantamab mafodotin, pregnancy test will be done weekly during the first month, then monthly thereafter in females with regular menstrual cycles or every 2 weeks in females
Disease Evaluation [every 4 weeks (±3 days) even if the cycle is delayed][14]					
SPEP (Serum Protein Electrophoresis)			X		
Serum Kappa, lambda free LC, FLC ratio			X		
Serum Immunofixation[15]			At time of suspected CR then until suspected PD		
UPEP (Urine Protein Electrophoresis) (on 24 h collected urine)			X		
Urine Immunofixation[15]			At time of suspected CR then until suspected PD		
Ca corrected for Albumin (Serum)			X		
IgG, IgM, IgA			X		
IgD/IgE[16]			X		

Study Assessments[1]	Cycle 1		Every 28 Days (Starting at Week 5[3] regardless of dosing)	Starting at Cycle 2[4] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm A belantamab mafodotin SPLIT dosing only)
	Day 1[2]	Day 8			
Imaging for extramedullary disease[17]			Week 13, 25, 37, 49 and then if clinically indicated		with irregular menstrual cycles. Subsequent pregnancy test on dosing days may be either serum or urine test. Each pregnancy test must be performed within 24 h prior to dosing. 12. SINGLE ECG performed pre-infusion on belantamab mafodotin dosing days. On days when belantamab mafodotin PK sampling is performed, PK samples should be drawn shortly after ECG. TRIPLICATE ECGs will be performed as described below, with SINGLE ECG performed at all other times. All ECGs will be collected centrally (refer to SRM for details). **Belantamab mafodotin Dose 1 (C1)** Day 1: TRIPLICATE ECGs Pre-infusion (within 30 min prior to SOI), EOI (up to 15 min after EOI), 2 h (±15 min) after SOI and 24 h (±2 h) after SOI. D4 (i.e. 72 h after D1 SOI [±24 h]): TRIPLICATE ECG performed before PK sample. D8: TRIPLICATE ECGs Pre-infusion (within 30 min prior to SOI), EOI (up to 15 min after EOI), 2 h (±15 min) after SOI and 24 h (±2 h) after SOI. D11 (i.e. 72 h after Day 8 SOI [±24 h]): TRIPLICATE ECG performed before PK sample. **Belantamab mafodotin Dose 2:** D1: SINGLE ECG pre-infusion D8: SINGLE ECG pre-infusion **Belantamab mafodotin Dose 3:** D1: TRIPLICATE ECGs pre-infusion (within 30 min prior to SOI), EOI (up to 15 min after EOI) D8: TRIPLICATE ECGs pre-infusion (within 30 min prior to SOI), EOI (up to 15 min after EOI) 13. ECHO will be performed every 12 weeks (±7 days) and locally. 14. Disease evaluation (except imaging and skeletal survey) will continue to be performed, every 4 weeks (±3 days) even if the cycle is delayed.
Skeletal Survey[18]			As clinically indicated		
Whole body PET/CT			Only once at time of achieving CR or sCR (whichever comes first) according to IMWG 2016		
Response assessment by IMWG[19]			X		
Bone Marrow Tests					
BM aspirate/biopsy for Disease Assessment[20,24]			At time of suspected CR or at time of suspected PD (only if PD not evident otherwise)		
BM biopsy to confirm sCR by IHC			Upon achieving CR		

Study Assessments[1]	Cycle 1		Every 28 Days (Starting at Week 5[3] regardless of dosing)	Starting at Cycle 2[4] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm A belantamab mafodotin SPLIT dosing only)
	Day 1[2]	Day 8			
BM aspirate for [redacted] testing[21]			At time of achieving VGPR or better		15. At time of first achieving SPEP or Urine M protein ~0 g/dl (suspected CR) and until suspected PD after CR or stringent Complete Response (sCR). 16. Only in participants with IgD/IgE myeloma. 17. Imaging is only required for participants with known extramedullary disease at week 13, 25, 37, 49 (±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 (i.e. if CT/PET scan was used as baseline, participant needs to be followed by CT/PET scans). Selected target lesion needs to be measured and followed over time. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For participants with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the Sum of the Products of the maximal perpendicular diameters of measured lesions (SPD). 18. Imaging of bones for lytic lesions by method aligned with institutional guidance (X-ray, CT or MRI). Survey results within 30 days prior to C1D1 date are acceptable. At later cycles, repeat as clinically indicated, or if worsening clinical symptoms suggest PD, by the same method used as at screening. 19. Response to treatment will be assessed every 4 weeks (±3 days), based on laboratory tests and imaging (if applicable), using IMWG criteria [Kumar, 2016]. 20. Whenever CR is assessed, if possible, a further BM aspirate sample may be taken at the same time for biomarker analysis. 21. [redacted]) to be performed by the central lab at the time of first achieving VGPR or better. Thereafter, [redacted] should be repeated every 6 months until PD or CR. In case of deepening of response from VGPR to CR, or achieving CR without prior VGPR, [redacted] should be performed at the time of achieving suspected CR and repeated every 6 months until PD.
Biomarkers					
[redacted]	X			X	
	X		At time of achieving VGPR or better[21]		
Optional					
Optional tissue sample at PD for BCMA expression and biomarker research[24]			X		
Genetic sample[25]	X				
PK and ADA					
Pharmacokinetic blood sampling for belantamab mafodotin[22,26]	X[26]	X[26]		X (at selected cycles)[26]	
Anti-drug antibodies (ADA)[27]	X[27]			X (at selected cycles)[27]	
Treatment					
Premedication if needed[28]	X			X	

Study Assessments[1]	Cycle 1		Every 28 Days (Starting at Week 5[3] regardless of dosing)	Starting at Cycle 2[4] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm A belantamab mafodotin SPLIT dosing only)
	Day 1[2]	Day 8			
Administration of belantamab mafodotin[29]	X	X		Day 1 and Day 8 of each 28-day cycle	Whenever possible, a further BM aspirate sample may be taken at the same time for biomarker analysis. Additionally, collect blood plasma for CCI analysis. CCI [redacted] 24. The optional PD tissue sample should contain tumor cells, either BM aspirate clot, or other tissue in case of extramedullary disease. Samples will be submitted to central lab for BCMA analysis, any remaining bone marrow and/or tissue sample will be used for biomarker research. 25. Informed consent for optional sub-studies (e.g. genetic research) must be obtained before collecting a sample. The sample will be collected at the first opportunity after a participant has met all eligibility requirements, before/ on C1D1 prior to infusion. If insufficient DNA was extracted, or the sample was damaged or otherwise could not be processed, the site may be requested to recollect the genetic sample where applicable. 26. PK samples to be taken in all participants for belantamab mafodotin measurement on: **Belantamab mafodotin Dose 1 (Cycle 1)** • Day 1: at pre-infusion (within 30 min prior to SOI), EOI (0 to 15 min after EOI), at 2 h (±15 min) after SOI and at 24h (± 2 h) after SOI. • Day 4 (i.e., 72 h after SOI [±24 h]), one PK sample to be taken after ECG performed. • Day 8: at pre-infusion (within 30 min prior to Day 8 SOI), EOI (0 to 15 min after Day 8 EOI), at 2 h (±15 min) after SOI and at 24h (±2 h) after SOI. • Day 11: One PK sample to be taken after ECG performed • Day 15 through and including on Day 21: One PK sample to be taken.
Administration of lenalidomide[30]	X	X		25 or 10 mg PO Days 1-21 of each 28-day cycle	
Administration of dexamethasone[31]	X	X		40 or 20 mg on Days 1, 8, 15, and 22 of each 28-day cycle	
Preservative-free artificial tears[32]	X				
Cooling eye masks[32]	X	X		X	
Venous Thrombo-Embolism (VTE) prophylaxis[33]	X	X	X	X	
Health Outcomes					
EORTC QLQ-C30 AND QLQ-MY20[34]	X		Every 8 weeks starting at W9		
PRO-CTCAE[34]	X		X		
OSDI and NEI-VFQ-25[34]	X		X		

Study Assessments[1]	Cycle 1		Every 28 Days (Starting at Week 5[3] regardless of dosing)	Starting at Cycle 2[4] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm A belantamab mafodotin SPLIT dosing only)
	Day 1[2]	Day 8			**Belantamab mafodotin Dose 2** • Day 1: at pre- infusion (within 30 min prior to SOI) and EOI (0 to 15 min after EOI). If Dose 2 is delayed, collect one PK sample on this day (Dose 1 Day 29) regardless of dosing. • Day 8: at pre- infusion (within 30 min prior to SOI) and EOI (0 to 15 min after EOI). **Belantamab mafodotin Dose 3** • Day 1: at pre- infusion (within 30 min prior to SOI) and EOI (0 to 15 min after EOI). • Day 8: at pre- infusion (within 30 min prior to SOI) and EOI (0 to 15 min after EOI). **Belantamab mafodotin Dose 6** • Day 1: at pre- infusion (within 30 min prior to SOI) and EOI (0 to 15 min after EOI). • Day 8: at pre- infusion (within 30 min prior to SOI) and EOI (0 to 15 min after EOI). **Belantamab mafodotin Dose 9** • Day 1 only: at pre- infusion (within 30 min prior to SOI). **Belantamab mafodotin Dose 12** • Day 1 only: at pre-infusion (within 30 min prior to SOI). For treatment beyond belantamab mafodotin Dose 12, pre-infusion samples will be collected on Day 1 only of every 6th Dose of belantamab mafodotin (Dose 18, Dose 24, Dose 30 and so on, until PD). CCI samples will be collected every time a belantamab mafodotin PK sample is collected. See footnote 22. **NOTE: All pre-dosing samples must be collected on D8 even if belantamab mafodotin dosing is delayed. Any samples that are pre-dose but dose not administered should be moved to unscheduled. If belantamab mafodotin**

Study Assessments[1]	Cycle 1		Every 28 Days (Starting at Week 5[3] regardless of dosing)	Starting at Cycle 2[4] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm A belantamab mafodotin SPLIT dosing only)
	Day 1[2]	Day 8			**D8 dosing is delayed and D8 PK sampling were planned for that dose, pre-dose and EOI sample must be taken on the day of dosing.** 27. All ADA samples will be collected prior to each belantamab mafodotin infusion at Dose 1, 2, 3, 6, 9 and 12 (at the same time as the pre-infusion belantamab mafodotin PK samples are taken); for treatment beyond 12 cycles, collect samples for ADA analysis prior to each infusion every 6th Dose of belantamab mafodotin (Dose 18, Dose 24, Dose 30 etc. until PD). **NOTE: ADA samples only apply to Day 1 dose, not the Day 8 dose.** 28. Premedication should be considered in any participant who experienced an IRR during the first or any subsequent infusion with belantamab mafodotin. 29. Belantamab mafodotin will be administered first as a 30 min to 1 h infusion followed by 1-2 h rest period. For D1, a window of ±3 days is acceptable for administration of study treatment after C1. For D8, belantamab mafodotin can be delayed and administered any time up to D15. Refer to Section 8.2 for dose modification guidance. Note: "SPLIT" Dosing Schedule: belantamab mafodotin will be split into two equal halves and each half dose will be administered on D1 and D8 of each cycle. For example: A "2.5 mg/kg SPLIT" dosing schedule will administer a 1.25 mg/kg dose on D1 and a 1.25 mg/kg dose on D8 of each cycle. A "3.4 mg/kg SPLIT" dosing schedule will administer a 1.7 mg/kg dose on D1 and a 1.7 mg/kg dose on D8 of each cycle. **NOTE: If the participant is unable to receive D1 dose, D8 dose must be withheld. If belantamab mafodotin was administered on D1, participant should always receive belantamab mafodotin on D8 of any SPLIT dosing cycle unless the investigator determines that the participant is clinically unfit to receive the dose (e.g., febrile neutropenia, active infection).** 30. Lenalidomide: 25 mg orally daily on Days 1 - 21 of each cycle in participants with >60 mL/min/1.73 m^2, or reduced to 10 mg daily if the eGFR is 40-60 mL/min/1.73 m^2. [Please refer to lenalidomide PI]. Refer to Section 8.2 for dose modification guidance.

Study Assessments[1]	Cycle 1		Every 28 Days (Starting at Week 5[3] regardless of dosing)	Starting at Cycle 2[4] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm A belantamab mafodotin SPLIT dosing only)
	Day 1[2]	Day 8			31. Dexamethasone: 40 mg weekly, orally on Days 1, 8, 15, 22 of each cycle, Participants who are >75y with BMI <18.5 kg/m^2, the dose of dexamethasone can be reduced to 20 mg weekly. If intolerance to dexamethasone develops, dexamethasone may be reduced to 20 mg. If 20 mg is not tolerated, the dexamethasone dose can be further reduced or permanently discontinued. Please refer to Section 8.2 for dose modification guidance. On days where only lenalidomide and dexamethasone are taken at home, they should be taken in the morning approximately at the same time each day. On C1D1, lenalidomide should be administered as close as possible to the end of the 1-2 h rest period after administration of belantamab mafodotin and no later than 6 h after the end of the rest period after administration of belantamab mafodotin. On subsequent lenalidomide and belantamab mafodotin co-administration days such as C2D1, C3D1 and thereafter, lenalidomide should be administered after the end of the 1-2 h rest period after administration of belantamab mafodotin. Participant Diary will be used to keep record of self-administered oral study treatment(s) at home. 32. Corneal Events Management (SPLIT Dose): - Prophylactic preservative-free artificial tears must be administered in each eye at least 4-8 times daily beginning on C1D1 until end of treatment. In the event of ocular symptoms (e.g., dry eyes), the use of artificial tears may be increased up to every 2 hours as needed. - At the start of each infusion, participants may apply cooling eye masks for approximately 1 h or as long as tolerated. 33. ASA or LMH or oral anticoagulants according to institutional guidance for the duration of treatment with lenalidomide. 34. EORTC QLQ-C30 AND QLQ-MY20 will be collected every 8 weeks, and PRO-CTCAE, OSDI and NEI-VFQ-25 will be collected every 4 weeks, even if cycle is delayed. Participants who cannot complete the self-administered version should use an Interviewer-Administered format. The interview may be administered

Study Assessments[1]	Cycle 1		Every 28 Days (Starting at Week 5[3] regardless of dosing)	Starting at Cycle 2[4] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm A belantamab mafodotin SPLIT dosing only)
	Day 1[2]	Day 8			
					over the telephone. If the Interviewer-Administered format is used, it should be read to the participants verbatim, and participant responses should be recorded directly without any interpretation. Refer to SRM for further details.

Table 7 Schedule of Activities - On Study Assessments for Arm B (belantamab mafodotin in combination with bortezomib plus dexamethasone) [21-Day Cycle] - belantamab mafodotin SINGLE Dosing Only

Study Assessments[1]	Cycle 1		Every 21 Days (Starting at Week 4[4] regardless of dosing)	Starting at Cycle 2[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin SINGLE dosing only)
	Day 1[2]	D4, D8 and D11[3]			
ECOG Performance Status			X		1. All assessments apply to Part 1 and 2 of the study, unless stated otherwise. 2. Screening Assessments do not need to be repeated on C1D1 unless otherwise specified. 3. C1 D4, D8, and D11 are dosing days for bortezomib. 4. All assessments starting at week 4 can be performed within 3 days prior to the scheduled date unless otherwise specified. 5. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. Physical Exam must be within 72 h prior to 1st dose of study drugs to be administrated in that cycle. Body weight at C1D1 (prior to dosing) will be used for dose calculation of belantamab mafodotin. Body weight to be measured prior to each dose. If the change of body weight is greater than 10%, the dose should be re-calculated based on
Adverse Events/SAEs[6]	X	X	Ongoing	Ongoing	
Concomitant Medications	X	X	Ongoing	Ongoing	
Safety					
Physical Exam	X		X	X[5]	
Ocular Exam[7]				X	
Vital Signs (BP, Heart rate Body Temperature)[8]	X	X		X (must also be done with each dose of bortezomib)	

Study Assessments[1]	Cycle 1		Every 21 Days (Starting at Week 4[4] regardless of dosing)	Starting at Cycle 2[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin SINGLE dosing only)
	Day 1[2]	D4, D8 and D11[3]			
Body Weight (BW) and Height	BW only			BW only	
Hematology[9]	X	X	X	X (must also be done with each dose of bortezomib)	
Clinical chemistry[9]	X	X	X	X	
HbA1c	As clinically indicated				
C-reactive Protein (CRP) [9]			X		
Urinalysis (dipstick)[9]	X		X		
Estimated Glomerular Filtration Rate (eGFR) by MDRD formula	X		X		
Spot urine for albumin/creatinine ratio[10]			X		
Pregnancy Test for WOCBP[11]	X		X	X	
12-lead ECG[12]	X	X		X	
ECHO – LVEF[13]			Every 12 weeks (At week 13, 25, 37, 49 and so on)		
Disease Evaluation [every 3 weeks (±3 days) even if the cycle is delayed][14]					
SPEP (Serum Protein Electrophoresis)			X		
Serum Kappa, lambda free LC, FLC ratio			X		

the actual body weight at the time of dosing. Up to 8 cycles of bortezomib and dexamethasone in combination with belantamab mafodotin are allowed; after the 8th cycle of Bor/Dex, participants will continue belantamab mafodotin monotherapy until progressive disease, intolerable AEs, or death occurs.

6. Treatment-related toxicities will be assessed for at least 70 days after the last dose regardless initiation of new anticancer therapy. All related SAEs are to be collected from consent through CC follow-up. For reporting of ocular events see the guidance provided in Appendix 8.
7. Participants will be assessed by a qualified eye care specialist (Appendix 12) on Day 1 of every cycle prior to dosing up to Dose 6 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 the time of Dose 6 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 Dose 6 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 10.6.7.1 for full details of ocular exam procedures.
8. On each belantamab mafodotin dosing day, vital signs must be assessed within 30 min prior to Start of Infusion (SOI), within 15 min after End of Infusion (EOI), and at 1 h (±15 min) after EOI. On days where vital sign time points align with PK sampling time points, vital signs should be assessed prior to belantamab mafodotin PK samples being drawn. Vital signs must be

Study Assessments[1]	Cycle 1		Every 21 Days (Starting at Week 4[4] regardless of dosing)	Starting at Cycle 2[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin SINGLE dosing only)
	Day 1[2]	D4, D8 and D11[3]			
Serum Immunofixation[15]			At time of suspected CR then until suspected PD		assessed within 30 mins before and within 15 min after each dose of bortezomib. 9. Hematology and clinical chemistry must be repeated if not within 24 h prior to 1st dose of study drugs to be administrated in that cycle. **Hematology must be repeated prior to each dose of bortezomib.** Starting at C9, Hematology must be repeated prior to each dose of belantamab mafodotin. An additional hematology sample must be collected on D15 ±24 h for Cycles 1-8. On Day 1 of any planned cycle, Absolute Neutrophil Count (ANC) must be ≥1.0×10^9/L to administer treatment. Refer to Table 27 for comprehensive list of lab tests. 10. Albumin/creatinine ratio (Spot urine from first void) every 3 weeks ±3 days (local lab, if local not available then central). 11. Perform only in 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 (as needed in WOCBP) 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 test on dosing days may be either serum or urine test. Each pregnancy test must be performed within 24 h prior to dosing. 12. SINGLE ECG performed pre-infusion on belantamab mafodotin dosing days.
UPEP (Urine Protein Electrophoresis) (on 24 h collected urine)			X		
Urine Immunofixation[15]			At time of suspected CR then until suspected PD		
Ca corrected for Albumin (Serum)			X		
IgG, IgM, IgA			X		
IgD/IgE[16]			X		
Imaging for extramedullary disease[17]			Week 13, 25, 37, 49 and then if clinically indicated		
Skeletal Survey[18]			As clinically indicated		

Study Assessments[1]	Cycle 1		Every 21 Days (Starting at Week 4[4] regardless of dosing)	Starting at Cycle 2[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin SINGLE dosing only)
	Day 1[2]	D4, D8 and D11[3]			
Whole body PET/CT			Only once at time of achieving CR or sCR (whichever comes first) according to IMWG 2016		On days when belantamab mafodotin PK sampling is performed, PK samples should be drawn shortly after ECG. TRIPLICATE ECGs will be performed as described below with SINGLE ECG performed at all other times. All ECGs will be collected centrally (refer to SRM for details). **Belantamab mafodotin Dose 1 (C1)** D1: TRIPLICATE ECGs Pre-infusion (within 30 min prior to SOI), EOI (up to 15 min after EOI), 2 h (±15 min) after SOI and 24 h (±2 h) after SOI. D4: TRIPLICATE ECG performed before PK sample. D11: TRIPLICATE ECG performed before PK sample. **Belantamab mafodotin Dose 2** D1: SINGLE ECG pre-infusion **Belantamab mafodotin Dose 3** D1: TRIPLICATE ECGs pre-infusion (within 30 min prior to SOI), and EOI (up to 15 min after EOI). D4: TRIPLICATE ECG performed before PK sample. D11: TRIPLICATE ECG performed before PK sample. 13. ECHO will be performed every 12 weeks (±7 days) and locally. 14. Disease evaluation (except imaging and skeletal survey) will continue to be performed, every 3 weeks (±3 days) even if the cycle is delayed. 15. At time of first achieving SPEP or Urine M protein ~0 g/dl (suspected CR) and until suspected PD after CR or stringent Complete Response (sCR). 16. Only in participants with IgD/IgE myeloma 17. Imaging is only required for participants with extramedullary disease at week 13, 25, 37, 49 (±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 (i.e., if CT/PET scan was used as baseline, participant needs to be followed by CT/PET scans). Selected target lesion needs to be measured and followed over time. Plasmacytoma
Response assessment by IMWG[19]			X		
Bone Marrow Tests					
BM aspirate/biopsy for Disease Assessment[20,24]			At time of suspected CR or at time of suspected PD (only if PD not evident otherwise)		
BM biopsy to confirm sCR by IHC			Upon achieving CR		
BM aspirate for CCI [redacted] testing[21]			At time of first achieving VGPR or better		
Biomarkers					
CCI [redacted]	X			X	

Study Assessments[1]	Cycle 1		Every 21 Days (Starting at Week 4[4] regardless of dosing)	Starting at Cycle 2[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin SINGLE dosing only)
	Day 1[2]	D4, D8 and D11[3]			
CCI [redacted]	X		At time of achieving VGPR or better[21]		measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For participants with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the Sum of the Products of the maximal perpendicular diameters of measured lesions (SPD).
Optional					18. Imaging of bones for lytic lesions by method aligned with institutional guidance (X-ray, CT or MRI). Survey results within 30 days prior to C1D1 date are acceptable. At later cycles, repeat as clinically indicated, or if worsening clinical symptoms suggest PD, by the same method used as at screening.
Optional tissue sample at PD for BCMA expression and biomarker research[24]			X		19. Response to treatment will be assessed every 3 weeks (±3 days), based on laboratory tests and imaging (if applicable), using IMWG criteria [Kumar, 2016].
Genetic sample[25]	X				
					20. Whenever CR is assessed, if possible, a further BM aspirate sample may be taken at the same time for biomarker analysis.
PK and ADA					
Pharmacokinetic blood sampling for belantamab mafodotin[22,26]	X[26]			X (at selected cycles)[26]	21. CCI [redacted]) to be performed by the central lab at the time of first achieving VGPR or better. Thereafter, CCI [redacted] should be repeated every 6 months until PD or CR. In case of deepening of response from VGPR to CR, or achieving CR without prior VGPR, CCI [redacted] should be performed at the time of achieving suspected CR and repeated every 6 months until PD. Whenever possible, a further BM aspirate sample may be taken at the same time for biomarker analysis. Additionally, collect blood plasma for CCI [redacted] analysis.
Pharmacokinetic blood sampling for bortezomib[27]	X[27]				
Anti-drug antibodies (ADA)[28]	X[28]			X (at selected cycles)[28]	
Treatment					
Premedication if needed[29]	X			X	
Administration of belantamab mafodotin[30]	X			Day 1 of each 21-day cycle	

CCI [redacted]

Study Assessments[1]	Cycle 1		Every 21 Days (Starting at Week 4[4] regardless of dosing)	Starting at Cycle 2[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin SINGLE dosing only)
	Day 1[2]	D4, D8 and D11[3]			
Administration of bortezomib[31]	X	1.3 mg/m^2 SC or IV on Days 1, 4, 8 and 11 of each 21-day cycle		1.3 mg/m^2 SC or IV on Days 1, 4, 8 and 11 of each 21-day cycle	24. The optional PD tissue sample should contain tumor cells, either BM aspirate clot, or other tissue in case of extramedullary disease. Samples will be submitted to central lab for BCMA analysis, any remaining bone marrow and/or tissue sample will be used for biomarker research. 25. Informed consent for optional sub-studies (e.g. genetic research) must be obtained before collecting a sample. The sample will be collected at the first opportunity after a participant has met all eligibility requirements, before/ on C1D1 prior to infusion. If insufficient DNA was extracted, or the sample was damaged or otherwise could not be processed, the site may be requested to recollect the genetic sample where applicable. 26. PK samples to be taken in all participants for belantamab mafodotin measurement on: **Belantamab mafodotin Dose 1 (Cycle 1)** **Day 1**: at pre-infusion (within 30 min prior to SOI, EOI (0 to 15 min after EOI), at 2 h (± 15 min) after SOI and 24h (±2 h) after SOI. **Day 4**: one PK sample to be taken prior to Bor/Dex administration **Day 11**: one PK sample to be taken prior to Bor/Dex administration **Belantamab mafodotin Dose 2** **Day 1**: at pre-infusion (within 30 min prior to SOI) and EOI (0 to 15 min after EOI). If Dose 2 is delayed, collect one PK sample on this day (Dose 1 Day 22) regardless of dosing. **Belantamab mafodotin Dose 3** **Day 1:** at pre-infusion (within 30 min prior to SOI) and EOI (0 to 15 min after EOI), **Day 4**: during visit to be taken prior to Bor/Dex administration **Day 11**: during visit to be taken prior to Bor/Dex administration
Administration of dexamethasone[32]	X	20 mg PO or IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle		20 mg PO or IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle	
Preservative-free artificial tears[33]	X				
Cooling eye masks[33]	X			X	
Antiviral prophylaxis[34]	X				
Health Outcomes					
EORTC QLQ-C30 AND QLQ-MY20 (Part 1 and Part 2)[35]	X		Every 6 weeks starting at W7		
PRO-CTCAE[35]	X		X		
OSDI and NEI-VFQ-25[35]	X		X		

Study Assessments[1]	Cycle 1		Every 21 Days (Starting at Week 4[4] regardless of dosing)	Starting at Cycle 2[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin SINGLE dosing only)
	Day 1[2]	D4, D8 and D11[3]			**Belantamab mafodotin Dose 6** **Day 1**: at pre-infusion (within 30 min prior to SOI) and EOI (0 to 15 min after EOI) **Belantamab mafodotin Dose 9:** **Day 1:** at pre-infusion (within 30 min prior to SOI) **Belantamab mafodotin Dose 12:** **Day 1**: at pre-infusion (within 30 min prior to SOI). For treatment beyond belantamab mafodotin Dose 12, pre-infusion samples will be collected every 6th Dose of belantamab mafodotin (Dose18, Dose24, Dose30 and so on, until PD).[CCI] samples will be collected every time a belantamab mafodotin PK sample is collected. See footnote 22. 27. Bortezomib PK sampling after the first bortezomib dose in C1: Serial PK samples will be collected at pre-dose (within 30 min prior to administration) and, after the administration of bortezomib at 5 (± 1 min), 15 (± 1 min), and 30 (±2 min) min,1 h (±5 min), 2 h (±5 min), 4 h (±5 min), 6 h (±5 min), 10 h (±2 h), 24 h (±2 h), 48 h (±2 h), and 72 h (± 2 h).The 72 h sample needs to be taken prior to bortezomib dosing on D4. 28. All ADA samples will be collected prior to each belantamab mafodotin infusion (at Dose 1 (C1) D1, Dose 2, 3, 6, 9 and 12) both in Part 1 and Part 2 (at the same time as the pre-infusion belantamab mafodotin PK samples are taken); for treatment beyond 12 cycles, 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). 29. Premedication should be considered in any participant who experienced an IRR during the first or any subsequent infusions with belantamab mafodotin. 30. Belantamab mafodotin will be administered first as a 30 min to 1 h infusion, followed by 1-2 h rest period. A window of ±3 days is acceptable for administration of study treatment after C1. Please refer to Section 8.2 for

Study Assessments[1]	Cycle 1		Every 21 Days (Starting at Week 4[4] regardless of dosing)	Starting at Cycle 2[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin SINGLE dosing only)
	Day 1[2]	D4, D8 and D11[3]			dose modification guidance. Note: "SINGLE" Dosing Schedule: belantamab mafodotin will be administered as a SINGLE full dose on Day 1 of each cycle. For example: A "2.5 mg/kg SINGLE" dosing schedule of belantamab mafodotin will administer a 2.5 mg/kg dose on D1 of each cycle. A "3.4 mg/kg SINGLE" dosing schedule will administer a 3.4 mg/kg dose on D1 of each cycle. 31. Bortezomib 1.3 mg/m^2 SC or IV (depending on participants' and institutional preference) on Days 1, 4, 8, and 11 of every 21-day cycle for a total up to 8 cycles. Please refer to Section 8.2 for dose modification guidance. Note: Participants will receive antiviral prophylaxis (for example acyclovir or other according to the institutional guidelines), for the entire duration of treatment with Bor/Dex (8 cycles). 32. Dexamethasone 20 mg PO or IV will be given on Days 1, 2, 4, 5, 8, 9, 11, and 12 of every 21-day cycle. Dexamethasone will be given for a total of up to 8 cycles. If dexamethasone is taken at home, it should be taken approximately at the same time each day. Participant Diary will be used to keep record of self-administer oral dexamethasone at home. Participants who are >75y with BMI <18.5 kg/m^2, the dose of dexamethasone can be reduced to 10 mg. If intolerance to dexamethasone develops, dexamethasone may be reduced to 10 mg. If 10 mg is not tolerated, the dexamethasone dose can be further reduced or permanently discontinued. Please refer to Section 8.2 for dose modification guidance. 33. Corneal Events Management: - Prophylactic preservative-free artificial tears must be administered in each eye at least 4-8 times daily beginning on C1D1 until end of treatment. In the event of ocular symptoms (e.g., dry eyes), the use of artificial tears may be increased up to every 2 hours as needed.

Study Assessments[1]	Cycle 1		Every 21 Days (Starting at Week 4[4] regardless of dosing)	Starting at Cycle 2[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin SINGLE dosing only)
	Day 1[2]	D4, D8 and D11[3]			- At the start of each infusion, participants may apply cooling eye masks for approximately 1 h or as long as tolerated. 34. Antiviral prophylaxis (for example acyclovir or other according to institutional guidelines) is required for the duration of bortezomib treatment. 35. EORTC QLQ-C30 AND QLQ-MY20 will be collected every 6 weeks, and PRO-CTCAE, OSDI and NEI-VFQ-25 will be collected every 3 weeks, even if cycle is delayed. Participants who cannot complete the self-administered version should use an Interviewer-Administered format. The interview may be administered over the telephone. If the Interviewer-Administered format is used, it should be read to the participants verbatim, and participant responses should be recorded directly without any interpretation. Refer to SRM for further details.

Table 8 Schedule of Activities - On Study Assessments for Arm B (belantamab mafodotin in combination with bortezomib plus dexamethasone) [21-Day Cycle] – belantamab mafodotin SPLIT Dosing Only

Study Assessments[1]	Cycle 1		Every 21 Days (Starting at Week 4[4] regardless of dosing)	Starting at Cycle 2[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin SPLIT dosing only)
	Day 1[2]	D4, D8 and D11[3]			
ECOG Performance Status			X		1. All assessments apply to Part 1 and 2 of the study unless stated otherwise. 2. Screening Assessments do not need to be repeated on C1D1 unless otherwise specified. 3. C1 D4, D8, and D11 are dosing days for bortezomib.
Adverse Events/SAEs[6]	X	X	Ongoing	Ongoing	
Concomitant Medications	X	X	Ongoing	Ongoing	

Study Assessments[1]	Cycle 1		Every 21 Days (Starting at Week 4[4] regardless of dosing)	Starting at Cycle 2[5] (Prior to the first dose of any study drugs at the given cycle)
	Day 1[2]	D4, D8 and D11[3]		
Safety				
Physical Exam	X	X (Day 8 only)	X	X[5]
Ocular Exam[7]				X
Vital Signs (BP, Heart rate Body Temperature)[8]	X	X		X (must also be done with each dose of Bortezomib)
Body Weight (BW) and Height	BW only			BW only
Hematology[9]	X	X	X	X (must also be done with each dose of Bortezomib)
Clinical chemistry[9]	X	X	X	X
HbA1c	As clinically indicated			
C-reactive Protein (CRP) [9]			X	
Urinalysis (dipstick)[9]	X		X	
Estimated Glomerular Filtration Rate (eGFR) by MDRD formula	X		X	
Spot urine for albumin/creatinine ratio[10]			X	
Pregnancy Test for WOCBP[11]	X		X	X
12-lead ECG[12]	X	X		X
ECHO – LVEF[13]			Every 12 weeks	

Notes (Arm B belantamab mafodotin SPLIT dosing only)

4. All assessments starting at week 4 can be performed within 3 days prior to the scheduled date unless otherwise specified.
5. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. Physical Exam must be within 72 h prior to 1st dose of study drugs to be administrated in that cycle. Body weight at C1D1 (prior to dosing) will be used for dose calculation of belantamab mafodotin. Body weight to be measured prior to each dose. If the change of body weight is greater than 10%, the dose should be re-calculated based on the actual body weight at the time of dosing. Up to 8 cycles of bortezomib and dexamethasone in combination with belantamab mafodotin are allowed; after 8 cycles of Bor/Dex, participants will be allowed to continue on belantamab mafodotin monotherapy until progressive disease, intolerable AEs, or death occurs.
6. Treatment-related toxicities will be assessed for at least 70 days after the last dose regardless initiation of new anticancer therapy. All related SAEs are to be collected from consent through CCI follow-up. For reporting of ocular events see the guidance provided in Appendix 8.
7. Participants will be assessed by a qualified eye care specialist (Appendix 12) on Day 1 of every cycle prior to dosing up to Dose 6 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 the time of Dose 6 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

Study Assessments[1]	Cycle 1		Every 21 Days (Starting at Week 4[4] regardless of dosing)	Starting at Cycle 2[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin SPLIT dosing only)
	Day 1[2]	D4, D8 and D11[3]			
			(At week 13, 25, 37, 49 and so on)		
Disease Evaluation [every 3 weeks (±3 days) even if the cycle is delayed][14]					
SPEP (Serum Protein Electrophoresis)			X		
Serum Kappa, lambda free LC, FLC ratio			X		
Serum Immunofixation[15]			At time of suspected CR then until suspected PD		
UPEP (Urine Protein Electrophoresis) (on 24 h collected urine)			X		
Urine Immunofixation[15]			At time of suspected CR then until suspected PD		
Ca corrected for Albumin (Serum)			X		
IgG, IgM, IgA			X		
IgD/IgE[16]			X		
Imaging for extramedullary disease[17]			Week 13, 25, 37, 49 and then if		

symptoms or vision changes at Dose 6 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 10.6.7.1 for full details of ocular exam procedures.

8. On each belantamab mafodotin dosing day, vital signs must be assessed within 30 min prior to Start of Infusion (SOI), within 15 min after End of Infusion (EOI), and at 1 h (±15 min) after EOI. On days where vital sign time points align with PK sampling time points, vital signs should be assessed prior to belantamab mafodotin PK samples being drawn. Vital signs must be assessed within 30 mins before and within 15 min after each dose of bortezomib.
9. Hematology and clinical chemistry must be repeated if not within 24 h prior to 1st dose of study drugs to be administered in that cycle. **Hematology must be repeated prior to each dose of bortezomib.** Starting at C9, Hematology must be repeated prior to each dose of belantamab mafodotin. An additional hematology sample must be collected on Day 15 ±24 h for Cycles 1-8. On Day 1 of any planned cycle, Absolute Neutrophil Count (ANC) must be ≥1.0×10^9/L to administer treatment. Refer to Table 27 for comprehensive list of lab tests.
10. Albumin/creatinine ratio (Spot urine from first void) every 3 weeks ±3 days (local lab, if local not available then central).
11. Perform only in 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 (as needed in WOCBP) should be performed at local lab to determine childbearing potential. WOCBP must have

Study Assessments[1]	Cycle 1		Every 21 Days (Starting at Week 4[4] regardless of dosing)	Starting at Cycle 2[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin SPLIT dosing only)
	Day 1[2]	D4, D8 and D11[3]			
			clinically indicated		
Skeletal Survey[18]			As clinically indicated		
Whole body PET/CT			Only once at time of achieving CR or sCR (whichever comes first) according to IMWG 2016		
Response assessment by IMWG[19]			X		
Bone Marrow Tests					
BM aspirate/biopsy for Disease Assessment[20,24]			At time of suspected CR or at time of suspected PD (only if PD not evident otherwise)		
BM biopsy to confirm sCR by IHC			Upon achieving CR		
BM aspirate for [redacted] testing[21]			At time of first achieving VGPR or better		

a negative highly sensitive serum pregnancy test within 72 hours of dosing on C1D1. Subsequent pregnancy test on dosing days may be either serum or urine test. Each pregnancy test must be performed within 24 h prior to dosing.

12. SINGLE ECG performed pre-infusion on belantamab mafodotin dosing days. On days when belantamab mafodotin PK sampling is performed, ECGs should be performed prior to PK samples being drawn. TRIPLICATE ECGs will be performed as described below with SINGLE ECG performed at all other times. All ECGs will be collected centrally (refer to SRM for details).
Belantamab mafodotin Dose 1 (C1)
Day 1: TRIPLICATE ECGs Pre-infusion (within 30 min prior to SOI), EOI (up to 15 min after EOI), 2 h (±15 min) after SOI and 24 h (±2 h) after SOI.
Day 4: TRIPLICATE ECG performed before PK sample.
Day 8: TRIPLICATE ECGs Pre-infusion (within 30 min prior to SOI), EOI (up to 15 min after EOI), 2 h (±15 min) after SOI and 24 h (±2 h) after SOI.
Day 11: TRIPLICATE ECG performed before PK sample.
Belantamab mafodotin Dose 2
D1: SINGLE ECG pre-infusion
D8: SINGLE ECG pre-infusion
Belantamab mafodotin Dose 3
D1: TRIPLICATE ECGs pre-infusion (within 30 min prior to SOI), EOI (up to 15 min after EOI).
D4: TRIPLICATE ECG performed before PK sample.
D8: TRIPLICATE ECGs pre-infusion (within 30 min prior to SOI), EOI (up to 15 min after EOI).
D11: TRIPLICATE ECG performed before PK sample.
13. ECHO will be performed every 12 weeks (±7 days) and locally.
14. Disease evaluation (except imaging and skeletal survey) will continue to be performed, every 3 weeks (±3 days) even if the cycle is delayed.

Study Assessments[1]	Cycle 1		Every 21 Days (Starting at Week 4[4] regardless of dosing)	Starting at Cycle 2[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin SPLIT dosing only)
	Day 1[2]	D4, D8 and D11[3]			
Biomarkers					
CCI [redacted]	X			X	
	X		At time of achieving VGPR or better[21]		
Optional					
Optional tissue sample at PD for BCMA expression and biomarker research[24]			X		
Genetic sample[23]	X				
PK and ADA					
Pharmacokinetic blood sampling for belantamab mafodotin[22,26]	X[26]	X (Day 8)[26]		X (at selected cycles)[26]	
Anti-drug antibodies (ADA)[27]	X[27]			X (at selected cycles)[27]	
Treatment					
Premedication if needed[28]	X	X		X	
Administration of belantamab mafodotin[29]	X	X (Day 8)		Day 1 and Day 8 of each 21-day cycle	

15. At time of first achieving SPEP or Urine M protein ~0 g/dl (suspected CR) and until suspected PD after CR or stringent Complete Response (sCR).
16. Only in participants with IgD/IgE myeloma
17. Imaging is only required for participants with extramedullary disease at week 13, 25, 37, 49 (±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 (i.e., if CT/PET scan was used as baseline, participant needs to be followed by CT/PET scans). Selected target lesion needs to be measured and followed over time. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable.
    For participants with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the Sum of the Products of the maximal perpendicular diameters of measured lesions (SPD).
18. Imaging of bones for lytic lesions by method aligned with institutional guidance (X-ray, CT or MRI). Survey results within 30 days prior to C1D1 date are acceptable. At later cycles, repeat as clinically indicated, or if worsening clinical symptoms suggest PD, by the same method used as at screening.
19. Response to treatment will be assessed every 3 weeks (±3 days), based on laboratory tests and imaging (if applicable), using IMWG criteria [Kumar, 2016].
20. Whenever CR is assessed, if possible, a further BM aspirate sample may be taken at the same time for biomarker analysis.
21. CCI [redacted]) to be performed by the central lab at the time of first achieving VGPR or better. Thereafter, CCI [redacted] should be repeated every 6 months until PD or CR. In case of deepening of response from VGPR to CR, or achieving CR without prior VGPR, CCI [redacted] should be performed at the time of achieving suspected CR and repeated every 6

Study Assessments[1]	Cycle 1		Every 21 Days (Starting at Week 4[4] regardless of dosing)	Starting at Cycle 2[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin SPLIT dosing only)
	Day 1[2]	D4, D8 and D11[3]			
Administration of bortezomib[30]	X	1.3 mg/m^2 SC or IV on Days 1, 4, 8 and 11 of each 21-day cycle		1.3 mg/m^2 SC or IV on Days 1, 4, 8 and 11 of each 21-day cycle	
Administration of dexamethasone[31]	X	20 mg PO or IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle		20 mg PO or IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle	
Preservative-free artificial tears[32]	X				
Cooling eye masks[32]	X	X (Day 8)		X	
Antiviral prophylaxis[33]	X				
Health Outcomes					
EORTC QLQ-C30 AND QLQ-MY20 (Part 1 and Part 2)[34]	X		Every 6 weeks starting at W7		
PRO-CTCAE[34]	X		X		
OSDI and NEI-VFQ-25[34]	X		X		

months until PD. Whenever possible, a further BM aspirate sample may be taken at the same time for biomarker analysis. Additionally, collect blood plasma for CCI analysis.

CCI [redacted]

24. The optional PD tissue sample should contain tumor cells, either BM aspirate clot, or other tissue in case of extramedullary disease. Samples will be submitted to central lab for BCMA analysis, any remaining bone marrow and/or tissue sample will be used for biomarker research.
25. Informed consent for optional sub-studies (e.g. genetic research) must be obtained before collecting a sample. The sample will be collected at the first opportunity after a participant has met all eligibility requirements, before/ on C1D1 prior to infusion. If insufficient DNA was extracted, or the sample was damaged or otherwise could not be processed, the site may be requested to recollect the genetic sample where applicable.
26. PK samples to be taken in all participants for belantamab mafodotin measurement on:

Belantamab mafodotin Dose 1 (C1)

- Day 1: at pre-infusion (within 30 min prior to SOI), End of Infusion (up to 15 min after EOI), at 2 h (± 15 min) after SOI and 24h (±2 h) after SOI.
- Day 4: one PK sample to be taken prior to Bor/Dex administration
- Day 8: at pre-infusion (within 30 min prior to SOI), End of Infusion (up to 15 min after EOI), at 2 h (± 15 min) after SOI and 24h (±2 h) after SOI.
- Day 11: one PK sample to be taken prior to Bor/Dex administration

Belantamab mafodotin Dose 2

Study Assessments[1]	Cycle 1		Every 21 Days	Starting at Cycle 2[5]	Notes (Arm B belantamab mafodotin SPLIT dosing only)
	Day 1[2]	D4, D8 and D11[3]	(Starting at Week 4[4] regardless of dosing)	(Prior to the first dose of any study drugs at the given cycle)	
					• Day 1: at pre-infusion (within 30 min prior to SOI) and EOI (up to 15 min after EOI). • If Dose 2 is delayed, collect one PK sample on this day (Dose 1 D22) regardless of dosing. **Belantamab mafodotin Dose 3** • Day 1: at pre-infusion (within 30 min prior to SOI) and EOI (up to 15 min after EOI), • Day 4: during visit to be taken prior to Bor/Dex administration • Day 8: at pre-infusion (within 30 min prior to SOI) and EOI (up to 15 min after EOI), • Day 11: during visit to be taken prior to Bor/Dex administration **Belantamab mafodotin Dose 6** • Day 1: at pre-infusion (within 30 min prior to SOI) and EOI (up to 15 min after EOI) **Belantamab mafodotin Dose 9** • Day 1: at pre-infusion (within 30 min prior to SOI) **Belantamab mafodotin Dose 12** • Day 1: at pre-infusion (within 30 min prior to SOI). For treatment beyond belantamab mafodotin Dose 12, pre-infusion samples will be collected every 6th Dose of belantamab mafodotin (Dose 18, Dose 24, Dose 30 and so on, until PD). CCI [redacted] samples will be collected every time a belantamab mafodotin PK sample is collected. See footnote 22. **NOTE: All pre-dosing samples must be collected on D8 even if belantamab mafodotin dosing is delayed. Any samples that are pre-dose but dose not administered should be moved to unscheduled. If belantamab mafodotin D8 dosing is delayed and D8 PK sampling were planned for that dose, pre-dose and EOI sample must be taken on the day of dosing.**

Study Assessments[1]	Cycle 1		Every 21 Days	Starting at Cycle 2[5]	Notes (Arm B belantamab mafodotin SPLIT dosing only)
	Day 1[2]	D4, D8 and D11[3]	(Starting at Week 4[4] regardless of dosing)	(Prior to the first dose of any study drugs at the given cycle)	
					27. All ADA samples will be collected prior to each belantamab mafodotin infusion (at Dose 1 (C1) Dose 2, 3, 6, 9 and 12) (at the same time as the pre-infusion belantamab mafodotin PK samples are taken); for treatment beyond 12 cycles, collect samples for ADA analysis prior to each infusion every 6th Dose of belantamab mafodotin (and so on, until PD). **NOTE: ADA samples only apply to Day 1 dose, not the Day 8 dose.** 28. Premedication should be considered in any participant who experienced an IRR during the first or any subsequent infusions with belantamab mafodotin. 29. Belantamab mafodotin administration: belantamab mafodotin will be administered first as a 30 min to 1 h infusion, followed by 1-2 h rest period. For D1, a window of ±3 days is acceptable for administration of study treatment after C1. For D8, belantamab mafodotin can be delayed and administered any time up to D15. Please refer to Section 8.2 for dose modification guidance. Note: "SPLIT" Dosing Schedule: belantamab mafodotin will be split into two equal halves and each half dose will be administered on D1 and D8 of each cycle. For example: A "2.5 mg/kg SPLIT" dosing schedule will administer a 1.25 mg/kg dose on D1 and a 1.25 mg/kg dose on D8 of each cycle. A "3.4 mg/kg SPLIT" dosing schedule will administer a 1.7 mg/kg dose on Day 1 and a 1.7 mg/kg dose on D8 of each cycle. **NOTE: If the participant is unable to receive Day 1 dose, D8 dose must be withheld. If belantamab mafodotin was administered on D1, participant should always receive belantamab mafodotin on D8 of any SPLIT dosing cycle unless the investigator determines that the participant is clinically unfit to receive the dose (e.g., febrile neutropenia, active infection).** 30. Bortezomib 1.3 mg/m^2 SC or IV (depending on participants' and institutional preference) on Days 1, 4, 8, and 11 of every 21-day cycle for a total up to 8 cycles. Please refer to Section 8.2 for instructions on dose delays.

Study Assessments[1]	Cycle 1		Every 21 Days	Starting at Cycle 2[5]	Notes (Arm B belantamab mafodotin SPLIT dosing only)
	Day 1[2]	D4, D8 and D11[3]	(Starting at Week 4[4] regardless of dosing)	(Prior to the first dose of any study drugs at the given cycle)	
					Note: Participants will receive antiviral prophylaxis (for example acyclovir or other according to the institutional guidelines), for the entire duration of treatment with Bor/Dex (8 cycles). 31. Dexamethasone 20 mg PO or IV will be given on Days 1, 2, 4, 5, 8, 9, 11, and 12 of every 21-day cycle. Dexamethasone will be given for a total of up to 8 cycles. If dexamethasone is taken at home, it should be taken approximately at the same time each day. Participant Diary will be used to keep record of self-administer oral dexamethasone at home. Participants who are >75y with BMI <18.5 kg/m^2, the dose of dexamethasone can be reduced to 10 mg. If intolerance to dexamethasone develops, dexamethasone may be reduced to 10mg. If 10mg is not tolerated, the dexamethasone dose can be further reduced or permanently discontinued. [Please refer to Section 8.2 for details]. 32. Corneal Events Management: - Prophylactic preservative-free artificial tears must be administered in each eye at least 4-8 times daily beginning on C1D1 until end of treatment. In the event of ocular symptoms (e.g., dry eyes), the use of artificial tears may be increased up to every 2 hours as needed. - At the start of each infusion, participants may apply cooling eye masks for approximately 1 h or as long as tolerated. 33. Antiviral prophylaxis (for example acyclovir or other according to institutional guidelines) is required for the duration of bortezomib treatment. 34. EORTC QLQ-C30 AND QLQ-MY20 will be collected every 6 weeks, and PRO-CTCAE, OSDI and NEI-VFQ-25 will be collected every 3 weeks, even if cycle is delayed. Participants who cannot complete the self-administered version should use an Interviewer-Administered format. The interview may be administered over the telephone. If the Interviewer-Administered format is used, it should be read to the participants verbatim, and participant responses should be recorded directly without any interpretation. Refer to SRM for further details.

Table 9 Schedule of Activities - On Study Assessments for Arm B (belantamab mafodotin in combination with bortezomib plus dexamethasone) [21-day Cycle] - belantamab mafodotin STRETCH and S/D STRETCH Dosing Only

Study Assessments[1]	STRETCH Dosing Schedule				Every 21 Days (Starting at Week 7[4] regardless of dosing)	Starting at Cycle 3[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin STRETCH and S/D STRETCH dosing only
	Cycle 1		Cycle 2				
	Day 1[2]	D4, D8 and D11[3]	Day 1[4]	D4, D8 and D11[3]			
ECOG Performance Status					X		1. All assessments apply to Part 1 and 2 of the study, unless stated otherwise.
Adverse Events/SAEs[6]	X	X	X	X	Ongoing	Ongoing	2. Screening Assessments do not need to be repeated on C1D1 unless otherwise specified.
Concomitant Medications	X	X	X	X	Ongoing	Ongoing	3. D4, D8, and D11 are dosing days for bortezomib.
							4. All assessments starting at C1D1 and week 7 can be performed within 3 days prior to the scheduled date unless otherwise specified.
Safety							5. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. Physical Exam must be within 72 h prior to 1st dose of study drugs to be administrated in that cycle. Body weight at C1D1 (prior to dosing) will be used for dose calculation of belantamab mafodotin. Body weight to be measured prior to each dose. If the change of body weight is greater than 10%, the dose should be re-calculated based on the actual body weight at the time of dosing. Up to 8 cycles of bortezomib and dexamethasone in combination with belantamab mafodotin are allowed; after the 8th cycle of Bor/Dex, participants will be allowed to continue on belantamab mafodotin monotherapy until progressive disease, intolerable AEs, or death occurs.
Physical Exam	X		X		X	X[5]	
Ocular Exam[7]			X		X	X	
Vital Signs (BP, Heart rate Body Temperature)[8]	X	X	X	X		X (must also be done with each dose of bortezomib)	
Body Weight (BW) and Height	BW only		BW only			BW only	
Hematology[9]	X	X	X	X	X	X (must also be done with each dose of bortezomib)	6. Treatment-related toxicities will be assessed for at least 70 days after the last dose regardless initiation of new anticancer therapy. All related SAEs are to be collected from consent through [redacted] follow-up. For reporting of ocular events see the guidance provided in Appendix 8.
Clinical chemistry[9]	X	X	X	X	X	X	
HbA1c	As clinically indicated						

Study Assessments[1]	STRETCH Dosing Schedule				Every 21 Days (Starting at Week 7[4] regardless of dosing)	Starting at Cycle 3[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin STRETCH and S/D STRETCH dosing only
	Cycle 1		Cycle 2				
	Day 1[2]	D4, D8 and D11[3]	Day 1[4]	D4, D8 and D11[3]			
C-reactive Protein (CRP)[9]					X		7. Participants will be assessed by a qualified eye care specialist (Appendix 12) on Day 1 (window of up to 5 days) of every 21-day cycle up to Dose 6 of belantamab mafodotin. All effort should be made to schedule the ophthalmologic exams prior to and as close to the belantamab mafodotin dosing as possible. If there are no significant ocular examinations findings, patient symptoms or vision changes at the time of the Dose 6 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 Dose 6 exam, the participants will have further ophthalmologic exams, at least every 21-day cycle (regardless of dosing) until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by the qualified eye care specialist. See Section 10.6.7.1 for full details of ocular exam procedures.
Urinalysis (dipstick)[9]	X				X		
Estimated Glomerular Filtration Rate (eGFR) by MDRD formula	X				X		
Spot urine for albumin/creatinine ratio[10]					X		
Pregnancy Test for WOCBP[11]	X		X		X	X	
12-lead ECG[12]	X		X			X	8. On each belantamab mafodotin dosing day, vital signs must be assessed within 30 min prior to Start of Infusion (SOI), within 15 min after End of Infusion (EOI), and at 1 h (±15 min) after EOI. On days where vital sign time points align with PK sampling time points, vital signs should be assessed prior to belantamab mafodotin PK samples being drawn. Vital signs must be assessed within 30 mins before and within 15 min after each dose of bortezomib.
ECHO – LVEF[13]					Every 12 weeks (At week 13, 25, 37, 49 and so on)		
Disease Evaluation [every 3 weeks (±3 days) even if the cycle is delayed][14]							
SPEP (Serum Protein Electrophoresis)					X		
Serum Kappa, lambda free LC, FLC ratio					X		
Serum Immunofixation[15]					At time of suspected CR then until suspected PD		9. Hematology and clinical chemistry must be repeated if not within 24 h prior to 1st dose of study drugs to be administrated in that cycle. **Hematology must be repeated prior to each dose of bortezomib.**

Study Assessments[1]	STRETCH Dosing Schedule				Every 21 Days (Starting at Week 7[4] regardless of dosing)	Starting at Cycle 3[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin STRETCH and S/D STRETCH dosing only
	Cycle 1		Cycle 2				
	Day 1[2]	D4, D8 and D11[3]	Day 1[4]	D4, D8 and D11[3]			
UPEP (Urine Protein Electrophoresis) (on 24 h collected urine)					X		Starting at C9, hematology must be repeated prior to each dose of belantamab mafodotin. An additional hematology sample must be collected on D15 ±24 h for Cycles 1-8. On Day 1 of any planned cycle, Absolute Neutrophil Count (ANC) must be ≥1.0×10^9/L to administer treatment. Refer to Table 27 for comprehensive list of lab tests. 10. Albumin/creatinine ratio (Spot urine from first void) every 3 weeks ±3 days (local lab, if local not available then central). 11. Perform only in 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 (as needed in WOCBP) 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 test on dosing days may be either serum or urine test. Each pregnancy test must be performed within 24 h prior to dosing. 12. SINGLE ECG performed pre-infusion on belantamab mafodotin dosing days. All ECGs will be collected centrally (refer to SRM for details). 13. ECHO will be performed every 12 weeks (±7 days) and locally. 14. Disease evaluation (except imaging and skeletal survey) will continue to be performed, every 3 weeks (±3 days) even if the cycle is delayed.
Urine Immunofixation[15]					At time of suspected CR then until suspected PD		
Ca corrected for Albumin (Serum)					X		
IgG, IgM, IgA					X		
IgD/IgE[16]					X		
Imaging for extramedullary disease[17]					Week 13, 25, 37, 49 and then if clinically indicated		
Skeletal Survey[18]					As clinically indicated		
Whole body PET/CT					Only once at time of achieving CR or sCR (whichever comes first) according to IMWG 2016		
Response assessment by IMWG[19]					X		

Study Assessments[1]	STRETCH Dosing Schedule				Every 21 Days (Starting at Week 7[4] regardless of dosing)	Starting at Cycle 3[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin STRETCH and S/D STRETCH dosing only
	Cycle 1		Cycle 2				
	Day 1[2]	D4, D8 and D11[3]	Day 1[4]	D4, D8 and D11[3]			
							15. At time of first achieving SPEP or Urine M protein ~0 g/dl (suspected CR) and until suspected PD after CR or stringent Complete Response (sCR).
Bone Marrow Tests							16. Only in participants with IgD/IgE myeloma
BM aspirate/biopsy for Disease Assessment[20,24]					At time of suspected CR or at time of suspected PD (only if PD not evident otherwise)		17. Imaging is only required for participants with extramedullary disease at week 13, 25, 37, 49 (±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 (i.e., if CT/PET scan was used as baseline, participant needs to be followed by CT/PET scans). Selected target lesion needs to be measured and followed over time. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For participants with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the Sum of the Products of the maximal perpendicular diameters of measured lesions (SPD).
BM biopsy to confirm sCR by IHC					Upon achieving CR		
BM aspirate for CCI [redacted] testing[21]					At time of first achieving VGPR or better		
Biomarkers							18. Imaging of bones for lytic lesions by method aligned with institutional guidance (X-ray, CT or MRI). Survey results within 30 days prior to C1D1 date are acceptable. At later cycles, repeat as clinically indicated, or if worsening clinical symptoms suggest PD, by the same method used as at screening.
CCI [redacted]	X		X			X	
	X				At time of achieving VGPR or better[21]		19. Response to treatment will be assessed every 3 weeks (±3 days), based on laboratory tests and imaging (if applicable), using IMWG criteria.
Optional							20. Whenever CR is assessed, if possible, a further BM aspirate sample may be taken at the same time for biomarker analysis.
Optional tissue sample at PD for BCMA expression and biomarker research[24]					X		

Study Assessments[1]	STRETCH Dosing Schedule				Every 21 Days (Starting at Week 7[4] regardless of dosing)	Starting at Cycle 3[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin STRETCH and S/D STRETCH dosing only
	Cycle 1		Cycle 2				
	Day 1[2]	D4, D8 and D11[3]	Day 1[4]	D4, D8 and D11[3]			
Genetic sample[25]	X						21. CCI [redacted] to be performed by the central lab at the time of first achieving VGPR or better. Thereafter, CCI [redacted] should be repeated every 6 months until PD or CR. In case of deepening of response from VGPR to CR, or achieving CR without prior VGPR, CCI [redacted] should be performed at the time of achieving suspected CR and repeated every 6 months until PD. Whenever possible, a further BM aspirate sample may be taken at the same time for biomarker analysis. Additionally, collect blood plasma for CCI [redacted] analysis.
PK and ADA							CCI [redacted]
Pharmacokinetic blood sampling for belantamab mafodotin[22,26]	X[26]		X[26]			X (at selected cycles)[26]	24. The optional PD tissue sample should contain tumor cells, either BM aspirate clot, or other tissue in case of extramedullary disease. Samples will be submitted to central lab for BCMA analysis, any remaining bone marrow and/or tissue sample will be used for biomarker research.
Anti-drug antibodies (ADA)[27]	X[27]					X (at selected cycles)[27]	25. Informed consent for optional sub-studies (e.g. genetic research) must be obtained before collecting a sample. The sample will be collected at the first opportunity after a participant has met all eligibility requirements, before/ on C1D1 prior to infusion. If insufficient DNA was extracted, or the sample was damaged or otherwise could not be processed, the site may be requested to recollect the genetic sample where applicable.
Treatment							26. PK samples to be taken in all participants for belantamab mafodotin measurement on:
Premedication if needed[28]	X					X	
Administration of belantamab mafodotin[29]	2.5 mg/kg on C1D1					2.5 mg/ kg STRETCH: 2.5 mg/kg on Day 1: at least 42 (±3) days between consecutive doses of belantamab mafodotin.	

Study Assessments[1]	STRETCH Dosing Schedule				Every 21 Days (Starting at Week 7[4] regardless of dosing)	Starting at Cycle 3[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin STRETCH and S/D STRETCH dosing only
	Cycle 1		Cycle 2				
	Day 1[2]	D4, D8 and D11[3]	Day 1[4]	D4, D8 and D11[3]			
						S/D STRETCH: 1.9 mg/kg on Day 1: at least 42 (±3) days between consecutive doses of belantamab mafodotin.	**Belantamab mafodotin Dose 1 (Cycle 1)** • Day 1: at pre-infusion (within 30 min prior to SOI), End of Infusion (0 to 15 min after EOI), at 2 h (± 15 min) after SOI and 24h (±2 h) after SOI. • Day 4: one PK sample to be taken prior to Bor/Dex administration • Day 11: one PK sample to be taken prior to Bor/Dex administration • Day 22 (C2D1): one PK sample to be taken prior to Bor/Dex administration **Belantamab mafodotin Dose 2** • Day 1: at pre-infusion (within 30 min prior to SOI) and EOI (0 to 15 min after EOI). • If Dose 2 is delayed, collect one PK sample on this day (Dose 1 Day 43) regardless of dosing. • Day 4: one PK sample to be taken prior to Bor/Dex administration • Day 11: one PK sample to be taken prior to Bor/Dex administration **Belantamab mafodotin Dose 3** • Day 1: at pre-infusion (within 30 min prior to SOI) and EOI (0 to 15 min after EOI). • Day 22: one PK sample to be taken prior to Bor/Dex **Belantamab mafodotin Dose 4** • Day 1: at pre-infusion (within 30 min prior to SOI) and EOI (0 to 15 min after EOI). **Belantamab mafodotin Dose 5** • **Day 1:** at pre-infusion (within 30 min prior to SOI).
	1.9 mg/kg on C1D1					1.9 mg/ kg STRETCH: 1.9 mg/kg on Day 1: at least 42 (±3) days between consecutive doses of belantamab mafodotin.	
Administration of bortezomib[30]	X	1.3 mg/m^2 SC or IV on Days 1, 4, 8 and 11 of each 21-day cycle	X	1.3 mg/m^2 SC or IV on Days 1, 4, 8 and 11 of each 21-day cycle		1.3 mg/m^2 SC or IV on Days 1, 4, 8 and 11 of each 21-day cycle	

Study Assessments[1]	STRETCH Dosing Schedule				Every 21 Days (Starting at Week 7[4] regardless of dosing)	Starting at Cycle 3[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin STRETCH and S/D STRETCH dosing only
	Cycle 1		Cycle 2				
	Day 1[2]	D4, D8 and D11[3]	Day 1[4]	D4, D8 and D11[3]			
Administration of dexamethasone[31]	X	20 mg PO or IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle	X	20 mg PO or IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle		20 mg PO or IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle	**Belantamab mafodotin Dose 6** • Day 1: at pre-infusion (within 30 min prior to SOI) and EOI (0 to 15 min after EOI) • Day 22: one PK sample to be taken prior to Bor/Dex **Belantamab mafodotin Dose 9:** • Day 1: at pre-infusion (within 30 min prior to SOI) For treatment beyond Dose 9 of belantamab mafodotin, pre-infusion samples will be collected every 3rd Dose of belantamab mafodotin (Dose 12, Dose 15, Dose 18 and so on, until PD). CCI samples will be collected every time a belantamab mafodotin PK sample is collected. See footnote 22.
Preservative-free artificial tears[32]	X						
Cooling eye masks[32]	X		X			X	
Antiviral prophylaxis[33]	X						
Health Outcomes							
EORTC QLQ-C30 AND QLQ-MY20 (Part 1 and Part 2)[34]	X				Every 6 weeks starting at W7		
PRO-CTCAE[34]	X				X		
OSDI and NEI-VFQ-25[34]	X				X		

27. All ADA samples will be collected prior to each belantamab mafodotin infusion (at Dose 1 (C1) D1, Dose 2, 3, 6, 9 and 12) both in Part 1 and Part 2 (at the same time as the pre-infusion belantamab mafodotin PK samples are taken); for treatment beyond 12 cycles, 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).
28. Premedication should be considered in any participant who experienced an IRR during the first or any subsequent infusion with belantamab mafodotin.
29. Belantamab mafodotin will be administered first as a 30 min to 1 h infusion, followed by 1-2 h rest period. A window of ±3 days is acceptable for administration of study treatment after C1. Please refer to Section 8.2 for dose modification guidance. Note: STRETCH Dosing Schedule: belantamab mafodotin will be administered as a full dose on D1 of every alternate 21-day cycle. For example: A 2.5 mg/kg STRETCH will administer a 2.5 mg/kg dose on Day 1 of every alternate 21-day cycles i.e. STRETCH (C1, C3, C5, C7 and so on). A

Study Assessments[1]	STRETCH Dosing Schedule				Every 21 Days (Starting at Week 7[4] regardless of dosing)	Starting at Cycle 3[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin STRETCH and S/D STRETCH dosing only
	Cycle 1		Cycle 2				
	Day 1[2]	D4, D8 and D11[3]	Day 1[4]	D4, D8 and D11[3]			
							S/D STRETCH will administer a 2.5 mg/kg dose on C1 D1 and for subsequent cycles a 1.9 mg/kg dose will be administered on Day 1 of all alternate 21-day cycles C3 onwards (C3, C5, C7 and so on). 1.9 mg/kg STRETCH will administer a 1.9 mg/kg dose administered on Day 1 of every alternate 21-day cycles i.e. STRETCH (C1, C3, C5, C7 and so on). 30. Bortezomib 1.3 mg/m^2 SC or IV (depending on participants' and institutional preference) on Days 1, 4, 8, and 11 of every 21-day cycle for a total up to 8 cycles. Please refer to Section 8.2 for dose modification guidance. Note: Participants will receive antiviral prophylaxis (for example acyclovir or other according to the institutional guidelines), for the entire duration of treatment with Bor/Dex (8 cycles). 31. Dexamethasone 20 mg PO or IV will be given on Days 1, 2, 4, 5, 8, 9, 11, and 12 of every 21-day cycle. Dexamethasone will be given for a total of up to 8 cycles. If dexamethasone is taken at home, it should be taken approximately at the same time each day. Participant Diary will be used to keep record of self-administer oral dexamethasone at home. Participants who are >75y with BMI <18.5 kg/m^2, the dose of dexamethasone can be reduced to 10 mg. If intolerance to dexamethasone develops, dexamethasone may be reduced to 10 mg. If 10 mg is not tolerated, the dexamethasone dose can be further reduced or permanently discontinued. Please refer to Section 8.2 for dose modification guidance. 32. Corneal Events Management: - Prophylactic preservative-free artificial tears must be administered in each eye at least 4-8 times daily beginning on C1D1 until end of treatment. In the event of ocular symptoms (e.g., dry eyes), the use of artificial tears may be increased up to every 2 hours as needed.

Study Assessments[1]	STRETCH Dosing Schedule				Every 21 Days (Starting at Week 7[4] regardless of dosing)	Starting at Cycle 3[5] (Prior to the first dose of any study drugs at the given cycle)	Notes (Arm B belantamab mafodotin STRETCH and S/D STRETCH dosing only
	Cycle 1		Cycle 2				
	Day 1[2]	D4, D8 and D11[3]	Day 1[4]	D4, D8 and D11[3]			
							- At the start of each infusion, participants may apply cooling eye masks to for approximately 1 h or as long as tolerated. 33. Antiviral prophylaxis (for example acyclovir or other according to institutional guidelines) is required for the duration of bortezomib treatment. 34. EORTC QLQ-C30 AND QLQ-MY20 will be collected every 6 weeks, and PRO-CTCAE, OSDI and NEI-VFQ-25 will be collected every 3 weeks, even if cycle is delayed. Participants who cannot complete the self-administered version should use an Interviewer-Administered format. The interview may be administered over the telephone. If the Interviewer-Administered format is used, it should be read to the participants verbatim, and participant responses should be recorded directly without any interpretation. Refer to SRM for further details.

Table 10 Schedule of Activities – End of Treatment & Follow-Up Assessments Both for Arm A (belantamab mafodotin in combination with lenalidomide plus dexamethasone) and Arm B (belantamab mafodotin in combination with bortezomib plus dexamethasone)

Study Assessments[1]	End of Treatment Visit[2]	CCI Follow-up Visit[3]	CC Follow-up Visit[4]	Notes (Arm A and Arm B End of Treatment and Follow-up)
ECOG Performance Status	X	X		1. All assessments apply to Part 1 and 2 unless stated otherwise. All assessments can be performed within 3 days prior to the scheduled date unless otherwise specified.
Adverse Events/ SAEs[5]	X	X		
Concomitant Medications	X	X		

Study Assessments[1]	End of Treatment Visit[2]	[redacted] Follow-up Visit[3]	[redacted] Follow-up Visit[4]	Notes (Arm A and Arm B End of Treatment and Follow-up)
Safety				2. **End of Treatment (EOT)** visit will occur within 45 days from the last dose of any study medication, or prior to initiation of new anti-cancer 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.
Physical Exam	X	X		3. The [redacted]) Follow-up Visit, (for participants who discontinue study treatment for a reason other than PD) should be conducted every 4 weeks (±3 days) for Arm A and every 3 weeks (±3 days) for Arm B until confirmed PD, death, start of a new anticancer treatment, withdrawal of consent, or end of the study whichever occurs first.
Ocular Exam[6]	X	X	X	4. The [redacted] Follow-up Visit will be performed in all participants who come off treatment completely. Participants will be followed for survival and subsequent anticancer therapy by chart review, phone call, or any form of communication every 3 months (±7 days) until study ends. Record the participant's survival status and whether subsequent treatment for disease was given. Participant does not need to come in for visit.
Vital Signs (BP, Heart rate Body Temperature)	X	X		5. Treatment-related toxicities will be assessed for at least 70 days after the last dose of treatment regardless initiation of new anticancer therapy. All related SAEs are to be collected from consent through [redacted] follow-up. For reporting of ocular events see the guidance provided in Appendix 8.
Body Weight (BW) and Height	BW only	BW only		6. End of Treatment visit ophthalmic exam to be performed by a qualified eye care specialist. Participants with corneal signs per the GSK scale at the End of Treatment Visit will be followed once every 3 months (±7 days) by a qualified eye care specialist until resolution to their baseline, starting another anti-cancer therapy, or up to 1 year (whichever comes first). See Section 10.6.7.1 for list of ophthalmic exam procedures and Appendix 12 for qualifications and requirements of the eye care specialist.
Hematology[7]	X	X		7. Refer to Table 27 for comprehensive list of lab tests.
Clinical chemistry[7]	X	X		8. Final pregnancy test (serum or urine) must be performed in women of child-bearing potential at the EOT Visit, the [redacted] Follow-up Visit, and (1) Arm A: 4 months after the last dose of belantamab mafodotin or 4 weeks after the last dose of lenalidomide, whichever is longer; or (2) Arm B: 4 months after the last dose of belantamab mafodotin or 7 months after the last dose of bortezomib whichever is longer (may be via a urine pregnancy test kit mailed to the participant's home with results reported by telephone).
HbA1c	As clinically indicated			
C-reactive Protein (CRP)[7]	X			
Urinalysis (dipstick)[7]	X	X		
Estimated Glomerular Filtration Rate (eGFR) by MDRD formula	X			
Pregnancy Test for WOCBP[8]	X	X	X	
12-lead ECG[9]	X			
ECHO – LVEF[10]	X			
Disease Evaluation[11]				
SPEP (Serum Protein Electrophoresis)	X	X		
Serum Kappa, lambda free LC, FLC ratio	X	X		
Serum Immunofixation[12]	At time of suspected CR until suspected PD	At time of suspected CR until suspected PD		
UPEP (Urine Protein Electrophoresis) (on 24 h collected urine)	X	X		
Urine Immunofixation[12]	At time of suspected CR, then until suspected PD	At time of suspected CR, then until suspected PD		
Ca corrected for Albumin (Serum)	X	X		

Study Assessments[1]	End of Treatment Visit[2]	CCI Follow-up Visit[3]	CC Follow-up Visit[4]
IgG, IgM, IgA	X	X	
IgD/IgE[13]	X	X	
Imaging for extramedullary disease[14]	As clinically indicated	As clinically indicated	
Skeletal Survey[15]	As clinically indicated	As clinically indicated	
Response assessment by IMWG[16]	X	X	
Bone Marrow Tests			
BM aspirate/biopsy for Disease Assessment[17,19]	At time of suspected CR or at time of suspected PD (only if PD not evident otherwise)	At time of suspected CR or at time of suspected PD (only if PD not evident otherwise)	
BM biopsy to confirm sCR by IHC	Only if CR has been achieved by this visit	Only if CR has been achieved by this visit	
BM aspirate for CCI [redacted] testing		X[18]	
CCI [redacted]	X		
	X		
Optional			
Optional tissue sample at PD for BCMA expression and biomarker research[19]	Optional at PD	Optional at PD	
PK and ADA			
Pharmacokinetic blood sampling for belantamab mafodotin[20]	X		

9. One SINGLE ECG at End of Treatment Visit.
10. ECHO to be performed locally.
11. Disease evaluation (except imaging) will continue to be performed, every 4 weeks (±3 days) for Arm A and every 3 weeks (±3 days) for Arm B, until confirmed PD, death, start of a new anticancer treatment, withdrawal of consent, or end of the study whichever occurs first.
12. At time of first achieving SPEP or Urine M protein ~0 g/dl (suspected CR) and until suspected PD after CR or sCR.
13. Only in participants with IgD/IgE myeloma.
14. Imaging is only required for participants with known extramedullary disease 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 (i.e., if CT/PET scan was used as baseline, participant needs to be followed by CT/PET scans). Selected target lesion needs to be measured and followed over time. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. A window of ± 7days is acceptable for imaging.
    For participants with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the Sum of the Products of the maximal perpendicular diameters of measured lesions (SPD).
15. Imaging of bones for lytic lesions by method aligned with institutional guidance (X-ray, CT or MRI). As clinically indicated, or if worsening clinical symptoms suggest PD, by the same method used as at screening.
16. Response to treatment will be assessed, based on laboratory tests and imaging (if applicable), using IMWG criteria [Kumar, 2016].
17. Whenever CR is assessed, if possible, a further BM aspirate sample may be taken at the same time for biomarker analysis.
18. CCI [redacted] is not to be done at each CCI visit. CCI [redacted]) to be performed by the central lab if the participant enters CCI with a VGPR or better. Thereafter, CCI [redacted] should be repeated every 6 months until PD, death, start of a new anticancer treatment, withdrawal of consent, or end of the study whichever occurs first. The 6-month window is intended to be a continuation of the interval whenever the CCI [redacted] was last performed prior to participant moving

Study Assessments[1]	End of Treatment Visit[2]	CCI Follow-up Visit[3]	CC Follow-up Visit[4]	Notes (Arm A and Arm B End of Treatment and Follow-up)
Anti-drug antibodies (ADA)[21]	X			into CCI follow-up. Whenever possible, a further BM aspirate sample may be taken at the same time for biomarker analysis. Additionally, collect blood plasma for CCI analysis.
				19. The optional PD tissue sample should contain tumor cells, either BM aspirate clot, or other tissue in case of extramedullary disease. Samples will be submitted to central lab for BCMA analysis, any remaining bone marrow and/or tissue sample will be used for biomarker research.
Health Outcomes				20. A pharmacokinetic sample will be collected from each participant at the EOT Visit. It should be accompanied by a CCI sample.
EORTC QLQ-C30 AND QLQ-MY20 (Part 1 and Part 2)[22]	X			21. A final ADA sample will also be drawn at the End of Treatment Visit.
PRO-CTCAE[22]	X			22. EORTC QLQ-C30, QLQ-MY20, PRO-CTCAE, OSDI and NEI-VFQ-25 will be collected at the EOT Visit. Participants who still show corneal signs per the GSK scale at EOT will continue to receive the OSDI and NEI-VFQ-25 assessments during follow-up visit or via **telephone** for up to 1 year or until ocular exams are completed (whichever comes first). For all measures, participants who cannot complete the self-administered version should use an Interviewer-Administered format. The interview may be administered over the telephone. If the Interviewer-Administered format is used, it should be read to the participants verbatim, and participant responses should be recorded directly without any interpretation. Refer to SRM for further details.
OSDI and NEI-VFQ-25[22]	X	X	X	
Others				
Survival Status phone call			X	
Subsequent anti-MM Treatment		X	X	

Abbreviations:
ADA = Anti-drug Antibody; BM= Bone marrow; BCMA= B-cell maturation antigen; BCVA = best-corrected visual acuity; BW = body weight; C1D1 = Cycle 1 Day 1, etc.CCI [redacted]; CRP = C-reactive protein; ECHO = Echocardiogram; EM = extramedullary; EOI = End of Infusion; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module; EORTC QLQ-MY20 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 20-item Multiple Myeloma module; FISH= Fluorescence-in-situ hybridization; FLC = free light chain; IHC = immunohistochemistry; IMWG = International Myeloma Working Group; LVEF = Left ventricular ejection fraction; CCI [redacted]; NEI-VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; OSDI = Ocular Surface Disease Index; PD = progressive disease; PET/CT = Positron emission tomography/computed tomography; PK = Pharmacokinetics; PO = orally; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events; QD = once/day (on specified days); SAEs = Serious adverse events; SOI = start of infusion; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; VGPR = Very good partial response; WOCBP = women of child-bearing potential.

4. INTRODUCTION

4.1. Study Rationale

The incorporation of proteasome inhibitors (PIs) and immunomodulatory drugs (IMIDs) into the standard of care (SoC) treatment has improved outcomes in patients with multiple myeloma over the past 10 years [Kumar, 2014; Kumar, 2008; Richardson, 2007], but most patients still eventually relapse and will require subsequent treatments [Moreau, 2015].

Bortezomib and lenalidomide are used in combination with dexamethasone to treat the relapsed disease. The recent addition of monoclonal antibodies (elotuzumab and daratumumab) to the treatment paradigm has demonstrated that the results achieved can be improved significantly. Elotuzumab, an immunostimulatory monoclonal antibody (that targets signaling lymphocytic activation molecule F7, or SLAMF7) has no anti-myeloma activity on its own, but when combined with lenalidomide-dexamethasone (Len/Dex) superior activity to Len/Dex alone was shown in a Phase 3 study (Eloquent-2 study) [Lonial, 2015]. The median Progression-free Survival (PFS) in the elotuzumab group was 19.4 months, versus 14.9 months in the control group; yielding a hazard ratio (HR) for progression or death in the elotuzumab group of 0.70 (95% CI: 0.57 to 0.85; $p<0.001$). The Overall Response Rate (ORR) in the elotuzumab group was 79%, versus 66% in the control group ($p<0.001$).

Similarly, the addition of daratumumab to lenalidomide and dexamethasone significantly lengthened PFS among patients with relapsed or refractory multiple myeloma (RRMM) [Dimopoulos, 2016]. A median follow-up of 13.5 months, and 169 events of disease progression or death were observed (in 53 of 286 patients [18.5%] in the daratumumab group vs. 116 of 283 [41.0%] in the control group; hazard ratio, 0.37; 95% CI: 0.27 to 0.52; $p<0.001$ by stratified log-rank test). The Kaplan-Meier rate of PFS at 12 months was 83.2% (95% CI: 78.3 to 87.2) in the daratumumab group, compared to 60.1% (95% CI: 54.0 to 65.7) in the control group. A significantly higher rate of overall response was observed in the daratumumab group than in the control group (92.9% vs. 76.4%, $p<0.001$). Daratumumab was associated with infusion-related reactions and a higher rate of neutropenia than the control therapy.

Daratumumab in combination with bortezomib and dexamethasone also resulted in significantly longer PFS than bortezomib and dexamethasone alone [Dimopoulos, 2016]. The 12-month PFS rate was 60.7% in the daratumumab group versus 26.9% in the control group. After a median follow-up period of 7.4 months, the median PFS was not reached in the daratumumab group, but was 7.2 months in the control group, with the HR for progression or death with daratumumab vs. control, 0.39 (95% CI: 0.28 to 0.53; $p<0.001$). The rate of overall response was higher in the daratumumab group than in the control group (82.9% vs. 63.2%, $p<0.001$). Treatment with daratumumab combined with bortezomib plus dexamethasone was associated with infusion-related reactions and higher rates of thrombocytopenia and neutropenia than bortezomib plus dexamethasone alone [Palumbo, 2016].

Belantamab mafodotin is an antibody drug conjugate targeting B cell maturation antigen (BCMA), which has demonstrated single-agent activity in the first-time-in-human trial (BMA117159) [Trudel, 2018; Trudel, 2019]. The ORR was 60% (95% CI: 42.1, 76.1) and the median PFS was 12 months in a heavily pretreated RRMM population (57% of patients had 5 or more prior lines of therapy). In the Phase 2 study 205678, at 2.5 mg/kg the ORR was 32% (97.5%CI: 21.7,43.6) and the median duration of response was 11.0 months (95%CI: 4.2,NR).

Given the previous experience with monoclonal antibodies, which exhibited lower single agent activity as monotherapy in similar populations, the combination therapy of belantamab mafodotin with SoC agents is an attractive option to explore for patients with RRMM who have been pre-treated with at least one prior line. The combination with SoC therapies (Len/Dex, or Bor/Dex) is expected to result in additive, or enhanced effects which could potentially translate into a deep and long lasting response over what has been achieved with other available agents. This study will evaluate the safety and tolerability profile of different doses and dosing schedule for belantamab mafodotin when administered in combination with approved regimens of either Len/Dex (Arm A) or Bor/Dex (Arm B). Part 2 of the study will evaluate the preliminary clinical activity at the multiple dose levels and schedules for belantamab mafodotin in combination with Len/Dex (Arm A) or Bor/Dex (Arm B) in additional participants with RRMM.

4.2. Background

4.2.1. Current Treatment of Multiple Myeloma

Multiple myeloma (MM) is an incurable malignancy and accounts for 1% of all cancers and for 10% of all hematologic malignancies. Worldwide, approximately 103,000 new cases are diagnosed annually, and an estimated 30,330 new cases and 12,650 deaths will occur in the U.S. in 2016 [Siegel, 2016]. Despite significant advances, current novel therapies and hematopoietic stem cell transplant (HSCT) cannot achieve cure, and most MM patients will die of relapse. Thus, new treatments are urgently needed.

A variety of drugs and combination treatments have been evaluated and found effective in treating multiple myeloma [Moreau, 2017; National Comprehensive Cancer Network, 2016]; however, most, if not all patients treated with these combinations inevitably relapse [Hanley, 2017; Jagannath, 2008; Richardson, 2003; Richardson, 2006]. 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 overall survival (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].

There is an urgent need to develop treatment combinations with mechanisms of action that do not overlap with the current SoC treatments, and where cross-resistance with prior treatments could be overcome. This approach is exemplified by the combination of

monoclonal antibodies (mAb) such as daratumumab (targeting CD38) or elotuzumab (targeting signaling lymphocyte activation molecule [SLAMF7]) in combination with standard of care drugs [Lokhorst, 2015; Lonial, 2014; National Comprehensive Cancer Network, 2016].

The immunomodulatory agents (IMIDs) and PIs which are often administered in combination with dexamethasone are considered corner stone treatments for MM, and are therefore good candidates for combinations where additional improvements in efficacy could be achieved when combined with belantamab mafodotin.

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

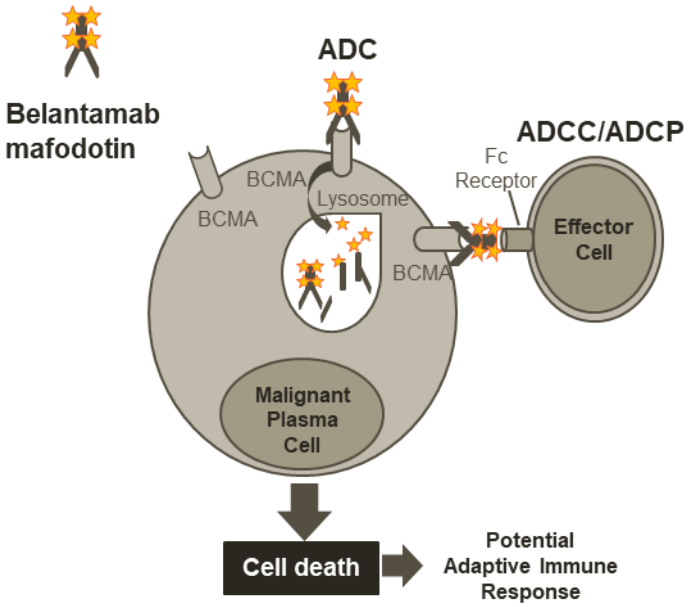
B-cell maturation antigen (BCMA), also designated as tumor necrosis factor receptor superfamily member 17 (TNFRSF17), is expressed on the surface of normal and malignant B lymphocytes at later stages of differentiation as they mature [Novak, 2004]. Ligands targeting BCMA such as B-cell activating factor (BAFF, TNFSF13B), along with a proliferation-inducing ligand (APRIL, TNFSF13) activate cell proliferation pathways and upregulate anti-apoptotic proteins in MM cell lines [Bellucci, 2005; Moreaux, 2004; Thompson, 2000]. CCI) is present in the serum of MM patients [Laurent, 2015], and its levels have been postulated to correlate with response to therapy and OS [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, 2015], and with belantamab mafodotin as single agent. Single-agent activity of belantamab mafodotin in heavily pre-treated RRMM patients has been shown in clinical trials [Trudel, 2019; Lonial, 2020].

4.2.3. Antibody-Drug Conjugate Belantamab Mafodotin

Belantamab mafodotin binds to BCMA and kills MM cells via a multi-modal mechanism including delivery of cytotoxic, MMAF (cysteine maleimidocaproyl MMAF [cys-mcMMAF]) to BCMA-expressing MM cells, thereby inducing apoptosis, enhancing antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, and inducing immunogenic cell death (Figure 3) [Tai, 2014; Montes De Oca, 2019]. Exposure of dendritic cells to tumor cells undergoing immunogenic cell death is expected to result in an antigen-specific T-cell response, enhancing the immunogenic response against MM.

Figure 3 Belantamab Mafodotin Mechanism of Action



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

4.2.4. 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 20Sep2019) 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.

4.2.4.1. Clinical activity in studies with belantamab mafodotin monotherapy

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 Number 2013N175128 V08, 2020; Trudel, 2019]. Estimated target engagement, as indicated by [redacted] binding >90%, was seen at doses of 1.92 mg/kg and higher.

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

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

As of the cut-off date of 31 January 2020, the study met its primary endpoint for ORR in both the 2.5 mg/kg [ORR 31% (97.5% CI 21.7,43.6)] and 3.4 mg/kg [ORR 35% (97.5% CI 24.8,47.0)] frozen treatments, and the benefit of belantamab mafodotin was supported by the secondary endpoints. The median DoR was 11.0 months (95% CI: 4.2, NR) at 2.5 mg/kg and 6.2 months (95% CI: 4.8, NR) at 3.4 mg/kg. The mPFS in this population was 2.8 months (95% CI: 1.6, 3.6) and 3.9 months (95% CI: 2.0, 5.8), respectively and the median Overall Survival (mOS) was 13.7 months (95% CI: 9.9, NR) at 2.5 mg/kg and 13.8 months (95% CI: 10.0, NR) at 3.4 mg/kg. Positive clinical activity was also demonstrated at the 3.4 mg/kg lyophilized dose [ORR 52% (97.5% CI 28.9,74.5)] [GSK Document Number 2013N175128 V08, 2020].

4.2.4.2. Clinical Safety in belantamab mafodotin monotherapy studies

Single-agent belantamab mafodotin was demonstrated to have a manageable safety profile in heavily pre-treated participants with RRMM. Safety data for single-agent belantamab mafodotin were pooled (data as of 20Sep2019) for DREAMM-2 study and supportive FTIH study DREAMM-1 by treatment cohorts of 2.5 mg/kg and 3.4 mg/kg [GSK Document Number 2013N175128 V08, 2020].

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

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

Adverse Events of Special Interest

Adverse events of special interest (AESIs) for belantamab mafodotin are corneal events, thrombocytopenia and infusion-related reactions, and are summarized in the IB [GSK Document Number 2013N175128 V08, 2020].

Corneal Events

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

In DREAMM-2 (data as of 31Jan2020), events in the Eye disorders SOC occurred in 78% of participants treated with belantamab mafodotin 2.5 mg/kg. The most common ocular AEs were keratopathy (71%, changes in corneal epithelium identified on eye exam, with or without symptoms), blurred vision (22%), and dry eye (13%). Decreased vision defined as Snellen score worse than 20/50 in the better seeing eye was reported in 18% of participants receiving belantamab mafodotin 2.5mg/kg. Severe vision loss defined as 20/200 or worse in the better seeing eye was reported in 1% of participants receiving belantamab mafodotin 2.5 mg/kg.

The median time to onset of Grade 2 or above corneal findings (best corrected visual acuity or corneal examination) was 36 days (range: 19 to 143 days) in participants receiving belantamab mafodotin 2.5 mg/kg. The median time to resolution of these corneal findings was 91 days (range: 21 to 201 days).

Participants with history of dry eye were more prone to develop corneal examination findings. Therefore, active management of dry eye symptoms prior to and during treatment is recommended (*i.e.* administration of preservative-free artificial tears).

The ocular sub-study of DREAMM-2 provided no evidence that corticosteroid eye drops are beneficial in preventing or mitigating corneal events.

Thrombocytopenia

In DREAMM-2 (data as of 31Jan2020), thrombocytopenic events (thrombocytopenia and platelet count decreased) occurred in 38% participants treated with belantamab mafodotin 2.5 mg/kg; severity ranging between Grade 1 and 4. The incidence of Grade 3 bleeding events was low (2%), with no Grade 4 or 5 events reported in participants treated with belantamab mafodotin 2.5 mg/kg.

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

Infusion-related reactions

Infusion-related reactions (IRRs) are expected for biologic agents. In DREAMM-2 (data as of 31Jan2020), IRRs occurred in 21% of participants in the belantamab mafodotin 2.5 mg/kg, which were Grade 1 - 3 in severity. Most IRRs occurred with the first infusion and few participants experienced IRRs with subsequent infusions.

Although not protocol-mandated, pre-medications for IRR prophylaxis (including paracetamol, antihistamines, and steroids) were administered to 26%–27% of participants. One participant (2.5 mg/kg cohort) discontinued treatment due to IRRs (Grade 3 IRRs at first and second infusion).

4.2.4.3. Pharmacokinetics and Pharmacodynamic in Humans

The pharmacokinetics and pharmacodynamics of belantamab mafodotin (antibody-drug conjugate, including complex) and total monoclonal antibody (total mAb; including complex) 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). There was limited accumulation (less than 2-fold) of belantamab mafodotin during subsequent cycles.

Belantamab mafodotin pharmacokinetics were well described by a linear, two-compartment population model, with a time-varying decrease in clearance in a population pharmacokinetic analysis. At Cycle 1, belantamab mafodotin had a systemic clearance of 0.924 L/day, steady-state volume of distribution of 10.8 L, and an elimination half-life of 11.8 days in participants with RRMM in Study 205678. Over time, clearance was reduced to 0.725 L/day, with an elimination half-life of 14.0 days. The time to 50% change in clearance was approximately 50 days.

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

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.

FreeCCI levels were measured in Study BMA117159 and Study 205678. All subjects exhibited reductions in free CCI concentration at end of infusion compared to baseline at Cycle 1, with a return to near-baseline level by seven days after dosing,

reflecting binding of belantamab mafodotin to [redacted]. Maximum decreases ranged from 2% to 97%, which were qualitatively dose-dependent, with larger reductions in free [redacted] at higher doses.

Exposure-response analyses performed for Study 205678 and/or Study BMA117159 found that ocular safety endpoints were most strongly associated with belantamab mafodotin exposure, while efficacy endpoints had a weaker association with belantamab mafodotin exposure. Both safety and efficacy endpoints were associated with patient characteristics. Belantamab mafodotin Ctau was associated with probability of corneal events and keratopathy. 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 concentration-QTc analysis demonstrated that belantamab mafodotin did not have a significant effect on cardiac repolarization.

Additional information related to belantamab clinical PK, PD, and exposure-response relationships can be found in the Investigator's Brochure [GSK Document Number 2013N175128 V08, 2020]

4.2.4.4. Clinical Summary

These results suggest that belantamab mafodotin has an acceptable safety profile and demonstrates significant clinical activity in RRMM that warrants further exploration in combinations with SoC.

Additional summaries of nonclinical and clinical findings and information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on belantamab mafodotin that may impact participant eligibility are provided in the Investigator's Brochure [GSK Document Number 2013N175128 V08, 2020].

4.3. Benefit/Risk Assessment

4.3.1. Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of belantamab mafodotin may be found in the Investigator's Brochure; more detailed information on lenalidomide, bortezomib, or dexamethasone may be found in their respective package inserts, provided in the SRM.

Table 11 Summary of Risk Assessment for the Combination Therapy of Belantamab Mafodotin with Len/Dex (Arm A) and Belantamab Mafodotin with Bor/Dex (Arm B)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Thrombocytopenia	Belantamab mafodotin may cause transient thrombocytopenia in some participants which, for most cases, recovered between doses. In the pooled safety population of study 205678, which included participants treated with belantamab mafodotin 2.5 and 3.4 mg/kg, thrombocytopenia was noted in 46% of participants and ranged between Grade 1 to 4 in severity.	Routine monitoring of hematologic panels as outlined in the SoAs. Supportive therapy per local medical practice (*e.g.,* platelet transfusion). Dose modification guidelines are outlined in Section 8.2.
Pneumonitis	Non-clinical safety experiments have demonstrated the presence of progressive microscopic changes in the lungs (prominent alveolar macrophages associated with eosinophilic material; mixed perivascular/neutrophilic inflammation) in rats at all doses tested. Cases of pneumonitis, including fatal events, have been observed with belantamab mafodotin although a causal association has not been established.	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 as described in Section 8.2 and further treatment with belantamab mafodotin delayed (refer to Section 8.2). An overall benefit/risk assessment should be considered for the participant prior to continuing belantamab mafodotin treatment. Further diagnostic tests and management will be implemented immediately in cases of suspected pneumonitis as described in Table 16.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Increased Infections due to Immunosuppression or neutropenia	In non-clinical studies, belantamab mafodotin has been associated with decrease in immunoglobulins in monkeys, at all doses. An increase in immunoglobulins was seen in rats (rats are not an antigen-specific species for belantamab mafodotin). Immunosuppression is frequently associated with an increased risk of infection. Serious and non-serious infections have been reported in belantamab mafodotin studies, including respiratory infections, pneumonia, and sepsis. Neutropenic events, including febrile neutropenia have been observed with belantamab mafodotin. In a study of belantamab mafodotin in combination with lenalidomide / dexamethasone, two fatal cases of severe infections associated with neutropenia were observed. Arm A subjects include belamaf,+len/dex.	Participants with an active infection are excluded. Monitoring for infections and immediate treatment of immunosuppression according to standard practice. Routine monitoring of hematologic panels as outlined in the SoA. Supportive therapy per local medical practice (e.g. growth factors). Prophylactic antibiotics, per local institutional guidance, in participants with Grade 3-4 neutropenia. Immediate hospitalization of participants with febrile neutropenia. Dose modification guidelines are outlined in Section 8.2
Keratopathy (changes to the corneal epithelium, potentially resulting in vision changes)	Changes in corneal epithelium on ocular examination have been frequently observed with belantamab mafodotin and was most commonly associated with keratopathy (changes in the corneal epithelium upon examination), blurred vision, dry eyes, photophobia, and changes in visual acuity. Participants with a history of dry eye were more prone to develop changes in the corneal epithelium.	Active monitoring of the corneal epithelium and visual acuity as outlined in the SoA. Evaluation and management by an eye care professional. Dose modification guidelines are outlined in Section 8.2.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Based on available follow-up data, vision returned to, or near, baseline in most cases.	
Infusion-Related Reactions (IRRs)	IRRs were reported in participants treated with belantamab mafodotin. Most IRRs were Grade 1-2 and manageable with medical treatment.	Close monitoring for signs of IRR. Consider premedication for IRR in participants at risk. If an IRR occurs, follow the guidance in Section 8.2.
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. Increased 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 (ACR). Education of participants on the need to maintain adequate urinary output. Dose modification guidelines for increased serum creatinine and urinary albumin/creatinine ratio are outlined in Section 8.2.

4.3.2. Benefit Assessment

As of 31 August 2018, results from the FTIH Study BMA117159 indicate that belantamab mafodotin monotherapy administered at 3.4 mg/kg (n=35) is active in the MM participant population and demonstrated an ORR of 60% with a 95% confidence interval (CI of 42.1% to 76.1%) and median PFS of 12 months. Preliminary data from the on-going Phase II study 205678 indicate that both dose levels of belantamab mafodotin (2.5 and 3.4 mg/kg) 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. The combination treatment of the highly active drug belantamab mafodotin with SoC is expected to result in improved outcomes, and to provide additional control of symptoms or disease progression. It is reasonable to hypothesize that such combination will benefit MM participants, who are refractory to currently available treatments.

4.3.3. Overall Benefit:Risk Conclusion

As of Amendment 03 there is limited clinical experience with the combination of belantamab mafodotin with Len/Dex and Bor/Dex. Preliminary safety data from Arm B of 207497 suggests that the combination of belantamab mafodotin 2.5 mg/kg IV Q3W with standard doses of bortezomib and dexamethasone has an acceptable safety profile, consistent with individual components. Belantamab mafodotin is a highly active agent in RRMM [Trudel, 2019; Lonial, 2020]. Taking into account the measures to minimize risks to participants in this study, the potential risks identified in association with belantamab mafodotin in combination with Len/Dex and Bor/Dex are justified by the anticipated benefits that may be afforded to participants with RRMM.

5. OBJECTIVES AND ENDPOINTS

The purpose of this Phase I/II dose escalation/dose expansion study is to determine if belantamab mafodotin can be safely administered in combination with two approved SoC regimes treatments for RRMM (Len/Dex or Bor/Dex in Part 1). The objective of Part 2 is to further evaluate the safety and preliminary clinical activity of selected doses of belantamab mafodotin with Len/Dex or Bor/Dex to identify the optimal dose(s) and schedule for each arm of combination treatment of belantamab mafodotin when administered with Len/Dex, or Bor/Dex.

The primary, secondary, and exploratory objectives, along with the corresponding endpoints for study 207497 are listed in Table 12.

Table 12 Objectives of Study 207497 – Dose Escalation and Dose Expansion

Objectives	Endpoints
Primary	
Dose Escalation Determine safety, tolerability of belantamab mafodotin in combination with either Len/Dex (Arm A) or Bor/Dex (Arm B) to establish a recommended dose range and schedule to evaluate in Dose Expansion for participants with RRMM	Number (%) of participants with DLTs. Number (%) of participants with AEs, changes in clinical signs and laboratory parameters.
Dose Escalation and Expansion[a] Select the dose(s) and dosing schedule for further investigation based on safety and tolerability of belantamab mafodotin in combination with either Len/Dex (Arm A) or Bor/Dex (Arm B) for participants with RRMM	A comprehensive determination based on safety and SAE/AEs.
Dose Expansion To determine preliminary clinical activity of belantamab mafodotin in combination with either Len/Dex (Arm A) or Bor/Dex (Arm B) for participants with RRMM	A specific determination based on ORR defined as percentage (%) of participants achieving ≥PR as defined by the IMWG Uniform Response Criteria for MM [Kumar, 2016].
Secondary **Dose Escalation and Expansion**	
To evaluate the pharmacokinetics profile of belantamab mafodotin when administered in combination with Len/Dex (Arm A) or Bor/Dex (Arm B) in participants with RRMM	Belantamab mafodotin PK parameters, as data permit
To evaluate the pharmacokinetics profile of lenalidomide when administered in combination with belantamab mafodotin and dexamethasone	Lenalidomide PK parameters, as data permit in Cycle 1
To evaluate the pharmacokinetics profile of bortezomib when administered in combination with belantamab mafodotin and dexamethasone	Bortezomib PK parameters, as data permit in Cycle 1
To assess anti-drug antibodies (ADAs) against belantamab mafodotin	Incidence and titers of ADAs against belantamab mafodotin pre-dose in Cycle 1 and selected subsequent cycles
To evaluate the effect and tolerability of belantamab mafodotin in combination with Len/Dex (Arm A) or Bor/Dex (Arm B) on	Changes from baseline in symptoms and related impacts as measured by OSDI, NEI-VFQ-25 and PRO CTCAE

Objectives	Endpoints
symptomatic adverse events in participants with RRMM	
To further characterize safety of belantamab mafodotin administered in combination with Len/Dex (Arm A) or Bor/Dex (Arm B) in participants with RRMM	Incidence of AEs, including SAEs and AEs of special interest (corneal events, thrombocytopenia and infusion related reactions). Ocular findings on ophthalmic exam
To evaluate the effect of belantamab mafodotin in combination with Len/Dex (Arm A) or Bor/Dex (Arm B) on health-related quality of life in participants with RRMM	Changes from baseline in health-related quality of life as measured by the EORTC QLQ-C30 and QLQ-MY20

CCI

[redacted]

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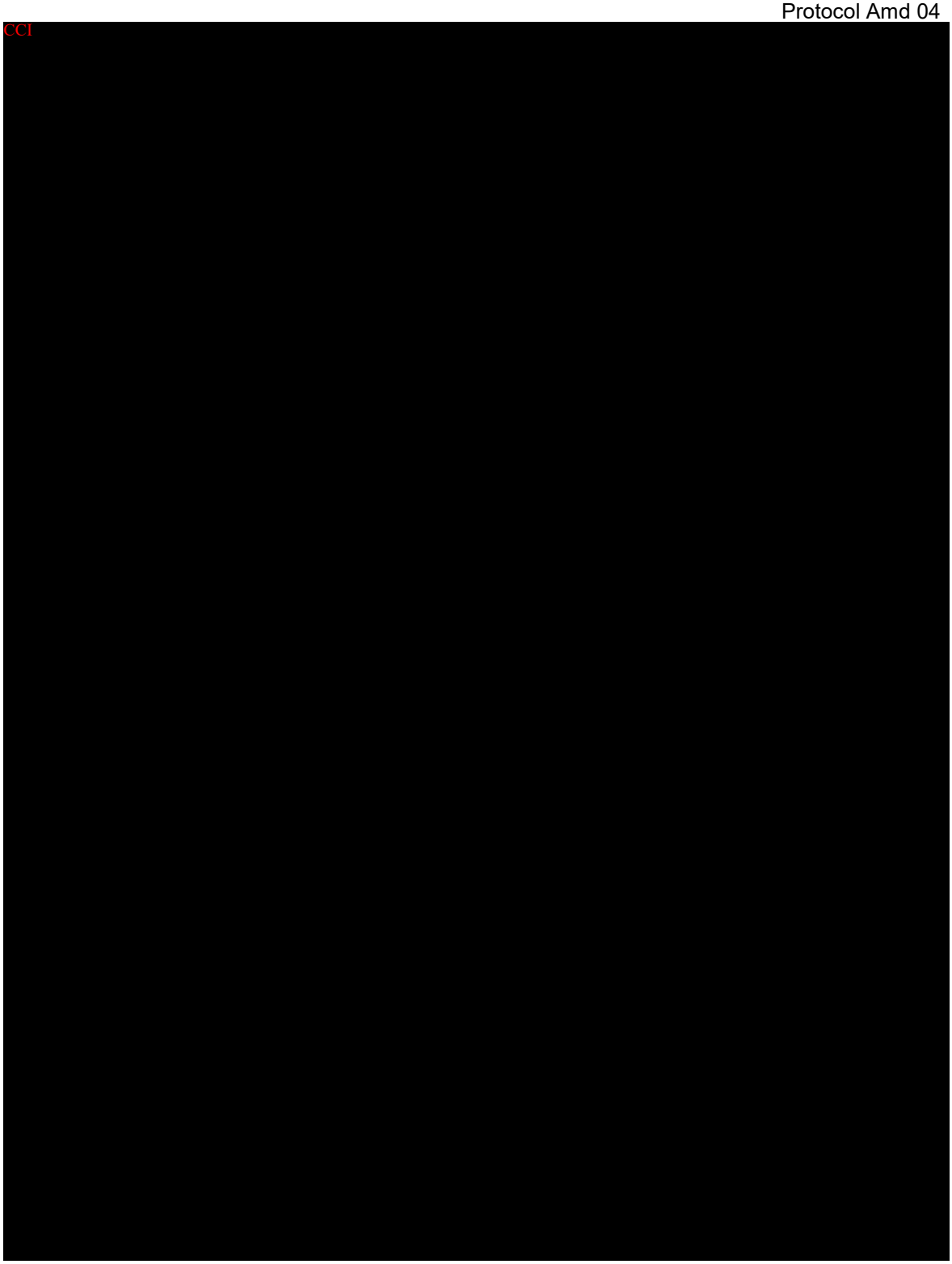


6. STUDY DESIGN

6.1. Overall Design

Part 1 of the study is a dose escalation phase to evaluate the safety and tolerability of up to 3 dose levels and up to 2 dosing schedules of belantamab mafodotin in combination with two SoC regimens (Arm A - belantamab mafodotin with Len/Dex [Figure 1] and Arm B - belantamab mafodotin with Bor/Dex [Figure 2]).

Part 2:

For Arm A (belantamab mafodotin with Len/Dex): **Part 2** of the study will further evaluate the safety and preliminary clinical activity of up to 2 dose levels and up to 3 dosing schedules of belantamab mafodotin with Len/Dex (Table 18). Additional dosing schedules may be considered if subsequent analyses of PK properties and the emerging safety profile support the exploration. Preclinical data with belantamab mafodotin suggest significantly greater activity when combined with lenalidomide in in vitro and in vivo in two established MM xenograft models [GSK internal data]. We hypothesize that the clinical combination of belantamab mafodotin with len/dex may result in significantly greater activity than that seen with the individual components. Given this and the emerging preliminary clinical data from evaluation of 2.5 mg/kg dosing cohorts in amendment 2, for Arm A, the maximum planned dose of belantamab mafodotin is 2.5 mg/kg and higher doses will not be investigated in this Arm. However, an alternate dosing schedule of STRETCH (Q8W) dosing may be explored for the 1.9 mg/kg dose level if emerging data (from either this study or across the program) suggests that this schedule may further optimize the tolerability or offers an improved benefit/risk profile.

For Arm B (belantamab mafodotin with Bor/Dex): **Part 2** of the study will further evaluate the safety and preliminary clinical activity of up to 3 dose levels and up to 4 dosing schedules of belantamab mafodotin with Bor/Dex (Table 18). Additional dosing schedules may be considered if subsequent analyses of PK properties and the emerging safety profile support the exploration. For Arm B, the maximum planned dose of belantamab mafodotin is 3.4 mg/kg, and higher doses will not be investigated in this study.

Administration of belantamab mafodotin at 2.5 mg/kg (Arm A & Arm B) and 3.4 mg/kg (Arm B only) as a SINGLE dose was tested in Protocol Amendment 1. It is hypothesized that the administration of belantamab mafodotin split into two equal halves with each half dose administered on Day 1 and Day 8 of each cycle could result in improvement of benefit/risk due to ~25% reduction in the maximum concentration while maintaining similar exposure over a cycle compared to the administration of a full dose on Day 1. To facilitate this, SPLIT dosing at the 3.4 mg/kg dose level (administering 1.7 mg/kg of belantamab mafodotin each at Day 1 and Day 8 of each dosing cycle) was introduced with Amendment 2 to deliver the same AUC of the dose with lowering of the Cmax. Accordingly, in addition to the planned 2.5 mg/kg SINGLE dosing of belantamab mafodotin, 2.5 mg/kg SPLIT dosing at belantamab mafodotin (administering 1.25 mg/kg of belantamab mafodotin each at Day 1 and Day 8 of each dosing cycle) is being tested under Protocol Amendment 2. SPLIT dosing will continue to be tested under Protocol

Amendment 3 to help explore alternative dosing schedules in order to optimize the administration of belantamab mafodotin in combination with SoC.

Although in Amendment 2, it was planned to test the 3.4 mg/kg dose as both SINGLE & SPLIT doses for Arm A, as described above, preclinical data from xenograft mouse models and emerging clinical data from Arm A in Amendment 2 suggests greater activity of belantamab mafodotin in combination with lenalidomide. Given this, in Amendment 3, the maximum planned dose of belantamab mafodotin in combination with lenalidiomide/dexamethasone in Arm A is 2.5 mg/kg and higher doses will not be investigated in Arm A.

For Arm B, however, with Amendment 3, to reduce increased exposure over time and potentially improve the benefit/risk for the participants, an extended inteval of 6 weeks (**STRETCH** schedule) between 2 consecutive planned doses of belantamab mafodotin will be evaluated in Arm B Part 2. As 6 weeks represents 3 half-lives of belantamab mafodotin, it is anticipated to lead to minimal accumulation. In addition, a Step-Down (S/D) STRETCH schedule with a first dose of 2.5 mg/kg at Cycle 1 Day 1 followed by 1.9 mg/kg every 6 weeks (42 [±3] days) from Cycle 3 onwards will also be studied as an alternative to 2.5 mg/kg repeating every 6 weeks (42 [±3] days). Similarly, dosing cohorts evaluating belantamab mafodotin 1.9 mg/kg dose every 3 weeks (1.9 mg/kg SINGLE) and 1.9 mg/kg dose every 6 weeks (1.9 mg/kg STRETCH) are also being introduced in Amendment 3.

For participants who discontinue study treatment for reasons other than PD, disease evaluations will continue to be performed at every 28 days (±3 days) for Arm A (belantamab mafodotin with Len/Dex) and at every 21 days (±3 days) for Arm B (belantamab mafodotin with Bor/Dex), until confirmed PD, death, start of a new anticancer treatment, withdrawal of consent, or end of the study, whichever occurs first. After PD is documented, participants will continue to be followed for survival and subsequent anticancer therapy every 3 months (±7 days) until the study ends.

Following 12 months post last subject first dose (LSFD), DREAMM-6 study will move into the post analysis continued treatment (PACT) phase. At that time, the collection of new data for all recruited participants who no longer receive study treatment will stop entirely and the clinical trial database will be closed. Those participants still benefiting from study drug in the opinion of their treating physician may continue to receive study drugs. In case the participant meets stopping criteria for belantamab mafodotin, the participant will discontinue all treatment and will continue to be monitored as per standard of care at the participant's particular study site. Only SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases, and pre-specified ocular data will be reported directly to GSK.

6.1.1. Arm A - Belantamab Mafodotin with Len/Dex

6.1.1.1. Part 1 Dose Escalation Phase

The modified Toxicity Probability Interval (mTPI) design [Ji, 2010] will be used to guide dose escalation in Part 1 with a slight modification (Figure 1). Up to 2 dose levels of belantamab mafodotin (1.9 mg/kg [dose -1]; 2.5 mg/kg [dose 1]) and alternate dosing

schedules are planned to be evaluated in combination with the fixed dose of the Len/Dex treatments. Based on emerging data under Protocol Amendment 1 from Arm A, the first dose investigated under Protocol Amendment 2 was 1.9 mg/kg (Dose Level -1). The design assumes the true underlying toxicity rate for maximum tolerated dose (MTD) of belantamab mafodotin falls within the range from 25% to 35% and centers at 30%. The rules for guiding dose escalations are provided in Figure 4. Columns provide the numbers of participants treated at the current dose level, and rows provide the corresponding numbers of participants experiencing toxicity. Cohorts will be recruited in blocks of three participants. Participants will be treated in a staggered approach with at least 1 day between each participant's first dose of belantamab mafodotin to minimize the risk of inadvertently exceeding the MTD in multiple participants.

In Part 1 up to 2 dose levels of belantamab mafodotin and up to 2 dosing schedules will be evaluated (Figure 1 and Table 13). Data from at least 3 DLT-evaluable participants are required before a decision is made to escalate to the next dose level. However, this is not required for enrollment of more participants at the same dose level in Part 2.

Figure 4 Dose-finding Criteria for the Modified Toxicity Probability Interval (mTPI) Dose-Finding Method

Number of DLTs	Number of Subjects treated at current dose					
	1	2	3	4	5	6
0	E	E	E	E	E	E
1	D	S	S	S	S	E
2		DU	D	S	S	S
3			DU	DU	D	S
4				DU	DU	DU
5					DU	DU
6						DU

The spreadsheet was generated based on a beta/binomial model and precalculated before trial initiation. The letters in different colors are computed based on the decision rules under the mTPI method and represent different dose-finding actions. In addition to actions de-escalate the dose (D), stay at the same dose (S), and escalate the dose (E), the table includes action unacceptable toxicity (DU), which is defined as the execution of the dose-exclusion rule in mTPI. Excerpted from Ji, et al. [Ji, 2010].

The entries of Figure 4 are dose-finding decisions (i.e., E, S, and D) representing escalating the dose, staying at the same dose, and de-escalating the dose. In addition, decision DU means that the current dose level is unacceptable because of high toxicity; the current dose level and any higher dose level should be excluded from the trial.

For example, when 1 of 3 participants experiences toxicity, the decision can be located at row 1 and column 3, which is S – to stay at the current dose level. Consequently, the next cohort of participants will be treated at the same dose level currently being used. If zero of three participants experience toxicity, the decision is at row 0 and column 3, which is E – to escalate. Thus, the next cohort of participants will be treated at the next-higher dose level. If 3 of 3 participants experience toxicity, the decision is DU – to de-escalate to the next-lower dose level and exclude the current dose and any higher dose from the trial, because toxicity levels are unacceptable. In dose escalation (E)/de-escalation (D), no dose skipping is allowed.

Table 13 Dose Levels: Arm A, Part 1

Dose Level	Belantamab mafodotin	Lenalidomide	Dexamethasone
Permissible Actions	Increase/Decrease	No changes	No changes
Dose Level -1 (de-escalation)	1.9 mg/kg IV q28 days	25 or 10 mg PO, QD on Days 1 to 21 of each 28-day cycle	40 or 20 mg/week PO or IV on Days 1, 8, 15, and 22 of each 28-day cycle
Dose Level 1	2.5 mg/kg IV q28 days[a]	25 or 10 mg PO, QD on Days 1 to 21 of each 28-day cycle	40 or 20 mg/week PO or IV on Days 1, 8, 15, and 22 of each 28-day cycle

IV = intravenous; PO = orally; QD = once daily; SC = subcutaneous

[a] Alternate dosing schedule could be investigated such as 2.5 mg/kg SPLIT dosing schedule where belantamab mafodotin will be administered at 1.25 mg/kg each on Day 1 and Day 8

Any participant from Part 1 in Arm A who received at least 1 full dose of belantamab mafodotin and at least 75% of planned doses of Len/Dex by the end of Cycle 1 (Day 28 for Arm A) is considered DLT-evaluable. Participants in Part 1 who have received less than 1 full dose of belantamab mafodotin, or <75% of planned doses of Len/Dex, or who have been withdrawn from the study for reasons other than toxicity but prior to completion of DLT observation period will be replaced.

Part 1 starts with a cohort of 3 participants at a dose level of 1.9 mg/kg SINGLE. Safety data over the first cycle of treatment for each participant will be evaluated. Data from at least 3 DLT evaluable-participants are required before a decision is made to escalate to the next dose level. The study will enroll participants in Part 1 will have staggered start times, but will run simultaneously as outlined below. If dose levels are open for both Part 1 and Part 2, priority for enrollment will be given to Part 1.

Rules for of mTPI dose escalation pertaining to Arm A only:

- If dose escalation decision is E, enrollment for Part 1 will be open at 2.5 mg/kg SINGLE and 2.5 mg/kg SPLIT. At the same time, Part 2 expansion could be opened to enroll additional participants at 1.9 mg/kg SINGLE.
- If dose escalation decision is S, three additional participants will be enrolled at 1.9 mg/kg SINGLE in Part 1 to achieve at least 6 DLT-evaluable participants at 1.9 mg/kg SINGLE. After review of data from the 6 participants:
    - If dose escalation decision is E, 2.5 mg/kg SINGLE and 2.5 mg/kg SPLIT will be open for enrollment in Part 1. Part 2 expansion will not be open for the 1.9 mg/kg SINGLE dose level unless emerging data suggest 2.5 mg/kg SINGLE and 2.5mg/kg SPLIT are not tolerable.
    - If dose escalation decision is S, enrollment will not open for dose levels higher than 1.9 mg/kg SINGLE in Part 1. Part 2 expansion will be open to enroll additional participants at 1.9 mg/kg SINGLE.
    - If dose escalation decision is D or DU, no more participants will be enrolled at 1.9 mg/kg SINGLE or higher dose levels in Part 1.

Once the 2.5 mg/kg SINGLE and 2.5 mg/kg SPLIT cohorts are open for enrollment in Part 1, a cohort of at least 3 participants will be enrolled for each dose. When Part 1 is

filled, Part 2 expansion will open for enrollment at 2.5 mg/kg SINGLE and 2.5 mg/kg SPLIT. Data from at least 6 DLT-evaluable participants at 2.5 mg/kg SINGLE and 2.5 mg/kg SPLIT are not required for enrollment of additional participants in Part 2.

Operating characteristics of the dose escalation rules are shown in Table 14.

Table 14 Operating Characteristics of the Dose Escalation Rules for Arm A

	Underlying True Toxicity Rate			Average n. of participants dosed at each dose level[1]			Prob. of Selecting as MTD[2]		
Scenario	1.9 SINGLE	2.5 SPLIT	2.5 SINGLE	1.9 SINGLE[3]	2.5 SPLIT	2.5 SINGLE	<1.9	1.9 SINGLE	2.5 SINGLE / 2.5 SPLIT
1	0.2	0.30	0.30	11	9	9	0.11	0.23	0.66
2	0.2	0.30	0.35	11	9	9	0.11	0.25	0.64
3	0.2	0.40	0.40	11	8	8	0.11	0.31	0.58
4	0.2	0.40	0.45	11	9	9	0.11	0.34	0.56
5	0.3	0.40	0.40	10	6	6	0.23	0.37	0.40
6	0.3	0.40	0.45	10	6	6	0.23	0.38	0.39
7	0.1	0.30	0.30	12	11	11	0.03	0.13	0.84
8	0.1	0.25	0.30	12	11	11	0.03	0.11	0.86
9	0.1	0.25	0.25	12	11	11	0.03	0.10	0.87
10	0.1	0.20	0.20	12	11	11	0.03	0.08	0.89
11	0.1	0.20	0.25	12	11	11	0.03	0.09	0.88

Red: Dose too toxic/n of participants exposed to a toxic dose/prob. of selecting toxic dose as MTD
Blue: True MTD dose/prob. of selecting true MTD as MTD

1. Average n. of participants dosed at each dose level include n. of participants dosed in Part 2 assuming participants for each dose level in Part 2 are enrolled before dose escalation decision is made in Part 1, except for dose 1.9 mg/kg, for which Part 2 will not open for enrollment prior to dose escalation decision.
2. Based on participants enrolled in Part 1 and assume the underlying true MTD is 30%.
3. Number in this column represents maximum estimate where dose is escalated to 2.5 mg/kg but is de-escalated to 1.9 mg/kg based on Part 1 and Part 2 data from 2.5 mg/kg.

6.1.1.2. Dose Escalation Decisions

During Part 1, the decisions on dose escalation will be made based on the mTPI guidance, as well as the totality of the safety, pharmacokinetics data as appropriate. The decisions will occur following review of all available data including participants data from Part 2 and joint discussion by the GSK medical monitor, participating investigators, and others as described in the Dose Escalation Plan.

The GSK study team, which includes but is not limited to, the GSK medical monitor, clinical scientist, safety physician, statistician and clinical pharmacologist, will review critical safety data defined in the Dose Escalation Plan prior to making a recommendation for dose escalation. This includes review of all adverse events including non-DLT toxicities, laboratory assessments and other defined safety evaluations, as well as PK and/or PD data, when appropriate. The results from the mTPI method will be included in the decision for dose modification as described in Section 12.4.8. Quality control of critical safety data will be described in the Dose Escalation Plan, which includes ongoing study monitoring visits, GSK review of the clinical database, and confirmation by participating investigators and/or delegate that the data are accurate and complete prior to making dose modification decisions.

The GSK medical monitor, in joint discussion with participating investigators, and others as described in the Dose Escalation Plan will be responsible for making dose escalation decisions. The dose-escalation decision and rationale for each cohort will be discussed with investigators during teleconference(s) and documented in writing, with copies maintained at each study site and in the study master file.

6.1.1.3. Part 2 Dose Expansion

Once Part 2 expansion is open for the 2.5 mg/kg SINGLE and 2.5 mg/kg SPLIT dose levels, up to 9 participants will be enrolled at each dosing schedule, unless enrollment is stopped based on emerging data.

In addition, up to 12 more participants maybe potentially enrolled to evaluate an extended (STRETCH) dosing schedule for belantamab mafodotin at the 1.9 mg/kg dose level if emerging data suggests that this schedule may further optimize the tolerability or offers an improved benefit/risk profile.

For STRETCH Dosing Schedule, belantamab mafodotin will be administered FIRST (prior to Len/Dex) as a single dose on Day 1 of every alternate 28-day cycle (C1, C3, C5, C7 and so on) as a 30-60 min infusion, followed by 1 to 2 h rest period. If a planned dose of belantamab mafodotin was held/missed due to any reason, the next dose can be administered at Day 1 of the next planned 28-day cycle, as long as the interval between 2 consecutive doses is at least 56 (±3) days.

Safety data from all enrolled participants will be closely monitored while the study is ongoing. In addition, participants permanently discontinuing study treatment within the first two cycles due to AEs related to belantamab mafodotin will be continuously monitored starting from when 5 participants are dosed at each dose level following pre-

defined safety stopping rules (Section 12.4.8.1). If safety concerns arise at a dose level, enrollment will stop for that dose level and higher dose level(s).

6.1.2. Arm B - Belantamab Mafodotin with Bor/Dex

6.1.2.1. Part 1 Dose Escalation Phase

A mTPI design will be implemented [Ji, 2010] to guide dose escalation in Part 1. Up to 3 dose levels of belantamab mafodotin (2.5 mg/kg [dose 1]; 3.4 mg/kg [dose +1]; 1.9 mg/kg [dose -1]), starting with 2.5 mg/kg, are planned to be evaluated in combination with the fixed dose of Bor/Dex. Cohorts will be recruited in blocks of three participants. Participants will be entered in a staggered approach with at least 1 day between each participant's first dose of belantamab mafodotin to minimize the risk of inadvertently exceeding the maximum tolerated dose (MTD) in multiple participants. A maximum of 6 participants will be assigned to each dose (Table 15).

Table 15 Dose Levels: Arm B, Part 1

Treatment Group and Dose Level	Belantamab mafodotin	Bortezomib	Dexamethasone
Permissible Actions	Increase/Decrease	No changes	No changes
Dose Level -1 (de-escalation)	1.9 mg/kg IV q21 days	1.3 mg/m^2 SC/IV on Days 1, 4, 8, and 11 of every 21-day cycle for a total of up to 8 cycles	20 mg PO or IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of every 21-day cycle for a total of up to 8 cycles.
Dose Level 1 Cohort	2.5 mg/kg IV q21 days[a]	1.3 mg/m^2 SC/IV on Days 1, 4, 8, and 11 of every 21-day cycle for a total of up to 8 cycles	20 mg PO or IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of every 21-day cycle for a total of up to 8 cycles.
Dose Level +1 Cohort	3.4 mg/kg IV q21 days[b]	1.3 mg/m^2 SC/IV on Days 1, 4, 8, and 11 of every 21-day cycle for a total of up to 8 cycles	20 mg PO or IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of every 21-day cycle for a total of up to 8 cycles.

IV = intravenous; PO = orally; QD = once daily; SC = subcutaneous

a. Alternate dosing schedule could be investigated such as SPLIT dosing schedule where belantamab mafodotin will be administered at 1.25 mg/kg each on Day 1 and Day 8

b. Alternate dosing schedule could be investigated such as SPLIT dosing schedule where belantamab mafodotin will be administered at 1.7 mg/kg each on Day 1 and Day 8

Evaluation of the available safety data over the first cycle of treatment for each participant enrolled in that dose level is required from at least 3 participants before a decision is made to enroll additional participants at the same or the subsequent dose level. However, this is not required for enrollment of more participants at the same dose level in Part 2.

The mTPI rule applied is explained in Section 6.1.1.1.

An additional dose level -1 of 1.9 mg/kg may be evaluated in case the starting dose of 2.5 mg/kg is considered not tolerated.

Rules for mTPI dose escalation pertaining to Arm B only:

- If 2.5 mg/kg is the current dose level and the decision is S, and if less than 6 participants have been evaluated for DLT and the planned maximum sample size is not reached, an additional cohort of 3 participants will be enrolled for DLT evaluation. If the dose escalation decision is S after this additional cohort, dose escalation is complete.
- If 2.5 mg/kg is the current dose level and the decision is U or DU, additional lower dose (e.g., 1.9 mg/kg) may be explored. If the dose of 1.9 mg/kg is not tolerated (i.e., results in excessive toxicity) the trial will be terminated early for lack of tolerability.
- If 3.4 mg/kg is the current dose level and the decision is E or S, and if less than 6 participants have been evaluated for DLT at the current dose, and the planned maximum sample size is not reached, an additional cohort of 3 participants will be evaluated for DLT at the current dose. If dose escalation is E or S after this additional cohort, dose escalation is complete.
- Otherwise, the dose escalation will continue until the planned maximum sample size (12 DLT-evaluable participants for each treatment) is reached. At the end of dose escalation, the rule proposed by Ji, et al. [Ji, 2010] used to guide the selection of the estimated MTD, from dose levels at which 3 or more participants have been evaluated for DLT.

During Part 1, the decisions on dose escalation will be made based on this guidance, as well as the totality of the safety, pharmacokinetics data as appropriate.

The decisions will occur following review of these data and joint discussion by the GSK medical monitor, participating investigators, and others as described in the Dose Escalation Plan.

Any participant in Arm B who received at least 1 full dose of belantamab mafodotin and ≥75% of planned doses of Bor/Dex by the end of Cycle 1 (Day 21) will be evaluated for DLTs. Participants who have received less than 1 full dose of belantamab mafodotin, or <75% of planned doses of Bor/Dex, or who have been withdrawn from the study for reasons other than toxicity but prior to completion of DLT observation period will be replaced.

The dose escalation of belantamab mafodotin will not include doses higher than 3.4 mg/kg.

6.1.2.2. Dose Escalation Decisions

The GSK study team, which includes but is not limited to, the GSK medical monitor, clinical scientist, safety physician, statistician and clinical pharmacologist, will review critical safety data defined in the Dose Escalation Plan prior to making a recommendation for dose escalation. This includes review of all adverse events including non-DLT toxicities, laboratory assessments and other defined safety evaluations, as well as PK

and/or PD data, when appropriate. The results from the mTPI method will be included in the decision for dose modification as described in Section 12.4.8. Quality control of critical safety data will be described in the Dose Escalation Plan, which includes ongoing study monitoring visits, GSK review of the clinical database, and confirmation by participating investigators and/or delegate that the data are accurate and complete prior to making dose modification decisions.

The GSK medical monitor, in joint discussion with participating investigators and GSK study team, will be responsible for making dose escalation decisions. The dose-escalation decision and rationale for each cohort will be discussed with investigators during teleconference(s) and documented in writing, with copies maintained at each study site and in the study master file.

6.1.2.3. Part 2 Dose Expansion

In Part 2 enrollment will proceed in multiple expansion cohorts to further evaluate the safety profile and to evaluate the preliminary clinical activity of belantamab mafodotin in combination with Bor/Dex at 3 dose levels and 4 dosing schedules (2.5 mg/kg SPLIT, 2.5 mg/kg SINGLE, 3.4 mg/kg SPLIT, 3.4 mg/kg SINGLE, 2.5 mg/kg STRETCH, S/D STRETCH, 1.9 mg/kg SINGLE and 1.9 mg/kg STRETCH) (Figure 2).

In Amendment 2, enrollment of each cohort was conducted by blocks of 3 participants each at 2.5 mg/kg SPLIT, 2.5 mg/kg SINGLE, 3.4 mg/kg SPLIT, and 3.4 mg/kg SINGLE with Bor/Dex for up to 12 participants each at 2.5 mg/kg SPLIT, 2.5 mg/kg SINGLE, 3.4 mg/kg SPLIT and up to 9 participants at 3.4 mg/kg SINGLE.

Similarly, in Amendment 3, enrollment of each cohort will be conducted by blocks of 3 participants each in 2.5 mg/kg STRETCH, S/D STRETCH, 1.9 mg/kg SINGLE and 1.9 mg/kg STRETCH, until approximately 12 participants are enrolled in each cohort.

For the SINGLE dosing schedule, belantamab mafodotin will be administered as a SINGLE full dose on Day 1 of each 21-day cycle. For example: A 3.4 mg/kg SINGLE dosing schedule will administer a 3.4 mg/kg dose on Day 1 of each cycle. A 2.5 mg/kg SINGLE dosing schedule of belantamab mafodotin will administer a 2.5 mg/kg dose on Day 1 of each cycle. A 1.9 mg/kg SINGLE dosing schedule of belantamab mafodotin will administer a 1.9 mg/kg dose on Day 1 of each cycle

For the SPLIT dosing schedule, belantamab mafodotin will be split into two equal halves and each half dose will be administered on Day 1 and Day 8 of each 21-day cycle. For example: A “2.5 mg/kg SPLIT” dosing schedule will administer a 1.25 mg/kg dose on Day 1 and a 1.25 mg/kg dose on Day 8 of each cycle. A “3.4 mg/kg SPLIT” dosing schedule will administer a 1.7 mg/kg dose on Day 1 and a 1.7 mg/kg dose on Day 8 of each cycle.

For STRETCH Dosing Schedule, belantamab mafodotin will be administered FIRST (prior to Bor/Dex) as a single dose on Day 1 of every alternate 21-day cycle (C1, C3, C5, C7 and so on) as a 30-60 min infusion, followed by 1 to 2 h rest period. If a planned dose of belantamab mafodotin was held/missed due to any reason, the next dose can be

administered at Day 1 of the next planned 21-day cycle, as long as the interval between 2 consecutive doses is at least 42 (±3) days.

For the S/D STRETCH schedule, belantamab mafodotin will be administered FIRST (prior to Bor/Dex) as a 2.5 mg/kg dose on Day 1 of Cycle 1, followed by 1.9 mg/kg S/D dose on Day 1 of all subsequent alternate 21-day cycles (C3, C5, C7 and so on), as a 30-60 min infusion, followed by 1 to 2 h rest period.

Safety data from all enrolled participants will be closely monitored while the study is ongoing. In addition, participants permanently discontinuing study treatment within the first two cycles due to AEs related to belantamab mafodotin will be continuously monitored starting from when 5 participants are dosed at each dose level following pre-defined safety stopping rules (Section 12.4.8.2). If safety concerns arise at a dose level, enrollment will stop for that dose level and higher dose level(s).

6.1.3. Criteria for Belantamab Mafodotin DLT in Part 1

Any participant in Part 1 who received at least 1 full dose of belantamab mafodotin and ≥75% of the planned doses of the combination with Len/Dex (Arm A), or Bor/Dex (Arm B) in Cycle 1 will be evaluated for DLTs using NCI-CTCAE Version 4.03 [National Cancer Institute, 2010]. Any participant that experiences a DLT in Cycle 1 prior to receiving a full dose of belantamab mafodotin or <75% of the respective Arm SoC (Len/Dex – Arm A or Bor/Dex – Arm B) will also be considered DLT-evaluable. Participants that are not DLT-evaluable will be replaced.

Dose-limiting toxicity (DLT) is assessed during DLT observation period defined as follows:

- The first 28 days (= 1 cycle) for Arm A
- The first 21 days (= 1 cycle) for Arm B

An event will be considered a DLT if it is attributed (definitely, probably, or possibly) to the investigational agent, occurs within the DLT reporting period, and meets one of the criteria provided in Table 16.

A participant who develops a DLT will be allowed to continue on study if the toxicity did not meet predefined stopping criteria and recovered to Grade ≤1 and if the investigator and Medical Monitor agree that for a given participant the potential benefits may outweigh the risks.

The lowest full dose of belantamab mafodotin to be evaluated in this study is 1.9 mg/kg IV. If 1.9 mg/kg is not tolerated, the respective treatment arm will be closed for lack of tolerability. Independent dose escalation rules will apply to each treatment arm.

Table 16 Dose-Limiting Toxicity Criteria for Belantamab Mafodotin in Part 1 Cycle 1

Criteria for Identification and Grading of Belantamab Mafodotin DLTs in Part 1	
Toxicity Type and Grade	**DLT Definition and Grade**

Hematologic	• Grade 3 or greater febrile neutropenia lasting >48 h despite adequate treatment:
	  • Grade 3 is defined as ANC <1.0×10^9/L with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 h.
	  • Grade 4 is defined as ANC <1.0×10^9/L with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 h, with life-threatening consequences and urgent intervention indicated.
	• Grade 4 Thrombocytopenia <25,000/mm^3 accompanied by clinically significant bleeding.

Non-hematologic except corneal events	• Any Grade 3 or greater non-hematologic toxicity (other than corneal events) which is more severe than expected for an individual agent * or which does not resolve with appropriate supportive treatment within 48 h
	• Any Grade 3 or greater non-hematologic laboratory value if
	  • The laboratory abnormality persists for >48 h despite supportive treatment
	  • The abnormality leads to hospitalization.

Corneal events	• Grade 4 per the GSK corneal grading scale provided in Table 33.
Other organ-specific toxicities	• Liver toxicity meeting prespecified GSK liver stopping criteria.
*For a list of most frequent adverse events for belantamab mafodotin see Investigator's Brochure, [GSK Document Number 2013N175128 V08, 2020]; for lenalidomide see Celgene Corporation (2019), REVLIMID Prescribing Information, and for bortezomib see VELCADE (bortezomib) Prescribing Information (2019).	

6.2. Number of Participants

Overall, it is estimated that approximately 152 treated participants will be enrolled in this two-part study (approximately 27 in Part 1, and approximately 125 in Part 2).

- Up to 27 DLT-evaluable participants with RRMM (approximately 14 participants in Arm A and approximately 13 participants in Arm B) will be evaluated during the Part 1 dose escalation phase.
- Part 2 will enroll approximately 125 participants with RRMM (approximately 31 participants in Arm A and approximately 94 participants in Arm B) in order to further evaluate the safety and preliminary clinical activity of the combination treatments.

At the time of Amendment 3 more participants have been added to Part 1 (Arms A and B) for the study due to non-DLT evaluable participants and the requirement for an additional replacement participant to assure an adequate assessment of DLTs. Two participants were added to Part 2 (Arms A and B) as a replacement for participants who either received an incorrect dose or failed to complete a full cycle.

6.3. Participant Study Completion, Study Analysis and End of Study

Participant Study Completion

A participant will be considered to have completed the study if he or she received at least one dose of study treatment and has progressed or died before the end of the study, has not been lost to Follow-up, or has not withdrawn consent from study participation, or the study or a treatment arm has been terminated.

A participant will be considered to have withdrawn from the study if the patient

- has not died and is lost to Follow-up, or
- has withdrawn consent, or
- is no longer being followed at the investigator's discretion

Documentation of the cause of death in the electronic case report form (eCRF) is required for all participants who die in the study regardless of the cause of death.

Study Analysis

Final analysis will be conducted approximately 12 months from the last subject first visit (LSFV) in either arm.

6.4. End of Study Definition

Following the final analysis, the study will move into the PACT phase and the clinical study database will be closed to new data. Participants who are receiving belantamab mafodotin monotherapy or in combination with Len/Dex (Arm A) or Bor/Dex (Arm B) may continue to receive belantamab mafodotin monotherapy or in combination with

either Len/Dex (Arm A) or Bor/Dex (Arm B) if they are gaining clinical benefit as assessed by the investigator until they meet any criterion for permanent discontinuation of study intervention (see section 9 and Section 10.2).

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

6.5. Scientific Rationale for Study Design

The recent addition of monoclonal antibodies (elotuzumab and daratumumab) to SoC treatments, such as Len/Dex or Bor/Dex has demonstrated that the results achieved can be improved significantly. [Lonial, 2015], [Dimopoulos, 2016].

Belantamab mafodotin is being studied in MM participants as monotherapy in the studies BMA117159 and 205678. The selected RP2D of 3.4 mg/kg was considered well tolerated in BMA117159. Belantamab mafodotin montherapy when used as a single agent in BMA117159 had an ORR of 60% (95% CI: 42.1, 76.1) and the median PFS was 12 months [Trudel, 2018; Trudel, 2019]. In the Phase 2 study 205678 in RRMM patients, belantamab monotherapy showed an ORR of 31% (97.5%CI: 20.8, 42.6) [Lonial, 2020].

Given the previous experience with monoclonal antibodies which exhibited lower single agent activity as monotherapy in similar populations, the combination therapy of belantamab mafodotin with SoC agents is an attractive option and is expected to result in additive, or enhanced effects which could potentially translate into a deep and long lasting response over what has been achieved with available agents.

Since belantamab mafodotin has not been combined with Len/Dex or Bor/Dex outside of this study, Part 1 will explore the safety and tolerability of escalating doses and alternate dosing schedule(s) of belantamab mafodotin administered in combination with Len/Dex (Arm A) or Bor/Dex (Arm B). Part 2 will further evaluate the safety and preliminary clinical activity of selected doses of belantamab mafodotin with Len/Dex or Bor/Dex to identify the optimal dose(s) and schedule for each arm in participants with RRMM who have relapsed or who are refractory to at least 1 prior line of treatment.

While there are some potential overlaps in the pattern of toxicities (primarily hematological) of the study treatments, these are expected to be manageable with appropriate supportive care. Combination therapy with these agents remains an attractive option to explore for the treatment of RRMM.

6.6. Dose Justification

6.6.1. Starting Dose of Belantamab Mafodotin

The starting dose for both arms of this study is 2.5 mg/kg, which is one dose level below the RP2D of 3.4 mg/kg for the monotherapy of belantamab mafodotin in the FTIH study BMA117159 when administered on a Q3W schedule. In addition to being safe and tolerated in a monotherapy setting, the starting dose of 2.5 mg/kg may potentially offer some benefit to participants if enhanced or additive effects occur with the combinations of belantamab mafodotin with Len/Dex or Bor/Dex, respectively. While the 2.5 mg/kg dose did not result in high ORR in the FTIH study BMA117159, this dose was later found to be effective in study 205678 with an ORR of 31% in a heavily pre-treated relapsed refractory patient population; 2.5 mg/kg Q3W is the proposed monotherapy dose for this population.

The starting dose of 2.5 mg/kg Q3W for this combination study will allow for careful assessment of safety, while still providing potential benefit to participants. It is to be noted that a dose of 1.9 mg/kg could also provide benefit as target engagement for this dose was greater than 90% at the end of the first infusion based on decrease from baseline in serum free soluble BCMA (BMA117159). Responses have also been seen at lower doses of 0.96 and 1.92 mg/kg (1 out of 3 and 1 out of 4 participants respectively) in that study.

Treatment in Arm B (combination with Bor/Dex) will be administered on a 21-day schedule which is identical as for monotherapy with belantamab mafodotin and aligned with dosing schedule of Bor/Dex.

Treatment in Arm A (combination with Len/Dex) will be administered on a 28-day schedule. The cycle length has been adjusted to reflect the schedule of administration for Len/Dex. Given the mechanism of action and the fact that responses achieved with monotherapy with belantamab mafodotin were durable even in participants who had prolonged intervals between dosings due to toxicity, it is felt that a cycle length of 28 days is appropriate for Arm A.

For Arm A, if Dose Level -1 combination regimen (1.9 mg/kg) is tolerable, escalation to the higher dose of 2.5 mg/kg will proceed and additional participants will be enrolled to this next dose cohort.

For Arm B, if Dose Level 1 combination regimen (2.5 mg/kg) is tolerable, escalation to the higher dose of 3.4 mg/kg will proceed and additional participants will be enrolled to this next dose cohort.

Safety assessments and dose escalation will proceed independently for Arm A and Arm B.

6.6.2. Alternate Schedule for Belantamab Mafodotin

SPLIT Dosing

Administration of belantamab mafodotin divided as two equal administrations a week apart (i.e. SPLIT dosing) will be evaluated to determine if this dosing schedule results in an improvement to the benefit/risk due to reduction in the maximum concentration while maintaining similar exposure over a cycle compared to the Q3W dosing. With anticipated accumulation, it is predicted that a 3.4 mg/kg dose administered with a SPLIT dosing of 1.7 mg/kg on Day 1 and Day 8 will lead to maximum concentration similar to the one observed with 2.5 mg/kg Q3W while achieving the same exposure (AUC) as 3.4 mg/kg Q3W.

STRETCH and S/D STRETCH Schedule:

Based on the population pharmacokinetics performed on the DREAMM-1 and 2 studies, belantamab mafodotin clearance decreases over time with an elimination half-life of 14 days after repeated administration. This leads to a moderate accumulation over time. It has been noted that safety events related to corneal toxicity occurred more frequently after repeated administration than after the first dose and tended to still occur after repeated administration at a reduced dose. These findings may be related to the long half-life and the decrease in clearance over time, both leading to drug accumulation.

To reduce increased exposure over time and potentially improve the benefit/risk, an extended interval of every 8 weeks for Arm A or 6 weeks for Arm B (STRETCH schedule) will be evaluated; 6-8 weeks represents 3-4 half-lives and is anticipated to lead to minimal accumulation. In addition, in Arm B, a S/D STRETCH schedule with a first dose of 2.5 mg/kg followed by 1.9 mg/kg every 6 weeks from Cycle 3 onwards will also be studied as an alternative to 2.5 mg/kg repeating every 6 weeks.

6.6.3. Standard of Care Dosing

6.6.3.1. Len/Dex Dose (Arm A)

Len/Dex will be administered at the approved and clinically used dose, and there will be no dose escalation for Len/Dex. Details on Len/Dex administration are provided in Section 8.1.1.2.

6.6.3.2. Bor/Dex Dose (Arm B)

Bor/Dex will be administered at the approved and clinically used dose, and there will be no dose escalation for Bor/Dex. Details on Bor/Dex administration are provided in Section 8.1.2.2.

7. STUDY POPULATION

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

7.1. Inclusion Criteria

The study will enroll adult participants with RRMM, who have undergone autologous stem cell transplant (SCT), or are considered transplant ineligible, and who have been previously treated with at least 1 prior line of therapy, and who have documented evidence of disease progression during or after their most recent therapy.

Inclusion Criteria

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

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. Male or female, 18 years or older (at the time consent is obtained).
3. Have confirmed diagnosis of Multiple Myeloma as defined by the International Myeloma Working Group (IMWG) [Rajkumar, 2016].
4. Eastern Cooperative Oncology Group (ECOG) performance status:
   - For Arm A only: 0 to 1 (Appendix 3, Section 14.3).
   - For Arm B only: 0 to 2 (Appendix 3, Section 14.3).
5. Have undergone autologous SCT or are considered transplant ineligible.
6. Have been previously treated with at least 1 prior line of MM therapy and must have documented disease progression during or after their most recent therapy.
7. Must have at least ONE aspect of measurable disease, defined as one of 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. Participants with a history of autologous stem cell transplant (SCT) are eligible for study participation provided the following eligibility criteria are met:
   a. Autologous SCT was >100 days prior to study enrollment
   b. No active bacterial, viral, or fungal infection(s) present
   c. Participant meets the remainder of the eligibility criteria outlined in this protocol

9. All prior treatment-related toxicities (defined by National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI-CTCAE], Version 4.03, 2010) must be Grade ≤1 at the time of enrollment, except for alopecia. Participants with Grade 2 neuropathy can be enrolled into Len/Dex treatment arm, but not into Bor/Dex treatment arm.
10. Adequate organ system functions as defined by the laboratory assessments listed in Table 17.

Table 17 Adequate Organ System Function Based on Safety Assessments

Organ System and Laboratory Tests	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)[a]	≥1.5 × 10^9/L
Hemoglobin [a]	≥8.0 g/dL
Platelets [a]	≥75 × 10^9/L
Hepatic	
Total bilirubin	≤1.5 × ULN; (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
ALT	≤2.5 × ULN
Renal	
eGFR[b]	≥40 mL/min/1.73 m^2
Spot urine (albumin/creatinine ratio from spot urine)	≤500 mg/g (56 mg/mmol)
Cardiac	
Left Ventricular Ejection Fraction (LVEF) by ECHO	≥40%

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

a. Without Growth factor support for the past 14 days, excluding erythropoietin. Transfusions are allowed
b. As calculated by Modified Diet in Renal Disease (MDRD) formula (Appendix 4, Section 14.4)

11. 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 one of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP)

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency (Appendix 7, Section 14.7) during the intervention period and for **4 months** after the last dose of

belantamab mafodotin 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.

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.

WOCBP Participants Assigned to Arm A

Due to lenalidomide being a thalidomide analogue with risk for embryo-fetal toxicity and prescribed under a pregnancy prevention/controlled distribution program, WOCBP participants will be eligible if they commit either to abstain continuously from heterosexual sexual intercourse or to use **two methods** of reliable birth control (one method that is highly effective; see Appendix 7, Section 14.7), beginning 4 weeks prior to initiating treatment with lenalidomide, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of lenalidomide treatment. Thereafter, WOCBP participants must use a contraceptive method that is highly effective (with a failure rate of <1% per year) for a **further 3 months**, and agree not to donate eggs (ova, oocytes) for the purpose of reproduction during this period.

Two negative pregnancy tests must be obtained prior to initiating lenalidomide therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing lenalidomide therapy.

WOCBP Participants Assigned to Arm B

WOCBP assigned to Arm B must have a negative highly sensitive serum pregnancy test within 72 hours of dosing on C1D1 and agree to use effective contraception during the study and for **4 months** after the last dose of belantamab mafodotin or 7 months from the last dose of bortezomib, whichever is longer.

12. 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:

- Arm A: from the time of first dose of study until **6 months** after the last dose of belantamab mafodotin 4 weeks after the last dose of lenalidomide, whichever is longer, to allow for clearance of any altered sperm:
- Arm B: from the time of first dose of study until **6 months** after the last dose of belantamab mafodotin or 4 months from the last dose of bortezomib (whichever is the longer) to allow for clearance of any altered sperm.

Refrain from donating sperm and either:

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

OR

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

Agree to use a male condom even if they have undergone a successful vasectomy and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 7, Section 14.7 when having sexual intercourse. Male participants should also use a condom with pregnant females.

If the female partner of the male participant is pregnant at the time of enrollment, or becomes pregnant during the trial, the male participant must agree to remain abstinent (if it is consistent with their preferred and usual lifestyle) or use a male condom.

7.2. Exclusion Criteria

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

1. Systemic anti-myeloma therapy (including systemic steroids) within ≤14 days, or plasmapheresis within 7 days prior to the first dose of study drug.
2. Use of an investigational drug within 14 days or five half-lives (whichever is longer) preceding the first dose of study drug.
3. Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study drugs.
4. Prior allogenic stem cell transplant.

   Note: Participants who have undergone syngeneic transplant will be allowed only if they have no history and no currently active, graft versus host disease (GvHD)
5. Evidence of active mucosal or internal bleeding.
6. Any major surgery within the last four weeks.
7. 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 fulfill criteria given in Table 17.
8. 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.
9. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, or otherwise stable chronic liver disease per investigator's assessment).
10. Participants with invasive malignancies other than multiple myeloma are excluded, unless the second malignancy has been considered medically stable for at least 2 years. The participant must not be receiving active therapy, other than hormonal therapy for this disease.

    Note: Participants with curatively treated non-melanoma skin cancer are allowed without a 2-year restriction.

11. Evidence of cardiovascular risk including any of the following:
    - Evidence of current clinically significant untreated arrhythmias, including clinically significant ECG abnormalities including 2nd degree (Mobitz Type II) or 3rd degree atrioventricular (AV) block.
    - History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within 3 months of Screening.
    - Class III or IV heart failure as defined by the New York Heart Association functional classification system (Appendix 5, Section 14.5).
    - Uncontrolled hypertension.
12. Known immediate or delayed hypersensitivity reaction or idiosyncratic reaction to drugs chemically related to belantamab mafodotin, or any of the components of the study treatment.
13. Pregnant or lactating female.
14. Active infection requiring treatment.
15. Known HIV infection.
16. Presence of hepatitis B surface antigen (HBsAg), or hepatitis B core antibody (HBcAb at Screening or within 3 months prior to first dose of study treatment)
17. Positive hepatitis C antibody test result or positive hepatitis C RNA test result at Screening or within 3 months prior to first dose of study treatment.

    Note: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained. Hepatitis RNA testing is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing

18. Current corneal disease except for mild punctate keratopathy (Appendix 8, Section 14.8).

    Note: Participants with mild punctate keratopathy are allowed.

Additional Exclusion Criteria for Participants Assigned to Arm A (belantamab mafodotin plus Len/Dex)

19. Participants unable to tolerate antithrombotic prophylaxis must be excluded.
20. Discontinuation of prior treatment with lenalidomide due to intolerable adverse events.

Additional Exclusion Criteria for Participants Assigned to Arm B (belantamab mafodotin plus Bor/Dex)

21. Unacceptable adverse effects from previous bortezomib treatment.
22. Ongoing Grade 2 or higher peripheral neuropathy or neuropathic pain from previous bortezomib treatment.
23. Intolerance or contraindications to anti-viral prophylaxis.

7.3. Lifestyle Restrictions

The following lifestyle restrictions apply while the participants are in the study:

- Contact lenses are prohibited while on the study treatment (from first dosing to the end of study treatment). Contact lens use may be restarted after the end of study treatment and a consultation with a qualified eye care specialist confirms there are no other contraindications. Use of bandage contact lenses is permitted during study treatment as directed by a qualified eye care specialist.
- Participants must not donate blood while receiving study treatment; Participants in Arm A must not donate blood for 28 days following discontinuation of lenalidomide.
- Intraocular pressure may become elevated with dexamethasone treatment in some individuals. Intraocular pressure should be monitored.

Injection Site:

When bortezomib in Arm B is administered via SC injection, sites for each injection (thigh or abdomen) should be rotated. New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.

If local injection site reactions occur following administration of bortezomib SC in Arm B, a less concentrated solution (1 mg/mL instead of 2.5 mg/mL) may be administered SC. Alternatively, the IV route of administration should be considered.

Meals and Dietary Restrictions

There are no recognized dietary restrictions for the individual components of Arm A or Arm B.

- For participants assigned to Arm A, lenalidomide capsules should be swallowed whole with water; the capsules should not be opened, broken, or chewed. Lenalidomide should be taken orally at approximately the same time each day [Celgene Corporation (2019), REVLIMID REVLIMID (lenalidomide) Prescribing Information, 2019] or most recent label.
- Lenalidomide capsules contain lactose. The risk-benefit of Arm A should be evaluated in participants with lactose intolerance.

Caffeine, Alcohol, and Tobacco

No restrictions

Activity

No restrictions

7.4. Screen Failures

Screen Failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to either Arm A or Arm B, or were assigned but did not receive treatment, because they did not satisfy all the Inclusion/Exclusion criteria provided in Section 7.

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: the participant ID number; demography; eligibility (Inclusion/Exclusion criteria failed); reason for screen failure; any serious adverse events (SAE) related to study participation; and protocol deviations, if any.

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. Rescreened participants should be assigned a different participant number from that assigned for the initial screening.

8. TREATMENTS

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

8.1. Treatments Administered

Details of the identity and characteristics of the individual components of the Study Treatments are shown in Table 19. A summary of the treatment regimens and schedules is contained in Table 18.

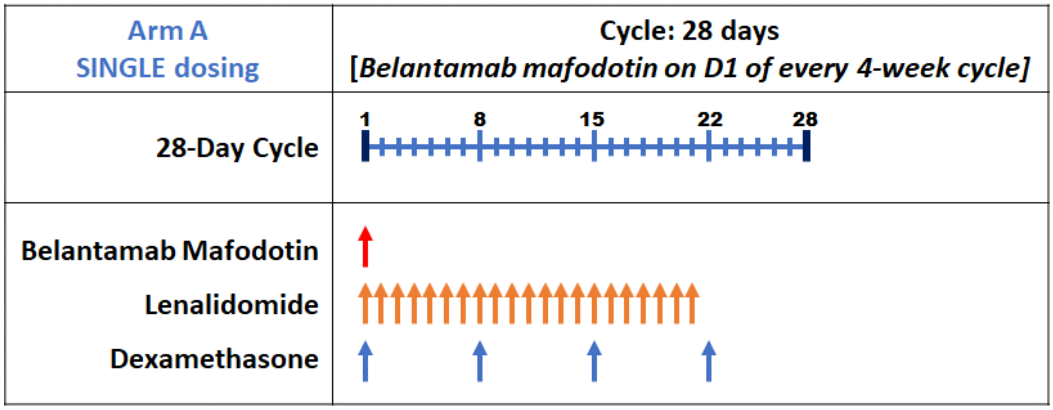
Table 18 Summary of Treatment Regimens and Schedules

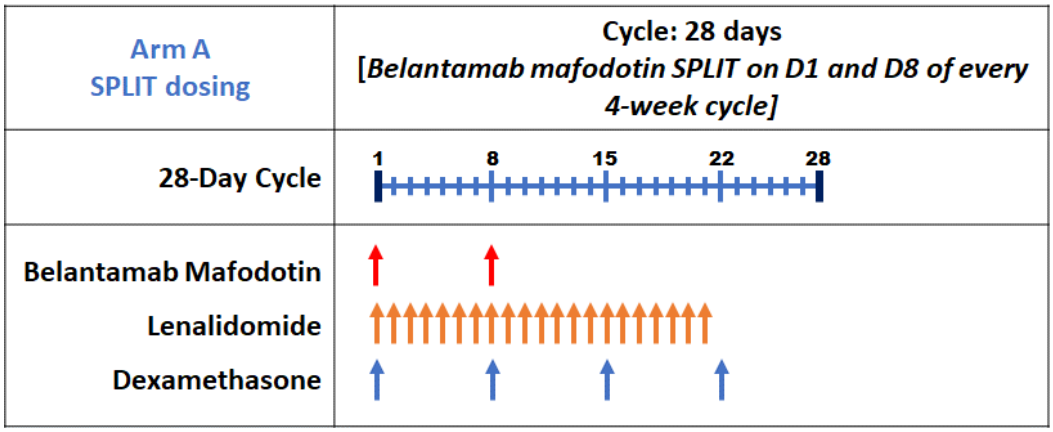
Treatment Arm	Part	Cohort	Dose of Belantamab Mafodotin	Schedule	SoA
Arm A: 28-Day Cycle Lenalidomide 25mg PO QD, D1-D21; Dexamethasone 20mg PO or IV, D1, 8, 15, 22	1 and 2	2.5 mg/kg SINGLE	2.5 mg/kg IV	Day 1	Table 5
	1 and 2	2.5 mg/kg SPLIT	1.25 mg/kg IV	Day 1, 8	Table 6
	1	1.9 mg/kg SINGLE	1.9 mg/kg IV	Day 1	Table 5
	2	*1.9 mg/kg STRETCH*	*1.9 mg/kg IV*	*Day 1 in every alternate 28-day cycle*	Table 5
Arm B: 21-Day Cycle Bortezomib 1.3mg/m^2 SC or IV BIW, D1, 4, 8, 11; Dexamethasone 20mg PO or IV QIW, D1, 2, 4, 5, 8, 9, 11, 12) Cycle 1-8 Monotherapy ≥ Cycle 9	1 and 2	3.4 mg/kg SINGLE	3.4 mg/kg IV	Day 1	Table 7
	2	3.4 mg/kg SPLIT	1.7 mg/kg IV	Day 1, 8	Table 8
	1 and 2	2.5 mg/kg SINGLE	2.5 mg/kg IV	Day 1	Table 7
	2	2.5 mg/kg SPLIT	1.25 mg/kg IV	Day 1, 8	Table 8
	2	1.9 mg/kg SINGLE	1.9 mg/kg IV	Day 1	Table 7
	2	2.5 mg/kg STRETCH	2.5 mg/kg IV	Day 1 in every alternate 21-day cycle	Table 9
	2	S/D STRETCH	Cycle 1: 2.5 mg/kg IV STRETCH Cycle 3+: 1.9 mg/kg IV STRETCH	Day 1 in every alternate 21-day cycle	Table 9
	2	1.9 mg/kg STRETCH	1.9 mg/kg IV	Day 1 in every alternate 21-day cycle	Table 9

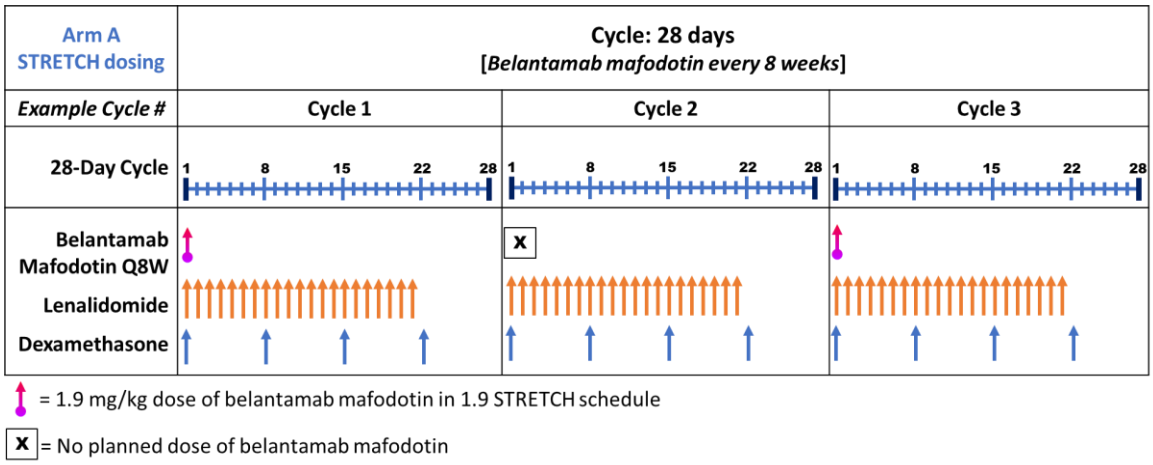
8.1.1. Belantamab Mafodotin and Len/Dex Combination (Arm A) 28-day Cycle: SINGLE,SPLIT, *and STRETCH* Schedules

The schedules for dosing of belantamab mafodotin and Len/Dex on a 28-day schedule is shown in Figure 5.

Figure 5 Arm A: 28-day Dosing Schedules







8.1.1.1. Belantamab mafodotin

For SINGLE day dosing schedule, belantamab mafodotin will be administered FIRST (prior to Len/Dex) in the clinic as a single full dose on Day 1 of each 28-day cycle as a 30-60 minute (min) infusion, followed by a 1 to 2 h rest period. For example, a 2.5 mg/kg SINGLE dosing schedule will administer a 2.5 mg/kg dose on Day 1 of each cycle.

For SPLIT day dosing schedule, belantamab mafodotin will be administered FIRST (prior to Len/Dex) in the clinic in two equal divided doses - one on Day 1 and the other on Day 8 of each 28-day cycle as a 30-60 min infusion, followed by a 1 to 2 h rest period. For example, a 2.5 mg/kg SPLIT dosing schedule will administer a 1.25 mg/kg dose on Day 1 and a 1.25 mg/kg dose on Day 8 of each cycle.

For the STRETCH dosing schedule, belantamab mafodotin will be administered FIRST (prior to Len/Dex) in the clinic on Day 1 of every alternate 28-day cycle as a 30-60 min infusion, followed by a 1 to 2 h rest period. A 1.9 mg/kg STRETCH dosing schedule will administer a 1.9 mg/kg dose on Day 1 of all alternate 28-day cycles (C1, C3, C5, C7 and so on).

Starting dose in Part 1 will be 2.5 mg/kg IV for belantamab mafodotin (Dose Level 1). If the 2.5 mg/kg dose is not tolerated an additional, lower dose (1.9 mg/kg [Dose Level –1]) will be evaluated. Additionally, alternate dosing schedules will also be explored, including SPLIT dosing where the belantamab mafodotin dose will be split into two equal halves with each half dose administered on Day 1 and Day 8 of each cycle.

Note: 2.5 mg/kg IV is the highest dose (dose level 1) that will be assessed in Arm A.

The actual body weight in kg at baseline (assessed on C1D1 prior to dosing) will be used for dose calculation of belantamab mafodotin in all participants during the treatment period. If the change of body weight is greater than 10%, the dose should be re-calculated based on the actual body weight at the time of dosing. Participants must be weighed prior to dosing for each cycle.

8.1.1.2. Len/Dex

Lenalidomide will be administered as 25 mg PO daily on days 1-21 of each 28-day cycle, in the participants with eGFR ≥60 mL/min/1.73 m^2. The dose of lenalidomide will be reduced to 10 mg daily on Days 1 to 21 in participants with eGFR of 40-60 mL/min/1.73 m^2. Lenalidomide is administered at a fixed dose level, with no adjustments needed for body weight or BSA [REVLIMID (lenalidomide) Prescribing Information 2019].

On lenalidomide and belantamab mafodotin co-administration days, lenalidomide should be administered as close as possible to the end of the 1-2 h rest period **after** administration of belantamab mafodotin and no later than 6 h after the end of the rest period after administration of belantamab mafodotin.

Dexamethasone will be given 40 mg weekly PO or IV on Days 1, 8, 15 and 22 of each cycle. Dexamethasone is administered at a fixed dose of 40 or 20 mg PO or IV, with no

adjustments needed for body weight or BSA. For dexamethasone refer to dexamethasone prescribing information.

Participants who are >75 years old, with BMI <18.5 kg/m^2, the dose of dexamethasone can be reduced to 20 mg at the discretion of the investigator.

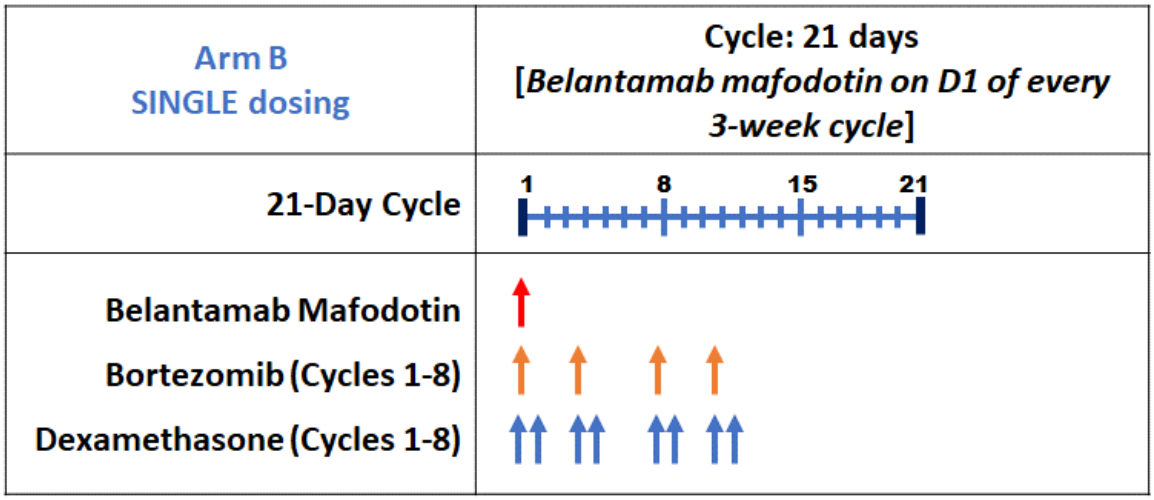
In the event of tolerability issues, the dose of dexamethasone can be reduced from 40 mg to 20 mg; if 20 mg is not tolerated, dexamethasone may be permanently discontinued.

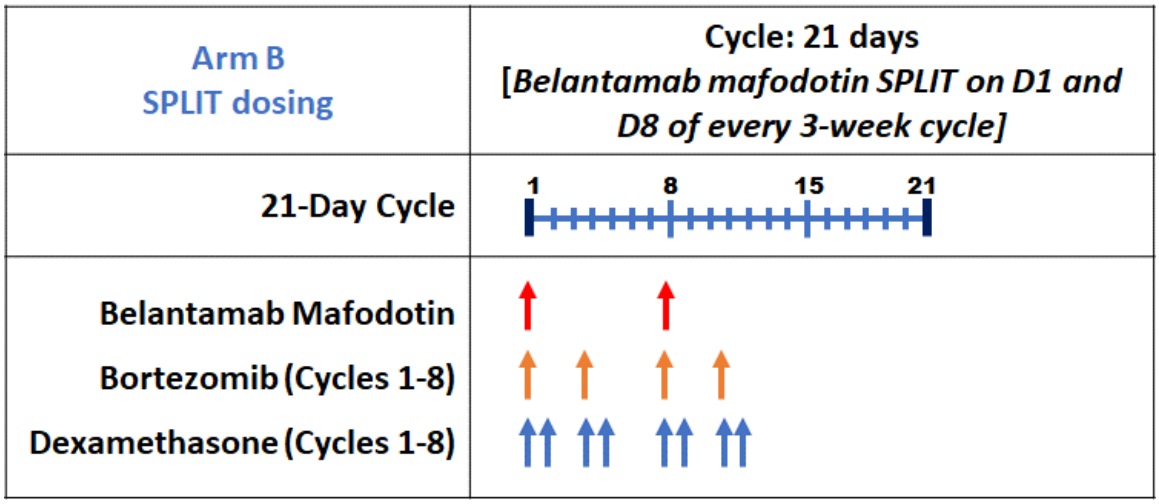
On days where only lenalidomide and dexamethasone are taken at home, they should be taken in the morning approximately at the same time each day. On days when lenalidomide PK samples will be collected, participants will be required to take their morning dose in the clinic. For Cycle 1, the 24 h post-dose lenalidomide PK sample must be collected before lenalidomide dosing on Cycle 1 Day 2.

8.1.2. Belantamab Mafodotin and Bor/Dex Combination (Arm B) 21-day Cycle: SINGLE and SPLIT Schedules

The schedules for dosing of belantamab and Bor/Dex on a 21-day schedule is shown in Figure 6

Figure 6 Arm B: 21-day Dosing Schedules





8.1.2.1. Belantamab Mafodotin

For SINGLE day dosing schedule, belantamab mafodotin will be administered FIRST (prior to Bor/Dex) in the clinic as a single full dose on Day 1 of each 21-day cycle as a 30-60 min infusion, followed by a 1 to 2 h rest period. For example, a 3.4 mg/kg SINGLE dosing schedule will administer a 3.4 mg/kg dose on Day 1 of each cycle, a 2.5 mg/kg SINGLE dosing schedule will administer a 2.5 mg/kg dose on Day 1 of each cycle, a 1.9 mg/kg SINGLE dosing schedule will administer a 1.9 mg/kg dose on Day 1 of each cycle.

For SPLIT day dosing schedule, belantamab mafodotin will be administered FIRST (prior to Bor/Dex) in the clinic in two equal divided doses - one on Day 1 and the other on Day 8 of each 21-day cycle as a 30-60 min infusion, followed by a 1 to 2 h rest period. For example, a 2.5 mg/kg SPLIT dosing schedule will administer a 1.25 mg/kg dose on Day 1 and a 1.25 mg/kg dose on Day 8 of each cycle, a 3.4 mg/kg SPLIT dosing schedule will administer a 1.7 mg/kg dose on Day 1 and a 1.7 mg/kg dose on Day 8 of each cycle.

The starting dose in Part 1 will be 2.5 mg/kg IV for belantamab mafodotin (Dose Level 1). If safety and tolerability of the starting dose is confirmed, an escalation of the dose of belantamab mafodotin to 3.4 mg/kg (Dose Level +1) will be performed in the next cohort of participants. If the 2.5 mg/kg dose is not tolerated, or if emerging data were to indicate potential improved benefit/risk at reduced dose, an additional, lower dose (1.9 mg/kg (Dose Level –1) will be evaluated.

Note: 3.4 mg/kg IV is the highest dose (Dose level +1) that will be assessed in Arm B

8.1.2.2. Bor/Dex

Bortezomib 1.3 mg/m^2 SC or IV (depending on participants' and institutional preference) will be administered on Days 1, 4, 8, and 11 of every 21-day cycle for a total of up to 8 cycles. The administration of bortezomib will be after belantamab mafodotin administration, approximately after 1 h and after assuring that participant is clinically stable. Bortezomib doses are calculated based on the participant's BSA (West, 2000), ranging from a recommended starting dose of 1.3 mg/m^2 to a reduced dose of 1.0 mg/m^2 or 0.7 mg/m^2 [VELCADE (bortezomib) Prescribing Information (2019)]. Formulae used to calculate the administered volume of bortezomib for SC or IV administration are given in Section 8.1.5.3.

For participants who experience an IRR during belantamab mafodotin, bortezomib administration will be delayed until the IRR has resolved, and the participant is considered clinically stable.

Dexamethasone will be administered at 20 mg PO or IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of every 21-day cycle. Dexamethasone is administered at a fixed dose of 20 mg PO or IV, with no adjustments needed for body weight or BSA. Dexamethasone dose may be reduced at investigator's discretion for participants who are older than 75 years of age, for participants who have BMI <18.5 kg/m^2, or for participants who had previous unacceptable side effects associated with glucocorticoid therapy. Dexamethasone will be given for a total of up to 8 cycles. For dexamethasone refer to dexamethasone prescribing information.

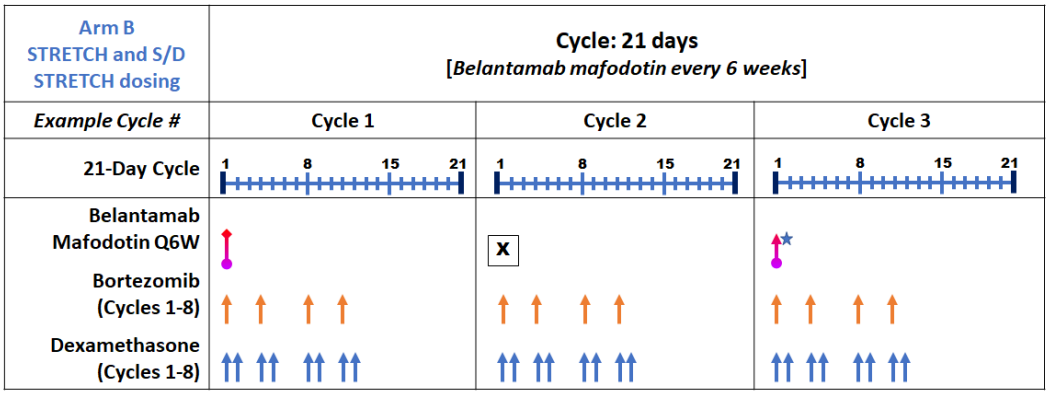
In case of lack of tolerability, dexamethasone can be reduced from 20 mg to 10 mg and if 10 mg is not tolerated, may be permanently discontinued.

Dexamethasone should be taken at the same time of the day and may be taken at home.

8.1.3. Belantamab Mafodotin and Bor/Dex Combination (Arm B) 21-day Cycle: STRETCH and S/D STRETCH Dosing Schedule

The schedule for dosing of belantamab mafodotin and Bor/Dex on a STRETCH schedule is shown in Figure 7.

Figure 7 Arm B: STRETCH Dosing Schedule



= 2.5 mg/kg dose of belantamab mafodotin in 2.5 STRETCH and S/D STRETCH schedule (or 1.9 mg/kg dose in 1.9 STRETCH schedule)

= 2.5 mg/kg dose of belantamab mafodotin in 2.5 STRETCH schedule, OR, 1.9mg/kg dose in S/D STRETCH and 1.9 STRETCH schedule

X = No planned dose of belantamab mafodotin

8.1.3.1. Belantamab mafodotin

For the STRETCH dosing schedule, belantamab mafodotin will be administered FIRST (prior to Bor/Dex) in the clinic on Day 1 of every alternate 21-day cycles as a 30-60 min infusion, followed by a 1 to 2 h rest period. A 2.5 mg/kg STRETCH dosing schedule will administer a 2.5 mg/kg dose on Day 1 of all alternate 21-day cycles (C1, C3, C5, C7 and so on). A 1.9 mg/kg STRETCH dosing schedule will administer a 2.5 mg/kg dose on Day 1 of all alternate 21-day cycles (C1, C3, C5, C7 and so on).

For the S/D STRETCH dosing schedule, belantamab mafodotin will be administered FIRST (prior to Bor/Dex) in the clinic at 2.5 mg/kg as a dose on Day 1 of Cycle 1 followed by 1.9 mg/kg step-down dose on Day 1 of all alternate 21-day cycles C3 onwards (C3, C5, C7 and so on), as a 30-60 min infusion, followed by a 1 to 2 h rest period.

8.1.3.2. Bor/Dex

Bortezomib 1.3 mg/m^2 SC or IV (depending on participants' and institutional preference) will be administered on Days 1, 4, 8, and 11 of every 21-day cycle for a total of up to 8 cycles. The administration of bortezomib will be after belantamab mafodotin administration, approximately after 1 – 2 h and after assuring that participant is clinically stable. Bortezomib doses are calculated based on the participant's BSA (West, 2000), ranging from a recommended starting dose of 1.3 mg/m^2 to a reduced dose of 1.0 mg/m^2 or 0.7 mg/m^2 [VELCADE (bortezomib) Prescribing Information (2019)]. Formulae used to calculate the administered volume of bortezomib for SC or IV administration are given in Section 8.1.5.3.

For participants who experience an IRR during belantamab mafodotin, bortezomib administration will be delayed until the IRR has resolved, and the participant is considered clinically stable.

Dexamethasone will be administered at 20 mg PO or IV on Days 1, 2, 4, 5, 8, 9, 11, and 12 of every 21-day cycle. Dexamethasone is administered at a fixed dose of 20 mg PO or IV, with no adjustments needed for body weight or BSA. Dexamethasone dose may be reduced at investigator's discretion for participants who are older than 75 years of age, for participants who have BMI <18.5 kg/m^2, or for participants who had previous unacceptable side effects associated with glucocorticoid therapy. Dexamethasone will be given for a total of up to 8 cycles. For dexamethasone refer to dexamethasone prescribing information.

In case of lack of tolerability, dexamethasone can be reduced from 20 mg to 10 mg and if 10 mg is not tolerated, may be permanently discontinued.

Dexamethasone should be taken at the same time of the day and may be taken at home.

8.1.4. Pharmaceutical Presentation

8.1.4.1. Belantamab mafodotin

Belantamab mafodotin solution, 20 mg/mL, 1.5 mL is supplied as a sterile, preservative-free aqueous solution of purified monoclonal ADC in type 1 untreated borosilicate clear glass, stoppered vials. The drug product solution appears as a clear or opalescent; colorless, yellow to brown liquid; essentially free from particles. The drug is supplied as a single-use vial. Each vial of belantamab mafodotin solution, 20 mg/mL; 1.5 mL is filled with 1.6 mL of solution to provide a 1.5 mL extractable volume.

Subjects continuing treatment during PACT phase after final analysis may receive lyophilized study drug. Lyophilized belantamab mafodotin 100 mg/vial is supplied as a white to yellow powder in a single-dose vial for reconstitution and further dilution.

8.1.4.2. Lenalidomide

Lenalidomide (REVLIMID) capsules, for oral use is available in 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg capsules for oral administration. For details of pharmaceutical presentation or prescribing information refer to the local prescribing information for lenalidomide.

8.1.4.3. Bortezomib

Bortezomib (VELCADE) for Injection is supplied as individually-cartoned 10 mL vials containing 3.5 mg of bortezomib as a white to off-white cake or powder. Retain in original package to protect from light. For details of pharmaceutical presentation or prescribing information refer to the local prescribing information for bortezomib.

8.1.4.4. Dexamethasone

Dexamethasone is available in a tablet formulation for oral administration and as Dexamethasone Sodium Phosphate Injection (USP), a sterile solution of dexamethasone sodium phosphate in water for injection for intravenous (IV) use. For details of pharmaceutical presentation or prescribing information refer to the local prescribing information for dexamethasone.

Table 19 Description and Identity of Study Treatments

Study Treatment Name	Belantamab mafodotin Arm A and Arm B	Arm A Standard of Care (28-Day Cycle)		Arm B Standard of Care (21-Day Cycle)	
		Lenalidomide	Dexamethasone	Bortezomib	Dexamethasone
Dosage Formulation	20 mg/mL, 1.5 mL vial or Lyophilized powder, 100 mg/vial in single-use vial for reconstitution (Subjects continuing treatment in PACT phase after final analysis may receive lyophilized study drug)	Capsules, for oral use	Tablets for oral administration / Injection for IV use	Solution for injection, for subcutaneous (2.5 mg/mL) or intravenous (1 mg/mL) use	Tablet for oral administration / Injection for IV use
Route of Administration	IV Infusion (See SRM for details)	Oral	Oral or IV	IV as a 3 to 5 second bolus Infusion or SC	Oral or IV
Dosing Instructions	30-60 min IV infusion	Days 1 to 21 of each 28-day cycle	Days 1, 8, 15, and 22 of each 28-day cycle	Days 1, 4, 8, and 11 of every 21-day cycle	Days 1, 2, 4, 5, 8, 9, 11, and 12 of every 21-day cycle
Packaging and Labelling	Open-label	Open-label	Open-label	Open-label	Open-label

Study Treatment Name	**Belantamab mafodotin** **Arm A and Arm B**	**Arm A Standard of Care (28-Day Cycle)**		**Arm B Standard of Care (21-Day Cycle)**	
		Lenalidomide	**Dexamethasone**	**Bortezomib**	**Dexamethasone**
Manufacturer/ Source of Procurement	GlaxoSmithKline/Baxter	Celgene Corporation (US & Europe) Refer to SRM for country-specific details	Refer to SRM for country-specific details	Millennium Pharmaceuticals, Inc. (US) Janssen Pharmaceutica (Europe) Refer to SRM for country-specific details	Refer to SRM for country-specific details

8.1.5. Preparation of Doses

8.1.5.1. Belantamab mafodotin

Belantamab mafodotin will be administered intravenously over 30 min to 1 h. The maximum dose to be administered to participants in this trial is 3.4 mg/kg. Dilute belantamab mafodotin solution in normal 0.9% saline to the appropriate concentration for the dose. For lyophilized powder, reconstitute belantamab mafodotin lyophilized powder 100 mg/vial 2.0mL of water for injection (WFI); dilute with saline to the appropriate concentration for the dose before use.

Refer to the SRM for more details on preparation and handling, and administration instructions for belantamab mafodotin.

8.1.5.2. Lenalidomide

Lenalidomide is administered at a fixed dose level of 25 or 10 mg PO, depending upon renal function. Refer to the SRM for more details on preparation, handling, and administration instructions for lenalidomide. Dose modifications may be required for safety; see Table 23 for further information.

8.1.5.3. Bortezomib

Bortezomib dosing is based on the participant's body surface area (BSA; 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, see Table 24 for further information.

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 Intravenous Administration (1 mg/mL concentration)

[bortezomib dose (mg/m^2) × participant BSA (m^2)] ÷ [1 mg⁄mL] = Total bortezomib volume (mL) 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

Refer to the SRM for more details on preparation, handling, and administration instructions for bortezomib.

8.1.5.4. Dexamethasone

Dexamethasone is administered at a fixed dose level of 40 mg or 20 mg (PO or IV) at the discretion of the investigator, and is not adjusted for weight or BSA. Refer to the SRM for more details on preparation and handling, and administration instructions for dexamethasone.

8.1.6. Treatment Duration

8.1.6.1. Arm A

For participants assigned to Arm A (belantamab mafodotin in combination with Len/Dex, 28-day cycle), participants may continue combination treatment until the occurrence of PD, intolerable AEs, consent withdrawal, death, or end of study.

8.1.6.2. Arm B

For participants assigned to Arm B (belantamab mafodotin in combination with Bor/Dex, 21-day cycle), participants may continue combination treatment for a total of up to 8 cycles, as per prescribing information for bortezomib for the treatment of RRMM. Participants completing 8 cycles of combination therapy will continue treatment with belantamab mafodotin as monotherapy until PD, intolerable AEs, consent withdrawal, death, or end of study.

8.1.6.3. Lack of tolerability in Arm A or B

In case a participant meets stopping criteria for Len/Dex or Bor/Dex treatment and cannot continue on Len/Dex or Bor/Dex treatment due to related safety/tolerability issues, the participant may continue on study with belantamab mafodotin monotherapy. In case the participant meets stopping criteria for belantamab mafodotin, the participant will discontinue all treatment but will continue to be monitored as described in the SoA tables for follow-up activities. Cross over between arms is not allowed.

8.2. Dose Modification

After the completion of Cycle 1, dose modifications for all study drugs are allowed (within restrictions) to manage tolerability or adverse events.

8.2.1. Dose Modification After Cycle 1

In both Part 1 and Part 2 of the study after Cycle 1, and dose modifications may be made for individual participants, based on safety findings. Dose interruptions and reductions are permitted throughout the study per guidance below.

The dose allowed for belantamab mafodotin may be reduced twice by 25% of the originally assigned dose. The rule of 25% dose reduction always refers to the originally assigned dose. If the participant is unable to tolerate at least a full dose of belantamab mafodotin 1.9 mg/kg (including SPLIT dose of 0.95 mg/kg on Day 1 and Day 8), they will be withdrawn from the trial due to unacceptable toxicity (Table 21).

For the S/D STRETCH dosing schedules, belantamab mafodotin will be administered at 2.5 mg/kg on D1 of Cycle 1 followed by 1.9 mg/kg dose in all subsequent alternate planned cycles starting at Cycle 3 Day 1 throughout the rest of treatment. As 1.9 mg/kg is the lowest full dose evaluated in this study, no dose reductions for belantamab mafodotin, except for dose delays and interruptions, will be allowed. If the participant is unable to tolerate the dose of belantamab mafodotin at 1.9 mg/kg, they will be withdrawn from the trial due to unacceptable toxicity (Table 21).

In Arm A, for the 1.9 mg/kg STRETCH dosing schedule, if a planned dose of belantamab mafodotin was held/missed due to any reason, the next dose can be administered at Day 1 of the next planned 28-day cycle, as long as the interval between 2 consecutive doses is at least 56 (±3) days.

In Arm B, for the S/D STRETCH, 2.5 mg/kg STRETCH and 1.9 mg/kg STRETCH dosing schedules, if a planned dose of belantamab mafodotin was held/missed due to any reason, the next dose can be administered at Day 1 of the next planned 21-day cycle, as long as the interval between 2 consecutive doses is at least 42 (±3) days.

- Detailed guidance for belantamab mafodotin dose reductions and delays is shown in Table 20, Table 21, and Table 22.
- Detailed guidance for lenalidomide dose reductions and delays is shown in Table 23.
- Detailed guidance for bortezomib dose reductions and delays is shown in Table 24.
- Detailed guidance for dexamethasone dose reductions and delays is shown in Table 25 (Arm A) and Table 26 (Arm B).

Dosing delays also are permitted for medical/surgical events or for logistical reasons not related to study therapy (e.g., COVID-19 related restrictions, ophthalmology services unavailable, elective surgery, unrelated medical events, participant vacation, and/or public holidays, but not for a participants' decision to delay treatment). The reason for any dose delay must be documented in the participant's eCRF and clinic records.

Refer to the SRM for more details on dose modification scenarios.

Table 20 Recommendations for Dose Reduction of Belantamab Mafodotin

	SINGLE Dosing			SPLIT Dosing		STRETCH Dosing		
Treatment Arm	**Arm A and Arm B**		**Arm B only**	**Arm A and Arm B**		**Arm A[a] and Arm B**	**Arm B only**	
Assigned Dose	1.9 mg/kg on Day 1	2.5 mg/kg on Day 1	3.4 mg/kg on Day 1	2.5 mg/kg SPLIT into 1.25 mg/kg on Day 1 and Day 8	3.4 mg/kg SPLIT into 1.7 mg/kg on Day 1 and Day 8	1.9 mg/kg STRETCH	2.5 mg/kg STRETCH	S/D STRETCH
Dose upon First 25% Dose Reduction from Assigned Dose	No dose reduction allowed	1.9 mg/kg (no dose reductions below a full dose of 1.9 mg/kg allowed)	2.5 mg/kg	1.9 mg/kg SPLIT into 0.95 mg/kg on Day 1 and Day 8 (no dose reductions below a full dose of 1.9 mg/kg allowed)	2.5 mg/kg SPLIT into 1.25 mg/kg on Day 1 and Day 8	No dose reduction allowed	1.9 mg/kg STRETCH (no dose reductions below a full dose of 1.9 mg/kg allowed)	No dose reduction below 1.9 mg/kg allowed
Dose upon Second 25% Dose Reduction from Assigned Dose	No dose reduction allowed	No dose reduction allowed	1.9 mg/kg (no dose reductions below a full dose of 1.9 mg/kg allowed)	No dose reduction allowed	1.9 mg/kg SPLIT into 0.95 mg/kg on Day 1 and Day 8 (no dose reductions below a full dose of 1.9 mg/kg allowed)	No dose reduction allowed	No dose reduction allowed	No dose reduction allowed

a. The 1.9 mg/kg STRETCH dosing schedule for Arm A may be evaluated if emerging data suggests that this schedule may further optimize the tolerability or offers an improved benefit/risk profile.

Table 21 Dose Modification Guidelines for Adverse Events Associated with Belantamab Mafodotin (Arm A and B)

Toxicity	Grade/Symptoms	Recommendations
Serum creatinine elevation which cannot be explained by concomitant sepsis, TLS, other severe infection with fever or dehydration	If absolute serum creatinine increase from baseline of >0.5 mg/dL	Repeat within 48 h • If confirmed: withhold therapy, institute treatment and monitoring as clinically indicated, and follow for resolution. • Discuss any further dosing with Medical Monitor[a].
Serum creatinine Grade >3	>3.0 mg/dL from baseline or 3.0-6.0 × ULN	• Provide appropriate medical treatment • Permanently discontinue treatment with belantamab mafodotin

Spot urine (creatinine / albumin ratios)	>2000 mg/g (224 mg/mmol)	• Re-test (at least 7 days apart)
		  • If not confirmed, continue belantamab mafodotin at 100% 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 25% dose reduction[b].
		  • If spot urine remains >2000 mg/g (224 mg/mmol) after 4 weeks, permanently discontinue belantamab mafodotin and withdraw participant from study; provide treatment as clinically indicated and follow for resolution.

Thrombocytopenia (on days of dosing) Graded according to NCI-CTCAE criteria	Grade 3	**SINGLE and 2.5 mg/kg STRETCH Dosing:** • No bleeding: continue treatment with 25% dose reduction[b]. Consider reverting to previous dose once thrombocytopenia recovered to Grade 2, or less. • With bleeding: withhold dose. Treatment with a 25% dose reduction[a] may continue after thrombocytopenia has recovered to Grade 2 or less. • Consider additional supportive treatment (*e.g.*, transfusion), as clinically indicated and per local practice.

Toxicity	Grade/Symptoms	Recommendations
		SPLIT Dosing: • **If noted on Day 1** of any cycle**,** follow guidance outlined above for SINGLE Day dosing for "No bleeding" vs "With bleeding" scenarios as appropriate. • **If noted on Day 8** of any cycle; ***and*** participant has received belantamab mafodotin on Day 1: o No bleeding: continue belantamab mafodotin Day 8 dosing with a 25% dose reduction[b]. Consider reverting to previous dose once thrombocytopenia recovers to Grade 2, or less. o If the dose is unable to be administered on Day 8 of the cycle, it can be withheld and administered at any time, up to, and including Day 15 of the same cycle, and once the investigator determines the participant is clinically fit to receive the dose. o If belantamab mafodotin is withheld on Day 8 through Day 15 due to clinical reasons, then belantamab mafodotin will not be administered until Day 1 of the next planned 28-day cycle for Arm A or Day 1 of the next planned 21-day cycle for Arm B. o With bleeding: withhold belantamab mafodotin and provide supportive care to stop the bleeding. o Continue treatment after recovery with the 25% dose reduction [b]. o If the dose is unable to be administered on Day 8 of the cycle, it can be withheld and administered at any time, up to, and including Day 15 of the same cycle, and once the investigator determines the participant is clinically fit to receive the dose. o If belantamab mafodotin is withheld on Day 8 and up to Day 15 due to clinical reasons, then belantamab mafodotin will not be administered until Day 1 of the next planned 28-day cycle for Arm A or Day 1 of the next planned 21-day cycle for Arm B. **S/D STRETCH and 1.9 mg/kg STRETCH Dosing:** • No bleeding: withhold dose. Treatment at 1.9 mg/kg dose may continue after thrombocytopenia has recovered to Grade 2 or less.

Toxicity	Grade/Symptoms	Recommendations
		• With bleeding: withhold dose. Treatment at 1.9 mg/kg dose may continue after thrombocytopenia has recovered to Grade 2 or less. • Consider additional supportive treatment (*e.g.*, transfusion), as clinically indicated and per local practice.
	Grade 4	• Withhold the belantamab mafodotin dose. Consider restarting with 25% dose reduction[a] if thrombocytopenia recovers to Grade ≤3 and **only** if there is no active bleeding at time of treatment restart. If thrombocytopenia is considered disease-related, and is not accompanied by concurrent bleeding, and which recovers following transfusion to >25 x10^9/L belantamab mafodotin treatment with 25-50% dose reduction[a] may be considered following discussion with the GSK Medical Monitor.
Febrile neutropenia Graded according to NCI-CTCAE criteria	Defined as: single temp of 38.3°C, or sustained 38°C for >1 h AND ANC <1.0×10^9/L	• Withhold belantamab mafodotin and immediately hospitalize participant with appropriate management, per local institutional guidance. • Consider additional supportive treatment per local practice (e.g. growth factors).[b] Upon recovery, consider a 25% dose reduction [a] of belantamab mafodotin, if neutropenia was drug-related.
Neutrophil Count Decreased (Neutropenia) Graded according to NCI-CTCAE criteria	Grade 3-4	• Defined as ANC <1.0x10^9/L **SINGLE, STRETCH and S/D STRETCH** Dosing: • If noted on Day 1 of any cycle, withhold belantamab mafodotin. Repeat hematology (CBC) as clinically indicated. • Resume belantamab mafodotin at pre-held dose once neutropenia recovers to Grade ≤ 2 (ANC ≥ 1.0x10^9/L) on Day 1 of the subsequent cycle. • Consider prophylactic antibiotics, per physician discretion and local institutional guidance, in participants with Grade 3-4 neutropenia (ANC <1.0x10^9/L), even if afebrile. Consider growth factors[b]. **SPLIT Dosing** • If noted on Day 1 of any cycle, follow guidelines as outlined above for single Day 1 dosing • If noted on Day 8 of any cycle, and participant has received belantamab mafodotin on Day 1, then continue belantamab mafodotin Day 8 dosing unless the investigator

Toxicity	Grade/Symptoms	Recommendations
		determines that the participant is clinically unfit to receive the dose (e.g., febrile neutropenia). • If the dose is unable to be administered on Day 8 of the cycle, it can be withheld and administered at any time, up to, and including on Day 15 of the same cycle, and once the investigator determines the participant is clinically fit to receive the dose. • If belantamab mafodotin is withheld on Day 8 up to Day 15 due to clinical reasons, then belantamab mafodotin will not be administered until Day 1 of the next planned 28-day cycle for Arm A or Day 1 of the next planned 21-day cycle for Arm B.
	For a subsequent drop in ANC to $<1.0 \times 10^9$ /L	• Consider 25% dose reduction [b] of belantamab mafodotin, if it was drug-related.
Infusion Reaction Graded according to NCI-CTCAE criteria	Note: If symptoms resolve within 1 h of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated at the next scheduled dose	
	Grade 2	• Stop infusion, provide medical treatment and continue at slower infusion 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 $\leq$ Grade 1 and with premedication, and extension of infusion time to 2-4 h. Any future infusion needs to be premedicated.
	Grade 4	• Permanently discontinue
Pneumonitis Graded according to NCI-CTCAE criteria	Grade 1	Withhold dose and follow recommendations below: • Obtain high resolution chest CT if possible. • CT scan (high-resolution with lung windows) recommended • Clinical evaluation and laboratory work-up for infection • Monitoring of oxygenation via pulse-oximetry recommended • Consultation with pulmonologist recommended • If resolved: Retreatment at the full dose is possible

Toxicity	Grade/Symptoms	Recommendations
	Grade 2	Withhold treatment with belantamab mafodotin Follow recommendations below: • Obtain high resolution chest CT if possible. • CT scan (high-resolution with lung windows) • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • Pulmonary function tests (PFT) – if abnormal, repeat every 8 weeks until back to baseline • Bronchoscopy with biopsy and/or bronchoalveolar lavage (BAL) recommended • Symptomatic therapy including corticosteroids if clinically indicated If resolved: Restart treatment with 50% dose reduction [b].
	Grade 3-4	Permanently discontinue treatment with belantamab mafodotin and follow recommendations below. • Obtain CT scan (high-resolution with lung windows) • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • PFT – if abnormal, repeat every 8 weeks until back to baseline bronchoscopy with biopsy and/or BAL if possible. • Symptomatic therapy including corticosteroids as clinically indicated

a. Medical monitor may consult GSK's Nephrology safety panel regarding treatment continuation.
b. Dose reduction strategy: see Table 20.

Table 22 Dose Modification Guidelines for Belantamab Mafodotin Treatment-Related Corneal Events

	Grade 1 per GSK Scale[a]	Grade 2 per GSK Scale[a]	Grade 3 per GSK Scale[a]	Grade 4 per GSK Scale[a]
Belantamab Mafodotin Dosing Actions	Continue treatment with current dose of belantamab mafodotin.	If **either** ophthalmic exam findings **or** visual acuity findings are **Grade 1,** continue dosing with belantamab mafodotin at current dose. If visual acuity **and** exam findings are **both** Grade2, **HOLD** belantamab mafodotin. • Upon improvement of either visual acuity or ophthalmic exam findings to Grade 1 or baseline, resume with current dose	Hold belantamab mafodotin. • Upon improvement of either visual acuity or ophthalmic exam findings to Grade 1 or baseline, resume with 25% dose reduction* (* for participants receiving 1.9 mg/kg dose continue at 1.9 mg/kg) In case of recurring ≥Grade 3 events, consult GSK Medical monitor	Stop treatment with belantamab mafodotin. Additional topical treatment may be prescribed, as recommended by ophthalmologist* Treatment re-start may be possible after discussion and agreement between the treating qualified eye care specialist, treating physician, the GSK Medical Monitor and possibly a GSK ophthalmologist
Corneal Management Care Regardless of Grade	**Preservative-free artificial tears:** • Increase to 1 drop as frequently as every 2 h, as needed **Cooling Eye Masks:** At the start of each infusion, participants may apply cooling eye masks to their eyes for approximately 1 h or as long as tolerated. **Steroid Eye Drops:** 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).			

a. See Appendix 8 for GSK Scale for belantamab mafodotin Corneal Events

Table 23 Dose Modification Guidelines for Hematologic and Other Toxicities Associated with Lenalidomide Plus Dexamethasone (Arm A)

Toxicity	Grade/Symptoms	Recommendations
Thrombocytopenia[a]	Platelets fall to <30 × 10^9 /L	• Interrupt lenalidomide, follow by weekly hematology assessment
	Platelets return to ≥30 × 10^9 /L	• Resume lenalidomide at next lower dose. Do not dose below 2.5 mg daily
	For each subsequent drop in platelets to <30 × 10^9 /L	• Interrupt lenalidomide treatment. Do not dose below 5 mg daily for Days 1 to 21 of 28-day cycle
	Platelets return to ≥30 × 10^9 /L	• Resume lenalidomide at 5 mg daily for Days 1 to 21 of 28-day cycle. Do not dose below 5 mg daily for Days 1 to 21 of 28-day cycle
Neutropenia[b] Absolute Neutrophil Counts (ANC)	ANC fall to <1.0 × 10^9 /L	• Interrupt lenalidomide, hematology (CBC) at least once a week • Consider prophylactic antimicrobials per physician discretion and institutional guidelines • Consider additional supportive treatment, per local practice (e.g., growth factors) • Immediate hospitalization for febrile neutropenia is required
	When ANC returns to ≥ 1.0 × 10^9 /L	• Resume lenalidomide at next lower dose, continuously for Days 1-21 of repeated 28-day cycle
	For a subsequent drop in ANC to <1.0 × 10^9 /L	• Interrupt lenalidomide treatment.
	When ANC returns to ≥1.0 × 10^9 /L	• Resume lenalidomide at next lower dose daily for Days 1 to 21 of 28-day cycle. Do not dose below 5 mg daily for Days 1 to 21 of 28-day cycle
Cutaneous Reactions	Grade 2-3	• Consider dose interruption or discontinue lenalidomide
	Grade 4	• Permanently discontinue lenalidomide
Hypersensitivity	Angioedema and anaphylaxis	• Permanently discontinue lenalidomide

Toxicity	Grade/Symptoms	Recommendations
For other non-hematological toxicities judged to be related to lenalidomide	Grade 3 to 4	• Hold lenalidomide treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to Grade ≤2

a. Note that in the REVLIMID (lenalidomide) PI, platelet counts and neutrophil counts are presented as 30,000/mcL; those values have been converted to 30×10^9/L to maintain consistency with protocol laboratory conventions.

b. Note that in the REVLIMID (lenalidomide) PI, platelet counts and neutrophil counts are presented as 1,000/mcL; those values have been converted to 1.0×10^9/L to maintain consistency with protocol laboratory conventions

Data Source: REVLIMID (lenalidomide) Approved Labelling.

Table 24 Dose Modification Guidelines for Hematologic and Other Toxicities Associated with Bortezomib Plus Dexamethasone (Arm B)

Toxicity	Grade[a]/Symptoms	Recommendations
Hematological toxicity Graded according to NCI-CTCAE criteria	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)[c]	Grade ≥ 3	• Withhold bortezomib therapy until symptoms of toxicity have resolved. Then, bortezomib may be reinitiated with 1 dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). • For bortezomib-related neuropathic pain and/or peripheral neuropathy, hold or modify bortezomib as outlined in the bortezomib Approved Labelling.
Peripheral Neuropathy[b]	Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	• No action
	Grade 1 with pain, or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living [ADL[c]])	• Reduce bortezomib to 1 mg/m^2

Toxicity	Grade[a]/Symptoms	Recommendations
	Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL[d])	• Withhold bortezomib therapy until toxicity resolves. When toxicity resolves, reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 once per week.
	Grade 4 (life threatening consequences; urgent intervention indicated)	• Discontinue bortezomib.

a. Criteria and Recommendations from bortezomib Approved Labelling.
b. Criteria and Recommendations for Peripheral Neuropathy from bortezomib Approved Labelling.
c. Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc.
d. Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Data Source: bortezomib Approved Labelling.

8.2.2. Dose Modification Guidelines for Dexamethasone

For participants who are intolerant to full dose of dexamethasone, the dose of dexamethasone can be reduced as per guidance below:

Table 25 Dose Modification Guidelines for Toxicities Related to Dexamethasone in Arm A

Toxicity	Recommendations
For participants who are >75 with BMI <18.5 kg/m2	Reduce the dose of dexamethasone by 50% (i.e. from 40 mg to 20 mg) at the discretion of the investigator.
Lack of tolerance or significant toxicities related to dexamethasone	Reduce dexamethasone dose by 50% (i.e. from 40 mg to 20 mg). If 20 mg is not tolerated, the dexamethasone dose can be further reduced, or permanently discontinued.

Table 26 Dose Modification Guidelines for Toxicities Related to Dexamethasone in Arm B

Toxicity	Recommendations
For participants who are >75 years, with BMI <18.5 kg/m2	Reduce the dose of dexamethasone by 50% (i.e. from 20 mg to 10 mg) at the discretion of the investigator.
Lack of tolerance or significant toxicities related to dexamethasone	Reduce dexamethasone dose by 50% (i.e. from 20 mg to 10 mg). If 10 mg is not tolerated, the dexamethasone dose can be further reduced or permanently discontinued.

8.3. Method of Treatment Assignment

A unique participant number will be assigned to all participants who sign the ICF and are screened in the study.

Participants, who satisfy the Inclusion and Exclusion criteria for entry, will be assigned to either Arm A or Arm B at the discretion of the investigator, until the maximum planned number of participants is obtained in each treatment group.

Crossover between arms is not permitted in this study.

Study treatment will be dispensed at the study visits summarized in the Schedule of Activities (Section 3). Returned study treatments (lenalidomide, bortezomib, or dexamethasone) should not be re-dispensed to the participants.

8.4. Blinding

This is an open-label study; therefore, no blinding of treatment identity is needed for either Arm A or Arm B.

8.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, designee, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the Investigator, where this is required by local laws, or is available upon request from GSK.

8.6. Treatment Compliance

When participants have parenteral study treatments (belantamab mafodotin or bortezomib or dexamethasone) administered at the site, they will receive study treatment in the clinic under supervision of the investigator or designee. The date and time of each dose administered in the clinic will be recorded in the participant's CRF and source documents. The dose of study treatment 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 treatment.

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

In addition, a complete list of all prior anti-cancer therapies will be recorded in the eCRF.

8.7. 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 End of the Study Treatment Visit. Any concomitant medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of 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.

8.7.1. Permitted Concomitant Medications and Therapies

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

Concomitant therapy with bisphosphonates is allowed.

Concomitant prophylactic treatment for tumor lysis syndrome (according to local standards) in participants with high tumor load should be considered.

Participants may receive local irradiation for pain control or stability control.

Several permitted concomitant medications may need special monitoring if used. Please refer to the SRM for details.

8.7.2. Prohibited Concomitant Medications and Therapies

Chronic treatment with oral steroids other than part of the study treatment is prohibited while the participant is on study with the exception of low dose prednisolone (<10 mg/d) as substitution in participants with adrenal insufficiency.

A short course (up to 7 days) of steroids is allowed to manage rash, treatment-induced diarrhea, or other acute complications. Steroids may be used to treat infusion related reactions. Inhaled steroids are allowed.

Plasmapheresis is prohibited from 7 days prior to first dose of study drug through the end of study treatment.

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.

Elimination pathways for belantamab mafodotin and cys-mcMMAF have not been characterized in humans; however, cys-mcMMAF was shown to be a substrate of P-gp and OATP transporters and to be a poor substrate of CYP enzymes *in vitro*. Caution should be exercised when belantamab mafodotin is combined with strong inhibitors of P-gp, and strong inhibitors of OATP should be avoided unless considered medically necessary.

A list of Prohibited Concomitant Medications is provided in SRM, based on known interactions or characteristics of each component of the Study Treatment.

8.7.3. Prohibited Devices

Contact lenses are prohibited while the participant is on study treatment.

8.8. Treatment After the End of the Study

Study participants that continue to benefit from study intervention beyond the DCO date will continue to have access to study intervention until the EOS as defined in Section 8.9. There is no planned intervention following the EOS.

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

Refer to End of Treatment & Follow-Up Assessments for participants who are to be followed for disease progression and/or survival after they permanently discontinue from study treatment (Table 10).

8.9. Continued Access to Study Intervention after Final Data cut

Participants receiving belantamab mafodotin monotherapy or in combination with either Len/Dex (Arm A) or Bor/Dex (Arm B) at the time of the final analysis data cut-off date, may continue to receive belantamab mafodotin monotherapy or in combination with either Len/Dex (Arm A) or Bor/Dex (Arm B), if in the opinion of their treating physician, they are continuing to derive clinical benefit from continued treatment. In case the participant meets stopping criteria for belantamab mafodotin, the participant will discontinue all treatment and will continue to be monitored as per standard of care at the participant's particular study site. Study treatment will continue until a study discontinuation (see Protocol Section 9.3) as assessed by the investigator has been met.

Participants who continue study treatment in the PACT phase will be cared for in accordance with local standard clinical practice Investigators must report all SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases until 70 days after receipt of their last dose of study treatment in accordance with Section 10.2.4 (Reporting of Serious Adverse Events). Pre-specified ocular data (refer to the SRM) will be reported for up to 12 months from the end of PACT treatment or until resolution (to Grade 1 or baseline), whichever comes first.

Post final analysis data cut-off, reporting and follow up of SAEs, AEs leading to treatment discontinuation, overdose and pregnancy cases and pre-specified ocular data will be done via paper forms (see SRM for details).

For dispensing of study treatment and drug accountability in the PACT phase please refer to the SRM.

9. DISCONTINUATION CRITERIA

9.1. Discontinuation of Study Treatment

All participants who discontinue from study treatment will have safety assessments at the time of discontinuation and during EOT Follow-up as specified in Table 10. Participants will receive study treatment until disease progression, death or unacceptable toxicity.

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

- Participant has met any of the protocol defined safety stopping criteria (Section 9.2)
- Deviation(s) from the protocol
- Request of the participant or proxy (withdrawal of consent by participant or proxy)
- Investigator's discretion
- Pregnancy
- Participant is lost to Follow-up
- The study is closed or terminated

If the participant voluntarily discontinues from treatment due to toxicity, 'adverse event (AE)' will be recorded as the primary reason for permanently discontinuation on the electronic case report form (eCRF).

Once a participant has permanently discontinued from study treatment, the participant will not be allowed to re-start taking study treatment.

9.1.1. Discontinuation of Individual Components of Combination Study Treatment

The primary reason study treatment was permanently discontinued must be documented in the participant's medical records and eCRF.

- At the discretion of the investigator and in consultation with the Medical Monitor, participants assigned to Arm A and meeting Stopping Criteria for lenalidomide plus dexamethasone may continue to receive belantamab mafodotin monotherapy on the approved schedule until PD, unacceptable toxicity, or death occurs. The primary reason each study treatment was discontinued must be documented in the medical record and on the eCRF.
- At the discretion of the investigator and in consultation with the Medical Monitor, participants assigned to Arm B and meeting Stopping Criteria for bortezomib plus dexamethasone prior to completing 8 cycles, may still continue to receive belantamab mafodotin monotherapy until PD, unacceptable toxicity, or death occurs. The primary reason each study treatment was discontinued must be documented in the medical record and on the eCRF.

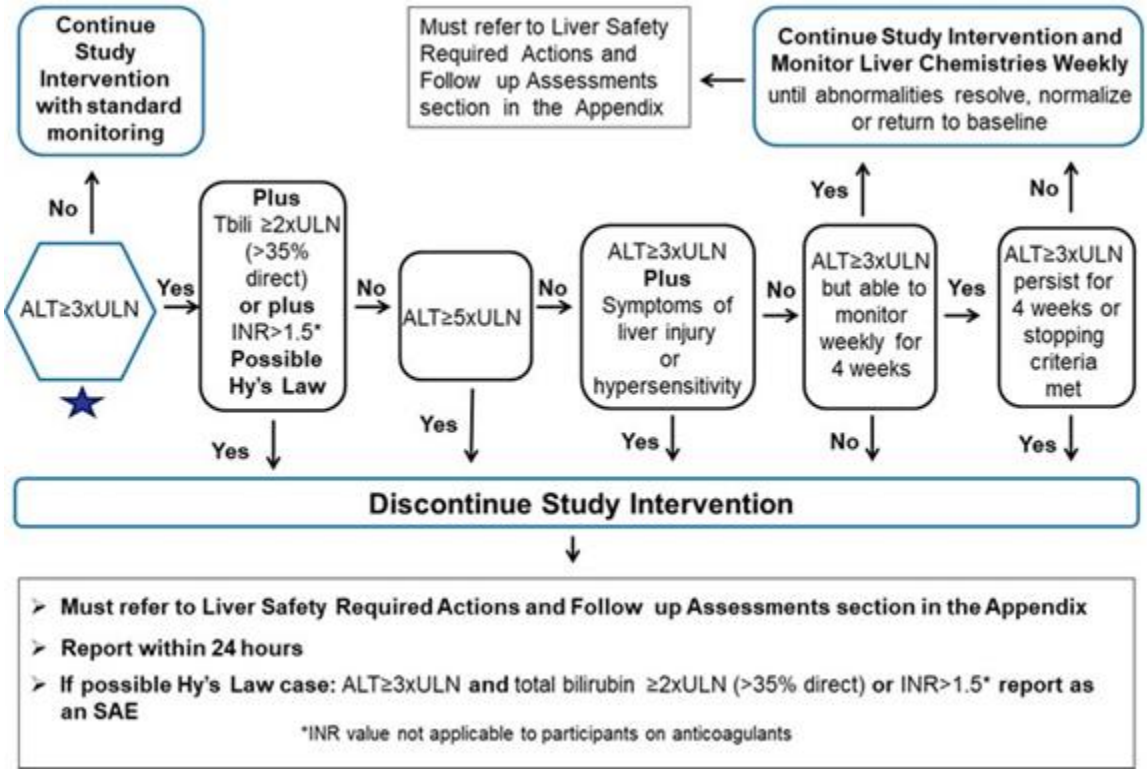
The reason for discontinuing each agent in the combination Arm A and B must be recorded independently; the reason for each component of the combination may differ from each other.

9.2. Safety Stopping Criteria

9.2.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance [Food and Drug Administration, 2009]). Discontinuation of study treatment for abnormal liver tests is required when the participant satisfies any of the stopping rules as shown in Figure 8.

Figure 8 Liver Stopping and Monitoring Event Algorithm



Refer to Appendix 9 (Section 14.9) for required Liver Safety Actions and Follow-up Assessments.

9.2.2. Study Treatment Restart or Rechallenge

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

- GSK approval **is granted** (see Section 9.1.1),
- Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval is obtained and
- Separate ICF for study intervention restart/rechallenge is signed by the participant and participant is informed of any associated risks

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

Refer to Study Procedural Manual for full guidance.

9.2.3. QTc Interval Stopping Criteria

If a participant that meets the corrected QT (QTc) interval duration criteria below, study treatment(s) will be withheld.

- QTcF >530 msec

Based on average QTcF value of triplicate electrocardiograms (ECGs) to include manual over-read.

For example, if an ECG demonstrates a prolonged QT interval, obtain 2 additional ECGs over a brief period (*e.g.*, within approximately 10 min of the abnormal ECG, if possible, and approximately 10 min apart from each other), and then use the averaged QTc values of the 3 ECGs to determine whether the participants should have study treatment(s) withheld. The QTc should be based on single or averaged QTc values of triplicate ECGs obtained over a brief (e.g., 5-10 min) recording period.

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

See the Schedule of Activities for data to be collected at the time of treatment discontinuation and Follow-up and for any further evaluations that need to be completed.

9.2.4. Left Ventricular Ejection Fraction (LVEF) Stopping Criteria

ECHO must be performed at Screening and then every 12 weeks (±7 days), and at the End of Study Treatment Visit as outlined in the Schedule of Activities (Section 3).

Participants who have an asymptomatic, absolute decrease of >10% in left ventricular ejection fraction (LVEF) compared with baseline and the ejection fraction is below the institution's lower limit of normal (LLN) should temporarily discontinue study treatment and have a repeat evaluation of LVEF within 1 week. ECHO should be repeated every 1 to 2 weeks for 4 weeks or until LVEF recovery to above institutional LLN and within 10% of baseline.

- If the LVEF recovers (defined as ≥LLN and an absolute decrease ≤10% compared with baseline) at any time during the next 4 weeks, after consultation and approval of the Medical Monitor, the participant may be restarted on study treatment at a reduced dose. For such participants, monitoring of LVEF will be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 16 weeks and then per protocol.
- If repeat LVEF does not recover within 4 weeks, study treatment should be permanently discontinued. Ejection fraction should be monitored every 4 weeks for a total of 16 weeks or until resolution.

Participants with Grade 3 or 4 (symptomatic) left ventricular systolic dysfunction must discontinue study treatment. Ejection fraction should be monitored every 4 weeks for a total of 16 weeks or until resolution. If recovery occurs (LVEF ≥institutional LLN and symptom resolution) within 4 weeks, then study treatment may be restarted at a reduce dose in consultation with the Medical Monitor.

ECHOs for participants who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is < institution's LLN will be reviewed by the Sponsor. Instructions for submitting qualifying ECHOs are provided in the SRM.

9.2.5. Corneal Event Stopping Criteria

Corneal events, which commonly manifests as a superficial microcystic keratopathy, has been observed with antibody drug conjugates, including those conjugated to MMAF.

Further information regarding corneal event associated with belantamab mafodotin, including the GSK grading scale and prophylactic measures are in Appendix 8, Section 14.8.

All belantamab mafodotin dose modifications and stopping criteria are to be based on the GSK Scale provided in Appendix 8, Section 14.8. Corneal events will be graded according to both CTCAE criteria for eye disorders and the guidelines provided in Appendix 8.

The treating physician or qualified eye care specialist (Appendix 12) must discuss the participants who develop a Grade 4 corneal event according to the GSK scale with the Medical Monitor or a GSK eye care specialist to determine whether the participant can be allowed to restart treatment with belantamab mafodotin or whether belantamab mafodotin should be permanently discontinued. If a participant is allowed to continue on study, the dose of belantamab mafodotin will be reduced after discussion with Medical Monitor. The decision will be documented in study files, together with individual assessment of risk-benefit.

9.2.6. Infusion-Related Reaction Management and Stopping Criteria

Premedication is not required prior to infusion unless deemed medically appropriate by the investigator. 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 administered with subsequent infusions per institutional guidelines. IRRs should be managed by guidelines provided in Table 20.

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

9.2.7. Allergic and Anaphylactic Reaction Stopping Criteria

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

9.3. Withdrawal from the Study

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

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

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

Refer to End of Treatment & Follow-Up Assessments (Table 6) for information to be collected at the time of study discontinuation.

9.4. Lost to Follow-Up

A participant will be considered lost to Follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site.

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

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

10. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (Section 3). Key assessments to be performed during the study are briefly described below, with more detailed information provided for some specific assessments in the Protocol Appendices or the SRM. Protocol waivers or exemptions for study assessments will not be allowed.

The investigators will maintain screening logs to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as appropriate. 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 Schedule of Activities (Table 4).

Where applicable country and local regulations and infrastructure allow, home healthcare and telemedicine may be permitted (Appendix 13 Section 14.13)

10.1. Assessments for Evaluation of Clinical Activity

Clinical activity will be evaluated in all participants in the study. Standard Response assessments for RRMM will be applied to clinical activity data, and will include: Overall Response Rate (ORR), CCI [redacted] – as defined by 2016 IMWG response criteria [Kumar, 2016], and as data permits. In addition, the number (%) of participants achieving CCI [redacted] will be assessed according to IMWG criteria 2011 and 2016 [Kumar, 2016], as data permits.

Clinical activity assessments and/or diagnostic criteria will be evaluated during treatment, per IMWG and other current practice guidelines for the management of RRMM [Bennett, 2016; Kumar, 2016; Moreau, 2017; National Comprehensive Cancer Network, 2016; Rajkumar, 2016]. These may include:

- Laboratory tests (serum and urine M-protein test, immunofixation, free light chains [FLC])
- Bone marrow (BM) aspirate/biopsy for disease assessment, CCI [redacted] testing
- Imaging for extramedullary disease and skeletal survey

10.1.1. Imaging

Imaging is only required for participants with extramedullary disease by either CT, MRI, or PET/CT per local guidance. The screening assessment may be performed up to 30 days prior to C1D1. The imaging method used at baseline should be used throughout the study (i.e. if CT/PET scan was used as baseline, the participant should be followed by CT/PET scans). A selected target lesion should be measured and followed over time. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans, where applicable. For participants with only skin

involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the Sum of the Products of the maximal perpendicular diameters of measured lesions (SPD).

10.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 6, Section 14.6.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (see Section 9.1).

Adverse events, including corneal events, will be graded by the investigator according to the NCI-CTCAE, (version 4.03). For dosing decisions, corneal events associated with belantamab mafodotin will also be graded according to the GSK grading scale provided in Appendix 8.

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

All SAEs 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 Schedule of Activities (SoA) (Section 3).

- However, any SAEs assessed as related to study participation (e.g., study treatment, 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 treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the electronic case report form (eCRF) not the AE section.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 h, as indicated in Appendix 6, Section 14.6. The investigator will submit any updated SAE data to the Sponsor within 24 h of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 6, Section 14.6.

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

10.2.2. Method of Detecting AEs and SAEs

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

10.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to Follow-up (as defined in Section 9.4). Further information on follow-up procedures is given in Appendix 6, Section 14.6.

10.2.4. 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 treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information e.g., summary or listing of SAE) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

10.2.5. Cardiovascular and Death Events

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

For any cardiovascular events detailed in Appendix 5, Section 14.5 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV medical dictionary for regulatory activities (MedDRA) terms. The CV information must be recorded in the specific cardiovascular section of the eCRF within 1 week of receipt of a CV Event data query prompting its completion.

10.2.6. 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 AESI will be graded using National Cancer Institute-Common Toxicity Criteria for Adverse Events (CTCAE, v4.03; Appendix 8). Severity of corneal events will also be graded using the GSK scale for corneal events provided in Table 33. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in Table 20.

10.2.7. Pregnancy

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

The need for a screening pregnancy test depends on whether a female participant is of childbearing potential or non-childbearing potential.

If a female participant is of childbearing potential, she must have a serum β-human chorionic gonadotropin (β –HCG) pregnancy test performed within 24 h prior to the first dose of study treatment. Participants with positive pregnancy test result must be excluded from the study. Participants with negative pregnancy test result must agree to use an effective contraception method as described below during the study until 4 months following the last dose of study treatment.

- Details of all pregnancies in female participants will be collected after the start of study treatment and
  - Arm A: for 4 months following last dose of belantamab mafodotin or 4 weeks after the last dose of lenalidomide, whichever is longer (by telephone for WOCBP only)
  - Arm B: for 4 months following last dose of belantamab mafodotin or 7 months following last dose of bortezomib whichever is longer (by telephone for WOCBP only)
- Details of all pregnancies for female partners of male participants will be collected after the start of study treatment and 6 months following the last dose of belantamab mafodotin (by telephone for WOCBP partners only)
- If a pregnancy is reported, the investigator must inform GSK within 24 h of learning of the pregnancy and must follow the procedures outlined in Appendix 7, as well as those outlined in REVLIMID (lenalidomide) Patient Exposure Registry (Refer to SRM).
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

10.2.8. Medical Device Incidents (including malfunctions)

Not applicable for this study

10.3. Treatment of Overdose

10.3.1. Belantamab Mafodotin Overdose

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

In the event of an overdose (defined as administration of more than the protocol-specified dose) of belantamab mafodotin, the investigator should:

- contact the GSK Medical Monitor immediately

- closely monitor the participant for AEs, SAEs, and laboratory abnormalities until they are resolved and belantamab mafodotin concentrations are predicted to be within the anticipated range in absence of the overdose
- obtain an additional PK and serum [redacted] sample as soon as the overdose situation is recognized and contact the GSK Medical Monitor for further guidance with regards to additional sample collection (determined on a case-by-case basis)
- document the quantity of the excess dose as well as the duration of the overdosing in the eCRF

Decisions regarding belantamab mafodotin or administration of SoC agents following an overdose will be made by the investigator in consultation with the GSK Medical Monitor based on the clinical evaluation of the participant.

10.3.2. Lenalidomide Overdose

There is no specific experience in the management of lenalidomide overdose in participants with MM. In dose-ranging studies in healthy participants, some were exposed to up to 200 mg (administered 100 mg BID) and in single-dose studies, some participants were exposed to up to 400 mg. Pruritis, urticaria, rash, and elevated liver transaminases were the primary reported AEs. In clinical trials, the dose-limiting toxicity was neutropenia and thrombocytopenia.

10.3.3. Bortezomib Overdose

There is no known specific antidote for bortezomib over-dosage. In humans, overdose of more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes. In the event of an overdose, the participant's vital signs should be monitored, and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or inotrophic agents) and body temperature.

10.3.4. Dexamethasone Overdose

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

10.4. Demographics and Medical History

Demographic and medical history data will be collected at Screening and verified pre-dose on Day 1 Cycle 1 in both Part 1 and Part 2.

Demographic data we can collect may differ in different regions but should include: year of birth, sex, and race/ethnicity (if permitted). The medical history data that may be collected can be divided into two sections:

- Standard Medical History of Prior Conditions: may include the condition/diagnosis, body system (if appropriate), date of diagnosis, intensity (if appropriate), date of resolution, and any interventions or treatments (with dates).

- History of RRMM and Current Comorbid Conditions may include: the condition/diagnosis (for non-RRMM), body system (if appropriate, for non-RRMM), date of diagnosis, intensity or Grade (as appropriate), prior treatment regimens with start and stop dates, and any interventions or treatments.

10.5. Daily Study Diary

Depending on assigned treatment, participant will be issued Daily Study Diary that will be reviewed at each clinic visit. Participant Diary will be used to record drug accountability information: doses of lenalidomide or dexamethasone taken at home during a treatment cycle; drug name, dose (or number of tablets or capsules), the date the dose was taken, and the time the dose was taken will all be recorded in the Diary.

10.6. Safety Assessments

10.6.1. Physical Examinations

Physical examinations will be performed during Screening, pre-dose on Day 1 (and on Day 8 for SPLIT dosing) of each Cycle, and upon discontinuation form Study Treatment (End of Treatment Visit and CCI [redacted] FU Visit). A physical examination will include, at a minimum, assessments of the head, eyes, ears, nose, throat, skin, thyroid, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured at Screening and recorded, with weight repeated at the start of each cycle (Schedule of Activities, Section 3). Body weight at C1D1 (prior to dosing) will be used for dose calculation of belantamab mafodotin. Body weight will also be measured prior to each dose. If the change of body weight is greater than 10%, the dose should be re-calculated based on the actual body weight at the time of dosing.

During the physical examinations, investigators should pay special attention to clinical signs related to previous serious illnesses and record any changes noted during study treatment, if any.

10.6.2. ECOG Performance Status

The participant's performance status will be assessed using the ECOG scale (Appendix 3, Section 14.3) as specified in the Schedule of Activities (Section 3).

10.6.3. Vital Signs

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

On each dosing day, vital signs must be assessed prior to each infusion of belantamab mafodotin at pre-dose, defined as within 30 min prior to start of infusion (SOI), within 15 min after End of Infusion (EOI), and at 1 h (±5 min) after EOI. On days where bortezomib is administered, vital signs must be assessed within 30 mins prior and within

15 min after each dose of bortezomib. On days where vital sign time points align with PK sampling time points, vital signs should be assessed prior to PK samples being drawn.

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

In case of IRRs monitoring will be performed with higher frequency (as clinically indicated).

10.6.4. New York Heart Association Functional Scale

Criteria for rating participants for heart failure status according to the New York Heart Association (NYHA) criteria are provided in Appendix 5, Section 14.5.

10.6.5. Electrocardiograms

Triple 12-lead electrocardiogram (ECGs) will be obtained at designated time points specified in the Schedule of Activities (Section 3) during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc) intervals.

At each assessment, a 12-lead ECG will be performed by qualified personnel at the site after the participant has at least a 5-min rest.

The QT interval should be corrected for heart rate by Fridericia's formula (QTcF). Refer to Section 9.2.3 for QTc withdrawal criteria. Refer to the Study Procedures Manual for details regarding ECG procedures.

Instructions for submission of ECGs are provided in the SRM.

10.6.6. Echocardiogram

ECHOs must be performed at baseline and then every 12 weeks (± 7 days) to assess cardiac ejection fraction for the purpose of study eligibility, as specified in the SoA. A final ECHO will also be performed at the End of Treatment Visit. The evaluation of the echocardiographer must include an evaluation for left ventricular ejection fraction (LVEF). If an ECHO is performed on study the results must be documented in the e-CRF.

10.6.7. Ophthalmic Examinations

Study sites are required to establish a close collaboration with a qualified eye care specialist who will be responsible for assessing participants while they are on-study and managing participants who develop a corneal event in close communication with the GSK Medical Monitor. Participants will be assessed by a qualified eye care specialist at screening/baseline and then on Day 1 of every cycle prior to belantamab mafodotin dosing up to Dose 6 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). For STRETCH schedule, belantamab mafodotin dosing is scheduled

on Day 1 of every alternate 21-day cycle, but participants will be assessed by a qualified eye care specialist on Day 1 of every 21-day cycle up to the Dose 6 of belantamab mafodotin regardless of dosing (assessment window of up to 5 days before Day 1 of every 21-day cycle prior to dosing, but all effort should be made to schedule as close to belantamab mafodotin dosing as possible). See Appendix 12 for qualifications and requirements of the eye care specialist.

- If there are no significant ocular examinations findings, patient's symptoms or vision changes at the time of the Dose 6 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 Dose 6 exam, the participants will have further ophthalmologic exams, at least every cycle until resolution (to Grade 1 or baseline) or more frequently as clinically indicated by the qualified eye care specialist.

Participants who have corneal signs per the GSK scale for Corneal Events at the End of Treatment Visit will be followed once every 3 months (±7 days) until full resolution of ophthalmic changes (Grade 1 or baseline) by a qualified eye care specialist or start a new anti-cancer therapy, or up to 1 year (whichever comes first).

10.6.7.1. Ocular Examinations and Procedures

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) and must include:

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

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

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

10.6.8. 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 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 80 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, as shown in the Schedule of Activities (Section 3). The PRO-CTCAE will be administered to participants in different regions based on the availability of translated versions. All participants will complete the self-

administered version of this assessment unless they are unable to do so due to site restrictions or the PI or site feels it is in the best interest of the participant not to come to the site. Participants who cannot complete the self-administered version should use an Interviewer-Administered format. The interview may be administered over the telephone. If the Interviewer-Administered format is used, it should be read to the participants verbatim, and participant responses should be recorded directly without any interpretation.

10.6.9. Visual Function Safety Assessment

The impact of potential ocular toxicity on function and health-related quality of life will be assessed with the use of 2 visual function questionnaires: the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25), and the Ocular Surface Disease Index (OSDI). All participants will complete the self-administered version of these two assessments, unless their vision prevents them from being able to complete the questionnaire on their own, they are unable to complete the self-administered version due to site restrictions, or the PI or site feels it is in the best interest of the participant not to come to the site. Participants who are not able to complete the self-administered version should use an Interviewer-Administered format. If the Interviewer-Administered format is used, it should be read to the participants 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.

10.6.9.1. National Eye Institute Visual Function Questionnaire-25

The NEI-VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. These include a global vision rating (1 item); difficulty with near vision activities (3 items); difficulty with distance vision activities (3 items); limitations in social functioning due to vision (2 items); role limitations due to vision (2 items); dependency on others due to vision (3 items); mental health symptoms due to vision (4 items); driving difficulties (3 items); limitations with peripheral vision (1 item), limitations with color vision (1 item); and Ocular pain (2 items). The NEI-VFQ-25 will be completed by the participants at the times shown in the Schedule of Activities (Section 3).

10.6.9.2. The Ocular Surface Disease Index

The Ocular Surface Disease Index (OSDI) is a 12-item questionnaire designed to assess both the frequency of dry eye symptoms and their impact on vision-related functioning [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 participative 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 (Section 3).

10.6.10. Laboratory Assessments

All protocol-required laboratory assessments should be performed according to the Schedule of Activities (Section 3).

Details for the preparation and shipment of samples are provided in the SRM.

Local laboratory results will be used to make decisions regarding treatment or management of AEs.

Prior to administration of the first dose of study treatment, results of laboratory assessments should be reviewed. Any laboratory test with a value outside the normal range may be repeated (prior to the first dose) at the discretion of the Investigator.

If additional non-protocol-specified laboratory assessments are performed at the institution's local laboratory and result in a change in participant management or are considered clinical significant by the investigator (for example SAE or AE or dose modification) the results must be recorded in the participant's CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values that are significantly abnormal during participation in the study or within 70 days after the last dose of study treatment should 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 should be identified and the Sponsor notified.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 27 with detailed instructions and timing in the SRM.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Table 27 List of Clinical Laboratory Tests

Hematology[1]		
Platelet Count	Red Blood Cell (RBC) Indices:	Automated WBC Differential:
Red Blood Cell (RBC) Count	MCV	Neutrophils
White Blood Cell (WBC) Count (absolute)	MCH	Lymphocytes
Reticulocyte Count	MCHC	Monocytes
Hemoglobin		Eosinophils
Hematocrit		Basophils

Clinical Chemistry[1]			
Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin
Creatinine	Chloride	Alanine aminotransferase (ALT)	Uric Acid
Glucose	Total carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
Magnesium	Phosphorous	Creatine kinase (CK)	LDH
Urinalysis[1]			
Specific gravity; pH, glucose, protein, blood and ketones by dipstick Microscopic examination (if blood or protein is detected by dipstick)			
Other Laboratory Tests			
Spot urine (albumin/creatinine ratios)[1, 3]; HbA1c[1]; C-reactive protein (CRP)[1]; Pregnancy Test (urine or blood)[1]; Follicle-stimulating hormone (FSH)[1] and estradiol[1] (as needed in women of non-child-bearing potential only); Hepatitis B (HbsAg)[1]; HbcAb, Hepatitis C antibody[1], Hepatitis C RNA test[1] (optional) Note: Hep C RNA testing is optional but may be done to determine participant eligibility if Hep C antibody positive. eGFR[1]			
PK and ADA[2]			
Pharmacokinetics (PK) Anti-Drug Antibodies (ADA)			
Disease Evaluation Laboratory Tests[1, 3]			
Beta2 microglobulin; SPEP (Serum Protein Electrophoresis); Serum M-protein calculation; Serum Kappa, lambda free LC, FLC ratio; Serum Immunofixation; UPEP (Urine Protein Electrophoresis); 24-h urine collection for M-protein; Urine Immunofixation; Ca corrected for Albumin (Serum); IgG, IgM, IgA, IgD/IgE[4]			
Bone Marrow Aspiration/Biopsy			
BM for FISH analysis[1, 3, 5]; BM aspirate for BCMA expression and biomarker research[2]; BM biopsy to confirm sCR (by IHC)[2]; BM aspirate for CCI [redacted] testing[2]			
Biomarker Measurements[2]			
CCI [redacted] Genetic Sample[6]			

1. To be performed at local laboratory
2. To be performed at central laboratory
3. If not available locally it can be performed centrally
4. Only for participants with IgD/E myeloma
5. FISH testing 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 regardless of timeframe, FISH for these translocations does not need to be repeated. FISH results for amp(1q), del(1p) and del(17p13) from samples taken within 60 days prior to first dose are acceptable.
6. Informed consent for optional sub-studies (e.g. genetic research) must be obtained before collecting a sample.

10.6.11. DNA Sampling for Genetic Testing

Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, and pending

the consent of the participant, a 6 mL of blood sample will be collected for DNA analysis. If insufficient DNA is extracted from the original sample, or if the sample was damaged or otherwise could not be processed, the site may be requested to recollect the genetic sample where applicable and if the participant consents.

DNA samples will be used for research related to belantamab mafodotin or RRMM and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to belantamab mafodotin and RRMM. Detailed Guidance relating to sampling, analysis of genetic material in this study is provided in Appendix 10 – Genetics.

Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (or analysis of the entire genome as appropriate). DNA samples will be analyzed by using appropriate descriptive and/or statistical analysis methods. A detailed description of any planned analyses will be documented in a RAP prior to initiation of the analysis. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to belantamab mafodotin or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.

The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on belantamab mafodotin (or study treatments of this class) or RRMM continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

10.6.12. Suicidal Risk Monitoring

Not applicable.

10.7. Pharmacokinetics

10.7.1. Blood Sample Collection for Pharmacokinetics

Blood samples for pharmacokinetic (PK) analysis of belantamab mafodotin (ADC and total antibody) and cys-mcMMAF will be collected for all participants at the time points indicated in the Schedule of Activities tables (Section 3).

For participants assigned to Arm A and receiving belantamab mafodotin Q4W, additional blood samples for lenalidomide pharmacokinetics will also be collected at Cycle 1 at the time points indicated in SoA (Table 5).

For participants assigned to Arm B and receiving belantamab mafodotin Q3W, additional blood samples for bortezomib pharmacokinetics will be also collected at Cycle 1 at the time points indicated in SoA (Table 7).

Each PK sample should be collected as close as possible to the planned time relative to the administration of the drug being measured on PK days (i.e., belantamab mafodotin samples collected relative to belantamab mafodotin dosing, lenalidomide samples collected relative to lenalidomide dosing, and bortezomib samples collected relative to bortezomib dosing). The actual date and time of each blood sample collection will be recorded. Details on PK blood sample collection including blood volumes, processing, storage, and shipping procedures are provided in the SRM.

CCI samples should be collected at all PK time points as close as possible to the belantamab mafodotin PK sample.

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

10.7.2. Pharmacokinetic Sample Analysis

Plasma analysis will be performed under the control of GSK, the details of which will be included in the SRM. Concentrations of belantamab mafodotin (ADC and total antibody) and cys-mcMMAF will be determined in plasma samples using the currently approved bioanalytical methodology. Concentrations of lenalidomide and bortezomib will be determined in plasma samples using validated bioanalytical methods. Raw data will be archived at the bioanalytical site (as described in the SRM).

Once the plasma has been analyzed for belantamab mafodotin (ADC and total antibody) and cys-mcMMAF, any remaining plasma may be analyzed for other compound-related metabolites and the results reported separately.

CCI

CCI

[redacted]

CCI

10.9. Immunogenicity Assessments

Serum samples for determination of anti- belantamab mafodotin antibodies will be taken from all participants at the time points specified in the Schedule of Activities (Section 3). 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. Additionally, plasma samples will be collected at the same time points (see SoA) as the immunogenicity samples and analyzed to determine the belantamab mafodotin plasma concentration. The belantamab mafodotin plasma concentration results will enable interpretation of the anti-belantamab mafodotin antibody data. Anti-belantamab mafodotin antibody samples will be disposed three months after final approved results are

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

10.11. Health-Related Quality of Life

Two validated health-related quality of life (QoL) instruments will be employed in this study, to assess disease severity, disease symptoms, adverse events associated with the study treatment, and general quality of life in study participants with RRMM assigned to either Arm A or Arm B. All participants will complete the self-administered version of these assessments unless they are unable to do so due to site restrictions or the PI or site feels it is in the best interest of the participant not to come to the site. Participants who cannot complete the self-administered version should use an Interviewer-Administered format. The interview may be administered over the telephone. If the Interviewer-Administered format is used, it should be read to the participants verbatim, and participant responses should be recorded directly without any interpretation.

10.11.1. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires

The symptoms related to multiple myeloma and its treatment, and the impact of these symptoms on daily functioning will be assessed using the European Organisation for

Research and Treatment of Cancer Quality of Life Questionnaires; EORTC QLQ-C30 and QLQ-MY20. The EORTC QLQ-C30 AND QLQ-MY20 will be completed at the times shown in the Schedule of Activities (Section 3).

10.11.1.1. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module (EORTC QLQ-C30)

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

10.11.1.2. European Organisation for Research and Treatment of Cancer 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 participants with multiple myeloma [Aaronson, 1993; Cocks, 2007]. The module comprises 20 questions that address four myeloma-specific HRQoL domains: Disease Symptoms, Side Effects of Treatment, Future Perspective, and Body Image. Three of the four QLQ-MY20 domains are multi-item scales: Disease Symptoms (includes bone aches or pain, back pain, hip pain, arm or shoulder pain, chest pain, and pain increasing with activity); Side Effects of Treatment (includes drowsiness, thirst, feeling ill, dry mouth, hair loss, upset by hair loss, tingling hands or feet, restlessness/agitation, acid indigestion/heartburn, and burning or sore eyes); and Future Perspective (includes worry about death and health in the future, and thinking about illness). The Body Image scale is a single-item scale that addresses physical attractiveness. 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 and Side Effects of Treatment represents a high level of symptomatology or problems, whereas a high score for Future Perspective and Body Image represents better outcomes [Proskorovsky, 2014].

11. DATA MANAGEMENT

For this study participant data will be entered into GSK-defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.

Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.

CRFs (including queries and audit trails) will be retained by GSK or designee and copies will be sent to the Investigator to maintain as the Investigator copy. Participant initials will not be collected or transmitted to GSK according to GSK policy.

12. STATISTICAL CONSIDERATIONS

This section briefly describes the planned analyses to be performed for Study 207497. Statistical analyses will either be performed separately or by combining data from Part 1 (Dose Escalation) and Part 2 (Dose Expansion) as well as being performed independently for Arm A and Arm B.

Actual analyses to be performed for each Treatment may be dependent on the outcomes of Part 1 and Part 2 for both Arm A and Arm B. Ultimately those analyses will be described fully in the Reporting and Analysis Plan (RAP) that will be finalized prior to the final database release or interim database release.

12.1. Hypothesis(es)

12.1.1. Arm A – Belantamab Mafodotin with Len/Dex

12.1.1.1. Part 1

No formal statistical hypotheses are being tested in Part 1. Analysis of the data obtained from Part 1 will only utilize descriptive methods.

12.1.1.2. Part 2

No formal statistical hypotheses are being tested in Part 2. Analysis of the data obtained from Part 1 will only utilize descriptive methods.

For Part 2, the number of participants who permanently discontinue study treatment due to AEs related to belantamab mafodotin within the first two cycles will be continuously monitored. For STRETCH dosing schedule, a cycle is a SoC cycle of 28 days. If the observed number of participants permanently discontinuing belantamab mafodotin is significantly higher than 12% (at 1-sided alpha of 0.01), then the combination treatment at that dose level or higher dose level will be considered to have unacceptable toxicity and the dose level as well as higher dosed levels will be closed.

12.1.2. Arm B – Belantamab Mafodotin with Bor/Dex

12.1.2.1. Part 1

No formal statistical hypotheses are being tested in Part 1. Analysis of the data obtained from Part 1 will only utilize descriptive methods.

12.1.2.2. Part 2

No formal statistical hypotheses are being tested in Part 2. Analysis of the data obtained from Part 2 will only utilize descriptive methods.

For Part 2, the number of participants who permanently discontinued study treatment due to AE related to belantamab mafodotin within the first two cycles will be continuously monitored starting from when 5 participants are dosed. For STRETCH dosing schedule, a cycle is a SoC cycle of 21 days. If the observed number of participants permanently discontinuing belantamab mafodotin is significantly higher than 12% (at 1-sided alpha of 0.01), then the combination treatment at that dose level or higher dose level will be considered to have unacceptable toxicity and the dose level as well as higher dose levels will be closed.

12.2. Sample Size Determination

12.2.1. Arm A – Belantamab Mafodotin with Len/Dex

12.2.1.1. Part 1

The total number of participants to be enrolled into Part 1 will depend on the number of participants needed to characterize individual dose cohorts. The sample size is not driven by statistical considerations. However, based on assumptions that 2 different dose levels will be evaluated, it is anticipated that approximately 14 evaluable participants will be enrolled in Part 1.

12.2.1.2. Part 2

The sample size is not driven by statistical considerations. Up to 2 dose levels and up to 3 dosing schedules will be evaluated, approximately 9 participants each will be enrolled at the 2.5 mg/kg SINGLE and, 2.5 mg/kg SPLIT dose levels.

- In addition, an alternate dosing schedule of STRETCH (Q8W) dosing may be explored for the 1.9 mg/kg dose level if emerging data (from either this study or across the program) suggests that this schedule may further optimize the tolerability or offers an improved benefit/risk profile. Up to 12 participants will be enrolled in this new cohort.

Approximately 31 participants will be enrolled in Part 2.

12.2.2. Arm B – Belantamab Mafodotin with Bor/Dex

12.2.2.1. Part 1

The total number of participants to be enrolled into Part 1 will depend on the number of participants needed to characterize individual dose cohorts. The sample size is not driven by statistical considerations. However, based on assumptions that 2 different dose levels will be evaluated, an additional lower dose level may be explored using the mTPI design. It is anticipated that approximately 13 evaluable participants will be enrolled in Part 1.

12.2.2.2. Part 2

The sample size is not driven by statistical considerations. Up to 3 dose levels and up to 4 dosing schedules will be evaluated and up to 12 participants will be enrolled at each dosing schedule (up to 9 participants in the 3.4 mg/kg SINGLE), it is anticipated that approximately 94 participants will be enrolled in Part 2.

12.2.3. Sample Size Sensitivity

There is no need to perform sample size sensitivity analysis.

12.2.4. Sample Size Re-estimation or Adjustment

Sample size re-estimation is not planned for this study.

12.3. Populations for Analyses

For purposes of analysis, the following populations are defined in Table 28. Each of the following population will be created separately for Arm A and Arm B and by each part as appropriate. Additional analysis populations may be defined in the RAP.

Table 28 Definitions of Study Analysis Populations

Population	Description
All Screened	All participants who sign the ICF to participate in the clinical trial. Participants in this population will be used for screen failure summary.
All Treated	All participants who take at least 1 dose of any study treatment. Analyses of demographic, baseline characteristics, safety and all efficacy endpoints will be based on this population.
Pharmacokinetic	Participants in the All Treated Population from whom at least one PK sample was obtained, analyzed, and was measurable. Separate PK populations will be defined for each drug (belantamab mafodotin, lenalidomide, and bortezomib). This population will be the primary population for PK analyses.

12.4. Statistical Analyses

All statistical analyses will be performed by GSK (sponsor) or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the clinical activity and safety data is outlined below. Statistical analyses will be performed for each treatment group separately. There will be no comparison between treatment groups or parts.

Data will be listed and summarized mostly by doses. In general, separate analyses will be provided for Part 1 and Part 2 where applicable. Data from Part 1 and Part 2 may be

combined at interim, and final analyses. Final analysis will be performed following 12 months post LSFD.

Specific details will be provided in the Reporting and Analysis Plan (RAP).

12.4.1. Analyses of Clinical Activity

The primary endpoint for Part 2 will be based on the responses assessed by the investigator.

The primary efficacy endpoint will be analyzed based on the All Treated Population unless otherwise specified.

The analytical methods planned for the primary efficacy endpoint are described in Table 29.

Table 29 Statistical Analysis Methods for Clinical Activity Endpoints (Part 2)

Endpoint	Statistical Analysis Methods
Primary	**Overall Response Rate (ORR)** defined as percentage (%) of participants with a confirmed PR or better (i.e., PR, VGPR, CR and sCR), according to the International Myeloma Working Group (IMWG) Response Criteria). The number and percentage of participants in the following response categories will be presented: 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 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.

12.4.2. Safety Analyses

All safety analyses will be performed on the All Treated Population. Complete details of the safety analyses will be provided in the RAP.

12.4.2.1. Exposure Duration

The number of participants administered study treatment will be summarized for Arm A and Arm B independently, according to the duration of therapy.

12.4.2.2. Adverse Events

All adverse events whether serious or non-serious, 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 Schedule of Activities (SoA). AEs will be recorded using standard medical terminology and graded according to the NCI-CTCAE, Version 4.03. For AE reporting, the verbatim

term used in the CRF by investigators to identify adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

12.4.2.3. Clinical Laboratory Evaluations

The evaluation of clinical laboratory tests will focus on selected laboratory analytes from the hematology and blood chemistry panel.

Descriptive statistics (mean, standard deviation, median, range) will be used to summarize observed laboratory values and change from baseline in observed value at each scheduled visit or worst-case postbaseline, as appropriate.

The worst-case toxicity grade in hematology and chemistry results during the treatment will be summarized according to NCI-CTCAE, Version 4.03 [National Cancer Institute, 2010]. Shift tables from baseline to the worst toxicity grade during treatment will be provided for each laboratory analyte as appropriate. Laboratory test results outside the reference ranges that do not have associated NCI-CTCAE criteria will be summarized using proportions. Further details will be provided in the RAP.

12.4.2.4. Other Safety Measures

Data for vital signs, ECGs and ECHOs 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. Further details will be provided in the Reporting and Analysis Plan (RAP).

12.4.3. Pharmacokinetic Analyses

12.4.3.1. Belantamab mafodotin pharmacokinetic

Belantamab mafodotin pharmacokinetic data will be reported separately for Arm A and Arm B as well as combined, if appropriate.

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

Derived Pharmacokinetic Parameters: Pharmacokinetic analyses will be the responsibility of Clinical Pharmacokinetics/Modelling and Simulation, GSK. Plasma belantamab mafodotin (ADC, total mAb) and cys-mcMMAF concentration-time data will be analysed using standard noncompartmental methods, data permitting.

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

Plasma belantamab mafodotin, total mAb, 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 then-current population pharmacokinetic model to generate post hoc pharmacokinetic parameter estimates. Summary exposure measures (e.g., Cmax, AUC) will also be computed. Results of this analysis may be provided in a separate report.

12.4.3.2. Lenalidomide

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

Derived PK Parameters: Lenalidomide pharmacokinetics in the presence of belantamab mafodotin will be analyzed using standard noncompartmental methods, data permitting, or using a published population pharmacokinetic model [Guglieri-Lopez, 2017]. Results of the population PK analysis, if performed, may be provided in a separate report.

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

12.4.3.3. Bortezomib

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

Derived PK Parameters: Bortezomib pharmacokinetics in the presence of belantamab mafodotin will be analyzed using standard noncompartmental methods, data permitting.

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

12.4.4. 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; data from this study may be combined with data from other

studies for these analyses. If data permit, the effects of covariates may be explored. Results may be reported separately.

12.4.5. Translational Research Analyses

The results of translational research investigations will be reported either within or separately from the main clinical study report (CSR). All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. Further details on the translational research analyses will be addressed in the RAP.

12.4.5.1. Novel Biomarker(s) Analyses

The results of these biomarker investigations may be reported separately from the main CSR. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. Additional exploratory analyses may be performed to further characterize novel biomarkers.

12.4.5.2. Genetic Analyses

Further details on genetic analyses can be found in Section 10.10

CCI

[redacted]

12.4.6. Immunogenicity Assessment

For each participant, the results and titers of anti- belantamab mafodotin binding antibodies will be listed for each assessment time point, along with plasma belantamab mafodotin concentration. The frequency and percentage of participants with positive and negative results will be summarized for each assessment time and overall for each participant by dose cohort. The detailed information will be included in the RAP.

12.4.7. Other Analyses

All other exploratory analyses will be described in the RAP.

12.4.8. Interim Analyses

12.4.8.1. Arm A – belantamab mafodotin with Len/Dex

Part 1

During dose escalation, no formal interim analysis will be performed. Data will be reviewed through data visualization tool to inform dose escalation decisions. The mTPI design will be utilized to guide dose escalation/de-escalation decisions. More details of the dose escalation procedure are described in Section 6.1.1.1.

Part 2

Continuous monitoring will be conducted for Part 2 starting from when 5 participants are dosed at each dose level within each arm. The observed number of participants permanently discontinuing study treatment within the first two cycles due to AE related to belantamab mafodotin will be compared against the safety stopping rule in Table 30. Enrollment may stop if the safety stopping rule is met based on totality of safety data. For example, if 4 or more out of 5 participants permanently discontinued study treatment within the first 2 cycles due to AE related to belantamab mafodotin, enrollment may stop after review of all safety data; otherwise enrollment will continue. Operating characteristics for the stopping rule are provided in Appendix 11.

Table 30 Safety Stopping Rules for Arm A Part 2

Number of dosed participants	Stop if number of participants discontinuing study treatment within the first two cycles due to AE related to belantamab mafodotin is larger or equal to this this number	Observed rate
5-8	4	0.5-0.8
9-12	5	0.42-0.56

An interim analysis may be conducted when the last participant within each arm is followed for at least 1 cycle to evaluate safety, efficacy and PK profiles at each dose level. Following the interim analysis, additional analyses may be performed to continue to evaluate safety, efficacy and PK profiles at each dose level, prior to the final analyses. If any dose level is not enrolled due to safety concerns, it will not be included in the interim or final analyses. Additionally, if enrollment is stopped within a dose group, data may be analyzed for participants within the dose group who take at least 1 dose of any study treatment.

12.4.8.2. Arm B – belantamab mafodotin with Bor/Dex

Part 1

During dose escalation, no formal interim analysis will be performed. Data will be reviewed through the data visualization tool to inform dose escalation decisions. The mTPI design will be utilized to guide dose escalation/de-escalation decisions. More details of the dose escalation procedure are described in Section 6.1.2.

Part 2

Continuous monitoring will be conducted for Part 2 starting from when 5 participants are dosed at each dose level within each arm. The observed number of participants permanently discontinuing study treatment within the first two cycles due to AE related to belantamab mafodotin will be compared against the safety stopping rule in Table 31. Enrollment may stop if the safety stopping rule is met based on totality of safety data. For example, if 4 or more out of 5 participants permanently discontinued study treatment within the first 2 cycles due to AE related to belantamab mafodotin, enrollment may stop after review of all safety data; otherwise enrollment will continue. Operating characteristics for the stopping rule are provided in Appendix 11.

Table 31 Safety Stopping Rules for Arm B Part 2

Number of dosed participants	Stop if number of participants discontinuing study treatment within the first two cycles due to AE related to belantamab mafodotin is larger or equal to this this number	Observed rate
5-8	4	0.5-0.8
9-12	5	0.42-0.56

An interim analysis may be conducted when the last participant within each arm is followed for at least 1 cycle to evaluate safety, efficacy and PK profiles at each dose level. Following the interim analysis, additional analyses may be performed to continue to evaluate safety, efficacy and PK profiles at each dose level, prior to the final analyses. If any dose level is not enrolled due to safety concerns, it will not be included in the interim or final analyses. Additionally, if enrollment is stopped within a dose group, data may be analyzed for participants within the dose group who take at least 1 dose of any study treatment.

12.4.9. Final Analysis

Final analysis of the data captured in Part 1 and Part 2 for both Arm A and Arm B will be undertaken following 12 months post LSFD. (Section 6.3). Within each arm, data from the two parts may be combined for some analyses at the final analysis, as appropriate.

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14. APPENDICES

14.1. Appendix 1: Abbreviations and Trademarks

14.1.1. Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA
REVLIMID
VELCADE

14.1.2. Abbreviations and Acronyms

Acronym	Definition
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
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
BCMA	B-cell maturation antigen
BCVA	Best-corrected visual acuity
BIB	Bioanalysis, immunogenicity and biomarkers
BID	Twice daily
BOR	Bortezomib
BM	Bone marrow
BMI	Body mass index
BSA	Body surface area
BW	Body weight
C1D1	Cycle 1 Day 1
CBC	Complete blood count
CCI [redacted]	
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
Cmax	Maximum plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Response
CRF	Case Report Form
CRP	C-reactive protein
CCI [redacted]	
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events

Acronym	Definition
CV	Cardiovascular
DCO	Data cut-off
Dex	Dexamethasone
DILI	Drug-Induced Liver Injury
DLT	Dose-limiting toxicities
[redacted]	
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
EOI	End of infusion
EOS	End of study
EOT	End of Treatment
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
GVHD	Graft-versus-host disease
GSK	GlaxoSmithKline
HbsAg	hepatitis B surface antigen
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormone replacement therapy
HSCT	Hematopoietic stem cell transplant
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
IHC	Immunohistochemistry
IMID	Immunomodulatory drugs
IMP	Investigational Medicinal Product
IMWG	International Myeloma Working Group
INR	International normalization ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
LDH	Lactate dehydrogenase
LEN	Lenalidomide
LLN	Lower limit of normal
LSFD	Last subject first dose
LSFV	Last subject first visit
LVEF	Left ventricular ejection fraction
MDRD	Modified Diet in Renal Disease

Acronym	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MM	Multiple myeloma
MMAF	Monomethyl auristatin-F
MoA	Mechanism of action
MR	Minimal Response
CCI [redacted]	
MSDS	Material Safety Data Sheet
MTD	Maximum tolerated dose
mTPI	modified Toxicity Probability Interval
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NOS	Not otherwise specified
NYHA	New York Heart Association
ORR	Overall Response Rate
CCI [redacted]	
OSDI	Ocular Surface Disease Index
PACT	Post analysis continued treatment
PCR	Polymerase chain reaction
PD	Progressive Disease
PE	Pulmonary embolism
PET	Positron Emission Tomography
CCI [redacted]	
PI	Proteasome inhibitors
PK	Pharmacokinetic(s)
PO	Per os (oral)
PR	Partial Response
PRO	Patient-Reported Outcome
PRES	Posterior Reversible Encephalopathy Syndrome
QD	Once daily
QID	Four times daily
QoL	Quality of life
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RP2D	Recommended Phase 2 dose
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
RRMM	Relapsed/Refractory Multiple Myeloma
SAE	Serious adverse event
SC	Subcutaneous
sCR	stringent Complete Response
SCT	Stem cell transplant
SD	Standard deviation of the mean
S/D	Step-down dosing
SoA	Schedule of Activities
SoC	Standard of Care
SOI	Start of infusion
SPEP	Serum Protein Electrophoresis
SPM	Second Primary Malignancies
SRM	Study Reference Manual

Acronym	Definition
t1/2	Serum half-life
TLS	Tumor lysis syndrome
tmax	Time to maximum plasma concentration
TNF	Tumor necrosis factor
[redacted]	[redacted]
TTP	Time to Disease Progression
[redacted]	[redacted]
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
VGPR	Very good partial response
VZIG	Varicella zoster immune globulin
WBC	White blood cell
WFI	Water for injection
WOCBP	Woman of child-bearing potential

14.2. Appendix 2: Study Governance Considerations and Informed Consent Process

Regulatory and Ethical Considerations

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

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.

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.
- Participants who are rescreened are required to sign a new ICF.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

Data Protection

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

Committees Structure

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.

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the CSR. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final 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.

Source Documents

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

Study and Site Closure

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

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

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

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

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

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655, [Oken, 1982]

14.4. Appendix 4: 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, S_{Cr} is serum creatinine expressed in mg/dL, and age is expressed in years.

The link below will auto-calculate the creatinine clearance:

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

14.5. Appendix 5: 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 one 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.

The Criteria Committee of the New York Heart Association (NYHA). 1994. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, Mass: Little, Brown & Co.; 1994:253-256.

14.6. Appendix 6: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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 it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses 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 fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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 fulfills 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.

A SAE is defined as any untoward medical occurrence that, at any dose:
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 Appendix 9, Section 14.9 for liver chemistry follow-up procedures.

Definition of Cardiovascular Events

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

Recording AE and SAE

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported (aside from corneal events) 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 noninvasive 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.

Corneal events associated with belantamab mafodotin will be graded according to the grading scale provide in Appendix 8.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very**

Assessment of Causality
important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK**.** • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.
Follow-up of AE and SAE
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to GSK within 24 h of receipt of the information.

Reporting of SAE to GSK

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

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

14.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study 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 one 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-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

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

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

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

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

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on the female partner of a male study participant who becomes pregnant while participating in this study. 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 h 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.
- Information will be recorded on the appropriate form and submitted to GSK within 24 h of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 6, Section 14.6. 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.

14.8. Appendix 8: Corneal Event Grading and Mitigation Strategy

Corneal events should be graded according to the guidelines provided in Table 33.

In order to minimize the corneal findings, prophylactic preservative-free artificial tears should be administered in each eye at least 4 to 8 times daily, beginning on C1D1 until the End of Treatment (EOT). Allow at least 5-10 min between administration of artificial tears and steroid eye drops (if administered). In the event of ocular symptoms (i.e., dry eyes), the use of artificial tears may be increased up to every 2 h as needed.

While not yet clinically demonstrated, it is theoretically possible that the application of a cooling eye mask during belantamab mafodotin administration, and in the first few hours after infusion may subsequently decrease ocular side effects. On the day of infusion, the following may be considered:

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

Contact lenses are prohibited while the participant is on study treatment.

The GSK grading scale for corneal events was developed to capture both corneal findings and visual acuity changes in participants treated with belantamab mafodotin and to provide recommendations for dosing decisions. This GSK scale is different from CTCAE criteria for eye disorders which relies mainly on participant's symptoms and participant's ability to attend to 'activities of daily living' and which (CTCAE) is to be used for grading of the adverse events.

A summary of prophylactic interventions for corneal events associated with belantamab mafodotin is provided in Table 32. In addition to reporting eye disorders using CTCAE 4.03 criteria, corneal events associated with belantamab mafodotin must also be graded according to the guidelines provided in Table 33. Additional guidance on visual acuity changes is provided in Table 34.

In the FTIH study (BMA117159), eye examinations showed that most participants continued to receive belantamab mafodotin dose when either a GSK Scale Grade 2 corneal examination finding ***or*** a 2-3-line decrease in visual acuity was reported. With this dosing paradigm, participants generally showed improvement in both corneal examination findings and visual acuity over time. Therefore, the dosing guideline has been adjusted to allow dosing with belantamab mafodotin if only one component on the GSK corneal event scale indicates Grade 2 corneal event.

Table 32 Prophylactic Measures for Corneal Events 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 5-10 min between administration of artificial tears and steroid eye drops
Cooling eye mask	May apply cooling eye mask to both eyes for approximately 1 h or as much as tolerated	During belantamab mafodotin infusion administration in the first hour for up to 4 h, as tolerated

a. Dose modifications and treatment for ocular toxicities are discussed in Section 8.2.1

Table 33 Grading Scale for Corneal Events Associated with Belantamab Mafodotin

Measure	Grade 1 per GSK Scale	Grade 2 per GSK Scale	Grade 3 per GSK Scale	Grade 4 per GSK Scale
Ophthalmic exam findings	Mild superficial keratopathy (change from baseline)	Moderate punctate keratopathy and/or Mild/patchy microcysts and/or Mild/patchy Epithelial or stromal edema and/or Sub-epithelial haze (peripheral) and/or Active stromal opacity (peripheral)	Severe punctate keratopathy and/or Diffuse microcysts and/or Diffuse Epithelial or stromal edema and/or Sub-epithelial haze (central) and/or Active stromal opacity (central)	Corneal ulcer
Visual Acuity [b, c]	Change of 1 line from baseline	Change of 2-3 lines from baseline and not worse than 20/200[b]	Change of more than 3 lines from baseline and not worse than 20/200[b]	Worse than Vision 20/200[b]

Note: Standardized guidance for grading ophthalmic findings associated with belantamab mafodotin is provided to sites in the ophthalmology SRM. Ophthalmic exam findings as described must be present in a participant to utilize GSK's scale.

a. Grading is based on most severe finding. If eyes differ in severity, GSK grading should be based on the more severe eye.
b. Change in visual acuity should be due to corneal events. If change in vision is for reason other than corneal events, ophthalmic exam findings will drive event grading.
c. See Table 34 for additional guidance on how to grade changes in visual acuity depending on baseline vision. If a participant has a baseline visual acuity of 20/200 or worse in an eye, ophthalmic exam findings will drive event grading.

Table 34 Guidance for Assessing Changes in Visual Acuity for GSK Grading Scale

Baseline Vision (best corrected)	Grade 1 per GSK scale	Grade 2 per GSK scale	Grade 3 per GSK scale	Grade 4 per GSK scale
20/15 to 20/16 From -0.12 to -0.1	20/20 0	20/25 to 20/30 or 20/32 0.1 to 0.18 or 0.2	20/40 to 20/200 0.3 to 1.0	Worse than 20/200 >1.0
20/20 0	20/25 0.1	20/30 to 20/40 0.18 to 0.3	20/50 to 20/200 0.4 to 1.0	Worse than 20/200 >1.0
20/25 0.1	20/30 to 20/32 0.18 to 0.2	20/40 to 20/50 0.3 to 0.4	20/60 to 20/200 0.48 to 1.0	Worse than 20/200 >1.0
20/30 to 20/32 0.18 to 0.2	20/40 0.3	20/50 to 20/60 or 20/63 0.4 to 0.48 or 0.5	20/70 to 20/200 0.56 to 1.0	Worse than 20/200 >1.0
20/40 0.3	20/50 0.4	20/60 to 20/70 or 20/80 0.48 to 0.56 or 0.6	20/100 to 20/200 0.7 to 1.0	Worse than 20/200 >1.0
20/50 0.4	20/60 to 20/63 0.48 to 0.5	20/70 to 20/100 0.56 to 0.7	20/125 to 20/200 0.8 to 1.0	Worse than 20/200 >1.0
20/60 to 20/63 0.48 to 0.5	20/70 to 20/80 0.56 to 0.6	20/100 to 20/125 0.7 to 0.8	20/150 to 20/200 0.88 to 1.0	Worse than 20/200 >1.0
20/70 to 20/80 0.56 to 0.6	20/100 0.7	20/125 to 20/150 or 20/1600.8 to 0.88 or 0.9	20/200 1.0	Worse than 20/200 >1.0
20/100 0.7	20/125 0.8	20/150 to 20/160 or 20/2000.88 to 0.9 or 1.0	N/A	Worse than 20/200 >1.0
20/125 0.8	20/150 to 20/160 0.88 to 0.9	20/200 1.0	N/A	Worse than 20/200 >1.0
20/150 to 20/160 0.88 to 0.9	20/200 1.0	N/A	N/A	Worse than 20/200 >1.0
Worse than 20/160 >/= 1.0	N/A	N/A	N/A	Any further reduction from baseline is considered Grade 4

Note: *The Visual acuity is presented as Snellen equivalent and logMAR value.*

14.9. Appendix 9: Liver Safety: Required Actions, Follow-up Assessments, and Study Treatment Rechallenge Guidelines

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

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

Required Actions and Follow-up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 h** • Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments as described in the Follow Up Assessment column • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) **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 h** • Monitor participants twice 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 transaminase values show downward trend • Blood sample for pharmacokinetic (PK) analysis of belantamab mafodotin and a blood sample for [redacted], obtained within 70 days after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH), gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin. • Fractionate bilirubin, if total bilirubin ≥2 x ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications

• A specialist or hepatology consultation is recommended **<u>For All other criteria (</u>bilirubin <2xULN and INR ≤1.5<u>):</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline **<u>RESTART/RECHALLENGE</u>** • **Restart/rechallenge is allowed per protocol but do not resume study intervention unless GSK approval is granted;** If restart/rechallenge is **not granted**, permanently discontinue study intervention and continue participant in the study for any protocol specified follow up assessments. Refer to Restart/Rechallenge guidelines in Appendix 9 Section 14.9	• 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**<u>::</u>** • 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 computerized tomography) and /or liver biopsy to evaluate liver disease: complete Liver Imaging and/or Liver Biopsy forms. • Liver biopsy may be considered and discussed with local specialist if available, for instance: o In patients when serology raises the possibility of autoimmune hepatitis (AIH) o In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In patients with acute or chronic atypical presentation: • If liver biopsy conducted complete liver biopsy form.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥3 x ULN **and** bilirubin ≥2 x ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3 x ULN **and** total bilirubin ≥2 x ULN (>35% direct bilirubin) or ALT ≥3 x ULN **and** INR >1.5, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE**; the INR threshold value 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. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
5. Record the date/time of the PK/CCI blood sample draw and the date/time of the last dose of study treatment 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/CCI sample cannot be collected in the time period indicated above, do not obtain a PK/CCI sample. Instructions for sample handling and shipping are in the SRM.

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

14.9.1. Liver Safety Drug Restart or Re-Challenge Guidelines

A participant who met liver chemistry stopping criteria cannot resume study treatment 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, and
- Separate ICF for study treatment restart/rechallenge is signed by the participant and the participant is informed of any associated risks.

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

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

Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies** [Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered 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)

- 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)

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

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

- The Principal Investigator (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 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 10.2.4 and Appendix 6 (Section 14.6).

14.9.1.2. 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:

- Principle 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 principle 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 treatment is approved by GSK in writing:

- The participant must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study file.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK for 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 the 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 10.2.4.

14.9.1.3. 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.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA et al. 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 et al. 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;43:2363–2369

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

14.10. Appendix 10: Genetics

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.

CCI

CCI

[redacted]

14.10.2. Study Population

Any participant who is enrolled in the study can participate in genetic research.

Participant participation in the genetic research is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the participant would otherwise be entitled.

14.10.3. Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no a priori hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 mL blood sample will be taken for Deoxyribonucleic acid (DNA) extraction.

A blood sample is collected at the baseline visit, after the participant has been provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study-specific number used to label other samples and data in the study. This number can be traced or linked back to the participant by the Investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last participant completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from

the study for the purpose stated in this protocol and in the ICF. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Participants can request their sample to be destroyed at any time.

14.10.4. Informed Consent

Participants who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

14.10.5. Participant Withdrawal from Study

If a participant who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to Follow-up, the participant will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a participant withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a participant withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

14.10.6. Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the participant does not meet the entry criteria for participation in the study, then the investigator should instruct the participant that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

14.10.7. Provision of Study Results and Confidentiality of Participant's Genetic Data

GSK may summarize the genetic research results in the CSR, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the participant, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the participant's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

14.10.8. Germline Control

US Food and Drug Administration states that an in vitro companion diagnostic device (IVD) could be essential for the safe and effective use of a corresponding therapeutic product to:

- Identify participants who are most likely to benefit from a particular therapeutic product;
- Identify participants likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product;
- Monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness;
- Identify participants in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population.

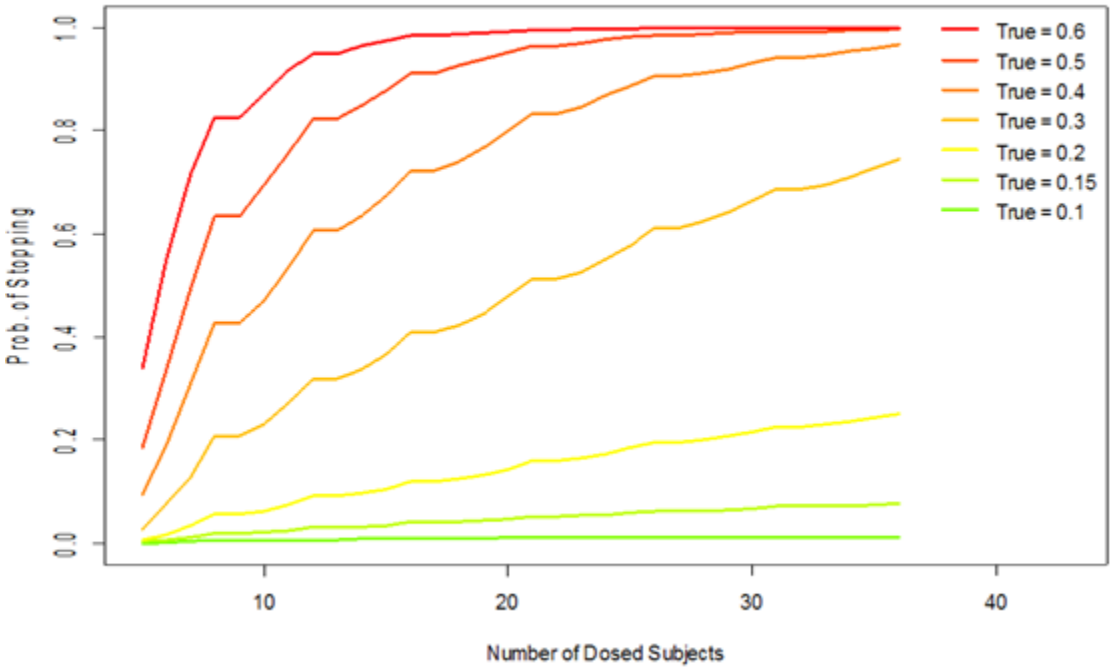
Global regulatory requirements for IVD companion diagnostic tests are evolving. If a DNA-based IVD companion diagnostic device might be needed to identify participants who are appropriate for the GSK medicinal product(s) under investigation in this protocol, then GSK should collect and retain DNA samples from participants who carry the genetic variant of interest as well as DNA samples from participants who do not carry the genetic variants of interest to validate the performance of the companion diagnostic. . Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis. Any IVD companion diagnostic research objectives should be described in participant ICFs.

14.10.9. References

Chen H, Yu KD, Xu GZ. Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis. PloS ONE. 2012;7:e42464

Gorin MB. Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics. Mol. Asp. Med. 2012;33:467-486.

14.11. Appendix 11: Operating Characteristics of Safety Stopping Rule for Expansion Cohort



14.12. Appendix 12: Eye care specialist's qualifications and requirements

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

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

14.13. Appendix 13: Alternative Health Care Approaches

Home Healthcare (General Visit)

Where applicable country, 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 practitioner, physician's assistant). Please refer to SRM for additional details.

Activities that may be done as part of a home healthcare visit will follow the schedule provided in the SoA (Section 3) and could 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
  - Biomarker, immunogenicity and genetic assessments
  - Pregnancy tests
  - 12-Lead ECG
  - Other assessments as clinically indicated

    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 treatments (subcutaneous delivery only, no i.v. or infusions).
- Administration of 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 Informed Consent Form if required by local law or regulations. 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 alternative location. Activities that may be done as part of remote eye exam must follow the schedule provided in the SoA (Section 3) and include (refer to SRM for additional details):

- Visual Acuity
- Slit lamp exam
- Ophthalmoscopy
- Other assessments as clinically indicated

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 if required 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, site staff or other qualified medical professionals and may be done in conjunction with visits from Home Healthcare personnel (see above). Refer to SRM for additional details.

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, site staff 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 if applicable and/or approve of this change in approach and the process documented in study files.

14.14. Appendix 14: Protocol Amendment History

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

14.14.1. Protocol Amendment 3 (13-Jul-2020)

Amendment 3: 13-JUL-2020

Where this Protocol Amendment applies:

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

Overall rationale for Amendment 3:

Protocol Amendment 3 includes updated duration of contraception for female participants to align with this guidance of child bearing potential based on review of guidelines on aneugens.

Additionally, upon review of safety data from Study 205678 (DREAMM-2), it was determined that ocular changes associated with belantamab mafodotin treatment were mostly limited to the corneal epithelium [GSK Document Number 2013N175128 V08, 2020]. Therefore, further collection of ocular safety data in belantamab mafodotin studies will be focused on corneal changes. Review of this data also indicated that the use of corticosteroid eye drops was ineffective in preventing or mitigating changes to the corneal epithelium associated with belantamab mafodotin [Lonial, 2020]. The discontinuation of corticosteroid eye drops as prophylaxis was communicated to the sites via a Protocol clarification letter dated 21 October 2019. Protocol Amendment 3 includes changes to ophthalmologic assessments based on these findings.

Preclinical data from xenograft mouse models and emerging clinical data from Arm A in Amendment 2 suggests greater activity of belantamab mafodotin in combination with lenalidomide. Given this, doses higher than 2.5 mg/kg of belantamab mafodotin will not be evaluated in combination with lenalidomide/ dexamethasone in Arm A in Amendment 3.

Furthermore, in order to reduce increased exposure of belantamab mafodotin over time and potentially improve the benefit/risk for participants, reduced dose levels and extended dosing schedules for belantamab mafodotin will be evaluated in Amendment 3.

- Arm A (Belantamab mafodotin + Len/Dex; 28-day cycle): As per above, in Arm A Part 2, an alternate dosing schedule of STRETCH (Q8W) dosing may be explored for the 1.9 mg/kg dose level if emerging data (from either this study or across the program) suggests that this schedule may further optimize the tolerability or offers an improved benefit/risk profile. To enable this, a potential extended dosing schedule has been introduced via this amendment, where belantamab mafodotin at 1.9 mg/kg will be administered once every 8 weeks (STRETCH) and will be evaluated dependent on emerging data. The cycle

duration will remain 28 days/4 weeks. Up to 12 participants will be enrolled in this new cohort.

- Arm B (Belantamab mafodotin + Bor/Dex; 21-day cycle): Similarly, in Arm B Part 2, 2 new dosing schedules (STRETCH and Step-Down [S/D] STRETCH) and one new (reduced) dose level (dose level -1 at 1.9 mg/kg) of belantamab mafodotin has been added. In the extended dosing schedule, belantamab mafodotin will be administered every 6 weeks (STRETCH). The cycle duration will remain 21 days/3 weeks. Additionally, a S/D STRETCH schedule with a first dose of 2.5mg/kg dose at C1D1 followed by subsequent planned doses of 1.9 mg/kg dose starting on Day 1 of alternate 21-day/3-week cycles C3 onwards (C3, C5, C7, and so on) will be evaluated. Furthermore, as target engagement and responses have been shown to occur at 1.9 mg/kg (and lower dose levels) in the first-time in human (FTIH) study BMA117159, belantamab mafodotin dose at a reduced dose level of 1.9 mg/kg in combination with SoC will be additionally explored in Arm B Part 2. To evaluate these additional dose levels and schedules, 4 new dosing cohorts (2.5 mg/kg STRETCH, 2.5 → 1.9 mg/kg S/D STRETCH, 1.9 mg/kg SINGLE (Q3W dosing) and 1.9 mg/kg STRETCH) are being added. Up to 12 participants will be enrolled in each of these 4 new cohorts.

Protocol Amendment 3 includes the following:

Section # and Name	Description of Change	Brief Rationale
Belantamab Mafodotin Program Level Changes		
Section 1, Treatment Groups and Treatment Duration, Section 8.1.6.1 and Section 8.1.6.2	Added “or end of study” to Arm A and Arm B text on continuing treatment until: “progressive disease (PD), intolerable AEs, consent withdrawal, or death”	To make text consistent with Section 6.3
Section 3, Table 4 and Table 10	Removed requirement for fasting glucose test at Screening. Fasting glucose and HbA1c to be done as clinically indicated and at End of Treatment	Glucose included in chemistry panel and fasting glucose/HbA1c to be assessed as clinically indicated on-treatment.
Section 3, Table 4 – Table 8, Table 10, Section 10.6.10, and Table 27	Removed troponin and B-type natriuretic peptide (BNP) testing.	Based on clinical experience to date with belantamab mafodotin, and as reviewed by the GSK cardiac safety panel, it was agreed that troponin and B-type natriuretic peptide (BNP) was not required unless clinically indicated
Section 3, Table 4	Acceptable BM aspirate/biopsy changed from within 21 to within 28 days prior to first dose.	Broaden window to avoid excessive procedures.
Section 3, Table 5 - Table 8	ECG footnote: timing for obtaining triplicate ECGs updated	Broaden collection period for ease of use in clinic

Section # and Name	Description of Change	Brief Rationale
Section 3, Table 5 – Table 8	PK blood sampling footnote: timing for obtaining EOI PK samples increased, language pertaining to collection following dosage delay clarified.	Clarification; Broaden collection period for ease of use in clinic
Section 3, Table 5 – Table 8, Table 10, Section 10.6.7	Ocular exams: timing for on-study exams changed from every 4 weeks prior to Day 1 dosing, to prior to belantamab mafodotin for the first 6 doses. Also changes to further exam schedule based on presence/absence of new corneal events.	Ocular substudy safety data from Study 205678 data indicated that participant symptoms should determine the need for ophthalmology exams. Additional collection of digital photography is not needed based on sufficient collection of ocular photography in Study 205678.
Section 3, Table 5 – Table 8; Section 4.3.1; Section 14.8	Corneal events management: removed text on prophylaxis with steroid eye drops.	Steroid eye drops not beneficial in preventing or mitigating corneal events associated with belantamab mafodotin, based on findings from ocular substudy from Study 205678.
Section 3, Table 5 – Table 8, and Section 10.6.11	Genetic sample: added text permitting recollection of genetic sample as necessary.	Enables genetic testing to proceed if original sample is damaged, unable to be processed, or if insufficient DNA was extracted.
Synopsis, Section 3 Table 10, Section 4.3.1, Section 7.1, Section 7.3, Section 10.2.8 and Appendix 7	Duration of contraception after last dose of belantamab mafodotin changed to 6 months for males and 4 months for females	Based on review of global guidelines on aneugens.
Synopsis, Section 4.2.3	Updated description of belantamab mafodotin ADC and MoA	Revised program language
Section 4.2.4	Updated clinical experience language for studies BMA117159 and 205678	Updated relevant clinical data available.
Section 4.3	Updated benefit/risk assessment	Incorporation of revised program safety language
Synopsis, Section 7.1, Table 17	Left ventricular ejection Fraction (LVEF) by ECHO value for adequate organ system function changed from 45% to 40%	Based on clinical experience to date with belantamab mafodotin, and as reviewed by the GSK cardiac safety panel, it was agreed that a reduction in LVEF was acceptable for participants enrolling in the study.
Synopsis, Section 7.2, Section 9.2.3	Removed exclusionary ECG QTcF parameter	Aligned with Cardiac Safety Panel recommendations (Dec 2019)

Section # and Name	Description of Change	Brief Rationale
Synopsis, Section 7.3	Lifestyle Restrictions • Clarified language regarding use of bandage contact lenses and when contact lenses may be restarted following end of study treatment • Moved the sentence about administration of live/live-attenuated vaccine to prohibited concomitant medication.	Program clarifications and revisions The text was moved to a more appropriate section
Section 8.2.1, Table 22	Removed the requirement for prophylactic corticosteroid eyedrops	Based on ocular substudy safety data from Study 205678 data
Section 8.2.1, Table 23	Inclusion of dose modification guidelines for cutaneous reactions and hypersensitivity associated with lenalidomide.	Aligned with updated approved lenalidomide labelling.
Section 8.7.2	Added administration of live/live-attenuated vaccine text. See the change for Section 7.3 above. Added restriction on use of live/attenuated virus vaccines for at least 70 days after the last dose of belantamab mafodotin	To enhance patients' safety, the period for prohibited use of live/live-attenuated vaccines has been extended
Section 9.2.6	Addition of reaction management language for belantamab mafodotin infusion reactions	Clarification
Section 10.3	Updates to belantamab mafodotin, lenalidomide and bortezomib overdose language; addition of dexamethasone overdose section	Clarification of overdose information
Section 10.6.7	Updated specifications for ophthalmic examinations	Revised safety language and adjustments for added cohorts
Study Design Changes		
Section 3, Section 10.2.1, Section 12.4.2.2 and Section 14.9	Adverse event assessment period increased from 45 days to at least 70 days after the last dose	Aligned with recent updated information regarding belantamab mafodotin half-life
Synopsis, Section 7.1	Removal of IMWG reference pertaining to disease progression in Inclusion Criteria #6	Due to varied global standards, wording in the listed criterion has been adjusted to introduce flexibility based on global differences
Section 3, Table 5 and Table 6	Serum pregnancy test collection window expanded to 10-14 days	To provide greater flexibility to sites in determining pregnancy status

Section # and Name	Description of Change	Brief Rationale
Section 3, Table 5 – Table 8	Criteria for collection of BM aspirate for CCI and CCI updated to achieving VGPR or better	Criteria for collection of BM aspirate for CCI and CCI updated to provide a more detailed disease response profile
CCI		
Synopsis, Table 1, Table 5, Figure 1, Section 6.1, Section 6.2, Section 6.5.2, Table 18, Section 8.1.1, Section 8.2.1, Section 12.2.1	Addition of a potential new treatment cohort with introduction of Q8W (STRETCH) schedule for Arm A (belantamab mafodotin with Len/Dex)	Evaluate other dosing regimens for optimal treatment
Synopsis, Table 2, Table 9, Figure 2, Section 6.1, Section 6.2, Section 6.5.2, Table 18, Section 8.1.2.1, Section 8.1.3, Section 8.2.1, Section 12.1.2, Section 12.2.2	Addition of new treatment cohorts and introduction of Q6W (STRETCH) and 2.5 → 1.9 mg/kg Step-Down (S/D) schedules for Arm B (belantamab mafodotin with Bor/Dex)	Evaluate other dosing regimens for optimal treatment
Section 6.1.1, Section 6.1.2, Section 6.5.1, Table 13, Section 8.1.1.1	SINGLE and SPLIT doses at 3.4 mg/kg removed from Arm A; Decreased number of dose levels for exploration and defined maximum dose as 2.5 mg/kg for belantamab mafodotin	3.4 mg/kg dose is not currently being explored
Synopsis, Section 6.2, Section 6.3, Section 12.2	Revised numbers of participants	Adjusted numbers to accommodate new dosing regimen cohorts and addition replacements for non-DLT evaluable participants
Section 6.5	Provide justification for lower dosing and different regimens for belantamab mafodotin treatment	Revised due to updated analysis of safety information
Synopsis, Section 7.1, Section 10.2.8	WOCBP and male participants in Arm B: change the restriction of contraceptive period after bortezomib	Added due to the changes in the bortezomib label
Section 7.3	The prohibition for blood donation in Arm A was changed from 120 days to 28 days	Alignment with lenalidomide label
Section 8.2.1, Table 20, Table 21	Removed requirement that dose modifications be “after Cycle 1” from Part 2.	To provide greater flexibility to sites in managing hematological toxicity

Section # and Name	Description of Change	Brief Rationale
Section 8.2.1, Section 8.6, Appendix 13, SoA Table 4 – Table 10	Added telemedicine and collection of data/follow-up by telephone	Covid-19-related changes
CCI [redacted]		
Section 10.9	Revised text for immunogenicity assessments	Update and clarification
Section 12.4.3.1	Pharmacokinetic analysis methods updated from population PK approach to standard noncompartmental analysis, data permitting.	Pharmacokinetic analysis methods and population PK approach updated to align with program level guidance
Section 12.4.4	Updated text on PK/PD assessments	Revised to match plans for analysis
Section 12.4.8.1.2 and Section 12.4.8.2.2	Interim analysis wording modified	Added additional details around planned interim analysis
Section 12.4.9	Final Analysis section added	Clarification
Section 12.4.5.3	Revised text on biomarkers analyses	Update and clarfication
Section 14.9	Actions and follow-up assessments modified in liver stopping events table	Clarification
Section 14.9.1.2	Addition of statement regarding liver stopping event due to hepatitis	Clarification of protocol in the event of alcohol-related hepatitis
Administrative Changes		
Title Page	Sponsor signatory changed	
Synopsis	Corrected dose reduction guideline for dexamethasone from ≥75 years of age to >75 years of age	Typographical error
Table 1 and Table 2; Figure 5, Figure 6, Figure 7; Table 18	Tables and figures to specify dosing regimens	Added to clarify cohort differences and schedules
Synopsis; Section 2, Section 6.1.2.3, Section 8.1.1.1,	Clarified dose descriptions administered on Day 1 of SINGLE dose and on Day 1 and Day 8 of SPLIT dose regimens.	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 8.1.2.1 and Table 18		
Synopsis; Section 3, Section 7.3, Section 8.2.1, Section 9.2.5, Section 10.6.7	Replaced reference to ophthalmologist and optometrist with "qualified eye care specialist"	To clarify the definition of an eye care professional
Section 6.5	Description of new dosing schedules in Arm B	Rationale added for explanation and justification
Synopsis; Section 7.1	Clarification of inclusion criteria contraception language pertaining to WOCBP in Arm A vs Arm B.	Clarification
Section 3, Table 4	Clarification to Pregnancy Test for WOCBP footnote regarding differences between Arm A and Arm B	Clarification
Section 3, Table 5-Table 8; Section 10.6.1	Clarification to Physical Assessment footnote that dose should be re-calculated for body weight change >10%.	Clarification
Section 3, Table 4-Table 9	CCI [redacted] testing footnote: clarification of CCI [redacted] testing requirements.	Clarification
Section 3, Table 4 – Table 8	BM aspirate footnote: clarified BM aspirate sampling	Clarification
Section 3, Table 5 – Table 8	Footnotes added to study assessments for BM aspirate, CCI [redacted] and PK blood sampling for belantamab mafodotin	Clarification
Section 3, Table 5 – Table 8	Corneal Events Management: Added "In the event of ocular symptoms (e.g., dry eyes), the use of artificial tears may be increased up to every 2 hours as needed" to footnote.	To align with existing language in Appendix 8
Section 3, Table 5 and Table 6	Updated Footnote #9: Day 21 corrected to Day 22	To align with standard of care (SoC; dexamethasone) dosing schedule
Section 3, Table 5 and Table 6	Pharmacokinetic sampling for belantamab mafodotin Dose 2: wording change for delay of Dose 2	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 3, Table 7 and Table 8	Administration of dexamethasone: footnote updated to remove "weekly" from "reduced to 10 mg weekly"	To align with SoC dosing schedule.
Section 3, Table 8	Hematology and clinical chemistry footnote: removed "to be performed every 3 weeks ±3 days" and corrected "72 h prior" to "24 h prior" EORTC QLQ-30 and QLQ-MY20 collected in Part 2 only changed to Part 1 and Part 2	Corrections
Section 3, Table 10	Addition of BM sampling considerations to BM aspirate/biopsy for Disease Assessment	
Section 4.3.1, Table 11	Updated Data summary/risk rationale and mitigation strategy items throughout table Added Embryo-fetal toxicity section to overlapping toxicities section	Updating to include recent information
Section 4.3.2	Added discussion of benefits from study 205678 to benefit assessment	Updating to include recent information
Section 4.3.3	Updated benefit/risk conclusions to include preliminary safety data from Arm B	Updating to include recent information
Section 6.3	Language regarding study completion, study analyses and end of study updated	Clarification
Section 8.1.1.2	Language throughout section streamlined for clarity	Clarification
Section 8.1.1.2 and Section 8.1.2.2, Section 8.1.4.4	For dexamethasone, added text referring to the product label and removed DECADRON reference.	Clarification
Section 8.1.3.2 and Section 8.1.4.3	Removed references to REVLIMID and VELCADE-specific product information, replaced with referral to local prescribing information	Broadened references for regional variance
Section 8.2.1, Table 21	Added missing footnote	Correction/clarification

Section # and Name	Description of Change	Brief Rationale
Section 8.2.1, Table 22	Added directions for use of cooling eye masks to reflect information in SOA	Clarification to align with SOA
Section 8.2.1, Table 23	Removed instruction to not dose below 5 mg daily for Days 1 to 21 of 28-day cycle.	Correction/clarification
Section 10.6.8, Secction 10.11	Updated text for PRO measures and HR-QoL assessments	Revised instructions and conduct
Section 10.7.1	Arm A, receiving belantamab mafodotin: Q3W corrected to Q4W	Correction to align with Arm A cycle length
Section 13	Reference list updated as necessary	Correction
Section 14.8, Table 34	Corrections to values for changes in visual acuity	Correction/clarification
Section 14.12	Appendix added to define eye care specialist qualifications and requirements	Definition of eye care specialist required due to language changes throughout document.
Section 14.13	Added appendix on telemedicine procedures	Added to facilitate adequate care and data collection
Editorial/Document Formatting Changes		
Whole document	Minor editorial and document formatting revisions	Minor, therefore have not been summarized
Whole document	GSK2857916, GSK'916 replaced with belantamab mafodotin	Use generic name
Whole document	Abbreviate the Step-Down regimen as S/D; Abbreviate Q6W regimen as 'STRETCH'	Ease of reference for dose regimen concepts

14.14.2. Protocol Amendment 2 (26-APR-2019) from the Final Version (28-FEB-2018)

Amendment 2 26-APR-2019

Where this Protocol Amendment Applies

Protocol Amendment 2 applies to all countries and sites.

Overall Rationale for the Amendment:

i) In December 2018, GSK paused enrolment in the belantamab mafodotin in combination with lenalidomide/dexamethasone (Arm A) of study 207497 due to two similar events of pneumonia and sepsis in the setting of febrile neutropenia resulting in

death in the first two patients enrolled in Arm A. The pause in enrolment in Arm A occurred per protocol, to assess the dose exploration in this treatment arm. GSK used this as an opportunity to review the data and conduct an evaluation to assess factors that led to these neutropenic/infection events while amending the protocol. Protocol for study 207497 is being amended to: a) to change ECOG eligibility criteria in Arm A from 0-2 to 0-1, b) to include additional guidance for management of neutropenia / prophylaxis of infections to be implemented across the study on resuming Arm A and c) more stringent hematological monitoring for both Arm A and Arm B.

ii) Regulatory feedback encouraged generation of additional data (safety, PK, PD, clinical activity) at lower dose levels of belantamab mafodotin to support dose selection for future Phase 3 studies with belantamab mafodotin in combination with standard of care (SoC) agents. Administration of belantamab mafodotin divided as two equal administrations a week apart will also be evaluated to see if this dosing schedule would result in improvement of benefit/risk due to ~25% reduction in the maximum concentration while maintaining similar exposure over a cycle compared to the full administration on Day 1.

iii) Protocol Amendment 2 also incorporates the Protocol Clarification letter (dated 28-Feb-2019) previously issued to study sites, that provided updated guidance on grading corneal events and dosing participants with belantamab mafodotin.

iv) Administrative corrections and general program updates are also included in Amendment 2.

Protocol Amendment 2 includes the following:

Section # and Name	Description of Change	Brief Rationale
Revised Study Design for 207497		
Section 2 Schedule of Activities Tables	Added SoA Tables 3 and 5 pertaining to the belantamab mafodotin SPLIT dosing cohorts based on the amendment 02-edited existing SoA tables (renumbered as Table 2 and Table 4, respectively). Additional PK timepoints were included for SPLIT dosing.	To align with revised study design regarding SPLIT dosing
Section 4 Objectives and Endpoints	Table 8: Combined previous Table 6 and Table 7 into a single table	To align with revised study design
Section 5.1 Overall Design	Revised study design	Based on emerging data
Section 5.1.1 Arm A	Figure 2: Replaced Figure with Study Design for Arm A Updated section to specifically refer	To clarify and to align with revised study design

Section # and Name	Description of Change	Brief Rationale
	to Arm A Figure 3: Updated dose-finding criteria pertaining to Arm A and changed number of figure from 4 to 3	 To align with revised study design and number of participants in the protocol
	Table 10: Added table for operating characteristics of the dose escalation rules for Arm A	To align with revised study design
Section 5.1.2 Arm B	Added section specific to Arm B Figure 4: Replaced Figure with Study Design for Arm B and updated figure number from 3 to 4	To clarify and to align with revised study design
Section 5.2 Number of Participants	Updated number of participants	To align with revised study design
Section 5.4 Scientific Rationale for Study Design	Edited rationale and removed reference to recommended phase 2 dose (RP2D)	To clarify the scientific rationale and to align with revised study design and strategy across the belantamab mafodotin development program
Section 5.5.1 Starting dose of belantamab mafodotin	Added language for divided administration of belantamab mafodotin (SPLIT dosing)	To align with revised study design
Section 7.1 Treatments Administered	Sections 7.1.1.1,Section 7.1.2.1 – Added guidance for SPLIT dosing schedule for belantamab mafodotin and language for potential exploration of alternate dosing schedule	To provide consistency and alignment with revised study design
Section 9.6.1 Physical Examinations	Included timeframe for the SPLIT dosing cohorts	To align with revised study design and new SoA Table 3 and Table 5 in Section 2
Section 11 Statistical Considerations	Edited section to include distinct sections for Arm A and Arm B	To align with revised study design
Section 11.1.1.2 (Arm A) and	Edited statistical hypotheses for Part	To align with revised study design

Section # and Name	Description of Change	Brief Rationale
11.1.2.2 (Arm B) Part 2	2	
Section 11.2.1.2 (Arm A) and 11.2.2.2 (Arm B) Sample size determination Part 2	Added language on sample size estimation	To clarify calculation of sample size
Section 11.3 Population for analysis	Removed definition of “all evaluable population”	To align with revised study design
Section 11.4.1 Analyses of clinical activity	Updated primary and secondary endpoints	To be consistent with changes in Section 4 - Objectives/Endpoints
Section 11.4.7 Section 11.4.7.1.1 (Arm A) and Section 11.4.7.2.1 (Arm B) Interim Analysis Part 1	Added language on analyses performed during dose escalation	To clarify based on the revised study design
Section 13 Appendices	Appendix 11– Appendix added to the protocol	To align with protocol updates
Study Specific Safety Changes		
Section 2 Schedule of Activities Tables	Table 2 & Table 4: Added requirement for ANC prior to dosing Table 2: Clarified lenalidomide administration timing in relation to belantamab mafodotin administration timing Table 2 & Table 4: Added an additional hematology sample collection on Day 15 for Cycles 1-8	Changes made following safety events and to enhance safety monitoring Information added to provide clarity and keep consistency with PK sample collection and add a safety window between administration of belantamab mafodotin and lenalidomide. Changes made to add additional safety monitoring
Section 3.3.1 Risk Assessment	Table 7: Updated table to highlight overlapping toxicities for belantamab mafodotin with SoC	To clarify risks associated with administration of belantamab mafodotin with Len/Dex and

Section # and Name	Description of Change	Brief Rationale
		Bor/Dex
	Table 7: Added language for methods of contraception in Arm A and B	Added clarification for method of contraception in accordance to the safety profile of each drug including requirements from REVLIMID REMS program.
	Table 7: Updated information on thrombocytopenia and neutropenia risks related to belantamab mafodotin and revised mitigation strategy	Updated based on data from the FTIH study BMA117159
Section 6.1 Inclusion Criteria	For Arm A, changed ECOG performance status from 2 to 1 Table 13: Increased limit for Absolute Neutrophil Count and Platelets Table 13: Removed Coagulation section and updated footnote Added language for contraception methods and female partner of male participants Added inclusion criteria for WOCBP participants assigned to treatment A	The changes were made following safety events and to enhance safety monitoring
Section 7.1 Treatments Administered	Added recommendation for time of administration of lenalidomide Added guidance for dose modification of dexamethasone	To clarify and to keep consistency with PK sample collection and add a safety window between administration of belantamab mafodotin and lenalidomide To provide guidance and align with addition of Section 7.2.2
Section 7.1.5.3 Lack of tolerability in Treatment A or B	Added language for participant who meets stopping criteria for belantamab mafodotin	To clarify follow up for participant who meets stopping criteria
Section 7.2.1 Dose Modification After Cycle 1	Table 16: • Added monitoring for Neutropenia	Updated based on emerging data

Section # and Name	Description of Change	Brief Rationale
	• Edited dose modification guidelines for thrombocytopenia to reflect the SINGLE day and SPLIT dosing schedules • Added immediate hospitalization for participants presenting with febrile neutropenia	
	• Corneal events monitoring removed and presented in a separate table (Table 17) • Added language clarifying infusion reaction symptoms Table 19: Added monitoring for hematological toxicity	To clarify recommendations for infusion reactions Updated information based on emerging data
Section 7.2.2 Dose Modification Guidelines for Dexamethasone	Added section, Table 20 and Table 21	To provide guidance for dose modifications for dexamethasone
Section 7.7.2 Prohibited Medication	Added caution statement for CYP inhibitors/inducers	Updated information based on emerging data
Section 8.1 Discontinuation of Study Treatment	Added Pregnancy and Safety stopping criteria to the list of reasons for discontinuation	To align with Section 9.2.8 and Appendix 7
Section 8.2.5 Corneal Supportive Care Guidelines	Removed section – content moved to Section 9.6.7 Ophthalmic Examinations	To provide cohesion and group related content
Section 11.4.7.1.2 (Arm A) and 11.4.7.2.2 (Arm B) Interim Analysis Part 2	Added language on safety monitoring and stopping rules during cohort expansion	To align with strategy across the belantamab mafodotin development program

Section # and Name	Description of Change	Brief Rationale
Belantamab Mafodotin Program Level Changes		
Section 2 Schedule of Activities Tables	Table 2 & Table 4: Edited hematologic examination timeframes to include additional testing during each cycle Table 2, Table 4, Table 6: Changed duration of collection of AE/SAE from 30 days to 45 days Table 2 & Table 4: Revised Corneal Event prophylaxis to also include prednisolone acetate	To align with strategy across the belantamab mafodotin development program Changed throughout the protocol Revised to align with duration of 5 half-lives of belantamab mafodotin To align with strategy across the belantamab mafodotin development program
Section 3.3.1 Risk Assessment	Table 7: Updated data and mitigation strategy on risks related to belantamab mafodotin (thrombocytopenic events, neutropenic events, IRR, cardiotoxicity, nephrotoxicity, pulmonary toxicity, immunosuppression, potential for other laboratory abnormalities)	Edited based on updated data from the FTIH study (BMA117159) and to align with strategy across the belantamab mafodotin development program
Section 6.2 Exclusion Criteria	Changed the definition of invasive malignancies to be excluded Increased QTcF from 470 msec to 480 msec	To clarify the definitions QTcF increased to align with GSK internal standards for oncology trials as determined by GSK Cardiac Safety Panel
	Changed uncontrolled arrhythmias to untreated arrhythmias Reduced timeframe for history of myocardial infarction, acute coronary syndromes prior to Screening	Based on emerging data as determined by GSK Cardiac Safety Panel

Section # and Name	Description of Change	Brief Rationale
Section 7.1 Treatments Administered	Sections 7.1.1.1, 7.1.2.1 and Table 11 – Changed duration of administration of belantamab mafodotin from “30 min” to “30 min to 1 h” Removed language indicating that participants will be removed from study for lack of tolerability	To add flexibility in the duration of administration of belantamab mafodotin To align with strategy across the belantamab mafodotin development program
Section 7.1.12.4 Participants Achieving CR	Removed section	Section not relevant for GSK2857916
Section 7.2.1 Dose Modification After Cycle 1	Table 15: Added table for recommendations for dose reduction of belantamab mafodotin Table 18: Added recommendation for use of prophylactic antimicrobials	To clarify and align with revised study design Changes to dose modification guidelines for belantamab mafodotin related to Corneal Events further clarified dose modifications based on visual acuity or findings on ophthalmic examination
Section 8.2.5 Corneal Event Stopping Criteria	Added clarity on use of GSK scale and CTCAE scale for AESI reporting purposes and dose modifications Removed duplicate text within section 8.2.5	Alignment throughout protocol. Both the CTCAE and GSK scale are to be utilized for reporting of corneal events and clarified that the GSK scale is to be utilized for dose modification decisions.
Section 9.2.7 Adverse Events of Special Interest	Added clarity on use of GSK scale and CTCAE scale	Alignment throughout protocol
Section 9.2.8 Pregnancy	Edited timeframe for performance of pregnancy test prior to the first dose of study treatment from 72 h to 24 h	To keep protocol consistency for pregnancy monitoring across the belantamab mafodotin development program
Section 9.6.10 Laboratory Assessments	Table 22: Removed INR analysis	To align with GSK liver monitoring requirements, INR test will not be required unless a liver event occurs

Section # and Name	Description of Change	Brief Rationale
Section 13 Appendices	Removed Appendix 3 – International Myeloma Working Group (IMWG) Criteria for Relapse-Refractory Multiple Myeloma	Included references to the IMWG Criteria in lieu of an appendix for clarification purposes
	Appendix 10 – Labelling changed to Appendix 8 - Added clarity on use of GSK scale and CTCAE scale – Updated GSK grading scale	To align with Section 9.2 and throughout the protocol
	Appendix 9 – PK collection updated from 30 days to 45 days (5 half-lives)	Revised to align with duration of 5 half-lives of belantamab mafodotin

Section # and Name	Description of Change	Brief Rationale
Additional Changes in Assessments		
Section 2 Schedule of Activities Tables	Table 1: Edited FISH testing to include identification of amplifications and deletions	Acceptability of positive results for high risk abnormalities by FISH has been extended beyond 60 days, as the listed abnormalities are myeloma-defining and do not change the course of the disease
	Table 2 & Table 4: Clarified timings for vital signs, ECG collections and PK sample collection	Additional ECG timepoints added to assess at the Cmax of the free cytotoxic drug (cys-mcMMAF) and to detect any delayed effects on QTc
	Table 2 & Table 4: Added additional PK timepoints	Additional PK timepoints added to capture the Cmax of the free cytotoxic drug (cys-mcMMAF) and to better define the kinetics of cys-mcMMAF and the elimination phase of ADC and cys-mcMMAF
	CCI [redacted]	
	Table 2 & Table 4: Added additional CCI [redacted] sample collection timepoint	To study the effect of genetic variations on response
Protocol Clarification and Alignment Changes		
Section 2 Schedule of Activities Tables	Table 2: Changed timeframe from pregnancy testing in WOCBP	To provide consistency and alignment throughout the protocol
Section 5.3 Participant and Study Completion	Edited definition of participant completion	To clarify study completion
	Edited definition for end of study for Arms A and B	To clarify definition for end of study
Section 5.5.2 Starting dose of	Added “planned” to “cycle”	To clarify between time bound assessments and cycle bound

Section # and Name	Description of Change	Brief Rationale
SOC		assessments
Section 6.1 Inclusion Criteria	Added “autologous” to “stem cell transplant”	To clarify inclusion criteria
Section 7.2.1 Dose Adjustments Due to Body Weight or Body Surface Area	Moved content to relevant context in Section 7.1	To clarify protocol
Section 7.2.2. belantamab mafodotin Dose Modification in Part 1 (Dose Escalation)	Moved content to Section 5.1	To clarify protocol
Section 5.1.3 Criteria for belantamab mafodotin Dose-Limiting Toxicity in Part 1	Moved this Section (previously Section 7.2.3) into Section 5.1	To clarify protocol
Section 7.2.1 Dose Modification After Cycle 1	Removed presented scenarios – to be provided as an Appendix to the SRM	To clarify protocol
Section 9.6.3 Vital Signs	Added language for timeframe of vital signs assessment on days of bortezomib administration	To provide consistency and alignment throughout the protocol
Section 9.6.7 Ophthalmic Examinations	Added clarification for supportive care.	To provide consistency and alignment throughout the protocol
Administrative Changes		
Title Page	Removed author list Removed Medical Monitor information and added reference to the Study Reference Manual	To follow current GSK template (i.e., Transcelerate protocol template)
Section 1 Synopsis	Changed text in Synopsis to reflect changes to the text of main body of	Refer to individual items listed throughout this table

Section # and Name	Description of Change	Brief Rationale
	the protocol	
Section 9.6.7 Ophthalmic Examinations	Clarification of examination requirement for each visit. Added statement on the central collection of photographs	Administrative change
Section 9.6.10 Laboratory assessments	Table 22: Removed "fasting" requirement for glucose analysis	Based on additional data, fasting glucose is not required at every visit as routine glucose is included in chemistry panel
Section 13 Appendices	Removed Appendix 7 – Calculation of Body Surface Area Appendix 12 – Included list of changes pertaining to Amendment 01	Removed to prevent copyright infringement To follow current GSK template (i.e., Transcelerate protocol template)
Editorial/Document Formatting Changes		
Whole document	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

14.14.3. Protocol Amendment 1 (7-MAY-2018):

Protocol Amendment 1 include following:

- additional authors who contributed to protocol amendment were added
- change in the Primary Medical Monitor
- Changes made in the Schedule of Activities tables. The SOA tables have been modified to reflect that the disease assessments need to be performed at regular intervals instead of being linked to the administration of study drugs. Revisions have also been made in the timings and frequency of some assessments.
- Minor correction made in the participants' eligibility criteria; participants with prior allogenic SCT will now be excluded (Section 6).
- Clarification made on dose delays of study drugs by giving examples of different scenarios (Section 7.2).
- All routine and disease evaluation related blood and urine tests now will be done locally; centrally only if unable to perform locally (Table 16)
- Administrative changes made throughout the document.

Section # and Name	Description of Change	Brief Rationale
Title Page	Authors list was updated.	Additional authors who contributed to protocol amendment were added to the list; authors who are no longer involved with the study were removed.
Medical monitor/Sponsor Information Page	GSK Medical Monitor change	Change in the Primary Medical Monitor
Section 2 **Schedule of Activities Tables**	Significant changes made in the Schedule of Activities tables. • The SOA Table 2 & Table 3 have been modified to reflect that the disease assessments need to be performed at regular intervals instead of being linked to the administration of study drugs. For this purpose, an additional column for fixed time interval assessments was added. • Time period windows have been added for vital signs, drug infusions, PK sampling and imaging. • Revisions have also been made in the timings and frequency of following assessments; Spot urine for albumin/creatinine ratio, ECHO, imaging and EORTC QLQ-C30 AND QLQ-MY20 questionnaires. • Timepoints for response assessments under disease evaluation modified. • Removal of flow cytometry for bone marrow aspirate. • Added whole body PET/CT to confirm CR, sCR. • Timings of Triplicate ECG at the End of Infusion (EOI) corrected. • Language on the genetic research	 • Cycle bound assessments have been separated from time bound assessments to clarify activities. • This change was made to avoid deviations from administration timings of these assessments. • To align the assessments in both treatment arms. • Per IMWG response criteria • Flow cytometry is not used in IMWG (Rajkumar 2016) • Based on IMWG (Rajkumar 2016) • ECG recordings must be made prior to EOI instead of post-infusion as stated in the original version of the protocol.

Section # and Name	Description of Change	Brief Rationale
	sample collection modified.	• To add more clarity.
Synopsis and Section 4 Secondary Objectives	Definition of CCI [redacted] modified.	The change was made to provide precise definition of CCI [redacted]
Section 6 **Study Population**	Minor correction made in the participants' eligibility criteria; participants with prior allogenic SCT will now be excluded. To reflect the above, inclusion criterion #9 deleted and exclusion criterion # 4 added in synopsis and main body of the protocol.	Participants with Allogenic SCT are now excluded to avoid unpredictable toxicity.
Section 7.2.4 Dose Modification After Cycle 1	Clarification provided regarding dose delays of study drugs by giving examples of different scenarios.	The change was made to provide guidance on dose interruptions and reductions.
Section 8.2.7 **Infusion Related Reaction Management and Stopping Criteria**	Clarification provided on management of infusion-related reactions and stopping criteria.	The change was made to add more clarity.
Section 9.2 **Adverse Events**	Guidance provided on the grading of adverse events.	Added language specifying grading for clarity
Section 9.2.6 **Disease-Related Events and/or Disease Related**	Sentence on the reporting of progression disease as a serious adverse event modified.	Updated text to ensure PD is not reported as a SAE
Section 9.6.7.1 **Ocular Examination and**	Added slit lamp in full anterior segment examination for clarity	The change was made to add more clarity.

Section # and Name	Description of Change	Brief Rationale
Procedures		
Section 9.7.1 **Blood Sample Collection for Pharmacokinetics**	Amount of blood volume needed for belantamab mafodotin, Lenalidomide and Bortezomib Pharmacokinetics samples removed.	Information on the PK blood volume will be contained in the SRM.
Table 16 **List of Clinical Laboratory Tests**	All routine and disease evaluation related blood and urine tests will now be done locally; they may be performed centrally only if unable to be performed locally	For ease of performing assessments and to provide more flexibility to sites.
Appendix 8 **Assessment of Intensity**	The intensity assessment scale for AE/SAE changed from mild, moderate and severe into grades.	Per new protocol template
Whole Document	Administrative corrections were made throughout the protocol to correct minor inconsistencies and rectify the typographical errors	Provide clarity and correction.

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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 30-Jun-2022 12:13:18 GMT+0000

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