Protocol Amendment 2

Study ID: 208887 Sub Study 6

Official Title of Sub Study 6: A Phase I/II, Randomized, Open-label Platform Study Utilizing a Master Protocol to Study Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination With Anti-Cancer Treatments in Participants With Relapsed/Refractory Multiple Myeloma (RRMM)-DREAMM5 - Sub-study 6 - Belantamab Mafodotin, Nirogacestat, Lenalidomide, and Dexamethasone in Combination

NCT ID of Sub Study 6: NCT07150091

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TITLE PAGE

Protocol Title: A Phase I/II, Randomized, Open-label Platform Study Utilizing a Master Protocol to Study Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination with Anti-Cancer Treatments in Participants with Relapsed/Refractory Multiple Myeloma (RRMM)–DREAMM5 – Sub-study 6 – Belantamab Mafodotin, Nirogacestat, Lenalidomide, and Dexamethasone in Combination

Protocol Number: 208887 / Amendment 2 for Sub-study 6

Compound Number or Name: Belantamab Mafodotin (GSK2857916), Nirogacestat, Lenalidomide, and Dexamethasone

Study Phase: 1/2

Short Title: Sub-study of Belantamab Mafodotin (GSK2857916) in Combination with Nirogacestat, Lenalidomide, and Dexamethasone in Participants with RRMM

Acronym: DREAMM-5 Sub-study 6

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Approval Date: 03 Sep 2024

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PROTOCOL AMENDMENT 2 SUB-STUDY 6 INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: 208887

AMENDMENT NUMBER: Protocol Amendment 2 for Sub-study 6

PROTOCOL TITLE: A Phase I/II, Randomized, Open-label Platform Study Utilizing a Master Protocol to Study Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination with Anti-Cancer Treatments in Participants with Relapsed/Refractory Multiple Myeloma (RRMM)–DREAMM5 – Sub-study 6 – Belantamab Mafodotin, Nirogacestat, Lenalidomide, and Dexamethasone in Combination

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigator Name:

_____

Investigator Address:

_____

_____

_____ _____

Investigator Signature Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 2 (Sub-study 6)	03 Sep 2024	TMF-19487484
Amendment 1 (Sub-study 6)	07 July 2023	TMF-15016838
Original Protocol (Sub-study 6)	21 January 2022	TMF-13841957

Amendment 2 (Sub-study 6): 03 Sep 2024

Overall Rationale for the Amendment:

This protocol has been amended (1) to include some changes regarding the study procedures in line with project-level updates, and (2) to comply with the new protocol template for oncology and latest regulatory requirements. These updates are summarized in the table below.

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities	Tables 4 & 6: Procedures related to health outcomes evaluation were removed. Table 6: A note to stop plasma PK sampling once enough data have been collected was added. Tables 5 & 6: Sampling for sBCMA and CMMC analyses was removed. Table 7: A note to stop sampling for MRD and biomarker research once enough data have been collected was added.	To update the study procedures in line with project-level updates.
Section 2.3.1. Summary of Risk Assessment	Some risks related to the study treatments (e.g., Belantamab mafodotin, Nirogacestat) were updated in the table of risk assessment.	To add the recent clinical experience with the study treatments.
Section 6.1. Study Treatment(s) Administered	The information regarding study treatments was updated.	To comply with the latest regulatory requirements.
Section 8.9. Health-related Quality of Life	Wording related to health outcomes evaluation was removed.	To align with the updates in study procedures.
Section 12.13. Appendix 13: Abbreviations, Trademarks, and Definitions of Terms	A list of definitions was included.	To define the terms used throughout the document.
Throughout the document	Editorial and wording updates.	Updates in wording were added to align with the new Sponsor's standard protocol template and ways of working.

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1. PROTOCOL SUMMARY

Please refer to the 208887 MP for the overall Protocol Summary for the study. Information and details specific to Sub-study 6 are in the subsections below (Table 1).

Table 1 Location of Sub-study 6 Specific Content

Section	Heading title	Brief description of content
1.2	Schema	Belantamab mafodotin, nirogacestat, lenalidomide, and dexamethasone study schema
1.3	Schedules of Activities	Comprehensive SoA tables specific for Sub-study 6
2.1	Rationale for the combination of Belantamab Mafodotin, Nirogacestat, Lenalidomide, and Dexamethasone	Explanation why treatment with belantamab mafodotin, nirogacestat, lenalidomide, and dexamethasone is expected to be complementary
2.2	Background	Available data on clinical pharmacology, safety, and clinical activity for nirogacestat
2.3	Benefit/Risk Assessment	Risk assessments for nirogacestat, lenalidomide and dexamethasone treatment; benefit assessment summary for the combination
4.1	Overall Design	Description of dose escalation and cohort expansion design for the combination treatment
4.3	Justification for Dose	Data for the basis of the planned belantamab mafodotin, nirogacestat, lenalidomide, and dexamethasone dosing
5.1	Inclusion Criteria	Inclusion criteria details specific to Sub-study 6
5.2	Exclusion Criteria	Exclusion criteria details specific to Sub-study 6
6.1	Study Treatment(s) Administered	Specifications for belantamab mafodotin, nirogacestat, lenalidomide, and dexamethasone IP
6.2	Administration of IP	Specifications for administration of belantamab mafodotin, nirogacestat, lenalidomide, and dexamethasone
6.3	Preparation / Handling / Storage / Accountability	Specifications for handling, storage, and accountability of nirogacestat, lenalidomide, and dexamethasone
6.5.2	Prohibited Concomitant Medications and Non-drug Therapies	Specifications of prohibited concomitant medications specific to Sub-study 6
6.6	Dose Modification	Detailed guidance for dose modifications per participant for combination treatment
8.3.7	Management of Pregnancy and Contraception	Detailed directions for management of pregnancy and guidance on contraception specific to Sub-study 6
8.3.10	AESI for Nirogacestat	Information on nirogacestat AESI
8.4	Treatment of Overdose	Guidance for potential drug overdose for nirogacestat, lenalidomide, and dexamethasone
8.8	Biomarkers	Summary of the biomarker research being conducted for Sub-study 6
12.9.1	Appendix 9: Liver Safety Event	Timeframe for PK sampling in case of liver safety event

1.1. Synopsis

Protocol Title: A Phase I/II, Randomized, Open-label Platform Study Utilizing a Master Protocol to Study Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination with Anti-Cancer Treatments in Participants with Relapsed/Refractory Multiple Myeloma (RRMM)–DREAMM5 – Sub-study 6 – Belantamab Mafodotin and Nirogacestat in Combination with Lenalidomide and Dexamethasone

Short Title: Sub-study of Belantamab Mafodotin (GSK2857916) in Combination with Nirogacestat, Lenalidomide, and Dexamethasone in Participants with RRMM

Rationale: The combination of belantamab mafodotin and nirogacestat was proposed in Sub-study 3 of DREAMM-5 and emerging data (belantamab mafodotin 0.95 mg/kg [Q3W] in combination with continuous nirogacestat 100 mg per oral [PO] twice daily [BID]) demonstrate that these 2 agents can be combined into a safe and effective regimen for patients with RRMM (data on file).

Furthermore, belantamab mafodotin has been evaluated in combination with standard-of-care combination partners, such as lenalidomide plus dexamethasone, in GSK-sponsored DREAMM-6. Preliminary safety data suggests that the combination of belantamab mafodotin at doses up to 2.5 mg/kg IV Q3W with standard doses of lenalidomide and dexamethasone has an acceptable safety profile, consistent with individual components in patients with RRMM. Nonclinical data demonstrated that the activity of belantamab mafodotin is enhanced by lenalidomide in cultured myeloma cell lines and patient myeloma cells. Additionally, nonclinical data with belantamab mafodotin suggest significant added benefit (efficacy and survival) when combined with lenalidomide and/or dexamethasone in established MM xenograft models.

Given the encouraging emerging data for belantamab mafodotin in combination with nirogacestat (data on file), the combination therapy of belantamab mafodotin plus nirogacestat with standard-of-care (SoC) agents is an attractive option to explore for participants with RRMM. The combination with SoC therapies (e.g., lenalidomide /dexamethasone) 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.

Dose Exploration will involve up to 3 belantamab mafodotin dosing regimens (3 belantamab mafodotin dosing levels with different schedules; Dose levels 1-3).

1.2. Schema

1.2.1. Platform Study

Please refer to 208887 MP Section 1.2 for the general design of the multiple myeloma platform study.

1.2.2. Belantamab Mafodotin, Nirogacestat, Lenalidomide, and Dexamethasone

Table 2 Dose Exploration Schematic for Belantamab Mafodotin, Nirogacestat, Lenalidomide, and Dexamethasone

Investigational Product	Dose Level 1 (Starting Dose)	Dose Level 2	Dose Level 3
Belantamab Mafodotin	0.5 mg/kg IV Q4W	1.0 mg/kg IV Q4W for Cycle 1 then Q8W or Q12W	1.4 mg/kg IV Q4W for Cycle 1 then Q8W or Q12W
Nirogacestat	100 mg PO BID Continuously dosed starting Day -2 Cycle 1	100 mg PO BID Cycle 1: Day -2 to D28 Subsequent cycles: D1 to D28 (regardless of whether Q8W or Q12W cycles)	100 mg PO BID Cycle 1: Day -2 to D28 Subsequent cycles: D1 to D28 (regardless of whether Q8W or Q12W cycles)
Lenalidomide	25 mg or 10 mg[1] PO QD on D1 to 21	25 mg or 10 mg[1] PO QD D1 to 21, QD D29 to 49 for Q8W and Q12W and QD D57 to 77 for Q12W only	25 mg or 10 mg[1] PO QD on D1 to 21, QD D29 to 49 for Q8W and Q12W and QD D57 to 77 for Q12W only
Dexamethasone	40 mg or 20 mg[2] weekly, PO or IV	40 mg or 20 mg[2] weekly, PO or IV	40 mg or 20 mg[2] weekly, PO or IV

1. If the eGFR is 40-60 mL/min/1.73 m^2.
2. Participants >75 years old or BMI <18.5 kg/m^2.

Dose level 1, 2 and 3: The first cycle with the lead-in dose will be 30 days (from Day -2 through Day 28). However, the DLT evaluation period initiates at C1D1 and goes through Day 28; specifically, DLT period initiates after all drugs of the combination treatment have been first administrated. Subsequent cycles from Cycle 2 for Dose Levels 2 and 3 will be 56 days for Q8W or 84 days for Q12W. Please refer to Section 4.1 for further details.

1.3. Schedule of Activities (SoA)

- The timing and number of planned study assessments (including safety, PK, ADA, biomarker or other assessments) may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations of study treatments administered) to ensure appropriate monitoring.
- Any changes in the timing of samples for PK and biomarker planned assessments must be documented and approved by the relevant team members and then archived in the sponsor and site study files but will not constitute a protocol amendment unless the number of samples required has increased. This will be to allow adjustments that may be needed to ensure the full PK and pharmacodynamic profile is defined.
- The Competent Authority and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the Informed Consent Form. The changes will be approved by the Competent Authority and the IRB / IEC before implementation.

Table 3 SoA – Screening for Dose Exploration (DE) and Cohort Expansion (CE) Phases: Belantamab Mafodotin, Nirogacestat, Lenalidomide, and Dexamethasone

Screening Study Assessments	Screening	Notes
Note: All Screening assessments must be performed within **30** days prior to Cycle 1 Day -2 unless otherwise specified. Informed Consent must be signed before any study-specific assessments are performed. Screening Assessment do not need to be repeated on C1D1 unless otherwise specified. All other assessments can be done ≤3 days prior to treatment unless otherwise specified. **If C1D1 Hem/Chem results are outside of the eligibility requirements, Medical Director to be contacted for review prior to dosing**.		
Informed Consent	X	1. Screening/baseline ocular examination will be performed by a qualified eye care specialist (ophthalmologist/optometrist 208887 MP Appendix 10) within 30 days prior to C1 Day -2 (see 208887 MP Section 8.2.7 for list of ophthalmic exam procedures). 2. Perform only in women of childbearing potential. Two serum pregnancy tests should be performed at Screening; the first test should be performed within 10-14 days of C1 Day-2, and the second must be performed within 24 hours of C1D1. 3. Refer to 208887 MP Appendix 2 for a comprehensive list of lab tests that must be collected for all participants. 4. eGFR as calculated by MDRD formula (208887 MP Appendix 6). 5. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥1+ at Screening, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab (first void). 6. If a participant tested hepatitis B core antibody positive, refer to Table 8 for additional procedures throughout the study. Hep C RNA testing is optional, but it will be performed to determine participant eligibility if Hep C antibody positive. If negative, participant is eligible (see Exclusion Criteria 12 for details). 7. Complete at Screening or within 12 weeks prior to C1 Day -2. 8. For participants who have been previously exposed to HIV, HIV viral load must be <400 copies/mL and CD4+ T-cell (CD4+) counts ≥350 cells/uL 9. Single ECG at Screening. 10. ECHO or MUGA scan for LVEF may be performed within 30 days prior to C1 Day -2. 11. SPEP and UPEP will include M-protein levels. 12. Serum FLC assay will include kappa/lambda ratio and quantification of involved and uninvolved light chains. 13. IgD/IgE testing is only required for participants with IgD/IgE myeloma. 14. Skeletal survey: Imaging of bones for lytic lesions by a method aligned with the institutional guidance (X-ray, CT, or MRI). X-ray is acceptable for lytic disease, but other methods are needed (CT, MRI,
Throughout the study, participants are educated about in lifestyle considerations (208887 MP Section 5.3) for the study and the need of maintaining adequate urinary output (208887 MP Section 2.3.1).	X	
Inclusion/Exclusion criteria	X	
Past and current medical conditions	X	
Concomitant Medication review	X	
Pregnancy Prevention Counseling	X	
Screening Safety Assessments		
Ocular Exam	X[1]	
ECOG Performance Status	X	
Vital Signs (BP, HR, Body Temperature)	X	
Weight and Height	X	
Serum Pregnancy Test (WOCBP only)	X[2]	
Hematology (CBC)	X[3]	
Clinical chemistry	X[3]	
Estimated Glomerular Filtration (eGFR)	X[4]	
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)	X[5]	
HBsAg, HBcAb[6], HCV[6] tests	X[7]	
HIV viral load and CD4+ count	X[8]	
12-lead ECG	X[9]	
ECHO or MUGA scan for LVEF	X[10]	

Screening Study Assessments	Screening	Notes
Note: All Screening assessments must be performed within **30** days prior to Cycle 1 Day -2 unless otherwise specified. Informed Consent must be signed before any study-specific assessments are performed. Screening Assessment do not need to be repeated on C1D1 unless otherwise specified. All other assessments can be done ≤3 days prior to treatment unless otherwise specified. **If C1D1 Hem/Chem results are outside of the eligibility requirements, Medical Director to be contacted for review prior to dosing**.		
Screening Disease Evaluation		PET/CT) for assessment of extramedullary disease. Skeletal survey results within 30 days prior to C1 Day -2 may be used for Screening. Same modality used at Screening should be used throughout study. 15. In participants with known or suspected extramedullary plasmacytoma, a whole-body scan (i.e., CT, MRI, or PET-CT) should be performed within 30 days prior to C1 Day -2. The same method should be used throughout the study (i.e., if a PET-CT scan was used as baseline scan, then the participants need to be followed by PET-CT scans). Selected target lesions need to be measured and followed over time. Whole body MRI is also acceptable, as long as it can be repeated over the duration of the study until confirmed disease progression. 16. Please refer to Table 7 for scheduled BM collection procedures to include aspirate and biopsy. 17. If FISH testing cannot be performed at a local lab the samples can be sent to the central lab. 18. MRD testing by NGS method.
Beta-2 microglobulin	X	
UPEP 24 hr urine collection	X[11]	
Urine immunofixation 24 hr urine collection	X	
SPEP	X[11]	
Serum immunofixation	X	
Serum FLC assay	X[12]	
IgG, IgM, IgA	X	
IgD or IgE, if applicable	X[13]	
Calcium corrected for albumin (serum)	X	
Skeletal survey	X[14]	
Extramedullary Plasmacytoma Assessment (by whole body CT or whole-body MRI or CT/PET)	X[15]	
BM Aspiration/Biopsy		
BM aspirate and/or core biopsy for local disease assessment	X[16]	
BM aspirate for local FISH testing	X[16,17]	
BM aspirate for BCMA expression and biomarker research	X[16]	
BM aspirate for MRD testing	X[16,18]	

Table 4 SoA – Treatment Period for DE and CE Phases: Belantamab Mafodotin, Nirogacestat, Lenalidomide, and Dexamethasone. Study assessments to be carried out regardless of whether participant is dosed

Study Assessments regardless of whether participant is dosed	Day 1 (Week 1)	Treatment Period until EOT	Notes
• All assessments will apply to both the DE and CE Phases unless otherwise specified. • Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. • If cycle length is Q8W or Q12W, determined by dosing of belantamab mafodotin, assessments within this table will be done Q4W. • Scheduled visit dates during the treatment period can be delayed or brought forward by a maximum of 5 days to be aligned with the next dosing date. If administration of study treatment is delayed ≤7 days, assessments indicated to occur at the dosing visit can be scheduled to occur when dosing occurs (every effort should be made to realign subsequent weekly visits with dosing visits). If administration of study treatment is delayed >7 days, dosing and weekly assessments may occur on the different days.			
AEs	Ongoing[1]		1. AEs/SAEs will be collected until at least 70 days after the last dose of study treatment. All SAEs related to study participation (e.g., protocol mandated procedures, tests, or change in existing therapy) are to be collected from consent through OS follow-up. All AEs/SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up. For the reporting of ocular events see the guidance provided in 208887 MP Appendix 3.
Concomitant Medications	Ongoing		
Throughout the study, participants are educated about in lifestyle considerations (208887 MP Section 5.3) for the study and the need of maintaining adequate urinary output (208887 MP Section 2.3.1)	X		2. Informed consent for optional genetic research must be obtained before collecting a sample. The sample will be collected on C1D1 prior to infusion.
Genetics	X[2]		3. On-study ocular exams to be performed by a qualified eye care specialist (see 208887 MP Appendix 10) for scheduled visits regardless of dosing, up to the sixth dose of belantamab mafodotin (assessment window up to 5 days prior to scheduled visit date, but all effort should be made to schedule as close to belantamab mafodotin dosing as possible). If there are no significant KVA Grade 2 or above treatment-related ocular examination findings, change in participant symptoms or vision at the time of the sixth dose exam, participants may have their ophthalmologic exams decreased to once every 3 months. See 208887 MP Section 8.2.7 for list of ophthalmic exam procedures and frequency of exams.
ECOG Performance Status		X	
Safety			
Ocular Exam		X[3]	
Hematology (CBC)	X[4]	X[4]	4. CBC and chemistry panel may be done more frequently as clinically indicated. Refer to 208887 MP Appendix 2 for comprehensive list of lab tests.
Clinical chemistry	X[4]	X[4]	
eGFR	X[5]	X[5]	5. eGFR as calculated by MDRD formula (208887 MP Appendix 6).
Urinalysis (dipstick) OR Spot Urine (albumin/creatine ratio)	X[6]	X[6]	6. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥2+, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab (first void).
ECHO or MUGA scan for LVEF		X[7]	7. ECHOs or MUGA scans for LVEF to be done if clinically indicated. The same procedure used at Screening should be used throughout the study.
Disease Evaluation (every 4 weeks even if a dose is delayed)			
UPEP 24 hr urine collection		X[8]	
Urine immunofixation 24 hr urine collection		X[9]	
SPEP		X[8]	

Study Assessments regardless of whether participant is dosed	Day 1 (Week 1)	Treatment Period until EOT	Notes
• All assessments will apply to both the DE and CE Phases unless otherwise specified. • Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. • If cycle length is Q8W or Q12W, determined by dosing of belantamab mafodotin, assessments within this table will be done Q4W. • Scheduled visit dates during the treatment period can be delayed or brought forward by a maximum of 5 days to be aligned with the next dosing date. If administration of study treatment is delayed ≤7 days, assessments indicated to occur at the dosing visit can be scheduled to occur when dosing occurs (every effort should be made to realign subsequent weekly visits with dosing visits). If administration of study treatment is delayed >7 days, dosing and weekly assessments may occur on the different days.			
Serum immunofixation		X[9]	8. SPEP must be performed Q4W, no matter the schedule of dosing for belantamab mafodotin.UPEP will only be performed Q4W for participants who had detectable M-protein only in the urine at Screening. For all other participants, if UPEP is negative at Screening, then UPEP will be performed only after a tumor response based on SPEP protein during treatment is observed, where UPEP on 24 hours urine sample is required to confirm the response per IMWG criteria. 9. To be performed when SPEP and UPEP are negative or not quantifiable. Also, to be performed to confirm objective response (PR or better). 10. Serum FLC assay will include kappa/lambda ratio and quantification of involved and uninvolved light chains; to be done every 4 weeks. 11. IgD/IgE testing is only required for participants with IgD/IgE myeloma. 12. Skeletal survey (as clinically indicated): Imaging of bones for lytic lesions by a method aligned with the institutional guidance (X-ray, CT, or MRI). X-ray is acceptable for lytic disease, but other methods are needed (CT, MRI, PET/CT) for assessment of extramedullary disease. Same modality used at Screening should be used throughout study. 13. Imaging is required for participants with extramedullary disease, as clinically indicated, to document disease response PR or better, or to confirm PD. Imaging is also required when there is a suspected appears of a new lesson (for confirmation of PD). 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 lesions need to be measured. 14. **Note**: Germany: no PET/CT to confirm CR or sCR will be performed until approval by the German Federal Office for Radiation Protection until further notice. 15. Please refer to Table 7 for scheduled BM collection procedures to include aspirate and biopsy.
Serum FLC assay		X[10]	
IgG, IgM, IgA		X	
IgD or IgE		X[11]	
Calcium corrected for albumin (serum)		X	
Skeletal survey		X[12]	
Extramedullary Plasmacytoma Assessment (by whole body CT or whole body MRI or CT/PET)		X[13, 14]	
MRI, CT or PET/CT upon achieving CR or sCR		Once after CR or sCR[14]	
BM Aspiration/Biopsy			
BM aspirate for BCMA expression and biomarker research		X[15]	
Bone marrow aspirate for MRD testing		X[15]	
BM aspirate and/or core biopsy for local disease assessment		X[15]	
BM core biopsy to assess sCR (local)		X[15]	

Table 5 SoA – Treatment Period on Dosing Days or After Dosing Only: Regarding Belantamab Mafodotin, Nirogacestat, Lenalidomide, and Dexamethasone

Study Assessments	Day -2 (prior to Cycle 1 Day 1)	Cycle 1 Day 1 (Week 1)	Cycle 1 Day 4 (±1 day) (DE only)	Cycle 1 Day 8 and Day 15	Cycle 2 to EOT	Notes
• All assessments will apply to both the DE and CE Phases unless otherwise specified. • Assessments completed on Day -2 do not need to be repeated on C1D1 with the exception of vital signs and PK. • Assessments should be done prior to drug administration, unless otherwise specified. • From Cycle 2, assessments can be performed ≤3 days prior to the scheduled date unless otherwise specified. • **Please note the first nirogacestat dose for Days -2, C1D1, C1D4 & C1D8 and every D1 onward starting with Cycle 2, MUST be administered in the clinic/hospital.** • **Nirogacestat, lenalidomide, and dexamethasone are dispensed every 28 days.** • **Regardless of belantamab mafodotin dosing schedule, participants will be assessed every 28 days.** • **If belantamab mafodotin is held for any reason, then nirogacestat will also be held (see Section 6.6.6 for exception).** • **If C1D1 Hem/Chem results are outside of the eligibility requirements, Medical Director to be contacted for review prior to dosing.**						
Safety						1. Measured after resting for at least 5 min. C1D1: Vital signs done at baseline, prior to predose PK sampling for nirogacestat, and prior to dose (within 30 min prior to SOI), then vital signs repeated at end of belantamab mafodotin infusion (EOI) (+0-10 min), and at 1 h post EOI (+0-10 min). For PK sampling collection details see footnote 7 (nirogacestat) and footnote 9 (belantamab mafodotin). For Day 1 of subsequent cycles, vital signs must be monitored prior to dose (within 30 min prior to SOI) PK collection for both nirogacestat and belantamab mafodotin and repeated at each EOI (+0-10 min), and 30 min post each EOI (+0-10 min) and as clinically indicated. On days with PK sampling time points, if vital signs assessments are conducted, they should be assessed prior to PK samples being drawn.
Physical Exam (full exam on treatment days Day 1 of each cycle, and C1D8 only)	X	X		X	X	
Vital Signs (BP, HR, Body Temperature)	X[1]	X[1]	X[1]	X[1]	X[1]	
Ocular Exam		X[2]			X[2]	2. On-study ocular exams to be performed by a qualified eye care specialist (see 208887 MP Appendix 10) regardless of dosing up to the sixth dose of belantamab mafodotin (assessment window 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 KVA Grade 2 or above treatment-related ocular examination findings, change in
Weight	X	X			X	
ECOG Performance Status	X	X			X	
Pregnancy Test	X[3]	X[3]		X[3]	X[3]	
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)		X[4]			X[4]	
Hematology (CBC)	X[5]	X[5]		X[5]	X[5]	
Clinical chemistry	X[5]	X[5]		X[5]	X[5]	
eGFR	X[6]	X[6]		X[6]	X[6]	
PK and ADA						
Plasma PK for nirogacestat	X[7]	X[7]		X[7]	X[7]	
Serum Immunogenicity (ADA) for belantamab mafodotin		X[8]			X[8]	

Study Assessments	Day -2 (prior to Cycle 1 Day 1)	Cycle 1 Day 1 (Week 1)	Cycle 1 Day 4 (±1 day) (DE only)	Cycle 1 Day 8 and Day 15	Cycle 2 to EOT	Notes
Plasma PK for belantamab mafodotin		X[9]		X[9]	X[9]	participant symptoms or vision at the time of the sixth dose exam, participants may have their ophthalmologic exams decreased to once every 3 months. See 208887 MP Section 8.2.7 for list of ophthalmic exam procedures and frequency of exams.
Biomarkers						3. Perform only in WOCBP. Pregnancy test will be done weekly during the first month, then every cycle thereafter (or every 2 weeks in females with irregular menses). Post-screening pregnancy tests may be either serum or urine test. Each pregnancy test must be performed within 24 hours prior to dosing. GSK should be made aware of any pregnancy within 24 hours. A pregnancy test performed at Cycle 1 Day -2 does not need to be repeated at C1D1.
Hematology (TBNK and/or enhanced TBNK cell activation panel)		X[10]			X[10]	
Treatment with Belantamab Mafodotin						4. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥2+, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab (first void).
Administration of belantamab mafodotin		X			Day 1 of each cycle[11]	
Premedication if needed		X[12]			X (at the start of each cycle)[12]	
Treatment prophylaxis and management: Preservative-free artificial tears and cooling masks		X[13]			X[13]	
Treatment with Nirogacestat						5. CBC and Clinical Chemistry may be done more frequently as clinically indicated. Refer to 208887 MP Appendix 2 for comprehensive list.
Administration of nirogacestat	X	X[14]	X[14]	X[14]	X[14]	
Patient Dosing Diary Card for nirogacestat, lenalidomide and dexamethasone	X[15]	X[15]	X[15]	X[15]	X[15]	6. eGFR as calculated by MDRD formula (208887 MP Appendix 6).
Treatment with Lenalidomide						7. Nirogacestat PK samples to be taken in all participants: Cycle 1 Day -2 – to be collected following baseline vital signs assessment: predose (within 30 min prior to nirogacestat dosing) and at 0.5 h (±5 min), 1 h (±5 min), 2 h (±15 min), and 4 h (±15 min) after nirogacestat first dose; C1D1, and C1D8 – predose (within 30 min prior to nirogacestat dosing). C2D1 – predose (within 30 min prior to nirogacestat first dose) and at 0.5 h (±5 min), 1 h (±5 min), 2 h (±15 min), and 4 h (±15 min) after nirogacestat dosing. On days with PK sampling time points, vital signs should be assessed prior to PK samples being drawn. If belantamab mafodotin dosing at C2D1 is
Administration of lenalidomide		X[16, 19]	X[16, 19]	X[16, 19]	X[16, 19]	
VTE prophylaxis		X[17]	X[17]	X[17]	X[17]	
Pregnancy Prevention Counseling		X			X	
Treatment with Dexamethasone						
Administration of dexamethasone		X[18, 19]		X[18, 19]	X[18, 19]	

Study Assessments	Day -2 (prior to Cycle 1 Day 1)	Cycle 1 Day 1 (Week 1)	Cycle 1 Day 4 (±1 day) (DE only)	Cycle 1 Day 8 and Day 15	Cycle 2 to EOT	Notes
						delayed, nirogacestat PK sample still to be collected. Pharmacokinetic and accompanying sBCMA sample collection may be terminated when sufficient data have been collected. 8. ADA serum samples will be collected predose (within 30 min prior to belantamab mafodotin SOI except for Cycle 1 which will be within 2 h prior to belantamab mafodotin SOI) at: Cycles 1, 2, 4, 6, 9, 12 and 18 or up to the primary cutoff date or closure of sub-study by sponsor, whichever comes first. 9. Belantamab mafodotin PK samples to be taken in all participants. Predose samples to be taken before nirogacestat dose. Vital signs should be assessed prior to PK samples being drawn. C1D1 – predose (within 30 minutes prior to belantamab mafodotin SOI), EOI (0 – 10 min after belantamab mafodotin EOI); at 2 h (±15 min) after belantamab mafodotin SOI;– C1D8 – anytime; C2D1 –predose (within 30 min prior to belantamab mafodotin SOI); C2D1 EOI (0 – 10 min after belantamab mafodotin EOI); C4D1, C6D1, C9D1, C12D1 – predose (within 30 min prior to belantamab mafodotin SOI) and EOI (0 – 10 min after belantamab mafodotin EOI) and C18D1 – predose (within 30 min prior to belantamab mafodotin SOI) or up to the primary cutoff date or closure of sub-study by sponsor, whichever comes first. Pharmacokinetic and accompanying sBCMA sample collection may be terminated when sufficient data have been collected. 10. To be collected prior to dosing at C1D1, C2D1, C3D1, and at PD. 11. Please refer to 208887 MP Section 6.6.3 for guidance on dose delays, reduction, and modification. For Q4W: The next scheduled dose must be administered every 28 days (+3-day window) since prior/last dose and cannot be given sooner/more frequently than this. For Q8W: The next scheduled dose must be administered every 56 days (+3-day window) since prior/last dose and cannot be given sooner/more frequently than this. For

Study Assessments	Day -2 (prior to Cycle 1 Day 1)	Cycle 1 Day 1 (Week 1)	Cycle 1 Day 4 (±1 day) (DE only)	Cycle 1 Day 8 and Day 15	Cycle 2 to EOT	Notes
						Q12W: The next scheduled dose must be administered every 84 days (+3-day window) since prior/last dose and cannot be given sooner/more frequently than this. If in the judgment of the investigator, treatment needs to be initiated prior to the next planned scheduled dose following a dosing delay and where clinical toxicity has resolved, please discuss with the Medical Director. Please see Section 6.2. All assessments should remain on schedule with the exception of those associated with dosing. Belantamab mafodotin will be administered as an IV infusion (see Section 6.1 for details) 12. Premedication should be considered and should be considered in any participant who experienced an infusion related reaction at first or any subsequent infusion with belantamab mafodotin or partner combination see Section 6.2. 13. Supportive Care information: a. Prophylactic preservative-free artificial tears should 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. Corticosteroid eye drops are not required but can be used if clinically indicated per the discretion of the qualified eye care specialist (see 208887 MP Appendix 10). Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops (if administered). b. At the start of each infusion, participants may apply cooling eye masks to their eyes for approximately 1 h or as long as tolerated. c. For participants with history of dry eyes, or participants who develop dry eye during study treatment, the eye care specialist should consider use of additional products/treatments as per local institutional guidance. 14. Administration of nirogacestat BID with the first administration to occur at least 1 hour before administration of belantamab

Study Assessments	Day -2 (prior to Cycle 1 Day 1)	Cycle 1 Day 1 (Week 1)	Cycle 1 Day 4 (±1 day) (DE only)	Cycle 1 Day 8 and Day 15	Cycle 2 to EOT	Notes
						mafodotin. A maximum gap of 12 hours is acceptable between belantamab mafodotin infusion and nirogacestat. 15. Patient Dosing Diary Card for nirogacestat, lenalidomide and dexamethasone to be provided to participant with start of every cycle and to be collected at the end of cycle. 16. Lenalidomide: 25 mg orally daily on Days 1 – 21 of each cycle in participants with eGFR >60 mL/min/1.73 m² or reduced to 10 mg daily if the eGFR is 40-60 mL/min/1.73 m². [Refer to lenalidomide PI]. Refer to Section 6.6 for dose modification guidance. 17. ASA, LMH or oral anticoagulants according to institutional guidance for the duration of treatment with lenalidomide. 18. Dexamethasone: 40 mg weekly, orally or intravenously, Participants who are >75 y with BMI <18.5 kg/m², 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 6.6 for dose modification guidance. 19. On days where only nirogacestat, lenalidomide and dexamethasone are taken at home, they should be taken 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.

Table 6 SoA – End of Treatment (EOT) and Follow-up for Sub-study 6: Belantamab Mafodotin, Nirogacestat, Lenalidomide, and Dexamethasone

Study Assessments	End of Treatment Visit[1]	PFS Follow-up[2]	OS Follow-up[3]	Notes
All assessments will apply to both the DE and CE Phases unless otherwise specified.				
Physical Exam	X	X		1. EOT safety assessments to occur within 30 days from when decision made to discontinue treatment and prior to the new anti-MM treatment (whichever occurs first). 2. PFS follow-up every 28 days (±7 days) for participants who discontinue study treatment for a reason other than PD. Disease evaluations will continue until confirmed PD, death, start of a new anti-cancer treatment, withdrawal of consent, or end of the study whichever occurs first. Once participant progresses, move to OS follow-up. 3. The survival for MM will be documented in medical charts. No visit necessary. Contacts will be made via phone calls, emails or other means of communications every 12 weeks (±14 days) until end of study. Participant does not need to come in for visit unless they are being followed for corneal signs that are present at the end of study treatment. 4. AEs/SAEs will be collected until at least 70 days after the last dose of study treatment. All SAEs related to study participation (e.g., protocol mandated procedures, tests, or change in existing therapy) are to be collected from consent through OS follow-up. All AEs/SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up. Concomitant medications administered after EOT should be recorded when given for SAEs/AESIs as defined in 208887 MP Section 8.3. 5. End of treatment ophthalmic exam to be performed by an eye care specialist. See 208887 MP Section 8.2.7 for list of exams. 6. Participants with a treatment-related corneal exam findings, ocular symptoms and/or change in vision at EOT will be followed every 3 months (±7 days), or more frequently if clinically indicated, until return to baseline, deemed clinically stable by the qualified eye care specialist (see 208887 MP Appendix 10), or up to 12 months (whichever comes first). Clinically stable is defined as changes ≤Grade 1. See 208887 MP Section 8.2.7 for list of exams. 7. CBC and chemistry panel may be done more frequently as clinically indicated. Refer to 208887 MP Appendix 2 for comprehensive list of lab tests. 8. Final pregnancy test (serum or urine) must be performed per 208887 MP Section 12.2. Follow-up pregnancy assessments should be performed per 208887 MP Section 12.7.3. 9. eGFR as calculated by MDRD formula (208887 MP Appendix 6).
AEs	X[4]	Related SAEs only[4]	Related SAEs only[4]	
Concomitant Medications	X	X		
Pregnancy Prevention Counseling	X	X	X	
Safety				
Ocular Exam	X[5]	X[6]	X[6]	
ECOG Performance Status	X	X		
Hematology (CBC)	X[7]	X[7]		
Clinical chemistry	X[7]	X[7]		
Pregnancy Test	X[8]	X[8]	X[8]	
eGFR	X[9]			
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)	X[10]			
ECHO or MUGA scan for LVEF	X[11]			
Disease Evaluation				
UPEP 24 hr urine collection	X[17]	X[17]		
Urine immunofixation 24 hr urine collection	X	X		
SPEP	X	X		
Serum immunofixation	X	X		
Serum FLC assay	X	X		

Study Assessments	End of Treatment Visit[1]	PFS Follow-up[2]	OS Follow-up[3]	Notes
All assessments will apply to both the DE and CE Phases unless otherwise specified.				
IgG, IgM, IgA	X	X		10. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥2+, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab (first void). 11. ECHO or MUGA for LVEF scan only done as clinically indicated. The same procedure used at Screening should be used throughout the study. 12. IgD/IgE testing is only required for participants with IgD or IgE myeloma. 13. Imaging of bones for lytic lesions by a method aligned with the institutional guidance (X-ray, CT, or MRI). X-ray is acceptable for lytic disease. 14. At the time of suspected disease progression or as clinically indicated. Same modality used at Screening should be used throughout study. 15. In participants with extramedullary MM, if the last radiographic assessment occurred ≥8 weeks prior withdrawal from study treatment, and PD has NOT been documented otherwise, a new assessment should be obtained at the time the participants withdrew from study treatment. 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). 16. Please refer to Table 7 for scheduled BM collection procedures to include aspirate and biopsy. 17. UPEP will only be performed for participants who had detectable M-protein only in the urine at Screening. For all other participants, if UPEP is negative at Screening, then UPEP will be performed only after a tumor response based on SPEP protein during treatment is observed, where UPEP on 24 hours urine sample is required to confirm the response per IMWG criteria.
IgD or IgE	X[12]	X[12]		
Calcium corrected for albumin (serum)	X	X		
Skeletal survey	X[13,14]	X[13,14]		
Imaging for Extramedullary Plasmacytoma Assessment (by whole body CT or whole-body MRI or CT/PET)	X[14,15]	X[14,15]		
PK and ADA				
Plasma PK for belantamab mafodotin	X			
Serum Immunogenicity (ADA) for belantamab mafodotin	X			
BM Aspiration/Biopsy				
BM aspirate for MRD testing		X[16]		
BM aspirate and/or core biopsy for Disease assessment	X[16]	X[16]		
BM core biopsy to assess sCR (local)	X[16]	X[16]		
BM aspirate for BCMA expression and biomarker research	X[16]			

Table 7 SoA - Bone Marrow Aspirate/Biopsy Collection

Timepoint	BM aspirate for FISH testing [1,3]	BM (core biopsy and/or aspirate) for disease assessment[1]	BM aspirate for MRD testing for disease assessment[2,6]	BM aspirate for BCMA expression and biomarker research[2]
Screening	X[4]	X[4]	X	X
Between C3D1 and C5D1 (predose belantamab mafodotin)				X[7]
VGPR or suspected CR/sCR	X[5]	X[5]	X	
Suspected PD (only if PD not evident otherwise)		X[5]		
PD				X[7]

1. These assessments will be performed at a local laboratory. For FISH testing, if testing cannot be performed at a local lab the samples can be sent to the central lab.
2. These assessments will be performed at a central laboratory.
3. See Table 31 in 208887 MP for details on FISH.
4. At Screening, IHC of bone marrow core biopsy is preferred for quantitative assessment of malignant plasma cells. However, bone marrow aspirate is acceptable and should be performed within 60 days of C1D1. Archival tissue from up to 60 days prior to C1D1 is acceptable.
5. At EOT or during PFS follow-up, only to confirm CR/sCR or suspected PD at this visit for plasma cell assessment by IHC or aspiration. For sCR in participants achieving a CR, BM core biopsy is required to confirm sCR by IHC for absence of clonal cells. Only 1 marrow procedure required for CR and sCR assessment.
6. MRD samples to be collected at Screening, and at the time of first achieving VGPR or better. Thereafter, MRD testing must be repeated every 6 months (±1 month) until PD. This also applies to participants who discontinue IP for reasons other than PD and have current disease response of VGPR or better. In case of deepening of response from VGPR to CR, or achieving CR without prior VGPR, MRD testing must be performed at the time of achieving suspected CR and repeated every 6 months (±1 month) until PD. Sample collection may be terminated when sufficient data have been collected, and this applies across all sub-studies. Note that MRD testing will be done by NGS method.
7. **Optional BM consent required.** Additional BM aspirate samples may be collected at any time during the study for biomarker research (as indicated for each sub-study) and if possible, as part of the same BM collection for disease assessments including MRD. Sample collection may be terminated when sufficient data have been collected.

Table 8 SoA – Additional Procedures for Participants HBcAb Positive

The procedures listed in this table apply ONLY to participants in Screening or who have been enrolled and who have positive HBcAb; all procedures must be done in addition to the required procedures for all participants detailed in Table 3 to Table 7.

HBV Study Assessments	During Screening / Prior to starting treatment	During Treatment	EOT	Notes
HBV-DNA testing	X	X	X	HBV-DNA testing prior to the start of belantamab mafodotin and subsequently every 3 months (may be grouped with closest study visit), or if liver function test elevations requiring increased monitoring or stopping criteria occur, or for any clinical suspicion of hepatitis reactivation.

2. INTRODUCTION

Please refer to the 208887 MP for the overall introduction to belantamab mafodotin and Platform Study design.

Information and details specific to Sub-study 6 are in Section 2.1, Section 2.2 and Section 2.3 below.

2.1. Rationale for the Combination of Belantamab Mafodotin, Nirogacestat, Lenalidomide, and Dexamethasone

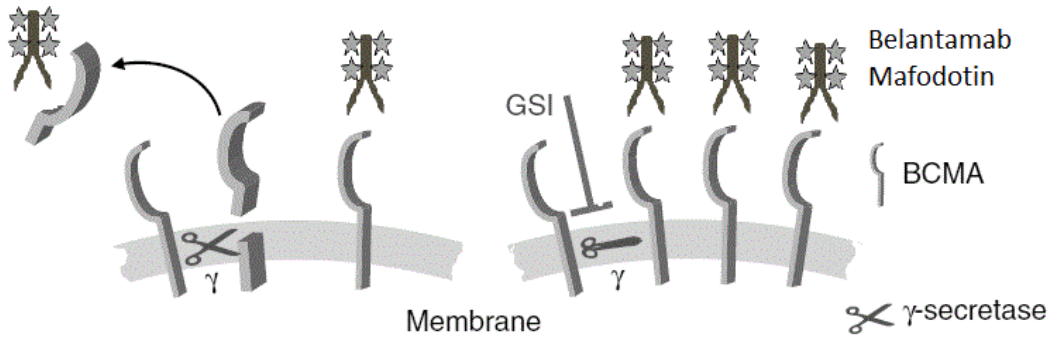
This sub-study will evaluate the safety and tolerability profile of belantamab mafodotin and nirogacestat when administered in combination with an approved SoC regimen of lenalidomide and dexamethasone in participants with RRMM.

2.1.1. Rationale for the Combination of Belantamab Mafodotin, Nirogacestat

The combination of belantamab mafodotin and nirogacestat was proposed in Sub-study 3 of DREAMM-5 and emerging data (belantamab mafodotin 0.95 mg/kg [Q3W] in combination with continuous nirogacestat 100 mg PO BID) demonstrate that these 2 agents can be combined into a safe and effective regimen for patients with RRMM.

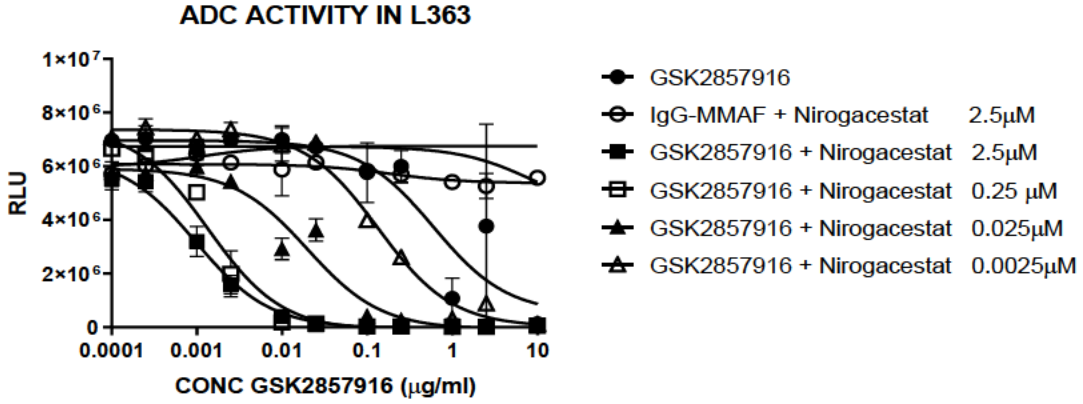
The mechanism for how GSI may potentially enhance the clinical activity of belantamab mafodotin is not yet determined but includes: 1) Increased cell surface expression of BCMA would increase the amount of belantamab mafodotin bound to the cell surface, potentially enhancing the ADCC mechanism of belantamab mafodotin through increased FcγR interaction and immune cell recruitment; 2) blocking shedding of BCMA would potentially enhance the delivery of the cys-mcMMAF toxin inside multiple myeloma cells leading to direct cell kill; and 3) reduced sBCMA concentrations in circulation would allow for more belantamab mafodotin availability to bind BCMA in MM cells (Figure 1).

Figure 1 **Enhancement of belantamab mafodotin mechanism of action by gamma-secretase Inhibition**



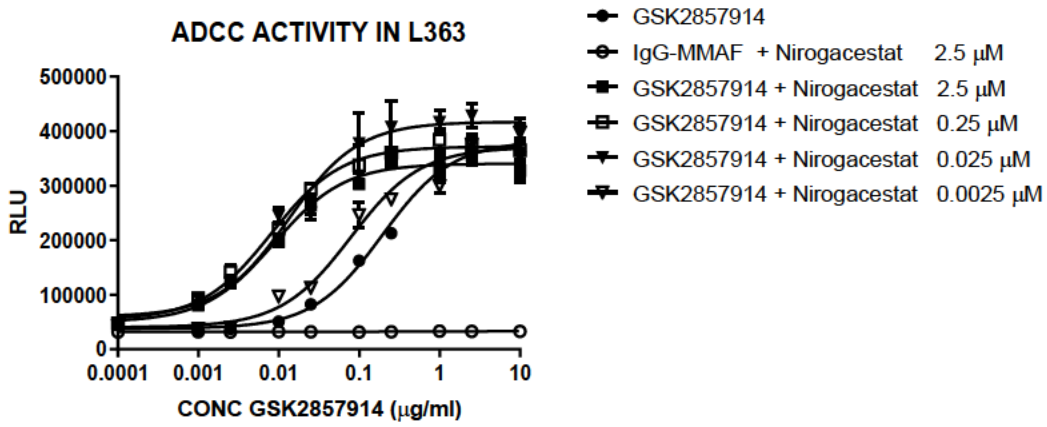
In preclinical experiments, using a panel of multiple myeloma and lymphoma cell lines with varying levels of BCMA expression, broad synergy was observed with combination treatment of nirogacestat and belantamab mafodotin in assays designed to measure ADC and ADCC activity. In the example shown in Figure 2 the multiple myeloma cell line L363 was pre-treated with 4 different concentrations of nirogacestat for 24 hours, then treated with a dose range of belantamab mafodotin or controls for an additional 72 hours and cell viability was measured. Nirogacestat alone or the combination of conjugated isotype antibody (IgG-MMAF) and nirogacestat had no effect on cell viability. However, a maximum 1,000-fold shift in EC50 was observed with the combination of nirogacestat and belantamab mafodotin over belantamab mafodotin alone. Similar log-fold shifts were observed with the combination of nirogacestat and belantamab mafodotin in 19 additional multiple myeloma and lymphoma cell lines with evidence of belantamab mafodotin activity.

Figure 2 **Viability of L363 cells treated with different concentrations of nirogacestat in combination with belantamab mafodotin or control IgG-MMAF**



In the example shown in Figure 3, ADCC activity of the unconjugated version of belantamab mafodotin, designated GSK2857914 or belantamab, in combination with nirogacestat was evaluated. L363 cells were pre-treated with different concentrations of nirogacestat for 24 hours, exposed to a dose range of belantamab, and FcγR engagement was evaluated with an engineered Jurkat cell line. The EC50 for FcγR engagement was enhanced 10-fold by the combination of nirogacestat and belantamab over belantamab alone. Therefore, preclinical data evaluating both ADC and ADCC modes of action support the mechanistic rationale for enhancing belantamab mafodotin therapeutic activity through γ-secretase inhibition.

Figure 3 **ADCC activity of L363 cells treated with different concentrations of nirogacestat in combination with GSK2857914 or control IgG-MMAF**



In additional preclinical studies, multiple myeloma cell lines produced sBCMA which was reduced in a dose-dependent manner by γ-secretase inhibition as measured by ELISA in cell culture supernatants. Moreover, continuous exposure of cell lines to a γ-secretase inhibitor did not result in any alteration of BCMA RNA expression (not shown), indicating that no regulatory feedback loop exists between BCMA cleavage, soluble BCMA levels and BCMA gene expression.

Gamma-secretase inhibition may also contribute to belantamab mafodotin activity through modulation of NOTCH signaling. Although nirogacestat has not been evaluated in RRMM to date, preclinical data support the role of NOTCH signaling in the pathophysiology of MM (reviewed in [Colombo, 2015]). Although NOTCH activating mutations are uncommon in multiple myeloma, results of in vivo preclinical experiments using other GSIs (e.g., RO4929097) have shown that NOTCH signaling attenuation in MM has favorable remodeling effects on the bone marrow tumor microenvironment, which results in MM plasma cell cytoreduction via anti-angiogenic and/or immune-mediated effects [Pisklakova, 2016]. Therefore, GSIs might have the additional potential to contribute to anti-myeloma effects in combination with belantamab mafodotin through NOTCH signaling inhibition in the bone marrow microenvironment.

2.1.2. Rationale for the Combination of Belantamab Mafodotin, Nirogacestat, Lenalidomide, and Dexamethasone

Furthermore, belantamab mafodotin has been evaluated in combination with lenalidomide plus dexamethasone in GSK-sponsored DREAMM-6 at, belantamab mafodotin doses of 1.9 mg/kg and 2.5 mg/kg; this combination has been demonstrated to be safe and effective in patients with RRMM. Nonclinical data demonstrated that the activity of belantamab mafodotin is enhanced by lenalidomide in cultured myeloma cell lines and patient myeloma cells [Tai , 2014; Tai, 2015]. Additionally, nonclinical data with belantamab mafodotin suggest significant added benefit (efficacy and survival) when combined with lenalidomide and/or dexamethasone in established MM xenograft models [GSK Document No. RPS-CLIN-105644, 2024].

Given the previous experience with monoclonal antibodies, which exhibited lower single agent activity as monotherapy in similar populations, the combination therapy of belantamab mafodotin plus nirogacestat with SoC agents is an attractive option to explore for participants with RRMM who have been pre-treated with ≥3 prior lines. The combination with SoC therapies (e.g., lenalidomide/dexamethasone) 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.

2.2. Background

2.2.1. Gamma-Secretase and BCMA

Gamma (γ)-secretase is an integral membrane protein complex with protease activity against single-pass transmembrane proteins within the transmembrane domain [Wolfe, 2010], such as amyloid precursor protein and the NOTCH receptor. Nirogacestat (PF-03084014) is a potent selective, non-competitive, reversible tetralin amino imidazole GSI, which belongs to a chemically heterogenous family of GSI small molecules, which inhibit the cleavage of several different cell surface receptors. Nirogacestat has been shown, when administered on a continuous dosing schedule in refractory solid tumors, T-cell acute lymphoblastic leukemia and desmoid tumors, to trigger disease responses that are consistent with downregulation of NOTCH target genes (e.g., HES4).

One of the substrates for γ-secretase is BCMA, the target for belantamab mafodotin [Laurent, 2015]. BCMA is unusual among γ-secretase substrates in that it does not require additional proteolytic steps either before or after γ-secretase cleavage for release of the extracellular domain of BCMA as a soluble form, known as sBCMA. Gamma secretase is the sole enzyme responsible for production of sBCMA and inhibition of γ-secretase reduces sBCMA and increases cell surface levels of BCMA on plasma cells, both in vitro and in vivo. In the context of multiple myeloma, the levels of sBCMA are elevated in multiple myeloma patients and this is correlated with the percentage of plasma cells in the bone marrow [Sanchez, 2018].

Sub-study 3, belantamab mafodotin in combination with nirogacestat, is investigating this combination based on the strong signals of therapeutic synergism demonstrated from in vitro preclinical experiments with belantamab mafodotin and nirogacestat.

2.2.2. Clinical Development of Nirogacestat in Monotherapy and Combination Studies

NOTCH pathway activation is a frequent occurrence in multiple human tumors. Over 50 clinical studies have been performed to date with GSIs in cancer. To date, nirogacestat has been investigated in >200 human participants in either Phase 1 or Phase 2 studies including normal healthy volunteers and patients with T-cell acute lymphoblastic leukemia and metastatic solid tumors, and its development in Alzheimer's disease was terminated due to its poor blood-brain barrier penetrance. Based on the favorable safety and preliminary efficacy results of a Phase 2 studies in aggressive fibromatosis (desmoid tumors) [Kummar, 2017], 150 mg BID nirogacestat continuous administration has been

evaluated in a randomized Phase 3 placebo-control desmoid tumor study that showed that nirogacestat had a significant progression-free survival benefit over placebo (hazard ratio for disease progression or death, 0.29; 95% confidence interval, 0.15 to 0.55; P<0.001) [Gounder, 2023].

As a combination treatment in solid tumors, a total of 32 participants have been exposed to nirogacestat in combination with either docetaxel (29 participants) or nab-paclitaxel (3 participants) in Phase 1 studies in triple negative breast cancer (NCT02299635 and NCT01876251) and metastatic pancreatic ductal adenocarcinoma (NCT02109445), respectively [Locatelli, 2017].

2.2.3. Nirogacestat Pharmacokinetics

Nirogacestat PKs were characterized by a rapid absorption with a median time of occurrence of Cmax (Tmax) values of 1 to 2.5 hour. Nirogacestat is eliminated slowly with a terminal half-life ranging from 22.6 to 38.6 hours in oncology patients. Nirogacestat exposure increased generally in a dose-proportional fashion between 20 and 330 mg BID. Following repeated BID administration, steady state was achieved by Day 8 and the median accumulation ratio ranged from 1.18 to 2.84.

2.2.4. Nirogacestat Monotherapy Safety Data

To date, important identified risks related to nirogacestat include Notch-related effects on reproductive function and female fertility, hematopoietic (immune) cells, GI function, and skin rash. Events of hypophosphatemia, hypokalemia, mucosal inflammation / stomatitis, and effects on the hepatic system, including potential liver cholestasis are also considered important identified risks. Important potential risks include effects on male fertility, embryo-fetal development, and effects on the musculoskeletal system.

To date, the safety profile of single-agent nirogacestat in participants with advanced cancer has been characterized by manageable and reversible toxicities. The most frequently reported AEs were diarrhea, fatigue, nausea, vomiting, hypophosphatemia, cough, and rash. The majority of the AEs were mild-to-moderate in intensity. In a Phase 2 study of nirogacestat administered as a single agent in the treatment of patients with advanced metastatic triple negative breast cancer, 19 participants received nirogacestat monotherapy at a starting dose of 150 mg BID given orally and continuously in 21-day cycles. In that study the most commonly reported treatment-emergent AEs (≥ 20% of participants), regardless of causality, were diarrhea (57.9%), fatigue and nausea (42.1% each), vomiting and hypophosphatemia (36.8% each), pyrexia (31.6%), and cough (26.3%). The most common treatment-emergent AEs deemed treatment-related were diarrhea (47.4%), nausea and vomiting (36.8% each), fatigue (31.6%), and hypophosphatemia (26.3%). Additionally, a Phase 2 (investigator-initiated) study in adult participants with desmoid tumors showed a similar AE profile [Kummar, 2017]. All participants in the study experienced at least 1 Grade 1 or Grade 2 AE; with the most commonly reported AEs being diarrhea and skin disorders.

Of the 64 participants with solid tumors, 62 experienced at least 1 AE, and 54 experienced at least 1 treatment-related AE (1 participant with a Grade 1 AE of upper respiratory infection was excluded from the analysis due to a database error). The most

common treatment-related AEs were diarrhea, nausea, fatigue, hypophosphatemia, vomiting, rash, and decreased appetite. The majority of these AEs were Grade 1 to Grade 3. Dose reductions due to treatment-related AEs were infrequent and were reported in 9 (14%) participants at various times during treatment (from Cycle 1 to Cycle 10). Across dose levels, 5 (7.8%) participants had Grade 2 or Grade 3 diarrhea that resolved with dose reduction. Temporary discontinuation occurred in 21 (32.8%) participants, 13 (20.3%) of which were for a treatment-related AE. All treatment-related AEs that led to temporary discontinuation (diarrhea, hypophosphatemia, rash, nausea, vomiting, and fatigue) or dose reduction were Grade 1 to Grade 3, and most resolved following temporary discontinuation or dose reduction. Seven (10.9%) participants permanently discontinued treatment primarily owing to an AE; of these, 4 (6.3%) participants discontinued for a treatment-related AE: 1 each for Grade 4 anaphylactic shock (100 mg BID) (an event thought to be related to co- administration of IV morphine), Grade 1 visual impairment (150 mg BID), Grade 3 drug hypersensitivity (220 mg BID), and Grade 3 rash (330 mg BID). The hypersensitivity reaction (rash associated with chest tightening and shortness of breath) resolved with intravenous steroid therapy after discontinuation of study treatment.

Preclinical toxicology studies utilizing nirogacestat have been conducted. In an embryo fetal developmental toxicity study in rats, nirogacestat induced significant embryo loss, resorptions and decreased fetal weights in surviving embryos. In a rat fertility study, nirogacestat decreased fertility due to decreased early embryo-fetal implantation and early embryonic loss. These effects occur at systemic exposures below those in humans administered 150 mg of nirogacestat BID.

Reproductive system effects have been observed in nonclinical and clinical studies with nirogacestat. In the repeat dose 1-month and 3-month toxicology studies in the rat, ovarian atrophy, a decreased number of follicles, asynchrony of the estrous cycle, and decreased ovarian weights were observed. In the repeat 3-month toxicology study in dogs, Sertoli cell degeneration in the testis, oocyte mineralization in the ovaries, and asynchrony of the estrous cycle were observed. These effects occurred at systemic exposures below those in humans administered 150 mg BID of nirogacestat. Events of primary ovarian insufficiency (e.g., hot flashes, amenorrhea, hormonal changes) have also been reported in clinical studies with nirogacestat. It is unknown if events of primary ovarian insufficiency are reversible after stopping nirogacestat. The effects on long term fertility are also unknown in males and females.

Participants may consider fertility preservation (egg or sperm preservation) prior to starting nirogacestat. Low dose selective serotonin reuptake inhibitors may be considered for the treatment of vasomotor symptoms associated with primary ovarian insufficiency as clinically indicated.

Additionally, risk measures are in place to minimize potential risks to study participants, and review of safety data will be conducted on an ongoing basis in order to identify new safety signals that may arise during the program.

More detailed information regarding toxicology and safety data in clinical studies with nirogacestat may be found in the IB [Nirogacestat, 2023].

Details regarding risks, and risk mitigation strategies for this study are described in Section 2.3.1.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of belantamab mafodotin may be found in the IB [GSK Document No. RPS-CLIN-105644, 2024].

2.3.1. Summary of Risk Assessment

Belantamab mafodotin: More detailed information about the known and expected benefits and risks and reasonably expected AEs of belantamab mafodotin may be found in the IB [GSK Document No. RPS-CLIN-105644, 2024]. Belantamab mafodotin risk assessment and mitigation strategies are in the 208887 MP Section 2.3.1.

Nirogacestat: Table 9 outlines the risk assessment and mitigation strategy for nirogacestat in this study.

Lenalidomide and dexamethasone: Details on risks for lenalidomide and dexamethasone can be found in respective prescribing information; see SRM.

Belantamab, nirogacestat, lenalidomide, dexamethasone combination: Table 10 outlines potential overlapping toxicities with the combination of belantamab, nirogacestat, lenalidomide, and dexamethasone.

Table 9 Risks Related to Nirogacestat

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risk related to Nirogacestat		
Effects on hematopoietic (immune) cells	In a healthy volunteer study, dose-related trends for increases in eosinophils and immature B-cell subsets were observed after administration of nirogacestat 95 mg daily. These observations although deemed clinically not important were interpreted as potentially indicative of the effects of nirogacestat on the Notch receptor. In single agent studies with nirogacestat, most hematologic abnormalities were mild to moderate in severity. Lymphopenia was the most common hematologic Grade 3 abnormality.	CBC will be monitored on Day 1 before each cycle, Day 8 for Cycles 1-6, and Day 15 for Cycles 1-2 per 28-day cycle and as clinically indicated.
Electrolyte Abnormalities Mainly hypophosphatemia, but can include hypokalemia and hypomagnesemia	Grade 3 hypophosphatemia was common in clinical studies of cancer patients occurring in 37.5-44.4% of participants. Most events were managed by oral phosphorus supplements. Hypophosphatemia has been observed with other GSIs and may be related to GI loss.	Electrolytes will be regularly monitored, with increased frequency as clinical indicated. Participants should be advised on clinical symptoms associated with hypophosphatemia and advised to contact the clinic should they experience such symptoms.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Electrolyte abnormalities will be promptly treated and monitored per local standard of care, including other potential clinical abnormalities associated with significant electrolyte derangements. Specialist metabolic advice should be sought by the investigator when managing and treating participants with severe (≥Grade 3) electrolyte insufficiencies or for persistent electrolyte deficiencies which are refractory to routine supplementation.
DDI with strong or moderate CYP3A4 inhibitors or inducers	Concomitant administration of the drugs listed in Section 6.5.2.1 could potentially either increase or reduce systemic exposure of nirogacestat dependent on whether the drug is a CYP3A4 inhibitor or inducer, respectively.	Concomitant administration of strong CYP3A4 inhibitors or inducers is not permissible in this sub-study. Guidance on concomitant moderate inhibitors is in Section 6.5.2.
Reproductive System Effects	Adverse effects to reproductive organs in repeat dose toxicology studies were observed in male dogs and female rats. Events of primary ovarian insufficiency have been reported. It is unknown if these events are reversible after stopping nirogacestat.	Participants may consider fertility preservation (egg or sperm preservation) prior to starting study medications. Contraception requirements detailed in 208887 MP Section 5.1, 208887 MP Appendix 7, and Section 8.3.7.

Table 10 Risks Related to the Combination

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential overlapping toxicities for belantamab mafodotin/nirogacestat/lenalidomide/dexamethasone		
Thrombocytopenia	**Belantamab mafodotin** may cause transient thrombocytopenia in some participants, which for most cases recovered between doses. In Study 205678, which included participants treated with belantamab mafodotin 2.5 mg/kg, thrombocytopenia was noted in 38 % of participants and ranged between Grade 1 to 4 in severity. **Lenalidomide** can cause significant thrombocytopenia.	Routine monitoring of hematologic panels as outlined in the SoA. Supportive therapy per local medical practice (e.g., platelet transfusion, growth factors). Prophylactic antibiotics, per local institutional guidance, in participants with Grade 3-4 neutropenia. Immediately hospitalization of participants with febrile neutropenia. Dose modification guidelines are outlined in Section 6.6.
Keratopathy (changes to the corneal epithelium, potentially resulting in vision changes)	**Belantamab mafodotin**: Changes in the corneal epithelium on ocular examination have been frequently observed with belantamab mafodotin, such as superficial punctate keratopathy,	Active monitoring of the corneal epithelium and visual acuity as outlined in the SoA.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	microcyst-like changes, sub-epithelial haze, corneal erosions, and corneal ulcers. These were most commonly associated with keratopathy (changes in the corneal epithelium upon examination), dry eyes, blurred vision, and changes in visual acuity. Participants with a history of dry eye were more prone to develop changes in the corneal epithelium. Based on available follow-up data, visual acuity returned to, or near baseline in most cases and no permanent loss of vision reported. Corneal ulcers or erosions are distinguished by the presence or absence of stromal involvement, respectively. The precise incidence has yet to be defined. The corneal defects (with or without stromal involvement) appeared as early as the second or third cycle but in most cases after 5 or more cycles of treatment. **Nirogacestat**: NOTCH and gamma-secretase are both present on corneal limbal stem cells and epithelial cells and are constitutively involved in corneal tissue repair after local injury. If nirogacestat is present at pharmacologically relevant concentrations in the tear film (this is unknown to date), there could be a potential risk that belantamab mafodotin-related microcystic epithelial keratopathy could be enhanced by nirogacestat. Nirogacestat monotherapy has not been associated with any anterior chamber ocular safety signals in previous human studies **Dexamethasone**: Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.	In the event of new-onset eye-related symptoms (such as pain, significant loss of visual acuity, or bothersome foreign body sensation), participants are to urgently seek medical attention by a qualified eye care specialist (appropriate testing includes slit lap examination [includes fluorescein staining] and measurement of visual acuity). Appropriate management should be initiated immediately as defined in 208887 MP Section 7.1.2.
GI: Diarrhea, nausea, vomiting or dyspepsia (gastroesophageal reflux), decreased appetite	**Nirogacestat**: In both rats and dogs, treatment-related intestinal tract changes consisting of epithelial hyperplasia and at higher doses, degeneration and necrosis were observed. These are considered mechanism-related and consistent with published effects of GSI on Notch. Treatment emergent GI symptoms have been observed in clinical study participants in both monotherapy and combination treatment studies, most commonly nausea, vomiting and diarrhea. Most were mild/moderate in intensity and responded to standard medication and temporary dosing interruptions or dose reductions.	Prophylactic use of an antidiarrheal medication to prevent diarrhea in patients receiving nirogacestat is therefore strongly recommended. If use of antidiarrheal medication for a particular participant is deemed by the investigator to be clinically inappropriate, please contact the medical director to discuss plan for diarrhea prevention. Diarrhea frequency will be monitored every 28 days/4 weeks, may utilize a

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Median time to onset of diarrhea is noted to be 9 days after the first dose of nirogacestat. **Lenalidomide:** Diarrhea, abdominal pain, nausea, and constipation are very commonly reported events. Grade 3 or 4 events of diarrhea, vomiting, and nausea are reported commonly.	stool chart if available or patient dosing diary. Body weight and eGFR will be evaluated per cycle with potential for increased frequency dependent on the frequency of GI/diarrheal symptoms ±hydration status of the participant. Dose interruption, delay and/or dose modification of nirogacestat is detailed in Section 6.6.3.1. Supportive measures for diarrhea: Intravenous hydration and electrolyte supplementation as clinically indicated. Use of Loperamide or similar anti-motility drugs. Use of systemic steroids for diarrhea which is refractory to loperamide and / or other supportive measures e.g., ≥Grade 2 diarrhea lasting for 7 consecutive days or longer despite other supportive measures. **Lenalidomide**: See Table 17 and Table 18 for dose modification guidelines.
Skin Rash	**Nirogacestat**: Skin rash is thought to arise as a result of NOTCH signaling inhibition in cutaneous stem cell compartments, and findings were consistent in rat studies. In single agent clinical studies, nirogacestat-associated skin rashes have occurred in a variety of different morphologies (rash, exfoliative rash, pruritic rash). Most reported to date were mild or moderate severity and were managed through standard medications (topical steroids and/or antihistamines) and temporary dosing interruptions or dose reductions. Median onset of rash is 13 days after first nirogacestat dose. **Lenalidomide**: Cases of allergic reactions including angioedema, anaphylactic reaction and severe cutaneous reactions including SJS, TEN and DRESS have been reported	Participants will be advised to contact the investigator should a rash of any type occur. **Nirogacestat**: Refer to Section 6.6.3.3 for skin rash stopping criteria, dose modification & dose delay guidance. Referral to a dermatologist and review for a potential skin biopsy is advisable for Grade 2 skin rashes lasting longer than 21 days and are refractory to topical steroids and/or antihistamines, or for Grade 3 rashes which are present for ≥72 consecutive hours. If hidradenitis suppurativa is suspected, referral to dermatologist is recommended for immediate antibiotic administration.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Lenalidomide: Refer to Section 6.6.4 (Table 17) for skin rash stopping criteria, dose modification & dose delay guidance.
Elevated Liver Enzymes	**Nirogacestat**: Abnormal LFTs (liver function tests; primarily transient ALT/AST elevations) have been reported in patients receiving nirogacestat. The majority of occurrences were Grade 1 or 2, asymptomatic, and resolved without treatment. Approximately 4% were Grade 3. Two SAEs were reported (worsening of hepatic enzymes and AST/ALT increased), both deemed possibly related to nirogacestat but were confounded by comorbid conditions. **Lenalidomide**: Abnormal liver function tests were commonly reported and were generally asymptomatic and reversible upon dosing interruption. **Belantamab mafodotin**: Elevated liver enzymes including AST, ALT, gamma glutamyl transferase and bilirubin have been observed in clinical studies with belantamab mafodotin.	Liver function tests will be monitored on 28-day/4-week basis and on Day 1 and Day 15 or more frequently as clinically indicated. GSK liver stopping and monitoring criteria will be used as described in the 208887 MP Section 7.1.1 and 208887 MP Appendix 9. **Nirogacestat**: dose modifications for LFT abnormalities may be found in Section 6.6.3.4.
Increased infections due to immunosuppression or neutropenia	**Belantamab mafodotin**: In nonclinical studies, belantamab mafodotin has been associated with decrease in immunoglobulins in monkeys, at all doses. An increase in immunoglobulins was seen in rats (rats are not an antigen-specific species for belantamab mafodotin). Immunosuppression is frequently associated with an increased risk of infection. Serious and non-serious infections have been reported in belantamab mafodotin studies, including respiratory infections, pneumonia, and sepsis. Neutropenic events, including febrile neutropenia have been observed with belantamab mafodotin. In a study of belantamab mafodotin in combination with lenalidomide / dexamethasone, 2 fatal cases of severe infections associated with neutropenia were observed. Severe neutropenia is associated with lenalidomide treatment. **Dexamethasone**: Patients who are on corticosteroids are more susceptible to infections or exacerbation of latent infections than healthy individuals. Chickenpox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids.	Patients with an active infection will be excluded. Monitoring for infections and immediate treatment according to standard practice. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin may be indicated. If exposed to measles, prophylaxis with immune globulin may be indicated.

2.3.2. Benefit Assessment

This is the first study testing the combination of nirogacestat, lenalidomide, dexamethasone, and belantamab mafodotin in participants with RRMM who have been treated with regimens incorporating standard therapies. Study participants may benefit from medical tests and Screening performed during the study. Any potential benefit of the addition of lenalidomide, dexamethasone, and nirogacestat to belantamab mafodotin in RRMM patients is unknown. Data obtained in this study may help identify individuals who may benefit or have side-effects from nirogacestat with belantamab mafodotin plus lenalidomide and dexamethasone.

2.3.3. Overall Benefit: Risk Conclusion

There is no previous data for the clinical activity and safety/tolerability of single-agent nirogacestat in RRMM. However, given the strong preclinical rational and demonstrative evidence of enhanced ADC and ADCC activity of belantamab mafodotin when combined with nirogacestat from in vitro experiments, and reduction of sBCMA upon nirogacestat treatment in vitro, inclusion of a belantamab mafodotin + nirogacestat sub-study in this platform study is scientifically justified. Furthermore, from a safety perspective, considering the absence of potentially overlapping hematological toxicities with belantamab mafodotin (e.g., thrombocytopenia), and the non-severe nature of most nirogacestat-related AEs from single-agent studies (including those which potentially overlap with belantamab mafodotin).

Belantamab mafodotin is a highly active agent in RRMM [Trudel, 2019; Lonial, 2020]. Emerging data for the combination of belantamab mafodotin and nirogacestat in Sub-study 3 of DREAMM-5 in vitro (belantamab mafodotin 0.95 mg/kg [Q3W] in combination with continuous nirogacestat 100 mg PO BID) demonstrates that these 2 agents can be combined into a safe and effective regimen for patients with RRMM.

Clinical experience with the combination of belantamab mafodotin and lenalidomide and dexamethasone [Dimopoulos, 2007] is currently being evaluated in DREAMM-6 (Study 207497). Preliminary safety data suggests that the combination of belantamab mafodotin at doses up to 2.5 mg/kg IV Q3W with standard doses of lenalidomide and dexamethasone has an acceptable safety profile, consistent with individual components. 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 lenalidomide and dexamethasone are justified by the anticipated benefits that may be afforded to participants with RRMM.

3. OBJECTIVES AND ENDPOINTS

The primary and secondary objectives, along with the corresponding endpoints for DE and the primary and secondary objectives and endpoints for CE are the same for this sub-study as the 208887 MP (see MP Section 3).

4. STUDY DESIGN

Please refer to the 208887 MP for the overall study design for the study.

Information and details specific to Sub-study 6 are in the Section 4.1 and Section 4.3 below.

4.1. Overall Design

Overall design encompasses the dose exploration of combination treatment belantamab mafodotin, nirogacestat, lenalidomide and dexamethasone being described in this sub-study as shown in Table 2.

4.1.1. Dose Exploration

Dose Exploration will involve 3 belantamab mafodotin dosing levels (refer to treatment schema Table 2). Enrollment into these cohorts will be according to criteria (see MP) except as noted below.

If findings from Sub-study 3 Cohort 3 DE Phase *(belantamab mafodotin 1.0 mg/kg C1 Q4W, from C2 Q8W+ nirogacestat 100 mg BID)* become available, a decision can be made to start enrolling participants for Dose Level 2. The enrollment for Dose Level 1 may be stopped. The observed Sub-study 3 Cohort 3 DE Phase data will be used to calculate the probability of true ocular event lower than a threshold. This probability, with all other available data including data outside of DREAMM-5, will be used to decide the belantamab mafodotin dose frequency (Q8W vs Q12W) for Dose Levels 2 and 3 Cycle 2 onwards. The decisions will occur following review of existing data and joint discussion by the study-specific GSK safety review team and investigators.

4.1.2. Cohort Expansion

Once each potential RP2D dose is selected from the DE Phase, participants may be enrolled in the CE Phase. Please refer to the 208887 MP for details.

4.2. Scientific Rationale for Study Design

Please refer to the 208887 MP.

4.3. Justification for Dose

4.3.1. Justification for Starting Dose of Belantamab Mafodotin

Preliminary data from Sub-study 3 Cohort 1, with the starting dose of belantamab mafodotin 0.95 mg/kg Q3W and nirogacestat 100 mg BID, demonstrated promising clinical activity with a positive risk/benefit profile (data on file). Safety data from the 8 DLT-evaluable participants permitted escalation to belantamab mafodotin 1.9 mg/kg

Q3W in combination with nirogacestat 100 mg BID; 1 out of 8 DLT evaluable participants experienced a DLT of infusion-related reaction.

Clinical investigation of belantamab mafodotin in combination with lenalidomide and dexamethasone is ongoing in DREAMM-6 with belantamab mafodotin doses ranging from 1.9 mg/kg to 2.5 mg/kg Q4W and less frequently. A starting dose of 0.5 mg/kg Q4W of belantamab mafodotin and 100 mg BID nirogacestat is considered appropriate for the combination therapy with lenalidomide and dexamethasone based on the above clinical experience with the following considerations:

- The starting dose of 0.5 mg/kg belantamab mafodotin in combination with nirogacestat, lenalidomide, and dexamethasone is expected to be safe as this dose level is several dose levels lower than the selected belantamab mafodotin monotherapy dose and the highest 2.5 mg/kg dose being evaluated in DREAMM-6 in combination with lenalidomide and dexamethasone in participants with RRMM.
- Doses with dose intensities as low as 0.5 mg/kg Q4W or 1.0 mg/kg Q4W for Cycle 1 then Q8W or Q12W are expected to be efficacious.
  - Based on in-vitro data (see Figure 2 and Figure 3 for manyfold potentiation of belantamab mafodotin activity by nirogacestat) it is anticipated that in combination with nirogacestat, belantamab mafodotin will have similar or increased efficacy at several-fold lower doses compared to monotherapy.
  - Results from the primary analysis of Sub-study 3 Cohort 1 demonstrated an encouraging response rate for 0.95 mg/kg Q3W belantamab mafodotin in combination with nirogacestat: 29% in the combination compared with 38% in the DREAMM-5 belantamab mafodotin monotherapy (2.5 mg/kg Q3W) control arm.
  - The addition of lenalidomide and dexamethasone further increases the efficacy potential in this sub-study.
- These clinical and pre-clinical data support assessing whether lower belantamab mafodotin dose intensities in this quadruplet combination could provide an improved benefit-risk profile, specifically reducing corneal toxicities and concomitant dose holds, while providing comparable or better efficacy than the selected 2.5 mg/kg Q3W monotherapy regimen.
- Based on *in-vitro* information, DDIs are not anticipated between lenalidomide and dexamethasone and belantamab mafodotin or cys-mcMMAF [GSK Document No. RPS-CLIN-105644, 2024]. No DDIs are anticipated between nirogacestat and lenalidomide and dexamethasone or belantamab mafodotin or cys-mcMMAF.
- With the low starting dose of 0.5 mg/kg Q4W and clinical experience with doses up to 2.5 mg/kg belantamab mafodotin (DREAMM-6) overlapping toxicities (see Section 2.3.1) between belantamab mafodotin, nirogacestat, lenalidomide, and dexamethasone are considered manageable in this RRMM participant population.
- The maximum belantamab mafodotin dose being tested in Sub-study 6 will be 1.4 mg/kg.

4.3.2. Justification for Starting Dose of Nirogacestat

The starting dose of nirogacestat used in this study is 100 mg BID PO.

The mean free (fraction unbound) EC50 for nirogacestat (2.48 nM) was determined in a set of in vitro studies measuring concentration-related increases in mbBCMA levels in several multiple myeloma cells lines (unpublished data from D. Green et al.). The *in vitro* free EC50 determined in these multiple myeloma cells is approximately equivalent to the mean unbound Ctrough concentration for nirogacestat (1.9 nM) observed at steady-state following a 100 mg BID dose (Study A8641014). These results suggest that the 100 mg BID dose of nirogacestat will maintain serum concentrations at or above the *in vitro* EC50 for increasing mbBMCA levels throughout the entire dosing interval leading to sustained increases in mbBCMA. In additional preclinical experiments in combination with belantamab mafodotin, nirogacestat concentrations as low as 2.5 nM exhibited broad synergy in assays designed to measure ADC and ADCC activity [Eastman, 2019]. Combined, these data indicate that the 100 mg BID dose should increase and sustain mbBCMA levels necessary to potentiate the activity of belantamab mafodotin.

Following a 95 mg QD dose of nirogacestat (Study A8641002), the mean maximum free concentration of nirogacestat was approximately 4.7 nM (~2-fold higher than the observed in vitro EC50). Therefore, at a 100 mg QD dose, nirogacestat is expected to inhibit cleavage of mbBCMA at Cmax and remain above the EC50 for approximately 2 hours post-dose. However, at the 100 mg QD dose, nirogacestat is not expected to sustainably inhibit cleavage of mbBCMA throughout the entire dosing interval. The duration of GSI inhibition required to increase mbBCMA levels on the multiple myeloma cells to sufficiently potentiate the activity of belantamab mafodotin is currently unknown.

At the proposed dose level of 100 mg BID, nirogacestat is expected to have a safety profile at least as well tolerated as the 150 mg BID dose used in the solid tumor studies that have had durations of treatment and follow-up longer than 5 years. In a dose-finding Phase 1 study, 2 participants had dose-limiting toxicity of Grade 3 diarrhea at 150 mg BID (n=6) and at 220 mg BID (n=6), respectively, while no participants in the 100 mg BID cohort (n=6) had DLTs of GI toxicity. The association of safety with dose was further characterized when enrollment was expanded to a total of 16 participants in the 220-mg BID group and to a total of 23 participants in the 150-mg BID group (dose-finding plus expansion cohorts). Treatment related Grade 3 AEs were reported in 62.5% of participants in the 220-mg BID group compared with 34.8% in the 150-mg BID group [Messersmith, 2015].

In the Phase 2 (investigator-initiated) study in adult participants with desmoid tumors treated with 150 mg BID of nirogacestat, all participants experienced Grade 1 and 2 AEs, notably, diarrhea (76%) and skin disorders (71%). Four participants met criteria for dose reduction2 participants received a reduced dose of 100 mg twice per day as a result of persistent Grade 2 nausea and diarrhea, but neither participant required corticosteroid therapy as symptoms fully resolved after dose reduction. One participant developed urticaria, which did not respond to dose reduction, and was taken off study because of an allergic reaction. One participant developed Grade 2 maculopapular rash, which resolved with dose reduction, and this participant continued on study for 2 years without recurrent or additional toxicity [Kummar, 2017].

Nirogacestat lead-in dosing before the first belantamab mafodotin dose was specified for Cohorts 3 and 4 to test whether lead-in dosing can enhance efficacy. Lead-in dosing will allow nirogacestat accumulation towards steady-state exposure levels and the realization of its pharmacodynamic effects on mbBCMA, such that by the first belantamab mafodotin dose, the nirogacestat potentiation of the belantamab mafodotin effect is near the maximal, steady-state level.

A nirogacestat starting dose of 100 mg BID is considered an appropriate dose for combination therapy with belantamab mafodotin based on the following:

- According to currently available data, the nirogacestat starting dose of 100 mg BID was assessed in the Phase 1 study alongside 150 mg BID and 220 mg BID and the rate and severity of AEs was found to be dose-related. Particularly of interest is that diarrhea was a DLT in both 150 mg BID and 220 mg BID doses, but not for 100 mg BID.
- In the Phase 2 solid tumor study, AEs occurring at 150 mg BID were successfully managed with dose reduction to 100 mg BID, and the 100 mg BID dose was tolerated over the long term.
- Based on in vitro data and human PK data, it is anticipated that the nirogacestat dose of 100 mg BID would be able to potentiate the effect of belantamab mafodotin.
- Based on in vitro information, nirogacestat demonstrated Pgp inhibition at clinically relevant concentration and therefore there is a small potential for nirogacestat to increase the exposure to free cys-mcMMAF.

4.3.3. Lenalidomide and Dexamethasone Dosing

Lenalidomide and dexamethasone will be administered at the approved and clinically used dose, and there will be no dose escalation for lenalidomide and dexamethasone. Details on lenalidomide and dexamethasone administration are provided in Table 2.

4.4. Participant Completion and End of Study Definitions

Please refer to the 208887 MP.

5. STUDY POPULATION

Please refer to the 208887 MP for the overall planned study population details for Study 208887.

5.1. Inclusion Criteria for Participants

The inclusion criteria below are in addition to the inclusion criteria already defined in 208887 MP Section 5.1.

For MP Inclusion Criterion 11: please note contraception requirements specific to Sub-study 6 (Section 8.3.7.2).

For MP Inclusion Criteria 7 (MP Table 15): For Sub-study 6 the platelets value for Adequate Organ System Function is ≥75 × 10^9/L.

5.2. Exclusion Criteria for Participants

The exclusion criteria #42 to #50, and #60 below are in addition to the exclusion criteria already defined in 208887 MP Section 5.2. The numbering in the criteria may not be sequential from the MP. Note: for Germany, female participants of childbearing potential using hormonal contraception at the time of inclusion/exclusion criteria screening are excluded.

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

42. Uncontrolled small and/or large intestinal disease
43. Uncontrolled skin disease
44. Any condition causing hypophosphatemia, hypokalemia or hypomagnesemia which is refractory to electrolyte replacement
45. Previous administration of a γ-secretase inhibitor
46. Concomitant administration of a strong CYP3A4 inhibitor or inducer (see Section 6.5.2.1).
47. Active or history of venous thromboembolism within the past 3 months.
48. Evidence of active mucosal or internal bleeding.
49. Contraindications to or unwilling to undergo protocol-required anti-thrombotic prophylaxis or unable to tolerate antithrombolytic prophylaxis,
50. Discontinuation of prior treatment with lenalidomide due to intolerable AEs.
60. Known HIV infection, unless the participant can meet **all** criteria listed in exclusion criterion 9 in the MP Section 5.2, in which case the participant would be eligible for CE Phase only.

    Note: for patients receiving nirogacestat, HIV drugs that are strong CYP3A4 inhibitors are prohibited. HIV drugs that are moderate CYP3A4 inhibitors, while permitted, should be co-administered with caution and must be accompanied by nirogacestat dose modifications outlined in Section 6.5.2.

5.3. Lifestyle Considerations

Please refer to the 208887 MP.

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

5.4. Screen Failures

Please refer to the 208887 MP.

6. STUDY TREATMENT

Please refer to the 208887 MP for the overall study treatment for the study.

Study treatment is defined as belantamab mafodotin administered with nirogacestat, lenalidomide and dexamethasone treatment and administered to a study participant according to the study protocol.

6.1. Study Treatments Administered

Specifications for belantamab mafodotin, nirogacestat, lenalidomide and dexamethasone treatment in this study are given in Table 11.

Table 11 Belantamab Mafodotin, Nirogacestat, Lenalidomide, and Dexamethasone Study Treatment Information

Intervention Label	Belantamab mafodotin	Nirogacestat	Lenalidomide	Dexamethasone
Intervention Name	GSK2857916 for Injection, 100mg	Nirogacestat tablet, 100mg	Capsule	Tablet
Intervention Description	Belantamab mafodotin (GSK2857916) is a powder for solution for infusion	Nirogacestat is orally formulated (tablets)	Orally formulated (capsules)	Orally formulated (tablets)
Type	Drug	Drug	Drug	Drug
Dose Formulation	Lyophilized powder for solution for infusion	Tablet	Capsule	Tablet
Unit Dose Strength(s)	100 mg/vial	50 mg or 100 mg	Available in 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg	Refer to local prescribing information for dexamethasone.
Dosage Level(s)	2.5 mg/kg Q3W	100 mg BID	25 mg or 10 mg[1]	40 mg or 20 mg[2]
Route of Administration	Delivered as IV solution and infused over 30-60 minutes	Oral (PO)	PO	PO or IV
Dosing instructions	Reconstitute belantamab mafodotin for Injection, 100 mg with 2.0 mL of sterile WFI, dilute with saline before use. Dilute GSK2857916 in normal 0.9% saline to the appropriate concentration for the dose. Doses of GSK2857916 are to be administrated as an IV infusion via an infusion pump. See Investigator's Brochure for compatible administration materials GSK2857916 IB [GSK Document No. RPS-CLIN-105644, 2024].	Not applicable	Not applicable	Not applicable or refer to prescribing information
Use	IMP	IMP	IMP	IMP
Authorized AxMP / Unauthorized AxMP	Not applicable	Not applicable	Not applicable	Not applicable
Sourcing	GSK	SpringWorks Therapeutics	Celgene Corporation (US & Europe) Lotus Pharmaceutical Refer to SRM for country-specific details.	Refer to SRM for country-specific details.
Packaging and Labeling	Study Treatment will be provided in vials. Each vial will be labeled as required per country requirement.	Study treatment will be provided in bottles. Each bottle will be labeled as required per country requirement.	Open label	Open label

Intervention Label	Belantamab mafodotin	Nirogacestat	Lenalidomide	Dexamethasone
Current / former name(s) or alias(es)	Not applicable	Not applicable	Refer to the Prescribing Information	Refer to the Prescribing Information

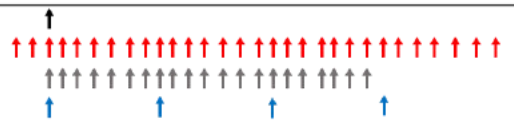
1. If the eGFR is 40-60 mL/min/1.73 m^2.
2. Participants >75 years old or BMI <18.5 kg/m^2.

6.2. Administration of IP

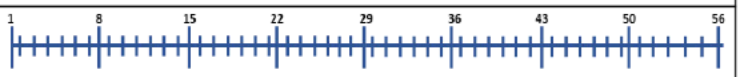
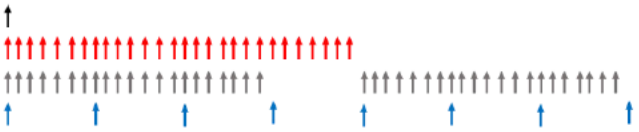
The dosing schedules for Sub-study 6 are depicted in below figures.

Figure 4 Dosing schedule

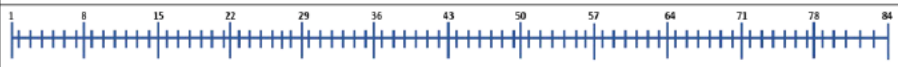
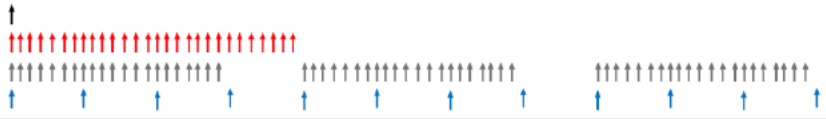
a. Dosing schedule of investigational product in Cycle 1

	Cycle 1: 28 days (Q4W or C1 Q4W from C2 Q8W) (Nirogacestat starts on Day -2, Belantamab mafodotin on D1)
28-Day Cycle	
Belantamab mafodotin Nirogacestat Lenalidomide Dexamethasone	

b. Dosing schedule of investigational product in Cycle 2 and beyond for Q8W dosing

	Cycle 2 and beyond: 56 days (C1 Q4W from C2 Q8W only) (Nirogacestat for first 28 days only, Belantamab mafodotin on D1 of every 8-week cycle)
56-Day Cycle	
Belantamab mafodotin Nirogacestat Lenalidomide Dexamethasone	

c. Dosing schedule of investigational product in Cycle 2 and beyond for Q12W dosing

	Cycle 2 and beyond: 84 days (C1 Q4W from C2 Q12W only) (Nirogacestat for first 28 days only, Belantamab mafodotin on D1 of every 12-week cycle)
84-Day Cycle	
Belantamab mafodotin Nirogacestat Lenalidomide Dexamethasone	

6.2.1. Belantamab Mafodotin

- Belantamab mafodotin will be administered to participants IV as mg/kg calculated dose at the study site. The dose to be administered is based on actual body weight calculation and may be reduced for toxicity according to protocol guidelines (Table 13).
- Administration will be documented in the source documents (208887 MP Appendix 1) and reported in the eCRF. The time of start and end of infusion will be documented in the eCRF.
- Belantamab mafodotin will be administered on Day 1 of each cycle at the assigned dose as an IV infusion (see Section 6.1 for details).
- Premedication is not required prior to each infusion unless deemed medically necessary by the investigator, in which case it should be administered according to institutional recommendations. In case of infusion related reactions related to belantamab mafodotin the rules outlined in the 208887 MP Section 7.1.4 and in 208887 MP Section 11 should be followed.
- The intended cycle time of belantamab mafodotin as a monotherapy is 21 days (+3 day window) and cannot occur more frequently.

6.2.2. Administration of Nirogacestat with Lenalidomide and Dexamethasone

Participants will be provided with a Patient Dosing Diary Card for oral (PO) dosing at home (nirogacestat, lenalidomide, and dexamethasone [if given orally]).

Dosing Instructions for Nirogacestat Administration

Nirogacestat will be administered BID orally in combination with belantamab mafodotin until disease progression. Nirogacestat will be discontinued if belantamab mafodotin is discontinued.

For Cycle 1 only, nirogacestat will be taken BID for 2 days prior to the first belantamab mafodotin infusion (on Days -2 and -1).

For Q8W cycles, nirogacestat will be taken BID from Day 1 through Day 28. Nirogacestat will not be taken from Days 29-56.

For Q12W cycles, nirogacestat will be taken BID from Day 1 through Day 28. Nirogacestat will not be taken from Days 29-84.

Instructions below will be provided to participants along with Patient Dosing Diary Card. 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.

- Participants will be instructed to swallow tablets whole and not to chew them prior to swallowing.
- No tablet should be ingested if it is broken, cracked, or otherwise compromised (i.e., not fully intact).
- Participants should take their dose orally without regard to food. **BID dose** should be taken approximately every 12 hours, same time every day.
- For **BID** dosing: If a participant misses a scheduled dose of study treatment, and it is within 6 hours of the scheduled dose, the participant should immediately administer the missed dose and resume study treatment in accordance with the normal administration schedule. If more than 6 hours have elapsed since the time of scheduled administration, the participant should be instructed not to administer the missed dose and to resume study treatment as prescribed.
- Participants should not take 2 doses together to "make up" for a missed dose.
- If a participant vomits any time after taking a dose, then they must be instructed not to take another dose to "make up" for vomiting, but rather to resume subsequent doses as prescribed.
- If a participant inadvertently takes 1 extra dose, then the participant should not take the next scheduled dose of study treatment.

Delivery of nirogacestat via nasogastric tube or gastrostomy tube is not allowed.

Dosing Instructions for Lenalidomide and Dexamethasone Administration

On lenalidomide and belantamab mafodotin co-administration days, lenalidomide should be administered as close as possible to the end of the 1 to 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.

Lenalidomide will be administered as 25 mg PO daily on days 1 to 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, 2019].

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, and from 20 mg to 10 mg (see Table 18); if 10 mg is not tolerated, dexamethasone may be permanently discontinued.

On days where only lenalidomide and dexamethasone are taken at home, they should be taken approximately at the same time each day. Additionally, when participants self-administer oral study treatment(s) at home, dosing with lenalidomide and dexamethasone 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.

6.2.3. Treatment Duration

- In case a participant meets stopping criteria for lenalidomide and dexamethasone treatment and cannot continue on lenalidomide and dexamethasone treatment due to related safety/tolerability issues, the participant may continue on study with belantamab mafodotin and nirogacestat.
- If participant meets stopping criteria for nirogacestat, may continue with belantamab mafodotin and lenalidomide and dexamethasone treatment.
- In case of overlapping toxicities of nirogacestat and lenalidomide, participants may continue with belantamab mafodotin and dexamethasone treatment.
- In case the participant meets stopping criteria for belantamab mafodotin, the participant will discontinue all treatments but will continue to be monitored as described in the SoA tables for follow-up activities.

6.2.4. Participant Transition from DE to CE

For participants enrolled in the DE Phase, once each potential RP2D has been established, intra-participant dose modification to the RP2D may be considered on a case-by-case basis, if the participant completed at least 2 cycles at the originally assigned dose and at least 1 disease assessment after the second cycle, has tolerated treatment well, and did not experience a treatment-related Grade 3 or higher toxicity. Approval must be obtained from a Medical Director. Dose-escalation decisions will be documented on a Dose Escalation/De-escalation Decision Form (see the SRM).

6.3. Preparation/Handling/Storage/Accountability

The first dose of oral nirogacestat and intravenous belantamab mafodotin (monotherapy or combination) will be administered to participants at the site. The second and subsequent doses of nirogacestat will be taken BID outside of the clinical setting. Fifty (50) mg nirogacestat tablets will be provided in 90 count, induction sealed high density polyethylene bottles. One hundred (100) mg nirogacestat tablets will be provided in 75 count, induction sealed high density polyethylene bottles. Administration will be documented in the source documents (208887 MP Appendix 1) and reported in the CRF. 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.

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 17 and Table 18 for further information.

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.

For further information regarding preparation/handling/storage/accountability refer to 208887 MP Section 6.3.

6.4. Measures to Minimize Bias: Randomization and Blinding

Please refer to the 208887 MP.

6.5. Concomitant Therapy

Please refer to the 208887 MP.

6.5.1. Permitted Concomitant Medications and Therapies

Please refer to the 208887 MP.

6.5.2. Prohibited Concomitant Medications and Non-Drug Therapies

Prohibited concomitant medications for lenalidomide are as per the prescribing information for this product.

Concomitant administration of any of the strong CYP3A4 inhibitors or inducers listed in Table 12 could either increase or reduce the systemic exposure of nirogacestat, respectively, and therefore, concomitant administration of the drugs in the strong inhibitors and strong inducers columns within Table 12 are not permissible in this sub-study. While CYP3A4 moderate inhibitors or inducers within Table 12 are not prohibited, caution should be used when co-administering with nirogacestat.

If co-administration of a moderate CYP3A4 inhibitor with nirogacestat is deemed medically necessary by the investigator, this decision must first be discussed with the Medical Director and the nirogacestat dose must be reduced from 100 mg BID to 50 mg QD. In cases where a moderate CYP3A4 inhibitor is discontinued while the participant is on study, the nirogacestat dose may be increased to 100 mg BID one week after discontinuation of the moderate CYP3A4 inhibitor.

Table 12 List of Moderate and Potent CYP3A Inhibitors and Inducers

	Strong inhibitors	Moderate inhibitors	Strong Inducers	Moderate Inducers
CYP3A	boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole	aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil	carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	bosentan, efavirenz, etravirine, modafinil

6.5.2.1. Medications to be Administered with Caution with Nirogacestat

Nirogacestat has been shown to increase exposure of a sensitive CYP3A4 substrate, midazolam, by approximately 50% following multiple daily doses of 95 mg QD. The potential for nirogacestat to inhibit CYP3A4 in vivo following BID dosing at 100 mg has not been evaluated in a clinical study. However, using physiological-based PK modeling, nirogacestat was predicted to be a mild to moderate inhibitor of CYP3A4 metabolism when administered at 150 mg BID resulting in increases in midazolam exposures ranging from 2- to 3.3-fold. Therefore, caution should be used when co-administering known CYP3A4 substrates with nirogacestat. Co-administration of CYP3A4 substrates with a narrow therapeutic index should be avoided if possible. If co-administration is unavoidable, monitor the participant closely for toxicity and consider reducing or titrating the dose of the substrate, as necessary.

Nonclinical studies suggest that nirogacestat may induce CYP2B6, CYP2C8, CYP2C9 and CYP2C19 enzymes. Drugs which are substrates of these enzymes may have a reduced exposure/efficacy when co-administered with nirogacestat. Dose adjustments should be considered when appropriate in discretion of treating physician.

Nonclinical studies have indicated that nirogacestat is a substrate for the drug efflux transporter Pgp. Therefore, caution should be used when co-administering nirogacestat with known Pgp inhibitors such as amiodarone, azithromycin, captopril, carvedilol, elacridar, felodipine, mibefradil, nitrendipine, quinidine, ranolazine, talinolol, and valspodar.

6.6. Dose Modification

6.6.1. Permitted Dose Reductions per Participant for Belantamab Mafodotin when in Combination with Nirogacestat, Lenalidomide, and Dexamethasone

- Belantamab mafodotin dose reductions will follow the details below in Table 13.
- For further details regarding belantamab mafodotin-associated dose modifications for other toxicities see Section 6.6 in the MP.
- No dose reduction is permissible from the belantamab mafodotin starting dose of 0.5mg/kg.

Table 13 Permitted Dose Reductions per Participant for Belantamab Mafodotin when in Combination with Nirogacestat, Lenalidomide, and Dexamethasone

Belantamab Mafodotin Dose Level	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
1.4 mg/kg	1.0 mg/kg	0.75 mg/kg	0.5 mg/kg
1.0 mg/kg	0.75 mg/kg	0.5 mg/kg	
0.75 mg/kg	0.5 mg/kg		
0.5 mg/kg			

- If the participant cannot tolerate the drug after the allowed dose reductions, he/she must be withdrawn from study treatment for lack of tolerability.
- Resuming treatment with belantamab mafodotin may be considered after the toxicity has resolved to Grade 1 or less.

6.6.2. Permitted Dose Reductions per Participant for Nirogacestat

There are no permitted dose reductions for nirogacestat in this sub-study.

Dosing will be on hold until recovery of event.

6.6.3. Nirogacestat-Associated Dose Modification Guidance

Dose modifications for nirogacestat for the following prespecified AESIs using grading from NCI-CTCAE (Version 5.0) are given below.

6.6.3.1. Gastrointestinal Toxicities

Refer to Risk Table in Section 2.3.1: All participants with diarrhea and other GI symptoms should be promptly reviewed by the investigator to determine the need for administration of intravenous hydration, electrolyte replacement, and / or loperamide treatment, and / or corticosteroid treatment.

Primary prophylaxis of nausea and vomiting is permitted in the first cycle. Primary prophylaxis in subsequent cycles is at the investigator's discretion. The choice of the prophylactic drug as well as the duration of treatment is up to the investigator with sponsor approval assuming there is no known or expected drug-drug interaction (DDI) and assuming the drug is not included in the prohibited medications and substances section (Section 6.5.2).

Gamma secretase inhibition by nirogacestat may affect the intestinal tract epithelium [Barker, 2007; Kurokawa, 2020], villus lacteals [Norden, 2021], and enteric nervous system [Barrenschee, 2015; Willem, 2016], resulting in diarrhea. Prophylactic use of an antidiarrheal medication to prevent diarrhea in patients receiving nirogacestat is therefore strongly recommended. If use of antidiarrheal medication for a particular participant is deemed by the investigator to be clinically inappropriate, please contact the medical director to discuss plan for diarrhea prevention.

The choice of anti-diarrheal drug(s), as well as the duration of treatment, is up to the investigator assuming there is no known or expected DDI. If a DDI is expected, then the drug(s) use must be approved by the Medical Director/sponsor.

Participants experiencing diarrhea considered associated with nirogacestat should be treated with loperamide, or other institutional standard of care. The recommended initial dose of loperamide is 4 mg followed by 2 mg after each unformed stool until the diarrhea is controlled, after which the dosage should be reduced to meet individual requirements. Loperamide should be dosed according to the treating physician's medical discretion.

Participants should also receive appropriate fluid and electrolyte replacement, including dietary phosphate supplementation, as needed.

If there are any concerns the Medical Director/sponsor should be contacted for guidance.

Table 14 Dose Modification for Nirogacestat - Diarrhea

Diarrhea Grade	Dose Modification / Delay
Grade 1 or Grade 2 ≤7 days; tolerating symptoms with clinical intervention	Not applicable
Grade 2 >7 days, despite therapeutic intervention, or Grade 2 not tolerating symptoms despite treatment	• Hold dose until recovered to Grade 1 or baseline
Grade ≥3	• Hold dose until recovered to Grade 1 or baseline

6.6.3.2. Hypophosphatemia

Serum phosphate levels should be monitored closely, and oral replacement instituted promptly for serum phosphate levels less than 2.0 mg/dL, or 0.6 mmol/L or earlier if clinically indicated (Table 15).

Replacement of phosphate should start prior to first dose of nirogacestat if indicated by phosphate level.

Table 15 Dose modification for nirogacestat - hypophosphatemia

Toxicity Grade CTCAE V.5		Dose Modification / Delay
1	Laboratory finding only and intervention not indicated	Not applicable
2	Oral replacement therapy indicated	Not applicable
≥3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated or life-threatening consequences	Hold dose if • ≥7 days despite maximal replacement therapy and in the absence of symptoms. • Symptomatic until Grade ≤2. • Resume dosing when recovered to Grade ≤2. • Continue with oral phosphorus replacement as indicated. • Monitor levels as clinically indicated.

6.6.3.3. Skin Rash

Refer to Risk Table in Section 2.3.1: Referral to a dermatologist is mandatory if development of hidradenitis suppurativa is suspected, or for the development of rashes that are refractory to topical/systemic corticosteroids.

All suspected Grade 4 rashes should be treated as a medical emergency and referred urgently to a dermatologist.

Dermatologist evaluation ±skin biopsy is recommended for Grade 2 skin rashes lasting longer than 21 days or for all Grade 3 rashes lasting longer than 72 hours.

Individual participant skin rash stopping criteria:

- Grade 4 rash
- Hidradenitis suppurativa

Table 16 Dose modification for nirogacestat – skin rash

Skin Rash Grade	Dose Modification / Delay
Grade 1 or Grade 2 <72 hours	Not applicable
Grade ≥2	• Hold dose until recovered to Grade 1 • For Grade 2 rashes lasting longer than 21 days and/or not responding treatment refer to dermatologist) • For Grade 3, refer directly to dermatologic evaluation

6.6.3.4. Elevated ALT

Refer to Risk Table in Section 2.3.1: Liver function tests will be monitored as per Table 4. Discontinuation or continuation of nirogacestat will follow the liver function test guidance in the master study protocol.

6.6.4. Lenalidomide-Associated Dose Modification Guidance

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

Refer to local prescribing information for further guidance on lenalidomide dose reduction.

Table 17 Dose Modification Guidelines for Hematologic and Other Toxicities Associated with Lenalidomide Plus Dexamethasone

Toxicity	Grade/Symptoms	Recommendations
Thrombocytopenia[1]	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, follow bi-weekly hematology assessment
	Platelets return to ≥30 × 10^9/L	• Resume lenalidomide at next lower dose. Do not dose below 2.5 mg
Neutropenia[2] 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	Nonblistering Rash Grade 2	• Consider holding until resolved to ≤ Grade 1. Consider treatment with antihistamines and/or low dose steroids as per institutional practice.
	Nonblistering Rash Grade 3 or 4	• Hold lenalidomide. Begin treatment with antihistamines and/or low-dose steroids as per institutional practice. • If the toxicity resolves to ≤ Grade 1, reduce dose by 1 level if not at lowest dose and restart lenalidomide. Continue antihistamines and/or low-dose steroids as per institutional practice. • For severe cases of rash, consider permanently discontinuing lenalidomide
	Desquamating/ blistering rash any grade (including exfoliative or bullous rash, erythema multiforme, SJS,	• Permanently discontinue lenalidomide

Toxicity	Grade/Symptoms	Recommendations
	TEN or DRESS is suspected)	
Hypersensitivity	Angioedema and anaphylaxis	• Permanently discontinue lenalidomide
For other non-hematological toxicities judged to be associated with 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

1. Note that in the 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.
2. Note that in the 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

Source: Lenalidomide approved labeling

6.6.5. 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 18 Dose Modification Guidelines for Toxicities Associated with Dexamethasone

Toxicity	Recommendations
For participants who are >75 with BMI <18.5 kg/m^2	Reduce the dose of dexamethasone by 50% (i.e., from 40 mg to 20 mg; from 20 mg to 10 mg) at the discretion of the investigator
Lack of tolerance or significant toxicities associated with dexamethasone	Reduce dexamethasone dose by 50% (i.e., from 40 mg to 20 mg; from 20 mg to 10 mg)

6.6.6. Dose Reductions and Delays

- No nirogacestat dose reduction less than 100 mg BID is permissible in this sub-study.
- Delayed dosing of nirogacestat will not affect the dosing schedule for belantamab mafodotin.
- If belantamab mafodotin is delayed then nirogacestat, lenalidomide, and dexamethasone will also be delayed. Exception when belantamab mafodotin is on hold for ocular toxicity, lenalidomide and dexamethasone may continue.

Investigators must contact the Medical Director for all Grade ≥3 clinically significant drug-related toxicities where interruption or permanent discontinuation of study treatment may be warranted according to the guidelines provided. Otherwise, investigators are encouraged to contact the Medical Director on a case-by-case basis to discuss any case that warrants separate discussion outside of the scope of these specific guidelines.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL FROM THE STUDY

Please refer to the 208887 MP for the overall discontinuation of study treatment and participant discontinuation/withdrawal for the study.

7.1. Discontinuation of Study Treatment

Please refer to the 208887 MP.

7.2. Participant Withdrawal from the Study

Please refer to the 208887 MP.

7.3. Lost to Follow-Up

Please refer to the 208887 MP.

8. STUDY ASSESSMENTS AND PROCEDURES

Please refer to the 208887 MP for the overall Study Assessments and Procedures for the study.

Information and details specific to Sub-study 6 are in Section 8.3.7, Section 8.3.10 and Section 8.4 below.

8.1. Efficacy Assessments

Please refer to the 208887 MP.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA tables (Section 1.3; Table 3, Table 4, Table 5, Table 6).

8.3. Adverse Events and Serious Adverse Events

Please refer to the 208887 MP.

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

Please refer to the 208887 MP.

8.3.2. Method of recording AE and SAE information

Please refer to the 208887 MP.

8.3.3. Method of Detecting AEs and SAEs

Please refer to the 208887 MP.

8.3.4. Follow-up of AEs and SAEs

Please refer to the 208887 MP.

8.3.5. Reporting of Potentially Life-Threatening AEs to the Medical Director

Please refer to the 208887 MP.

8.3.6. Regulatory Reporting Requirements for SAEs

Please refer to the 208887 MP.

8.3.7. Management of Pregnancy and Contraception

Please refer to the 208887 MP.

8.3.7.1. Pregnancy in Sub-study 6

Female Participants

Details of all pregnancies for female participants will be collected after the start of study treatment and for 6 months following last dose of combination study treatment or 4 weeks after the last dose of lenalidomide, whichever is longer. In the event of discontinuation of nirogacestat and continuation of belantamab mafodotin as single agent therapy, details of all pregnancies will be collected after the start of study treatment and for 4 months following last dose of belantamab mafodotin.

Women should not donate or harvest their eggs (ova, oocytes) while participating in this study and for at least 6 months after receiving combination study drug treatment. In the event of discontinuation of nirogacestat and continuation of belantamab mafodotin as single agent therapy, women should not donate or harvest their eggs (ova, oocytes) for 4 months following last dose of belantamab mafodotin.

Male Participants

Details of all pregnancies for female partners of male participants will be collected after the start of study treatment and for 6 months following last dose of combination study treatment. In the event of discontinuation of nirogacestat and continuation of belantamab mafodotin as single agent therapy, details of all pregnancies for female partners of male participants will be collected after the start of study treatment and for 6 months following last dose of belantamab mafodotin for male participants.

Men should not donate or preserve their sperm while participating in this study and for at least 6 months after receiving combination study drug treatment. In the event of discontinuation of nirogacestat and continuation of belantamab mafodotin as single agent therapy, men should not donate or preserve their sperm while participating in this study and for at least 6 months after last dose of belantamab mafodotin.

8.3.7.2. Contraception in Sub-study 6

Female Participants

Contraception Requirements for Female Participants Receiving Lenalidomide

Two methods of reliable birth control (one method that is highly effective and 1 additional effective (barrier) method), beginning 4 weeks prior to initiating treatment with lenalidomide, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of lenalidomide treatment.

Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing the start of lenalidomide therapy. The participant should not receive lenalidomide until the investigator has verified that the results of these pregnancy tests are negative. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.

Participants receiving lenalidomide must register with any pregnancy prevention/controlled distribution program in place locally (see SRM for details).

Female participants of childbearing potential must agree to use 1 of the approved methods of contraception outlined below from the start of study treatment throughout the study, and for 6 months after the last dose of combination study treatment.

The approved methods of birth control for female participants in Sub-study 6 are:

- Total abstinence
- Female sterilization
- Hormonal contraceptive (oral, injectable, implanted, intravaginal, or transdermal). Note: This method of birth control is not approved for Germany.
- Intrauterine device

- Male partner who has undergone surgical sterilization/vasectomy with medical confirmation of procedure efficacy/success, and this male partner is sole sexual partner of female study participant.

If using hormonal contraception, *an additional barrier method must be used as taking hormonal contraception with nirogacestat may decrease the effectiveness of the hormonal contraception*. Barrier methods include condoms (male or female) or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream or vaginal suppository.

In the event of discontinuation of nirogacestat and continuation of belantamab mafodotin as single agent therapy, use of approved highly effective contraception should be used throughout study treatment and for 4 months following last dose of belantamab mafodotin, or 6 months following the last dose of nirogacestat, whichever is longer, in female participants of childbearing potential (see 208887 MP Section 5.1 and 208887 MP Appendix 7 for further details on contraceptive guidance and definitions).

Male Participants

Male participants must agree to use 1 of the approved methods of contraception outlined below from the start of study treatment throughout the study, and for 6 months after the last dose of combination study treatment.

The approved methods of birth control for male participants in Sub-study 6 are:

- Total abstinence.
- Male condom use (regardless of whether the participant has undergone male sterilization).

One of the approved methods of birth control below must be used by female partners of male participants:

- Total abstinence.
- Female sterilization.
- Hormonal contraceptive (oral, injectable, implanted, intravaginal, or transdermal).
- Intrauterine device.

In the event of discontinuation of nirogacestat and continuation of belantamab mafodotin as single agent therapy, use of highly effective contraception should be used throughout study treatment and for 6 months following last dose of belantamab mafodotin for male participants (see 208887 MP Section 5.1 and 208887 MP Appendix 7 for further details on contraceptive guidance and definitions).

8.3.8. Cardiovascular and Death Events

Please refer to the 208887 MP.

8.3.9. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Please refer to the 208887 MP.

8.3.10. Adverse Events of Special Interest

Information on belantamab mafodotin AESIs are contained in the 208887 MP Section 8.3. Information on nirogacestat AESIs will no longer be collected for sub-study protocol amendment 01.

8.4. Treatment of Overdose

Guidelines for management of belantamab mafodotin overdose are contained in the 208887 MP Section 8.4.

In the case of accidental overdosing with nirogacestat, vital functions should be monitored carefully in an appropriate health care facility. Special attention should be given to hematological (complete blood counts with differential) and GI functions. Obtain an additional plasma sample for PK analysis if requested by the Medical Director.

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 studies, the dose-limiting toxicity was neutropenia and thrombocytopenia.

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.

8.5. Pharmacokinetics

Please refer to the 208887 MP.

8.6. Pharmacodynamics

Please refer to the 208887 MP.

8.7. Genetics

Please refer to the 208887 MP.

8.8. Immunogenicity Assessments

Please refer to the 208887 MP.

8.9. Biomarkers

Please refer to the 208887 MP Section 8.8 for description and details of biomarker research common among the sub-studies.

8.9.1. Plasma Soluble (s)BCMA Sample Analysis

Biomarker research in this sub-study will involve peripheral blood (whole blood, cells, serum, and plasma), bone marrow and tumor biopsies, as described in the MP.

The BCMA receptor undergoes γ-secretase mediated cleavage, leading to release of the BCMA extracellular domain as sBCMA into the circulation [Laurent, 2015]. Levels of sBCMA in serum will be evaluated in more detail in this sub-study as a direct pharmacodynamic biomarker of nirogacestat target engagement and will be compared to the belantamab mafodotin monotherapy arm. There is strong preclinical data demonstrating enhanced belantamab mafodotin ADC and ADCC activities, and dose-dependent decreases in sBCMA after nirogacestat treatment. Additionally, the BMA117159 first time in human study showed a dramatic decrease in free sBCMA levels after belantamab mafodotin infusion that returned to or around baseline at Day 8 or Day 15 after end of infusion [internal data]. Given nirogacestat's ability to block BCMA cleavage, we hypothesize that in contrast to the first time in human BMA117159 study and to the belantamab mafodotin monotherapy arm in this Sub-study, the levels of free sBCMA will remain low to negligible and/or recovery to the baseline level will be significantly delayed with the combination of belantamab mafodotin plus nirogacestat.

Samples will be collected to measure concentrations of sBCMA at the timepoints specified in the SoA (Table 5 and Table 6) using a validated assay. Details of sample preparation, storage and analysis will be provided in the SRM. Raw data will be archived at the bioanalytical site (detailed in the SRM).

8.9.2. NOTCH Gene Expression Analysis

NOTCH signaling modulates the expression of several target genes. Gene transcription analysis for regulation of NOTCH target genes by nirogacestat might be performed in this sub-study on the basis that previous studies have shown this as a prototypical pharmacodynamic biomarker in peripheral blood for GSIs (including nirogacestat) [Messersmith, 2015; Krop, 2012]. This analysis could be correlated to nirogacestat plasma concentrations in support of a mechanistic effect and/or to patient responses and would complement our evaluation of sBCMA levels.

8.9.3. Tumor Related Biomarker Analysis

While BCMA expression is present in multiple myeloma cells, there is some variability in the expression, as well as the membranous/cytosolic localization pattern. Therefore, it is important to determine if there is any association between the expression levels of BCMA on multiple myeloma cells and clinical responses. Furthermore, BCMA is cleaved from the tumor cell surface by γ-secretase reducing BCMA in the surface of tumor cells for belantamab mafodotin recognition and releasing sBCMA, limiting

belantamab mafodotin efficacy. GSI administration to MM patients has been shown to increase the percentage of BCMA+ tumor cells and the levels of BCMA surface expression resulting in enhanced BCMA CAR T-cell efficacy [Pont, 2019].

Given that the addition of nirogacestat to belantamab mafodotin is expected to increase the density of BCMA on the surface of MM plasma cells leading to potentially enhanced pharmacodynamic activity of belantamab mafodotin, we propose to explore the expression of BCMA and/or pharmacodynamic effects in plasma (and/or myeloma) cells at baseline and after treatment with the belantamab mafodotin plus nirogacestat combination. These analyses would support evaluation of mechanistic effects of the combination and/or association to patient responses. To this end, bone marrow samples will be collected during this study, at the time points indicated in the SoA and Table 7 and will be analyzed by flow cytometry. Evaluations may also include IHC or related technologies (e.g., DNA or RNA sequencing) for expression of BCMA, or relevant biomarkers on tumor cells and/or phenotypic and functional markers on immune cell populations.

8.10. General guidance for treatment continuity when participants are unable to come into the clinic

Please refer to the 208887 MP.

9. STATISTICAL CONSIDERATIONS

Please refer to the 208887 MP for the overall statistical considerations for the study.

9.1. Statistical Hypotheses

Please refer to the 208887 MP.

9.2. Sample Size Determination

Please refer to the 208887 MP.

9.3. Populations for Analyses

Please refer to the 208887 MP.

9.4. Statistical Analyses

Please refer to the 208887 MP.

9.5. Interim Analyses

At the first CE interim analysis, in addition to the futility assessment specified in 208887 MP, additional assessments will be evaluated as described below. The sub-study may be considered for termination for having convincing evidence that the combination treatment is more beneficial than the monotherapy if the conditions below are met:

1. Efficacy: Observed ORR is at least 45% across all participants in DE and any of the CE combination treatment participants at the first interim analysis, who have at least 3 post-baseline efficacy assessments or have at least 2 planned doses.
2. Ocular Toxicity: Posterior probability is greater than 90% that the (true toxicity rate for combination) < (true toxicity rate for monotherapy).
    a. Ocular toxicity criteria: Grade 3 or above. Details of the criteria will be finalized in the Statistical Analysis Plan prior to initiation of the CE Phase.
    b. This will be calculated using available data from the combination participants and all monotherapy CE participants at the first CE interim analysis.
    c. Toxicity rate will be assumed to have a beta distribution with parameters as follows:
        i. Combination therapy: parameters will be based on data from the DE Phase
        ii. Monotherapy: parameters will be based on DREAMM-2 data (42%, n=97)

The operating characteristics of the efficacy criteria are summarized in Table 19 and the operating characteristics of the toxicity criteria as well as the joint toxicity and efficacy criteria, assuming true ORR=0.70, are summarized in Table 20.

Table 19 Operating Characteristics of the Efficacy Criteria

True ORR	Probability of meeting efficacy stopping criteria
0.30	0.15
0.40	0.37
0.50	0.62
0.60	0.83
0.70	0.95
0.80	0.99

Table 20 Operating Characteristics of the Toxicity Criteria

Toxicity Rate		Probability of meeting stopping criteria	
Monotherapy	Combination treatment	Probability of meeting the toxicity criteria	Probability of meeting the toxicity and efficacy criteria *
0.42	0.42	0.096	0.092
0.42	0.3	0.364	0.348
0.42	0.2	0.718	0.686
0.42	0.15	0.869	0.830
0.42	0.1	0.959	0.915

*Assuming True ORR=0.70

9.6. Sample Size Sensitivity

Please refer to the 208887 MP.

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11. GUIDELINES FOR DOSE MODIFICATION AND OTHER PARTNER COMBINATION TREATMENTS FOR ALL SUB-STUDIES

Please refer to the 208887 MP for the overall Guidelines for Dose Modification for the study.

12. APPENDICES: SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Please refer to the 208887 MP for the overall supporting documentation and operational considerations for the study.

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

Please refer to the 208887 MP.

12.2. Appendix 2: Clinical Laboratory Tests

Please refer to the 208887 MP.

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

Please refer to the 208887 MP.

12.4. Appendix 4: ECOG Performance Status

Please refer to the 208887 MP.

12.5. Appendix 5: NYHA Functional Classification System

Please refer to the 208887 MP.

12.6. Appendix 6: Modified Diet in Renal Disease

Please refer to the 208887 MP.

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

Please refer to the 208887 MP.

12.8. Appendix 8: Genetics

Please refer to the 208887 MP.

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

Please refer to the 208887 MP.

12.9.1. Liver Safety Event

PK sampling required for partner agent with Liver Safety Event as outlined in Table 30 in the 208887 MP Appendix 9 should be performed approximately 5 days following the last dose of nirogacestat.

12.10. Appendix 10: Eye Care Specialist- Qualifications and Requirements

Please refer to the 208887 MP.

12.11. Appendix 11: Decentralized and Remote Assessment Approaches

Please refer to the 208887 MP.

12.12. Appendix 12: Third Parties and Subcontractors

Please refer to the 208887 MP.

12.13. Appendix 13: Abbreviations, Trademarks, and Definitions of Terms

ADA	Anti-drug antibody
ADC	Antibody drug conjugate
ADCC	Antibody dependent cellular cytotoxicity
AE	Adverse event
AESI	Adverse events of Special Interest
ALT	Alanine aminotransferase
ANC	Absolute Neutrophils count
APP	Amyloid precursor protein
AST	Aspartate aminotransferase
BP	Blood Pressure
BCMA	B-cell maturation antigen
BID	Twice a day
BM	Bone marrow
BMI	Body mass index

BSA	Body surface area
C	Cycle
CBC	Complete blood count
CE	Cohort Expansion (Phase)
Cmax	Maximum plasma drug concentration
CMMC	Circulating multiple myeloma cells
CR	Complete response
CRF	Case report form
CT	Computer tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CYP	Cytochrome P450
Cys-mcMMAF	cys Monomethyl auristatin F
D	Day
DDI	Drug-drug interactions
DE	Dose Exploration (Phase)
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
EC50	Concentration associated with 50% maximal effect
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration
ELISA	Enzyme linked immunosorbent assay
EOI	End of infusion
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires 30-item Core Module
FISH	Fluorescence in situ hybridization;
FLC	Free light chain
FTIH	First time in human
GI	Gastrointestinal
GSI	Gamma secretase inhibitor
GSK	GlaxoSmithKline
GSK2857914	GSK anti-BCMA antibody (CA8 J6M0 Potelligent)
HBsAg	Hepatitis B surface antigen
HBc	Hepatitis B core
HbcAb	Hepatitis B core antibody
HBV	Hepatitis B virus
HCV	Hepatitis C virus
IB	Investigator's Brochure
Ig	Immunoglobulin
IgG-MMAF	immunoglobulin G-Monomethyl auristatin F
IHC	Immunohistochemistry
IV	Intravenous
LFT	Liver function test

LVEF	Left ventricular ejection fraction
mbBCMA	Membrane-bound BCMA
Mc	Maleimidocaproyl
MDRD	Modified diet in renal disease
MM	Multiple Myeloma
MMAF	Monomethyl auristatin F
MP	Master Protocol
MRD	Minimal residual disease
MRI	Magnetic resonance Imaging
NCI-CTCAE	National Cancer Institute – Common Toxicity Criteria for Adverse Events
NYHA	New York Heart Association
OS	Overall survival
OSDI	Ocular Surface Disease Index
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
Pgp	P-glycoprotein
PK	Pharmacokinetic(s)
PO	Per Oral
PR	Partial response
PRO	Patient reported outcome
Q3W	Every 3 weeks
Q4W	Every 4 weeks
QD	Once daily
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
RRMM	Relapsed/refractory multiple myeloma
SAE	Serious adverse event
sBCMA	Soluble B-cell maturation antigen
sCR	Stringent complete response
SoA	Schedule of Activities
SJS	Stevens-Johnson syndrome
SOI	Start of infusion
SPEP	Serum protein electrophoresis
SRM	Study research manual
TEN	Toxic epidermal necrolysis
Tmax	Time to maximum drug concentration
UPEP	Urine protein electrophoresis
VGPR	Very good partial response
VTE	Venous thrombo-embolism
WOCBP	Women of childbearing potential

Trademark Information

Trademarks of the GSK group of companies	Trademarks not owned by the GSK group of companies
NONE	REVLIMID (lenalidomide)

Term	Definition
Auxiliary Medicinal Product (AxMP)	Medicinal products used in the context of a clinical trial but not as IMPs, such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess endpoints in a clinical trial. AxMPs should not include concomitant medications, i.e., medications unrelated to the clinical trial and not relevant for the design of the clinical trial. Authorized AxMP = Medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any member state concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product. Note: Safety reporting with regard to authorized AxMPs shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC. Unauthorized AxMP = Medicinal product not authorized in accordance with Regulation (EC) No 726/2004 Safety reporting for unauthorized AxMPs will follow the same processes and procedures as SUSAR safety reporting.
Blinding	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. In an open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned.
Combination product	Combination product comprises any combination of: • drug • device • biological product. Each drug, device, and biological product included in a combination product is a constituent part.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Investigational Medicinal Product (IMP)	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual(s) or party(ies) to perform those study-related duties and functions.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine[s]/product[s]/control). Synonym: subject

Term	Definition
Pharmacogenomics (PGx)	The ICH E15 Guidance for Industry defines PGx as "the study of variation of DNA and RNA characteristics as related to drug or treatment response." Pharmacogenetics, a subset of PGx, is "the study of variations in DNA sequence as related to drug response." PGx biomarkers include germline (host) DNA and RNA as well as somatic changes (e.g., mutations) that occur in cells or tissues. PGx biomarkers are not limited to human samples but include samples from viruses and infectious agents as well as animal samples. The term pharmacogenomic experiment includes both the generation of new genetic or genomic (DNA and/or RNA) data with subsequent analysis as well as the analysis of existing genetic or genomic data to understand drug or treatment response (PK, pharmacodynamics, safety, efficacy or effectiveness, mode of action). Proteomic and metabolomic biomarker research is not PGx.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Standard of care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries.
Study intervention	Term used throughout the clinical study to cover all types of investigational and non-investigational products, including medical devices and vaccines, intended to be administered to the study participants during the study conduct. Procedures conducted to manage participants or to collect data are excluded from the usage of this term.
SUSAR	In a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., IB for an unapproved IMP). All ADRs that are both serious and unexpected are subject to expedited reporting.

12.14. Appendix 14: Country-Specific Requirements

Please refer to the 208887 MP.

12.15. Appendix 15: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current Sub-study 2 Amendment 2 is located directly before the Table of Contents (TOC).

Amendment 01 (Sub-study 6): 07 July 2023

Overall Rationale for the Amendments:

The Sub-study 6 protocol has been amended to make corrections to typographical errors and inconsistencies, to add clarifications in line with program level changes, and to add administrative and safety updates, which are summarized in the table below.

Section # and Name	Description of Change	Brief Rationale
Throughout document	Changed all instances of Medical Monitor to consistently refer to the Medical Director, and updated medical director contact information	Correction of typographical or consistency error
Throughout document	Minor editorial and document formatting revisions; applied GSK style guide for abbreviations, date format, etc.	Correction of typographical or consistency errors
Throughout document	The term GSK'916 (used for laboratory samples) was replaced by belantamab mafodotin	Clarification of wording
Throughout document	Updated amendment numbering in sub-study to be unique and not identical to MP	Correction of typographical or consistency error
Throughout document	Updated reference to GSK2857916/ belantamab mafodotin Investigator's Brochure	To refer to the most recent version of the IB
Investigator Protocol Amendment Agreement Page	Included sub-study title for consistency with title page	Correction of typographical or consistency error
Section 1 Protocol Summary	Protocol amendment SOC Table, cannot refer to a previous version of the protocol. Country specific requirements should be incorporated in the main protocol.	Correction of typographical or consistency error
Section 1.2.2 Belantamab Mafodotin, Nirogacestat, Lenalidomide, and Dexamethasone	Clarified that DLT period is 28 days from C1D1 (not from Cycle 1 Day -2)	Clarification for study conduct
Section 1.3 Schedule of Assessments	Removed extraneous text from Table 2 footnote 1	Correction of typographical or consistency error
Section 1.3 Schedule of Assessments	In Table 5, aligned the time window for PK sampling with the one for vital signs measurement and added clarifications on the time window for predose PK sampling	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarification that Screening assessments should be conducted at Cycle 1 Day -2 (not C1D1) unless otherwise indicated in Table 3	Clarification for study conduct
Section 1.3 Schedule of Activities	Footnote for hepatitis tests incorrectly broken into 2 footnotes	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	In Table 3 and Table 5, clarified that anytime C1D1 Hem/Chem results are outside of eligibility requirements, MD should be contacted prior to dosing. Removed "at Screening" for clarity.	Clarification for study conduct
Section 1.3 Schedule of Activities	Correction of footnotes and references to footnotes in Table 3, footnote 6 onwards	Correction of typographical or consistency error

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Removed pharmacokinetic and soluble B cell maturation antigen sampling from Cycle 1 Day 4 (DE only) in Table 4	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarified guidance regarding realignment of scheduled weekly visits and dosing visits in Table 4	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 4, modified footnote for urine and serum immunofixation to include "not quantifiable"	Clarification for study conduct
Section 1.3 Schedule of Activities	Removed extraneous text from Table 4, footnote 4	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	In Table 4 (footnote 8) and Table 6 (footnote 21), decreased frequency of UPEP assessments	Program level changes
Section 1.3 Schedule of Activities	Revised language related to imaging for skeletal surveys and for participants white extramedullary disease in Table 4, footnotes 12 and 13	Clarification for study conduct
Section 1.3 Schedule of Assessments	Added details on treatment dispensation to note in Table 5.	Clarification for study conduct
Section 1.3 Schedule of Assessments	Removed details from footnote regarding sBCMA sampling in Table 5	Clarification for study conduct
Section 1.3 Schedule of Activities	Revised window for PK sampling to 0-10 minutes to align with vital sign window in Table 5	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarified that on PK sampling visits, if vital signs assessments are conducted, they should be assessed prior to PK samples being drawn in Table 4, footnote 1 and Table 5	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 5 footnote 7 and 9, clarified if belantamab mafodotin dosing at C2D1 is delayed, nirogacestat or PK samples should still be collected and belantamab mafodotin PK sample does not need to be collected	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 5 footnote 9, removed C18D1 EOI PK sample	Clarification for study conduct
Section 1.3 Schedule of Activities	Table 5 footnote 1, clarified that vital signs must be monitored within 30 minutes prior to start of infusion	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 5, updated nirogacestat dosing in footnote 16	Clarification for study conduct

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Removed detail regarding LFTs from Table 5, footnote 4	Clarification for study conduct. LFTs should be assessed as a part of hematology.
Section 1.3 Schedule of Activities	Revised guidance for home administration of lenalidomide and dexamethasone to be taken approximately the same time each day removing reference to be taken in the morning in Table 5, footnote 21	Clarification for study conduct
Section 1.3 Schedule of Activities	Removed reference to footnotes 23 and 25 in Table 5	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Aligned row heading of hematology (enhanced TBNK panel) with 208887 MP	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Updated guidance on pregnancy testing and collection of pregnancy information in Table 5, footnote 3 and Table 6, footnote 8	Clarification for study conduct
Section 1.3 Schedule of Activities	Revision to indicate change in timing of EOT to within 30 days from when decision to discontinue treatment in Table 6, footnote 1	Clarification for study conduct
Section 1.3 Schedule of Activities	Revision to clarify timing of follow-up OSDI questionnaires following the end of treatment in Table 6, footnote 18	Clarification for study conduct
Section 1.3 Schedule of Activities	Corrected the term in the Schedule of Activities to refer to the 'end of treatment' instead of 'end of study' in Table 6, footnote 19	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Updates to MRD, biomarker assessments, and optional bone marrow research in Table 5 and Table 7	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 7, the term "suspected VGPR, CR/sCR" was corrected to "VGPR or suspected CR/sCR".	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Details regarding FISH testing were removed from Table 7 footnote 3 and reference to Table 31 has been provided.	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 7 created separate rows PD and Suspected PD and added timing of corresponding assessments.	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 7, clarified that BM aspirate/biopsy collection between C3D1 and C5D1 is predose of belantamab mafodotin	Clarification for study conduct

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Clarified the timing of HBV-DNA testing to allow for grouping with the closest study visit in Table 8	Clarification for study conduct
Section 1.3 Schedule of Assessments	Updates to Table 3 Table 4, Table 5 and Table 6 to clarify the timing of ocular exams	Clarification for study conduct
Section 1.3 Schedule of Activities	Updates related to biomarker assessments (Table 3, Table 4, Table 6 remove core biopsy), Table 5 (clarified timing of sBCMA sampling)	Clarification for study conduct
Section 1.3 Schedule of Activities	Removed the need for bone marrow aspiration at end of study visit for MRD assessment in Table 6. Clarified conditions for MRD testing at screen and during study. Added a ±1 month window for follow-up MRD testing in Table 7. Update of timing of BM aspirate to occur between C3D1 and C5D1 from Cycle 1 Day 1 in Table 7.	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarified when the sample is collected for urine immunofixation in Table 3, Table 4, Table 6	Clarification of study conduct
Section 1.3 Schedule of Activities	Clarified that the core biopsy to assess sCR will be tested at a local lab	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Update of timing of bone marrow aspirate to occur between C3D1 and C5D1 from Cycle 1 Day 1 in Table 7 and at PFS follow-up in Table 6.	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Belantamab mafodotin program safety language to be used throughout protocols. AE/SAEs will be collected until at least 70 days post last dose (Table 4 and Table 6)	Clarification of study conduct
Section 1.3 Schedule of Activities, Section 5.2 Exclusion criteria, Section 6.5.2 Prohibited Concomitant Medications and Non-Drug Therapies	Added HIV testing at screening to Table 3 footnote 8 and Section 5.2 to conform with FDA guideline for inclusion of patients with previous exposure to HIV. Updated nirogacestat dose modifications when HIV drugs are co-administered.	Program level changes
Section 2.2.2 Clinical Development of Nirogacestat in Monotherapy and Combination Studies	Included results of nirogacestat Phase 3 study and corresponding reference	Inclusion of updated information
Section 2.3.1 Summary of Risk Assessment	In Table 10, updated the mitigation strategy for diarrhea related to nirogacestat	Clarification of study conduct

Section # and Name	Description of Change	Brief Rationale
Section 4.1.2 Cohort Expansion, Section 6.2.4 Participant Transition from DE to CE	Removed specification on how many CEs will be done for each sub-study. The decision of opening a CE is made by iDRC and DEC based on observed data during DE.	Clarification of study conduct
Section 4.3.1 Justification for Starting Dose of Belantamab Mafodotin	Corrected reference to DREAMM-6 that used lenalidomide	Correction of typographical or consistency error
Section 4.3.1 Justification for Starting Dose of Belantamab Mafodotin	Corrected reference to x/y to 29%	Correction of typographical or consistency error
Section 4.3.1 Justification for Starting Dose of Belantamab Mafodotin	Removed reference to EU approval	Correction of typographical or consistency error
Section 5.2 Exclusion Criteria for Participants	Added note that numbering for exclusion criteria may not be sequential from the MP	Correction of typographical or consistency error
Section 5.2 Exclusion Criteria for Participants	Added a note to clarify that female of childbearing potential using hormonal contraception at the time of Screening are excluded	Alignment with the German Addendum
Section 5.3 Lifestyle Considerations	Added guidance that participants must not donate blood during treatment with lenalidomide and 4 weeks following discontinuation	Clarification for study conduct
Section 6.1 Study Treatment(s) Administered	In Table 11, updated language concerning dose formulation.	Clarification for study conduct
Section 6.2.2 Administration of Nirogacestat with Lenalidomide and Dexamethasone	Revised guidance for home administration of lenalidomide and dexamethasone to be taken approximately the same time each day, removing reference to be taken in the morning	Clarification for study conduct
Section 6.2.2 Administration of Nirogacestat with Lenalidomide and dexamethasone Section 1.3 Schedule of Assessments	In Section 6.2.2 and Table 5 footnote 17, removed statements that diary cards are located in SRM, which is no longer accurate	Clarification for study conduct
Section 6.3 Preparation/Handling/Storage/Accountability	Stated that 100 mg nirogacestat tablets will be provided in 75 count, induction sealed high-density polyethylene bottles	Clarification for study conduct
Section 6.3 Preparation/Handling /Storage/Accountability	Removed “within a 21-day cycle” from second dose and onwards of nirogacestat. In addition to Table 17, identified Table 18 as a source for further information on dose modifications for safety purposes.	Correction of typographical or consistency error
Section 6.6.3.1 Gastrointestinal Toxicities	Updated section heading from “Diarrhea” to “Gastrointestinal Toxicities”	Correction of typographical or consistency error

Section # and Name	Description of Change	Brief Rationale
Section 6.6.3.1 Gastrointestinal Toxicities	Recommended use of antidiarrheal medication in patients receiving nirogacestat	Clarification for study conduct
Section 6.6.4 Lenalidomide-related Dose Modification Guidance	Reference added to refer to lenalidomide local prescribing information regarding guidance on dose reductions	Clarification for study conduct
Section 6.6.1 Permitted Dose Reductions per Participant for Belantamab Mafodotin when in Combination with Nirogacestat, Lenalidomide, and Dexamethasone Section 6.6.3 Nirogacestat-Associated Dose Modification Guidance Section 6.6.4 Lenalidomide-Associated Dose Modification Guidance Section 6.6.5 Dose Modification Guidelines for Dexamethasone	Revised safety language to be “associated (with)” drug in place of “related (to)”	Correction of typographical or consistency error
Section 8.3.10 Adverse Events of Special Interest	Revised to remove detail regarding adverse of special interest for nirogacestat	Clarification for study conduct. Development partner no longer collecting this data.
Section 8.3.7.1 Pregnancy in Sub-study 6	Updated the time period for pregnancy information collection	Alignment with current Nirogacestat IB
Section 8.3.7.2 Contraception in Sub-study 6	Added a note to the list of approved methods of birth control to clarify that hormonal contraceptives are not approved in Germany	Alignment with the German Addendum
Section 9.5 Interim Analyses	Clarification that participants would be considered evaluable for the futility analysis after they have had 3 efficacy assessments (1 baseline and 2 post-baseline assessments)	Correction of typographical or consistency error
Section 10 References	Added references; applied GSK style guide for references	Correction of typographical or consistency errors
Section 12 Supporting Documentation and Operational Considerations	Added single statement in beginning of appendix 12 to “Please refer to the 208887 MP for the overall supporting documentation and operational considerations for the study.”	Correction of typographical or consistency error
Section 12.12 - Appendix 12	Listing of all third parties and subcontractors who are supporting this study	Program level update

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