Protocol Amendment 7

Study ID: 208887 Sub Study 3

Official Title of Sub Study 3: 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 3 - Belantamab Mafodotin and Nirogacestat in Combination

NCT ID of Sub Study 3: NCT07084896

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NCT ID of Master Protocol: NCT04126200

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 3 – Belantamab Mafodotin and Nirogacestat in Combination

Protocol Number: 208887 / Amendment 7 for Sub-study 3

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

Study Phase: 1/2

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

Acronym: DREAMM-5 Sub-study 3

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Approval Date: 03 Sep 2024

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PROTOCOL AMENDMENT 7 SUB-STUDY 3 INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: 208887

AMENDMENT NUMBER: Protocol Amendment 7 for Sub-study 3

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 3 – Belantamab Mafodotin and Nirogacestat 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 7 (Sub-study 3)	03 Sep 2024	TMF-19471520
Amendment 6 (Sub-study 3)	07 July 2023	TMF-15016834
Amendment 5 (Sub-study 3)	22 February 2022	TMF-13841951
Amendment 4 (Sub-study 3)	14 December 2020	2020N453268_00
Amendment 3 (Sub-study 3)	08 July 2020	2017N352487_03
Amendment 2 (Sub-study 3)	16 December 2019	2017N352487_02
Amendment 1 (Sub-study 3)	24 June 2019	2017N352487_01
Original Protocol	12 March 2019	2017N352487_00

Amendment 7 (Sub-study 3): 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 3 & 5: Procedures related to health outcomes evaluation were removed. Tables 4 & 5: A note to stop plasma PK sampling once enough data have been collected was added. Tables 4 & 5: Sampling for sBCMA and CMMC analyses was removed. Table 6: 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 6.1. Study Treatment(s) Administered	The information regarding study treatments was updated.	To comply with the latest regulatory requirements.
Section 8.10. Health-related Quality of Life	Reference 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 3 are in the subsections below (Table 1).

Table 1 Location of Sub-study 3 Specific Content

Section	Heading title	Brief description of content
1.2	Schema	Belantamab mafodotin and nirogacestat study diagram
1.3	Schedules of Activities	Comprehensive SoA tables specific for Sub-study 3
2.1	Rationale for Belantamab Mafodotin and Nirogacestat Sub-study	Explanation why treatment with belantamab mafodotin and nirogacestat is expected to be complementary
2.2	Background	Available data on clinical pharmacology, safety and clinical activity
2.3	Benefit/Risk Assessment	Risk assessments for nirogacestat treatment; benefit assessment summary
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 and nirogacestat dosing
5.2	Exclusion Criteria	Five additional exclusion criteria were defined for Sub-study 3
6.1	Study Treatment(s) Administered	Specifications for belantamab mafodotin and nirogacestat investigational product
6.2	Administration of Belantamab Mafodotin and Nirogacestat	Specifications for administration of belantamab mafodotin and nirogacestat
6.3	Preparation/Handling/Storage/Accountability	Specifications for handling, storage and accountability of nirogacestat
6.5.2	Prohibited Concomitant Medications and Non-drug Therapies	Specifications of prohibited concomitant medications specific to Sub-study 3
6.6	Dose Modification	Detailed directions 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 3
8.3.10	AESI for Nirogacestat	Information on nirogacestat AESI
8.4	Treatment of Overdose	Guidance for potential drug overdose for nirogacestat
12.9.1	Appendix 9: Liver Safety Event	Timeframe for PK sampling in case of liver safety event
12.13	Appendix 13: Protocol Amendment History	Summary of Changes Tables for Sub-study 3 specific amendments

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 3 – Belantamab Mafodotin and Nirogacestat in combination

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

Rationale: Gamma (γ)-secretase is an integral membrane protein complex with protease activity against single-pass transmembrane proteins within the transmembrane domain, such as amyloid precursor protein and the NOTCH receptor. Nirogacestat (PF-03084014) is a potent selective, non-competitive, reversible tetralin amino imidazole γ-secretase inhibitor (GSI), which belongs to a chemically heterogenous family of GSI small molecules, which inhibit the cleavage of several different cell surface receptors. One of the substrates for γ-secretase is B-cell maturation antigen (BCMA), the target for belantamab mafodotin. Gamma-secretase is the sole enzyme responsible for production of the extracellular domain of BCMA as a soluble form, known as soluble B-cell maturation antigen (sBCMA). 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 (BM).

The addition of nirogacestat to belantamab mafodotin is expected to increase the density of BCMA on the surface of multiple myeloma (MM) plasma cells leading to potentially enhanced pharmacodynamic activity of belantamab mafodotin.

Dose Exploration (DE) in this sub-study will involve 4 potential dosing cohorts of belantamab mafodotin in combination with nirogacestat (Cohorts 1-4).

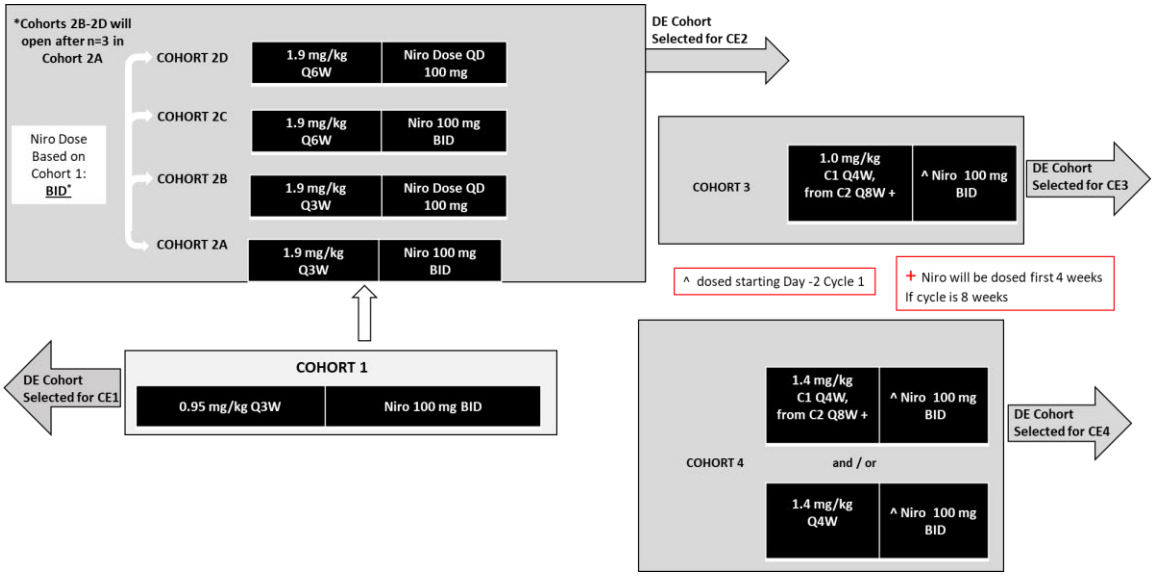
1.2. Schema

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 and Nirogacestat

Figure 1 Dose exploration and cohort expansion schematic for belantamab mafodotin and nirogacestat



Please refer to Section 4.1 for further details.

Nirogacestat lead-in dosing before the first belantamab mafodotin dose applies to Cohorts 3 and 4. 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 both agents have been administrated together on C1D1.

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 is to allow adjustments that may be needed to ensure the full PK and pharmacodynamic profile is defined.
- The Competent Authority and the IRB/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 CA and the IRB/IEC before implementation.

Table 2 SoA – Screening for DE and CE Phases: Belantamab Mafodotin and Nirogacestat

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 Assessments 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).
Demography	X	
Medical History (includes substance abuse)	X	
Full Physical Exam	X	2. Perform only in WOCBP. A pregnancy test must be performed at Screening. If the test is completed within 72 hours prior to the first dose, this assessment needs not to be repeated on C1D1.
Throughout the study, participants are educated about in life style considerations (208887 MP Section 5.3) for the study and the need of maintaining adequate urinary output (208887 MP Section 2.3.1).	X	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).
Inclusion/Exclusion criteria	X	
Past and current medical conditions	X	
Concomitant Medication review	X	
Screening Safety Assessments		6. If a participant tested hepatitis B core antibody positive, refer to Table 7 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).
Ocular Exam	X[1]	
ECOG Performance Status	X	
Vital Signs (BP, HR, Body Temperature)	X	7. Complete at Screening or within 12 weeks prior to C1 Day -2.
Weight and Height	X	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
Serum Pregnancy Test (WOCBP only)	X[2]	
Hematology (CBC)	X[3]	9. Single ECG at Screening.
Clinical chemistry	X[3]	10. ECHO or MUGA scan for LVEF may be performed within 30 days prior to C1 Day -2.
eGFR	X[4]	11. SPEP and UPEP will include M-protein levels.
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)	X[5]	12. Serum FLC assay will include kappa/lambda ratio and quantification of involved and uninvolved light chains.
HBsAg, HBcAb[6], HCV[6] tests	X[7]	13. IgD/IgE testing is only required for participants with IgD/IgE myeloma.
HIV viral load and CD4+ count	X[8]	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, PET/CT) for assessment of extramedullary disease. Skeletal survey results within 30 days prior to
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 Assessments 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		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 6 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 3 SoA – Treatment Period for DE and CE Phases: Belantamab Mafodotin and Nirogacestat. 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 (Cohorts 3 and 4 from Cycle 2 onwards), 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 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 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		
Genetics	X[2]		2. Informed consent for genetic research must be obtained before collecting a sample. The sample will be collected on C1D1 prior to infusion.
ECOG Performance Status		X	
Safety			
Ocular Exam		X[3]	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.
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]	
Disease Evaluation (every 3 or 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]	
Serum immunofixation		X[9]	
Serum FLC assay		X[10]	
IgG, IgM, IgA		X	
IgD or IgE		X[11]	

Study Assessments regardless of whether participant is dosed	Day 1 (Week 1)	Treatment Period until EOT
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]
BM 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]

Notes

7. ECHOs or MUGA scan for LVEF to be done if clinically indicated. The same procedure used at Screening should be used throughout the study.
8. SPEP must be performed Q3W or Q4W depending on cohort dosing scheme. 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.
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 3 weeks or every 4 weeks depending on cohort dosing scheme.
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 appearance of a new lesion (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 will be performed until approval by the German Federal Office for Radiation Protection
15. Please refer to Table 6 for scheduled BM collection procedures to include aspirate and biopsy.

Table 4 SoA – Treatment Period on Dosing Days or After Dosing Only: Regarding Belantamab Mafodotin and Nirogacestat

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 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 is dispensed every 21 or 28 days (see Table 2).** • **Regardless of belantamab mafodotin dosing schedule, participants will be assessed every 21 or 28 days (see Table 2).** • **If belantamab mafodotin is held for any reason, then nirogacestat will also be held (see Section 6.6.3.5 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) (+010 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) and repeated at each EOI (+0-10 min), and 30 min post each EOI (+0-10 min). On days with PK sampling time points, if vital signs assessments are conducted, they should be assessed prior to PK samples being drawn. 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 participant symptoms or vision at the time of the sixth dose exam, participants may have their ophthalmologic exams decreased to once every 3 months.
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]	
Weight	X	X			X	
ECOG Performance Status	X	X			X	
Pregnancy Test	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[4]	

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 Day 15	Cycle 2 to EOT
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]
Plasma PK for belantamab mafodotin		X[9]		X[9]	X[9]
Biomarkers					
Hematology (TBNK and/or enhanced TBNK cell activation panel)		X[10]			X[10]
Treatment with Belantamab Mafodotin					
Administration of belantamab mafodotin		X			Day 1 of each dose[11]
Premedication if needed		-			X (at the start of each dose)[12]
Treatment prophylaxis and management: Preservative-free artificial tears and cooling masks		X[13]			X[13]

Notes

See 208887 MP Section 8.2.7 for list of ophthalmic exam procedures and frequency of exams.

3. Perform only in WOCBP. Pregnancy tests may be either predose serum or urine and should be performed within 72 h prior of dosing. A pregnancy test performed at Cycle 1 Day -2 does not need to be repeated at C1D1.
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).
5. CBC and Clinical Chemistry may be done more frequently as clinically indicated. Refer to 208887 MP Appendix 2 for comprehensive list of lab tests.
6. eGFR as calculated by MDRD formula (208887 MP Appendix 6).
7. Nirogacestat PK samples to be taken in all participants. Vital signs should be assessed prior to PK samples being drawn.
   C1D1 (Cohorts 1 and 2) or D -2 (Cohorts 3 and 4) – 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, **Cohorts 3 and 4 only:** C1D1 – predose (within 30 min prior to nirogacestat dosing). **All Cohorts:** 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 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.

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 Day 15	Cycle 2 to EOT	Notes
Treatment with Nirogacestat						C1D1 – predose, 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; C2D1 EOI (0 – 10 min after belantamab mafodotin EOI); Cycles 4, 6, 9, and 12– 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.
Administration of Nirogacestat	X	X[14]	X[14]	X[14]	X[14]	10. To be collected prior to dosing at C1D1, C2D1, C3D1, and at PD.
Patient Dosing Diary Card for Nirogacestat-	X[15]	X[15]	X[15]	X[15]	X[15]	11. Please refer to 208887 MP Section 6.6.3 for guidance on dose delays, reduction and modification. **For Q3W:** The next scheduled dose must be administered every 21 days (+3-day window) since prior/last dose and cannot be given sooner/more frequently than this. **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. 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 can 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).

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 Day 15	Cycle 2 to EOT	Notes
						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 or QD with the first administration to occur at least 1 hour before administration of belantamab mafodotin. A maximum gap of 12 hours is acceptable between belantamab mafodotin infusion and Nirogacestat from C2D1 onwards. 15. Patient Dosing Diary Card for nirogacestat, to be provided to participant with start of every cycle and to be collected at the end of cycle.

Table 5 SoA – End of Treatment (EOT) and Follow-up for Sub-study 3: Belantamab Mafodotin and Nirogacestat

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 at least prior to the new anti-MM treatment (whichever occurs first). 2. PFS follow-up every 21 or 28 days (±7 days) at the time of disease assessment (as indicated in specific dose level) 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 the 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. 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		
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[2]				
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		
IgG, IgM, IgA	X	X		
IgD or IgE	X[12]	X[12]		

Study Assessments	End of Treatment Visit[1]	PFS Follow-up[2]	OS Follow-up[3]	Notes
Calcium corrected for albumin (serum)	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 scan for LVEF 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 6 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. 18. Pharmacokinetic and accompanying sBCMA sample collection may be terminated when sufficient data have been collected.
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[18]	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 6 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 BM core biopsy is preferred for quantitative assessment of malignant plasma cells. However, BM 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 PFS Follow-up Visit, 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. Note that MRD testing will be done by NGS method. Sample collection may be terminated when sufficient data have been collected, and this applies across all sub-studies.
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 7 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 2 to Table 6.

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

2.1. Rationale for Belantamab Mafodotin and Nirogacestat Sub-Study

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. Therefore, there are 2 main objectives for this sub-study:

1. Increase the ORR in participants treated with belantamab mafodotin and nirogacestat combination compared to the belantamab mafodotin monotherapy control arm, without a marked comparative worsening of the overall combination safety profile.
2. Evaluate a lower dose of belantamab mafodotin in combination with nirogacestat to improve the overall safety profile, including reducing the rate of ≥Grade 2 corneal toxicity.

2.2. Background

2.2.1. Gamma-Secretase and BCMA

Gamma-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-ALL, 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 BM [Sanchez, 2018].

It is the intention of this sub-study to investigate these hypotheses based on the strong signals of therapeutic synergism demonstrated from in vitro preclinical experiments with belantamab mafodotin and nirogacestat (see Section 2.2.2).

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-ALL 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 study in aggressive fibromatosis (desmoid tumors) [Kummar, 2017], 150 mg BID nirogacestat continuous administration bas 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 PK 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 Safety

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.

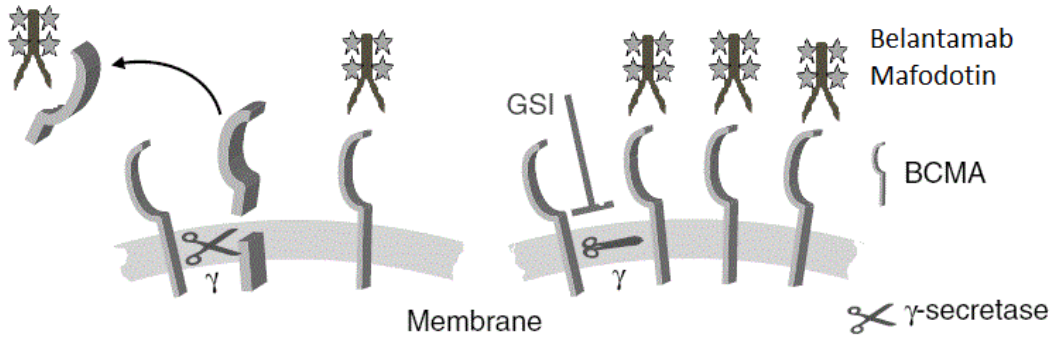
More detailed information regarding toxicology and safety data in clinical studies with Nirogacestat may be found in the IB [Nirogacestat, 2023].

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

2.2.5. Rationale for the Combination of Belantamab Mafodotin with Nirogacestat

GSI may potentially enhance the clinical activity of belantamab mafodotin through several mechanisms: 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 2).

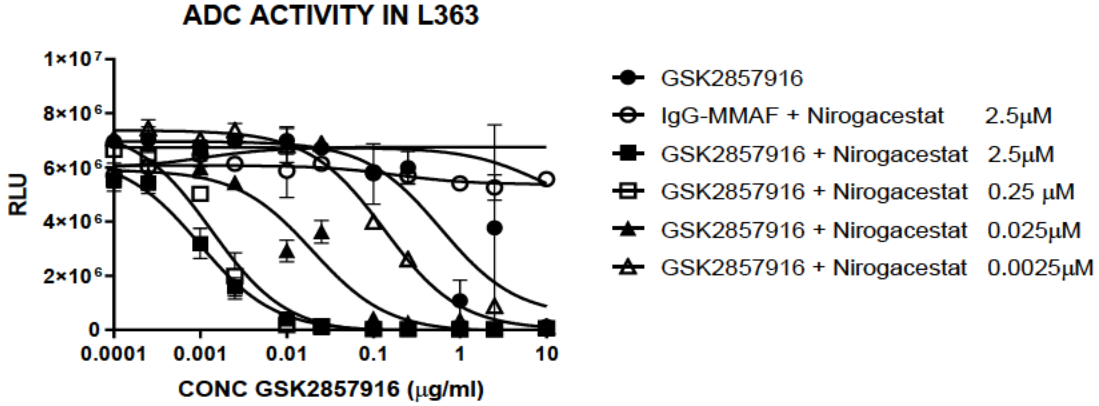
Figure 2 Enhancement of belantamab mafodotin mechanism of action by gamma-secretase inhibition



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 3, 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,

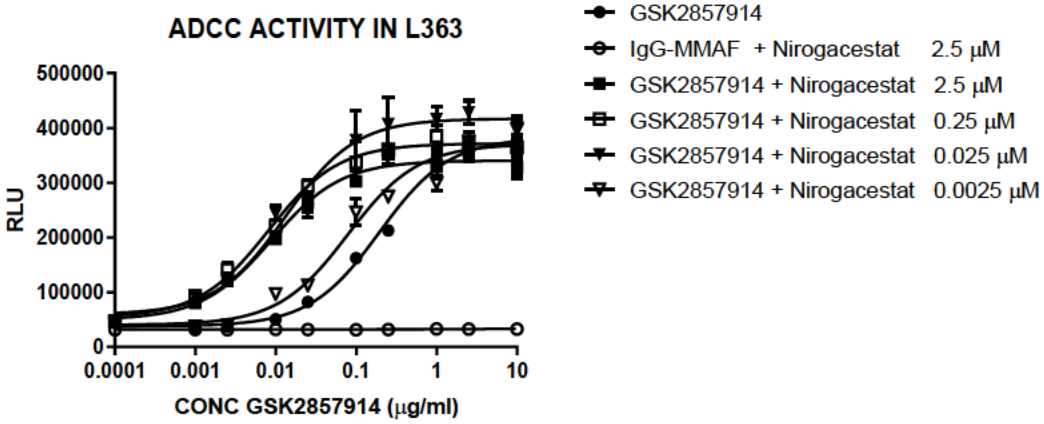
a maximum 1,000-fold shift in EC50 was observed with the combination of nirogacestat and belantamab mafodotin over belantamab mafodotin alone. Similar log-fold shifts were observed with the combination of nirogacestat and belantamab mafodotin in 19 additional multiple myeloma and lymphoma cell lines with evidence of belantamab mafodotin activity.

Figure 3 **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 4, 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 4 **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 BM 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 BM microenvironment.

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

Table 8 outlines the risk assessment and mitigation strategy for nirogacestat in this study. Belantamab mafodotin risk assessment and mitigation strategies are in the 208887 MP Section 2.3.1.

Table 8 Table of Risks Related to Nirogacestat

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risk related to nirogacestat		
Potential Effects of nirogacestat on belantamab mafodotin-related changes in corneal epithelium	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.	Monitoring/dosing guidelines are provided in the 208887 MP Section 6.6.3. Corneal toxicity Grade profile & time to resolution will be evaluated in CE between treatment groups on an ongoing basis.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 21 or 28-day cycle (refer to Table 2) and as clinically indicated.
GI: Diarrhea, nausea, vomiting or dyspepsia (gastroesophageal reflux), decreased appetite	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 GS inhibitors 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. Median time to onset of diarrhea is noted to be 9 days after the first dose of nirogacestat.	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 21 days/3 weeks, may utilize a 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.
Electrolyte Abnormalities	Grade 3 hypophosphatemia was common in clinical studies of cancer patients occurring in	Electrolytes will be regularly monitored, with increased frequency as clinical indicated. Participants should be advised on clinical

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Mainly hypophosphatemia, but can include hypokalemia and hypomagnesemia	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.	symptoms associated with hypophosphatemia and advised to contact the clinic should they experience such symptoms. 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.
Skin Rash	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.	Participants will be advised to contact the investigator should a rash of any type occur. 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.
Elevated Liver Enzymes	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.	Liver function tests will be monitored on 21-day/3-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.
Drug-Drug Interactions (DDI) with strong or moderate	Concomitant administration of the drugs listed in Section 6.5.2 could potentially either increase or reduce systemic exposure of	Concomitant administration of strong CYP3A4 inhibitors or inducers is not permissible in this sub-study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
CYP3A4 inhibitors or inducers	nirogacestat dependent on whether the drug is a CYP3A4 inhibitor or inducer, respectively.	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 nirogacestat. See Contraception requirements in 208887 MP Section 5.1, 208887 MP Appendix 7 and Section 8.3.7.

2.3.2. Benefit Assessment

This is the first study testing the combination of nirogacestat plus 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 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 plus belantamab mafodotin.

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), addition of nirogacestat to belantamab mafodotin in this sub-study is justified by the anticipated benefits that may be afforded to participants with RRMM in comparison to participants in the belantamab mafodotin monotherapy common control arm.

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 3 are in Section 4.1 and Section 4.2 below.

4.1. Overall Design

Overall design encompasses the dose exploration and cohort expansion of combination treatment belantamab mafodotin co-administered with nirogacestat being described in this sub-study as shown in Figure 1.

4.1.1. Dose Exploration

Dose Exploration will involve 4 potential belantamab mafodotin dosing cohorts (Cohorts 1-4).

Cohort 1: Nirogacestat dose-finding cohort has a starting dose of 0.95 mg/kg Q3W belantamab mafodotin and 100 mg BID nirogacestat with 2 dose de-escalation levels of nirogacestat 100 QD and 50 mg QD.

Cohort 2 is divided into 1 of 2 potential arms (depending on nirogacestat dose identified in Cohort 1) with up to 4 sub-cohorts exploring 1.9 mg/kg belantamab mafodotin Q3W or Q6W in combination with nirogacestat BID or QD dose selected from Cohort 1 as follows:

- Cohort 2A: 1.9 mg/kg belantamab mafodotin (Q3W) in combination with 100 mg BID nirogacestat.
- Cohort 2B: 1.9 mg/kg belantamab mafodotin (Q3W) in combination with the selected nirogacestat dose from Cohort 1 as a QD dose (50 mg or 100 mg).
- Cohort 2C: 1.9 mg/kg belantamab mafodotin (Q6W) in combination with 100 mg BID nirogacestat.
- Cohort 2D: 1.9 mg/kg belantamab mafodotin (Q6W) in combination with the selected nirogacestat dose from Cohort 1 as a QD dose (50 mg or 100 mg).

Cohort 3 will explore 1.0 mg/kg belantamab mafodotin (Cycle 1 Q4W then Q8W from Cycle 2 onward) in combination with nirogacestat 100 mg (BID).

Cohort 4 will explore 1.4 mg/kg belantamab mafodotin (Cycle 1 Q4W then Q8W from Cycle 2 onward) in combination with nirogacestat 100 mg (BID) and/or 1.4 mg/kg belantamab mafodotin (Q4W every cycle) in combination with nirogacestat 100 mg (BID).

4.1.2. Nirogacestat Dose Selection for Cohorts 2-4

Findings from Cohort 1 will inform nirogacestat dose selection in Cohort 2.

Evaluation of the totality of the data including but not restricted to PK, serum sBCMA levels, and safety from up to 10 participants, each administered the first 2 cycles of combination treatment in Cohort 1 (including if applicable Dose Levels -1 or -2) will be

used to select either the nirogacestat QD or BID dose for combination with escalating belantamab mafodotin doses in Cohort 2.

Findings from Cohort 1 will inform belantamab mafodotin and nirogacestat dose schedule.

Nirogacestat dosing will be 100 mg BID for both Cohort 3 and 4.

DE Algorithm

Dose escalation decisions between cohorts will be based on the following actions alongside the mTPI:

1. **Cohort 1/-1/-2: Dose and/or schedule exploration of nirogacestat with belantamab mafodotin 0.95 mg/kg Q3W**
    a. Dose de-escalation will be determined as per mTPI.
    b. Selected nirogacestat dose and schedule will be taken forward into Cohort 2.
2. **Cohort 2: Parallel dose exploration of belantamab mafodotin 1.9 mg/kg Q3W/Q6W + nirogacestat selected dose and schedule**
    a. If *nirogacestat 100 mg BID is selected* from Cohort 1, Cohort 2A (belantamab mafodotin 1.9 mg/kg Q3W + nirogacestat 100 mg BID) will open to 3 participants:
        - If nirogacestat 100 mg BID + belantamab mafodotin 1.9 mg/kg Q3W is tolerated, that is, mTPI suggests Stay or Escalate, Cohort 2A will expand up to 15 participants AND
            i. Three parallel cohorts (2B, 2C and 2D) will open for dose exploration of 1.9 mg/kg Q3W/Q6W with nirogacestat dose 100 mg BID or QD dose. If nirogacestat 100 mg BID + belantamab mafodotin 1.9 mg/kg Q3W is not tolerated, that is, mTPI suggests De-escalating, then staggered initiation of Cohorts 2B, 2C and 2D with 3 participants will be determined by the GSK study team based on the Dose Escalation Plan.
            ii. If *nirogacestat 50 mg or 100 mg QD is selected* from Cohort 1, then Cohort 2B will open to 3 participants: If nirogacestat 50 mg or 100 mg QD + belantamab mafodotin 1.9 mg/kg Q3W is tolerated in first 3 participants, cohort 2D only will be initiated.
            iii. If nirogacestat 50 mg or 100 mg QD + belantamab mafodotin 1.9 mg/kg Q3W is <u>not</u> tolerated, dose reductions will be determined based on AE relatedness to treatment.

    Selection of the nirogacestat dose and schedule to take forward into Cohort 3 will be based on the totality of the data (including but not restricted to PK, serum sBCMA levels, safety and ORR of up to 15 participants evaluated within each cohort).

Cohorts 3 and 4A/4B: Cohorts 3 and 4A will be initiated at the same time based on the emerging safety and efficacy data from Cohorts 1 and 2.

3. **Cohort 3: Belantamab mafodotin 1.0 mg/kg (Q4W for Cycle 1 then Q8W from Cycle 2 onward) in combination with nirogacestat 100 mg (BID).**

   Considering that Cohort 3 belantamab Mafodotin dose is similar and less frequent than the belantamab mafodotin dose in Cohort 1, the decision has been made to enroll up to 15 participants without requiring sentinel participants. Participants will be monitored based on mTPI design and DLT criteria as per protocol.

4. **Cohort 4: Belantamab mafodotin 1.4 mg/kg (Q4W Cycle 1 then Q8W from Cycle 2 onward) + nirogacestat 100 mg (BID) (4A) and/or belantamab mafodotin 1.4 mg/kg Q4W + nirogacestat 100 mg (BID) (4B).**

   Cohort 4A and 4B have identical DLT period (28 days) and for that reason at least 3 participants will be enrolled initially into Cohort 4A and follow mTPI criteria. If the safety profile in the first 3 participants is deemed to be favorable as per the mTPI by the Safety Review Team, then up to 12 additional participants can be enrolled in Cohort 4A, and Cohort 4B can enroll. Sentinel participants are not required for Cohort 4B.

4.1.3. Additional Nirogacestat Schedules

a. Option to Initiate Nirogacestat Dose Modification for Cohort 2

In the event of frequent and clinically significant treatment-emergent AEs (e.g., >Grade 2 diarrhea) being reported in DE Cohorts 2inclusive, new dosing cohort(s) with a lower dose density and intensity of nirogacestat can be initiated at the same belantamab mafodotin dosing schedule.

This will be at the discretion of the Medical Director in consultation with the principal investigator and SpringWorks Therapeutics, and will be based on the following criteria:

1. **Nirogacestat 100 mg BID:** In the event of an emergent unacceptable safety/tolerability profile at nirogacestat 100 mg BID in any DE Cohort 2, de-escalation to a new 100 mg QD dosing cohort can be initiated at the same belantamab mafodotin dosing schedule.
2. **Nirogacestat 100 mg QD:** In the event of an emergent unacceptable safety profile at nirogacestat 100 mg QD in any DE Cohort 2, de-escalation to a new 50 mg QD dosing cohort, can be initiated at the same belantamab mafodotin dosing schedule.

No further nirogacestat dose schedule modifications/reductions are permissible if continuous dosing with 50 mg QD, is deemed to be intolerable.

Please see Section 4.1.2 for details of decision making during the DE Phase.

4.1.4. Cohort Expansion (CE)

This sub-study has up to 3 potential CE arms.

CE1: 0.95 mg/kg belantamab mafodotin once every 3 weeks, in combination with the selected 100 mg nirogacestat BID, 100 mg QD, or 50 mg QD dose from Cohort 1.

CE2: 1.9 mg/kg belantamab mafodotin once every 3 weeks or once every 6 weeks, in combination with 100 mg nirogacestat BID, 100 mg QD, or 50 mg QD as selected from Cohort 1.

CE3: 1.0 mg/kg belantamab mafodotin once every 4 weeks for first cycle then once every 8 weeks from cycle 2 onwards, in combination with 100 mg nirogacestat BID.

CE4: 1.4 mg/kg belantamab mafodotin either once every 4 weeks for first cycle then once every 8 weeks from cycle 2 onwards and/or once every 4 weeks, in combination with 100 mg nirogacestat BID.

As per the MP, provided there are no unacceptable safety concerns in any DE cohort, the minimum requirement to select the CE doses may be ≥2/10 responders (i.e., ≥PR status per International Myeloma Working Group criteria) in DE.

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

The MP describes the justification for selecting 1.9 mg/kg Q3W belantamab mafodotin as the starting dose in Study 208887.

A lower starting dose of belantamab mafodotin of 0.95 mg/kg has been selected for this sub-study. The clinical activity of belantamab mafodotin monotherapy doses <1.9 mg/kg is predicted to be low based on Bayesian logistic regression modeling of the FTIH study data although a parsimonious number of participants were treated at doses lower than 1.9 mg/kg (e.g., n=3 at 0.48 mg/kg, n=4 at 0.96 mg/kg). While the starting dose of 0.95 mg/kg is expected to only have limited efficacy on its own, it is anticipated that nirogacestat will potentiate the effect of belantamab mafodotin. The rounded dose of 1.0 mg/kg is considered similar to 0.95 mg/kg with only minor relative difference in dose well within the exposure variability.

In this sub-study, doses lower than 1.9 mg/kg dose and alternative dosing schedules will be explored. Evaluation of belantamab mafodotin doses lower than 1.9 mg/kg in combination with nirogacestat and extended dosing schedules of belantamab mafodotin in this sub-study can be justified on the basis that a lower dose could have an improved safety profile compared to the higher doses used in belantamab mafodotin monotherapy studies, while still providing hematological efficacy (see Figure 2 and Figure 3 for manyfold potentiation of belantamab mafodotin activity by nirogacestat).

Reducing the belantamab mafodotin-related toxicity burden for participants, particularly corneal toxicities, could lead to potentially important improvements in QoL provided the overall benefit-risk profile of the doublet combination is not markedly worse than the belantamab mafodotin monotherapy dose in the common control arm.

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 Gil 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 reduction—two 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. Dose Exploration (DE) & Cohort Expansion (CE) for Belantamab Mafodotin in Combination with Nirogacestat

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.

Data obtained in the FTIH study were evaluated using the BLRM of efficacy and corneal toxicity (Grade 2 and higher). These data indicated that while the clinical activity of belantamab mafodotin is predicted to be low for doses ≤1.9 mg/kg (data were limited at doses lower than 1.9 mg/kg), the corneal toxicity events are likely to be associated with a lower rate of Grade ≥2 events compared to the higher dose of 2.5 mg/kg, which is associated with higher predicted levels of hematologic response. As it is anticipated that nirogacestat will potentiate the effect of belantamab mafodotin, evaluation of a single lower belantamab mafodotin dose <1.9 mg/kg (i.e., 0.95 mg/kg) in this sub-study can be justified on the basis that a lower dose could have an improved safety profile compared to the higher doses used in belantamab mafodotin monotherapy studies, while still providing hematological efficacy due to the anticipated potentiation with nirogacestat.

On this basis, there are 2 objectives for this sub-study:

- **Belantamab mafodotin + nirogacestat efficacy > efficacy of the belantamab mafodotin monotherapy dose in the common control arm:**

  Evaluate whether doses of belantamab mafodotin below the labeled monotherapy dose (2.5 mg/kg), when administered in combination with nirogacestat, have higher efficacy than the belantamab mafodotin monotherapy dose in the common control arm, as per the statistical criteria of success in the MP.

- **Belantamab mafodotin + nirogacestat ocular safety is better than the ocular safety profile in the monotherapy common control arm while maintaining efficacy:**

  Reducing the belantamab mafodotin-related toxicity burden for participants, particularly corneal toxicities, could lead to potentially important improvements in QoL provided the overall benefit-risk profile of the doublet combination is not markedly worse than the belantamab mafodotin monotherapy dose in the common control arm.

4.4. Participant Completion and End of Study Definitions

There is no change in this section from the 208887 MP.

4.4.1. Participant Completion Definitions

A participant is considered to have completed the study if they received at least 1 cycle of combination study treatment, and the participant is followed until death (even after starting a new anti-cancer treatment) or until the end of the study.

4.4.2. Study Completion

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

There are no additional inclusion criteria for Sub-study 3.

For Inclusion Criterion 11: please note contraception requirements specific to Sub-study 3 (Section 8.3.7.2).

5.2. Exclusion Criteria

The exclusion criteria #29, #30, #31, #32, #33, and #60 below are in addition to the exclusion criteria already defined in 208887 MP Section 5.2. Please note: 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:

29. Uncontrolled small and/or large intestinal disease.
30. Uncontrolled skin disease.
31. Any condition causing hypophosphatemia, hypokalemia or hypomagnesemia which is refractory to electrolyte replacement.
32. Previous administration of a γ-secretase inhibitor.
33. Concomitant administration of a strong or moderate CYP3A4 inhibitor or inducer (see Section 6.5.2).

    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.

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 treatment and administered to a study participant according to the study protocol.

6.1. Study Treatments Administered

Specifications for belantamab mafodotin and oral nirogacestat treatment in this study are given in Table 9.

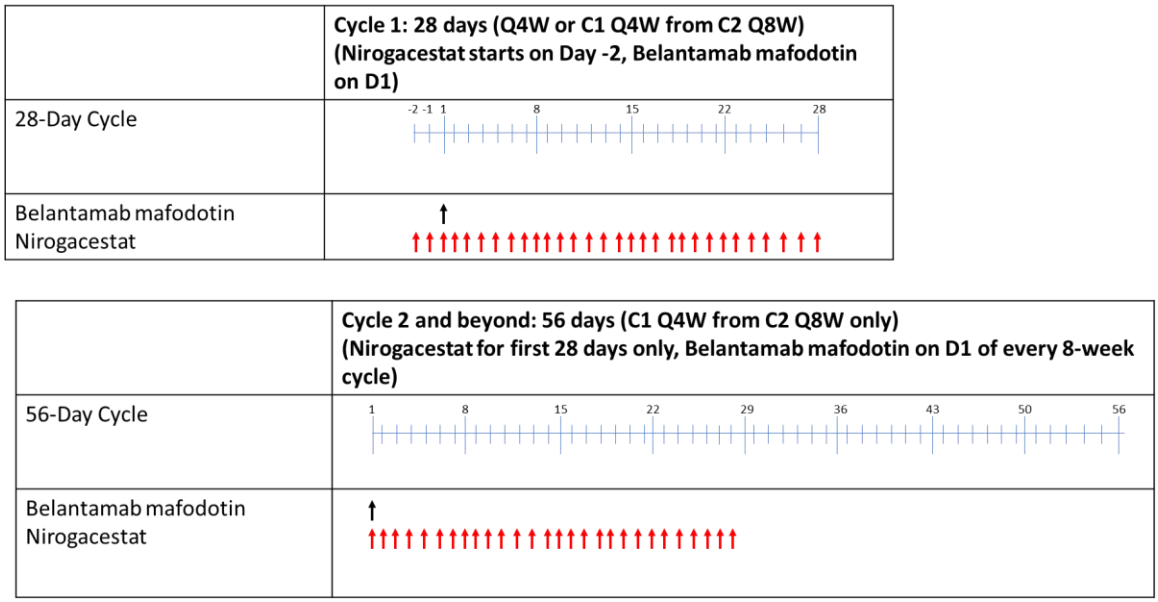
Table 9 Belantamab Mafodotin and Nirogacestat Study Treatment Information

Intervention Label	Belantamab mafodotin	Nirogacestat
Intervention Name	GSK2857916 for Injection, 100mg	Nirogacestat tablet, 100mg
Intervention Description	Belantamab mafodotin (GSK2857916) is a powder for solution for infusion	Nirogacestat is orally formulated (tablets)
Type	Drug	Drug
Dose Formulation	Lyophilized powder for solution for infusion	Tablet
Unit Dose Strength(s)	100 mg/vial	50 mg or 100 mg
Dosage Level(s)	2.5 mg/kg Q3W	100 mg BID
Route of Administration	Delivered as IV solution and infused over 30-60 minutes	Oral (PO)
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
Use	IMP	IMP
Authorized AxMP / Unauthorized AxMP	Not applicable	Not applicable
Sourcing	GSK	SpringWorks Therapeutics
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.
Current / former name(s) or alias(es)	Not applicable	Not applicable

6.2. Administration of Belantamab Mafodotin and Nirogacestat

The dosing schedule for Sub-study 3 is depicted in Figure 5.

Figure 5 Dosing schedule for Sub-study 3 during Cycle 1, Cycle 2 and beyond



- Belantamab mafodotin will be administered to participants intravenously 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.
- 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.
- Nirogacestat will be administered BID or QD orally in combination with belantamab mafodotin until disease progression. Nirogacestat will be discontinued if belantamab mafodotin is discontinued.
- Participants will be provided with a Patient Dosing Diary Card for oral nirogacestat dosing at home- this diary card will be provided at the start and collected at the end of each cycle.

6.2.1. Administration of Nirogacestat with Belantamab Mafodotin

Cohorts 1 and 2:

For C1D1 dosing only: Since the Tmax of nirogacestat after administration of a single dose is ~1 hour, belantamab mafodotin will be administered starting ~1 hour after the dose of nirogacestat.

For subsequent cycles: Nirogacestat is to be taken at the start of belantamab mafodotin infusion.

Cohorts 3 and 4:

For Cycle 1 only in Cohorts 3 and 4 only, nirogacestat will be taken BID for 2 days prior (Cycle 1 Day -2 and Cycle 1 Day -1) to the first belantamab mafodotin infusion on Cycle 1 Day 1.

For Q8W from Cycle 2 onwards, nirogacestat will be taken BID from Day 1 through Day 28. Nirogacestat will not be taken from Days 29-56.

Dosing Instructions for Nirogacestat Administration

Instructions below will be provided to participants along with Patent Dosing Diary Card, to be included in the SRM:

- 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 (e.g., 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 **QD dose**, should be taken every 24 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. For **QD** dosing: If a participant misses a scheduled dose of study treatment, and it is within 12 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 12 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.

6.2.2. Treatment Duration

Participants enrolled in the DE Phase and the CE Phase will be treated until disease progression, intolerable toxicity, informed consent withdrawal, the end of the sub-study or death.

6.2.3. 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 within a cycle (21, 28 or 56 days) will be taken BID or QD outside of the clinical setting. 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.

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

6.5.1. Permitted Concomitant Medications and Therapies

Please refer to the 208887 MP.

6.5.2. Prohibited Concomitant Medications and Non-Drug Therapies

Concomitant administration of any of the strong CYP3A4 inhibitors or inducers listed in Table 10 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 10 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 10 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

Nirogacestat was shown to increase exposure of a sensitive CYP3A4 substrate, midazolam, by approximately 50% following multiple daily doses of 95 mg QD nirogacestat. A combination of in vitro data and clinical PK data for nirogacestat, including the data from this midazolam study, were used to develop and verify a PBPK model to predict the potential for DDI under various scenarios. After the model development and verification steps were considered adequate, the model was applied to simulate the effects of nirogacestat, dosed at 100 mg BID for 15 days, on midazolam exposure. Similar to the 95 mg QD study, nirogacestat is expected to be a weak inhibitor of CYP3A4 at the 100 mg BID regimen. Therefore, concomitant use of nirogacestat with CYP3A4 substrates that have a narrow therapeutic index should be avoided.

Clinical studies were not conducted to evaluate the effects of nirogacestat-mediated induction of CYP2B6, CYP2C8, CYP2C9, and CYP2C19. A PBPK model developed for nirogacestat, which included in vitro data from hepatocyte induction studies, was considered suitable to predict the effects of these interactions in a clinical setting. No meaningful interaction was predicted for CYP2C19 when assuming the maximum induction value, however a weak-to-moderate induction effect was predicted for substrates when using a sensitivity analysis simulation to overestimate the observed in vitro effect. In the absence of a clinical study, this result predicts that nirogacestat could have a weak-to-moderate induction effect on CYP2C19 under worst case scenarios. Therefore, therapeutic alternatives to CYP2C19 substrates should be considered as appropriate; however, strict avoidance of concomitant use with nirogacestat is not necessary.

The effects of nirogacestat on P-gp inhibition were evaluated in a clinical study with healthy participants. No meaningful effect from nirogacestat was found on the exposure to total dabigatran, a P-gp substrate. Therefore, no dose modifications are recommended.

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

For further details regarding dose modifications see Section 6.6 of the MP.

- Belantamab mafodotin dose reductions will follow the details below in Table 11.

Table 11 Permitted Dose Reductions per Participant for Belantamab Mafodotin when in Combination with Nirogacestat

Belantamab Mafodotin Dose Level	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction	4th Dose Reduction
1.9 mg/kg	1.4 mg/kg	1.0 mg/kg	0.75 mg/kg	0.5 mg/kg
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		

- 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 dose reductions allowed. Dosing will be on hold until event had resolved to Grade 1 or less.

6.6.3. Nirogacestat-Associated Dose Modification Guidance

Dose modifications for nirogacestat for the following pre-specified 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: Events of diarrhea have been commonly reported in patients receiving nirogacestat.

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.

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 to be 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 diarrhea is Grade $\geq$ 3 diarrhea and persists $\geq$ 3 days despite maximal medical therapy, nirogacestat should be held until the diarrhea is resolved to Grade $\leq$1 or baseline, then restarted at the same dose of 100 mg BID.

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

Table 12 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 13).

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

Table 13 Dose Modification for nirogacestat - Hypophosphatemia

Toxicity Grade CTCAE (Version 5.0)		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 14 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 to 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.

6.6.3.5. 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 will also be delayed.

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 3 are in Section 8.3.7, Section 8.3.10 and Section 8.4 below.

8.1. Efficacy Assessments

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA tables (Section 1.3; Table 2, Table 3, Table 4, Table 5).

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 3

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. 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 3

Female Participants

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 3 are:

- Total abstinence.
- Female sterilization.

- Hormonal contraceptive (oral, injectable, implanted, intravaginal, or transdermal). Note: For Germany, female participants of childbearing potential using hormonal contraception at the time of inclusion/exclusion criteria screening are excluded.
- 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 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 3 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 8.4. Information on nirogacestat AESIs will no longer be collected for sub-study 3 Protocol Amendment 06.

8.3.11. Contact information for reporting SAEs, AESIs, and pregnancies

Please refer to the 208887 MP.

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.

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 8.9 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), BM 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 FTIH 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 FTIH 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 4 and Table 5) 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, BM samples will be collected during this study, at the time points indicated in the SoA and Table 6, 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

Success Criteria for CE1 - this will be based on:

- For the exploratory efficacy endpoint of the low dose, the estimated difference in ORR will be tested using normal approximation of the binomial proportion. On the RP2D combination arm for the low dose combination, we would expect at least as good efficacy as the monotherapy arm. Therefore, the hypothesis to be tested is H0: $p1 - p0 \leq 0$ vs H1: $p1 - p0 > 0$, where p1 is the response rate in the combination arm and p0 is the response rate in the control monotherapy arm. Success would be achieved if the lower bound of the 97.5% confidence interval exceeds the null value of 0.

  And

- The safety evaluation for the low dose will be based on the totality of the data. However, a comparison of corneal toxicity AEs will be reported, focusing on the rate of belantamab mafodotin-related ≥Grade 2 corneal toxicity on the combination arm in comparison to the belantamab mafodotin monotherapy dose in the common control arm. A two-sample proportion test will be performed to compare the Grade 2 and higher corneal events rate between CE1 combination dose and belantamab mafodotin monotherapy. Data from DREAMM-2 showed 64% corneal events (Grade 2 and higher) on 2.5 mg/kg of belantamab mafodotin monotherapy (n=95). Therefore, based on these data, on the combination arm we would expect at least a 10% reduction in corneal events compared with monotherapy alone. The hypothesis for testing 2 proportions using the Z-test with unpooled variance will be H0: p1 – p0 ≥0 vs H1: p1 – p0 <0, where p1 denotes the proportion of corneal events on the combination arm and p0 denotes the proportion on the monotherapy control arm. The power to detect a reduction in events from 3% to 33% ranges from 15% up to 95% at a significance level of 0.10 (Table 15).

Table 15 Impact on Power for a Range of Differences in Proportion of Corneal Events

Number of participants per arm	p0	p1	Difference in proportions	Power
35	0.63	0.30	0.33	0.95
35	0.63	0.35	0.28	0.88
35	0.63	0.40	0.23	0.76
35	0.63	0.45	0.18	0.60
35	0.63	0.50	0.13	0.43
35	0.63	0.55	0.08	0.27
35	0.63	0.60	0.03	0.15

As part of a sensitivity analysis in CE1, the two-sample proportion test will also be performed using pooled data from DE cohort 1 and CE.

Success Criteria for CE2, CE3 and CE4: As per the MP, this is statistically defined as the posterior probability of ORR in the experimental combination arm selected as a potential RP2D being higher than in the monotherapy common control arm being at least 90%.

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

Please refer to the 208887 MP.

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 belantamab mafodotin.

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
AST	Aspartate aminotransferase
BCMA	B-cell maturation antigen
BID	Twice a day
BLRM	Bayesian logistic regression modeling
BM	Bone marrow
BP	Blood pressure
C	Cycle

CBC	Complete blood count
CE	Cohort Expansion (Phase)
CI	Confidence interval
Cmax	Maximum plasma drug concentration
CMMC	Circulating multiple myeloma cells
CR	Complete response
CRF	Case report form
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Trough plasma concentration
CYP	Cytochrome P450
Cys-mcMMAF	cys Monomethyl auristatin F
D	Day
DE	Dose Exploration (Phase)
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
EC50	Concentration associated with 50% maximal effect
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration
ELISA	Enzyme-linked immunosorbent assay
EM	Extramedullary
EOI	End of infusion
EORTC IL52	European Organisation for Research and Treatment of Cancer Item Library 52
EORTC QLQ-30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires 30-item Core Module
EOT	End of treatment
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)
GSK2857916	GSK anti-BCMA antibody drug conjugate (CA8 J6M0 Potelligent MMAF)
HBc	Hepatitis B core
HbcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B
HCV	Hepatitis C
IB	Investigator’s Brochure
IDSL	Integrated Data Standards Library
IEC	Institutional ethics committee

Ig	Immunoglobulin
IHC	Immunohistochemistry
IP	Investigational product
IRB	Institutional review board
IV	Intravenous
KVA	Keratopathy Visual Acuity
LFT	Liver function test
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
mbBCMA	membrane-bound B-cell maturation antigen
MDRD	Modified diet in renal disease
MI	Myocardial infarction
MM	Multiple Myeloma
MMAF	Monomethyl auristatin F
MP	Master Protocol
MR	Minimal response
MRD	Minimal residual disease
MRI	Magnetic resonance Imaging
mTPI	Modified toxicity probability interval
MUGA	Multiple gated acquisition
NAG	N-Acetyl-β-D-glucosaminase
NCI-CTCAE	National Cancer Institute – Common Toxicity Criteria for Adverse Events
N-CRM	A modification of the Continual Reassessment Method (CRM) proposed by Neuenschwander et al.
NF-□B	Nuclear factor kappa light chain enhancer of activated B cells
NHV	Normal healthy volunteers
NICD	NOTCH intracellular domain
NK	Natural killer
NONMEM	Non-linear mixed effects modeling
NT-proBNP	N-terminal B-type natriuretic peptide
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
OSDI	Ocular Surface Disease Index
PBMC	Peripheral blood mononuclear cells
PBPK	Physiological-based pharmacokinetic
PC	Plasma cell
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
Pgp	P-glycoprotein
PK	Pharmacokinetic(s)
PR	Partial response
Q3W	Every 3 weeks
Q4W	Every 4 weeks

Q6W	Every 6 weeks
QD	Once daily
QoL	Quality of life
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
RRMM	Relapsed/refractory multiple myeloma
SAE	Serious adverse event
sBCMA	Soluble B-cell maturation antigen
SoA	Schedule of Activities
SOI	Start of infusion
SPEP	Serum protein electrophoresis
SRM	Study research manual
TBNK	T-cell, B-cell and Natural Killer cells
Tmax	Time to maximum drug concentration
UPEP	Urine protein electrophoresis
VGPR	Very good partial response
WOCBP	Women of childbearing potential
γ	Gamma

Trademark Information

Trademarks of the GSK group of companies
NONE

Trademarks not owned by the GSK group of companies
NONE

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.

Term	Definition
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
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 amendment is located directly before the Table of Contents (TOC).

Amendment 06 (Sub-study 3): 07 July 2023

Overall Rationale for the Amendment:

The Sub-study 3 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 and stylistic revisions; applied GSK style guide for abbreviations, date format, reference details, 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 reference to GSK2857916/ belantamab mafodotin and Nirogacestat Investigator's Brochure	To refer to the most recent version of the IB
Throughout document	Added references to the MP where missing, or to streamline text	Correction of typographical or consistency error
Section 1.2.2 Belantamab Mafodotin and Nirogacestat	Clarified that DLT period is 28 days from C1D1 (not from Cycle 1 Day -2)	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 2	Clarification for study conduct
Section 1.3 Schedule of Assessments	Clarified that FISH testing can be done in the central lab in Table 2	Correction of typographical or consistency error
Section 1.3 Schedule of Assessments	Clarified that MRD testing is done by NGS in Table 2	Correction of typographical or consistency error
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 Activities	In Table 2 and Table 4, 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	Added that disease evaluation should occur every 3 or 4 weeks in Table 3	Clarification for study conduct

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Assessments	In Table 3, clarified that the EORTC QLQ-C30 and EORTC IL52 questionnaires should be first performed on Day 1 (Week 1)	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Removed details regarding treatment period from Table 3 heading	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 3 (footnote 8) and Table 5 (footnote 21), decreased frequency of UPEP assessments	Program level changes
Section 1.3 Schedule of Activities	Removed extraneous text from Table 3, footnote 4	Correction of typographical or consistency error
Section 1.3 Schedule of Assessments	In Table 4, aligned the time window for PK sampling with the one for vital signs measurement	Clarification for study conduct
Section 1.3 Schedule of Assessments	Added ocular exam to Table 3 (footnote 3) and Table 4 (footnote 2), clarified timing of ocular exams in relation to dosing.	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarified guidance regarding realignment of scheduled visits during treatment and dosing visits in Table 3	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 3, modified footnote for urine and serum immunofixation to include "not quantifiable"	Clarification for study conduct
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	Removed details from footnote regarding sBCMA sampling in Table 4	Clarification for study conduct
Section 1.3 Schedule of Assessments	In Table 3 footnote revised wording regarding informed consent for genetic research	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Clarified that on PK sampling visits that if vital signs assessments are conducted, they should be assessed prior to PK samples being drawn in Table 4, footnote 1	Clarification for study conduct
Section 1.3 Schedule of Activities	Table 4, 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	Removed detail regarding LFTs from Table 4, footnote 4	Clarification for study conduct. LFTs should be assessed as a part of hematology.
Section 1.3 Schedule of Activities	In Table 4 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 4 footnote 9, removed C1D4 PK sample and C18D1 EOI PK sample, added C18D1 PK sample and changed window for PK samples to be drawn to 0-10 min	Clarification for study conduct
Section 1.3 Schedule of Activities	Revised language related to imaging for Skeletal surveys and for participants with extramedullary disease in Table 3, footnotes 12 and 13	Clarification for study conduct
Section 1.3 Schedule of Activities	Aligned row heading of hematology (enhanced TBNK panel) with 208887 MP	Correction of typographical or consistency error

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Removed footnote 17 attribution related to nirogacestat administration on Cycle 1 Day -2 in Table 4	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 5, footnote 1	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarified in Table 5 footnote 2 that PFS follow-up at the time of disease assessment could be every 21 or 28 days (±7 days).	Clarification for study conduct
Section 1.3 Schedule of Activities Sections 8.3.7.1 Pregnancy in Sub-Study 3 Section 8.3.7.2 Contraception in Sub-Study 3	Updated guidance on pregnancy testing and collection of pregnancy information in Table 2 footnote 2 and Table 4, footnote 3, as well as Sections 8.3.7.1 and 8.3.7.2	Clarification for study conduct and alignment with current Nirogacestat IB
Section 1.3 Schedule of Activities	Deleted the footnote “To be done every 3 weeks until suspected PD” which was associated with serum FLC assay for PFS follow-up because this is covered by revisions to footnote 2 which also applies to serum FLC assay for PFS follow-up.	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 5, 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 5, footnote 19	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Clarified in Table 5 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 6 and at PFS follow-up in Table 5	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	In Table 6, 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	Removed the need for BM aspiration at end of study visit for MRD assessment in Tables 5. Clarified conditions for MRD testing at screen and during study. Added a ±1 month window for follow-up MRD testing in Table 6	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 6, created separate rows PD and Suspected PD and added timimng of corresponding assessments.	Clarification for study conduct
Section 1.3 Schedule of Activities	Details regarding FISH testing were removed from Table 6 footnote 3 and reference to 208887 MP Table 31 has been provided.	Clarification for study conduct
Section 1.3 Schedule of Activities	Removed extraneous text from Table 6, footnote g	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Clarified the timing of HBV-DNA testing to allow for grouping with the closest study visit in Table 7	Clarification for study conduct
Section 1.3 Schedule of Activities	Updates related to bone marrow aspirate/biopsy collection in Table 2 and Table 3	Clarification for study conduct

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Updates related to biomarker assessments in Table 5 (remove BM biopsy at EOT visit for BCMA expression and biomarker research), Table 4 (clarified timing of sBCMA sampling) and TBNK sampling in Table 4, footnote 10 and 11	Clarification for study conduct
Section 1.3 Schedule of Activities	Updates to MRD, biomarker assessments, and optional BM research in Table 4 and Table 6	Clarification for study conduct
Section 1.3 Schedule of Assessments	In Table 3 and Table 5, AEs/SAEs will be collected until at least 70 days post EOT	Program level changes
Section 1.3 Schedule of Assessments	In Tables 2,Table 3, and Table 5, clarified that urine immunofixation should be done on 24 hr urine collection sample	Clarification for study conduct
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 8, updated the mitigation strategy for diarrhea related to nirogacestat; and mitigation strategy for concomitant administration of CYP34A4 inhibitors or inducers	Clarification for study conduct
Section 4.1.2 Nirogacestat Dose Selection for Cohorts 2-4	Throughout the document and in mTPI table (Table 13) updates made to extend the number of participants in the DE phase to include up to 15 participants	Clarification for study conduct
Section 5.1 Inclusion Criteria	Reference to Inclusion criteria 9 corrected to Inclusion criteria 11	Correction of typographical or consistency error
Section 5.2 Exclusion criteria	Section 5.2 Added note that use of legally authorized representative is not applicable for Germany	Clarification for study conduct
Section 1.3 Schedule of Assessments, Section 5.2 Exclusion criteria, Section 6.5.2 Prohibited Concomitant Medications and Non-Drug Therapies	Added HIV testing at screening to Table 2 and Section 5.2 (Exclusion Criterion #60) 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 6.1 Study Treatment(s) Administered	In Table 9, updated language concerning dose formulation.	Clarification for study conduct
Section 6.2 Administration of Belantamab mafodotin and Nirogacestat and Section 1.3 Schedule of Assessments	In Section 6.2 and Table 4 footnote 17, removed statements that diary cards are located in SRM, which is no longer accurate	Clarification for study conduct
Section 6.2.1 Administration of Nirogacestat with Belantamab Mafodotin	Clarified administration of nirogacestat for Cycle 2 onwards for Cohorts 3 and 4	Clarification for study conduct
Section 6.2.2 Treatment Duration	Added a description of treatment duration.	Correction of typographical or consistency error
Section 6.2.3 Participant Transition from DE to CE, Section 9.1 Statistical Hypotheses	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 for study conduct

Section # and Name	Description of Change	Brief Rationale
Section 6.6.1 Permitted Dose Reductions per Participant for Belantamab Mafodotin when in Combination with Nirogacestat	Updated the permitted dose reductions in Table 11 to replace 0.95 mg/kg with 1.0 mg/kg	Correction of typographical or consistency error
Section 6.6.3 Nirogacestat-Associated Dose Modification Guidance	Revised safety language to be "associated (with)" drug instead of "related (to)"	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 6.6.3.1 Gastrointestinal Toxicities	Recommended use of antidiarrheal medication in patients receiving nirogacestat	Clarification for study conduct
Section 8.3.7.2 Contraception in Sub-study 3	Hormonal contraceptives are not an approved method of contraception for German female participants. Timelines for use of approved methods of contraception have been updated from 4 months to 6 months.	Clarification of study conduct
Section 8.3.10 Adverse Events of Special Interest	Revised to remove detail regarding AESI for nirogacestat	Clarification for study conduct. Development partner no longer collecting this data.
Section 9.1 Statistical Hypothesis	Updated DREAMM-2 data in accordance to final analysis CSR	Updated information
Section 9.1 Statistical Hypothesis	Simplified success criteria for CE2, CE3, and CE4	Clarification of study conduct
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

Amendment 05 (Sub-study 3): 22 February 2022

Overall Rationale for the Amendments:

The protocol has been amended to include a 1.4 mg/kg dose level as well as a stretch Q8W dosing of belantamab mafodotin which may provide comparative efficacy and/or lower of incidence of adverse events compared to higher doses ≥1.9 mg/kg. In addition, changes were made in line with program level changes, administrative updates, updates to reflect new dose modification guidance for belantamab mafodotin, and safety updates.

Changes listed in the table below are for the Sub-study 3 protocol only. Changes for Protocol Amendment 5 that are related to the 208887 Master Protocol and specific sub-studies are tabulated at the beginning of each relevant sub-study module.

Section # and Name	Description of Change	Brief Rationale
Throughout document	Updated reference to GSK2857916/belantamab mafodotin Investigator's Brochure	To refer to the most recent version of the IB
	Minor editorial and document formatting revisions	To improve overall clarity and correct typographical errors
	Renumbering of Tables and Footnotes	As a result of the changes within the document

Section # and Name	Description of Change	Brief Rationale
1.2 Schema	Updated to reflect the revisions made to the study design with additions of cohort 3 and 4	To align with updates in Section 4.1.
1.3 Schedule of Activities (SoA)	Added Table 7 for additional procedures for participants who are positive for Hepatitis B core Antibody.	To align with the latest regulatory guidance
	Added allowance for multiple gated acquisition (MUGA) scan. Clarified text for the Treatment Period for belantamab mafodotin monotherapy CE Phase for performing the same procedure (ECHOs or MUGA scans) at Screening to be throughout the study	Updated in line with cardiac monitoring requirements across belantamab mafodotin program, based on emerging safety data
	Updated guidance on bone marrow/core biopsy sample collection	To clarify language
	Updated text to reflect the serum protein electrophoresis (SPEP) to be performed at Q3W and the urine protein electrophoresis [UPEP]) to be performed to confirm objective response (PR or better) or if there is concern for disease progression, during the Treatment Period for belantamab mafodotin monotherapy CE Phase Clarified the text suggesting the Serum Immunofixation to be performed when SPEP or UPEP are negative; and performed to confirm objective response (PR or better).	To clarify language
	Clarified Cycle 1 24 hour, and Cycle 1 Day 4 collection timepoint for PK and Biomarker during the treatment period is only for the DE Phase	To reduce collection of blood samples and reduce patient burden
	Updated the schedule for bone marrow aspiration and sample collection, throughout the study Clarified the optional BM research wording	To clarify language
	Revised the ocular exam follow-up time period for participants with a treatment-related change in vision at the end of treatment visit from every 6 weeks to every 3 months	To align with program level updates
2.2.4 Nirogacestat Safety	Updated safety data for nirogacestat.	To align with current Nirogacestat IB.
2.3.1 Summary of risk assessment	Updated the table 8: Table of risks related to nirogacestat	Updated according to recent Nirogacestat IB 2021.
4.1 Overall Design	Added new cohorts: Cohort 3 and Cohort 4, with 1.0 and 1.4 mg/kg starting dose of belantamab mafodotin in combination with nirogacestat, respectively. Provided details for DE and CE for Cohorts 3 and 4.	To allow further dose exploration of belantamab mafodotin.
4.3.1 Justification for Starting Dose of Belantamab Mafodotin	Justification provided for the new 1.0 and 1.4 mg/kg starting dose of belantamab mafodotin in Cohort 3	To allow further dose exploration of belantamab mafodotin.
4.3.2 Justification for Starting Dose of Nirogacestat	Justification updated. Justification for lead in dosing of nirogacestat added	To align with Nirogacestat IB 2021.
6.1 Study Intervention(s) Administered	Updated the dosing instructions of belantamab mafodotin and nirogacestat	For clarification

Section # and Name	Description of Change	Brief Rationale
6.2 Administration of Belantamab mafodotin and Nirogacestat	Added figure illustrating dosing days for belantamab mafodotin and nirogacestat for especially Cohorts 3 and 4.	To provide dosing details for new cohorts.
6.2.1 Administration of Nirogacestat with Belantamab Mafodotin	Added instructions for dosing of Nirogacestat in Cohorts 3 and 4	To clarify language
6.5.2 Prohibited Concomitant Medications and Non-Drug Therapies	Allow moderate CYP3A4 inhibitors or inducers with caution.	To expand list of permitted medications.
6.6.1 Permitted Dose Reductions per Participant for Belantamab mafodotin when in Combination with Nirogacestat	Added new dose modification guidance for belantamab mafodotin in combination with nirogacestat	To reflect new changes of the lower dose of belantamab mafodotin
6.6.2 Permitted Dose Reductions per Participant for Nirogacestat	Updated as no dose reduction is allowed	More clarification
6.6.3 Nirogacestat-Related Dose Modification Guidance	Updated the guidance	Updated as per Nirogacestat IB 2021
8.3.7.1 Pregnancy in Sub-study 3	Updated the duration of collection of pregnancy information to 4 months following last dose of study treatment	As per recent information
8.3.10 Adverse Events of Special Interest for Nirogacestat	Modified the criteria for reporting AESI	More clarification added
8.5 Pharmacokinetics	Removed reference to 12.9.1 liver safety event from sub-study protocol	Corresponding text added to Appendix 9 of the MP
8.8.3 Tumor Related Biomarker Analysis	Added information for BCMA expression analysis by IHC or flow cytometry. Added text confirming that remaining aspirate and/or biopsy sample to be used for biomarker research	To add clarity
9.1 Statistical Hypothesis	Success criteria for CE1 updated to reflect new information. Success criteria for CE3 added.	To align with updated data
Appendix 13: Protocol Amendment History	Addition of Summary of Changes from amendment 04 in the appendix, as per template requirements	Template Alignment

Amendment 04 (Sub-study 3) 14 December 2020

Overall Rationale for the Amendment:

The protocol has been amended to revise design for Sub-study 3 and to convert to a modular document format with separate Master Protocol (MP) and Sub-study modules. The organizational changes for Sub-study 3 are mapped in the table below.

Section # for Prot-Amend 3 and Name		Section # for Prot-Amend 4 and Name	
13.1	Protocol Amendment 3 Summary of Changes Specific to Sub-study 3	12.13	Appendix 13: Protocol Amendment History

Section # for Prot-Amend 3 and Name		Section # for Prot-Amend 4 and Name	
13.2	Schedule of Activities (SoA) for Belantamab mafodotin + Nirogacestat	1.3	Schedule of Activities (SoA)
13.3	Objectives of Belantamab mafodotin and Nirogacestat Sub-study	2.1	Rationale for Belantamab mafodotin and Nirogacestat Sub-study
13.4	Gamma-secretase and BCMA	2.2.1	Gamma-secretase and BCMA
13.5	Rationale for the Combination of Belantamab Mafodotin with Nirogacestat	2.2.5	Rationale for the Combination of Belantamab Mafodotin with Nirogacestat
13.6	Biomarkers	8.8	Biomarkers
13.7	Background Clinical Information for Nirogacestat	2.2	Background
13.7.1	Clinical Development of Nirogacestat in Monotherapy and Combination Studies	2.2.2	Clinical Development of Nirogacestat in Monotherapy and Combination Studies
13.7.2	Nirogacestat Pharmacokinetics	2.2.3	Nirogacestat Pharmacokinetics
13.7.3	Nirogacestat Safety	2.2.4	Nirogacestat Safety
13.8	Starting Dose Justification for Belantamab mafodotin and Nirogacestat	4.3.1	Justification for Starting Dose for Belantamab mafodotin
		4.3.2	Justification for Starting Dose for Nirogacestat
13.9	DE and CE for Belantamab mafodotin in Combination with Nirogacestat	4.3.3	Dose Exploration (DE) & Cohort Expansion (CE) for Belantamab mafodotin in Combination with Nirogacestat
13.9.1	Sub-study Design	4.1.1	Dose Exploration
		4.1.4	Cohort Expansion (CE)
Fig. 8	Dose Exploration and Cohort Expansion Schematic for Belantamab Mafodotin and Nirogacestat	Fig.	Dose Exploration and Cohort Expansion Schematic for Belantamab Mafodotin and Nirogacestat
13.9.1.2	Nirogacestat Dose Selection for Cohorts 2-3	4.1.2	Nirogacestat Dose Selection for Cohorts 2-3
13.9.1.3	DE Cohorts 2 and 3	4.1.2	Nirogacestat Dose Selection for Cohorts 2-3
13.9.1.4	Additional Nirogacestat Dosing Modification Schedules	4.1.3	Additional Nirogacestat Dosing Modification Schedules
13.9.2	Cohort Expansion (CE)	4.1.4	Cohort Expansion (CE)
13.10	Study Interventions Administered	6.1	Study Interventions Administered
13.11	Administration of Belantamab mafodotin and Nirogacestat	6.2	Administration of Belantamab mafodotin and Nirogacestat
13.11.1	Administration of Nirogacestat with Belantamab mafodotin	6.2.1	Administration of Nirogacestat with Belantamab mafodotin
13.11.2	Treatment Duration	6.2.2	Treatment Duration
13.11.3	Permitted Dose Reductions per Participant for Belantamab mafodotin	6.6.1	Permitted Dose Reductions per Participant for Belantamab mafodotin
13.11.4	Permitted Dose Reductions per Participant for Nirogacestat	6.6.2	Permitted Dose Reductions per Participant for Nirogacestat
13.11.5	Nirogacestat-Related Dose Modification Guidance	6.6.3	Nirogacestat-Related Dose Modification Guidance
13.11.6	Participant Transition from DE to CE	6.2.3	Participant Transition from DE to CE
13.11.7	Concomitant Medications with Nirogacestat	6.5	Concomitant Therapy
13.11.8	Treatment of Overdose	8.4	Treatment of Overdose
13.11.9	Liver Safety Event-PK sample	12.9	Appendix 9: Liver Safety: Required Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines
13.12	Preparation/Handling/Storage/Accountability	6.3	Preparation/Handling/Storage/Accountability - content identical to the 208887 MP was deleted
13.13	Adverse Events of Special Interest for Nirogacestat	8.3.10	Adverse Events of Special Interest for Nirogacestat
13.14	Benefit/Risk Considerations	2.3	Benefit/Risk Assessment

Section # for Prot-Amend 3 and Name		Section # for Prot-Amend 4 and Name	
13.15	Additional Inclusion/Exclusion Criteria for Nirogacestat Sub-study	5.1	Inclusion Criteria for Participants
		5.2	Exclusion Criteria
13.16	Management of Pregnancy and Contraception	8.3.7	Management of Pregnancy and Contraception

Changes listed in the table below are for the Sub-study 3 protocol only. Changes for Protocol Amendment 4 that are related to the 208887 Master Protocol and specific sub-studies are tabulated at the beginning of each relevant Sub-study module.

Section # and Name	Description of Change	Brief Rationale
Revised Study Design		
1.1 Synopsis, 1.2 Schema, 1.3 Schedule of Activities-Table 4, 4.1 Overall Design, 4.3.2 Justification for Starting Dose of Nirogacestat, 6.2 Administration of belantamab mafodotin and nirogacestat, 6.3 Preparation/handling/storage/accountability, 6.5.2.1 Medications to be Administered with Caution with Nirogacestat, 6.6.2 Permitted Dose Reductions per Participant for Nirogacestat, 6.6.3. Nirogacestat-Related Dose Modification Guidance, 9.1 Statistical Hypotheses	Replaced intermittent dosing with continuous QD dosing for nirogacestat de-escalation of Cohort 1. Cohort 2 divided in 4 sub-cohorts with staggered initiation, with the addition of QD dosing for nirogacestat in Cohort 2 and potentially Cohort 3.	Based on nirogacestat half-life and potential to optimize dose/schedule for combination
	Removal of 150 mg BID of nirogacestat	Based on observed safety data in participants of clinical trials on desmoid tumors
	Addition of extended dosing schedule (Q6W) for belantamab mafodotin in Cohorts 2 and 3	To allow for scheduling optimization to potentially reduce ocular/corneal events
Safety Changes		
2.2.4 Nirogacestat Safety	Updated section based on information for nirogacestat	To align with nirogacestat IB
6.2.1 Administration of Nirogacestat with Belantamab mafodotin	Clarified timeframe of nirogacestat administration for C1D1 vs subsequent cycles	To clarify administration of initial dose of nirogacestat for C1D1
8.3.7 Management of Pregnancy and Contraception	Added language on contraception for female participants, regarding male partners that have undergone sterilization/vasectomy	Further clarification of approved contraceptive methods
Changes in Assessments and SoAs		
1.3 Schedule of Activities	Clarification of assessments to be done in case of belantamab mafodotin Q6W dosing schedule (Table 4)	To clarify assessments based on updated design
	Clarification of vital signs assessments and PK collection for nirogacestat and belantamab mafodotin dosing at C1D1	To clarify assessments
	Extraction of information regarding BM Assessments in a separate table (current Table 6)	To clarify assessments
	Clarified FISH assessments that are to be completed at Screening (Table 6) based on availability on previous results	In line with other protocols in the program.
	Clarified language on definition of resolution of ophthalmic findings (to baseline instead of Grade 1)	To align with GSK belantamab mafodotin program language

Section # and Name	Description of Change	Brief Rationale
Protocol Clarification and Alignment		
8.3.7	Split guidelines for management of pregnancy and contraception in sections specific to "female participants" and "male participants"	To clarify requirements by gender
Editing, format, style changes		
Throughout	Correction of typos and technical document aspects	Minor changes; no impact on content

Protocol Amendment 3 (08 July 2020)

Protocol Amendment 03 Summary of Changes Specific to Sub-study 3

Section # and Name	Description of Change	Brief Rationale
Revised Study Design		
Section 13.9, Section 13.10, Section 13.11.3	Removal of 3.4 mg/kg dose from figures and text	See Lonial, 2020 reference for monotherapy recommended dose
Section 13.9	Revisions to statistical analyses and hypotheses added for efficacy and safety	Incorporating data from 205678 study
Safety Changes		
Section 13.2, Table 42 and Table 44	AEs/SAEs will be collected until at least 70 days post EOT	As per belantamab mafodotin program safety language
Section 13.2, Table 44	Change EoT pregnancy restriction from 9 months to 4 months	As per belantamab mafodotin program safety language
Section 13.11.8	Added section on overdose	To provide guidance on overdose
Section 13.13, Table 54	Added Reproductive System Effects as AESI category	Updated safety guidance
Section 13.14, Table 55	Added Reproductive System Effects to table of risks	Updated safety guidance
Changes in Assessments and SoAs		
Section 13.2	Revised assessments and descriptions, including: Urinalysis assessment and description Removal of post-baseline ECG assessments, thyroid testing, NT-proBNP, troponin Description of MRI, CT, PET/CT scans for disease assessment in Germany Serum immunofixation and serum FLC assay	Provide clarification and more specific guidance
Section 13.2	Bone Marrow sample for BCMA expression-added biopsy in addition to aspirate collection for biomarker research. Replaced aspirate clot by aspirate.	Change in sample type due to observed assay failure secondary to hemodilution in bone marrow aspirate clots. BCMA IHC is validated in bone marrow biopsy samples
Section 13.2	Added additional timepoints for cytokines, whole blood RNA, PBMCs and CMMC.	To provide consistency across substudies and a more comprehensive longitudinal analysis of these samples
Section 13.2	Removal of Qualitative phone interview during treatment; Added optional follow-up Qualitative phone interview after EoT	Revised timepoints and qualified application of phone interview
Section 13.2, Section 13.11	Patient Dosing Diary Card added	To allow patient recording of daily oral nirogacestat treatment at home
Section 13.2	Removal of post EOT ADA assessments for belantamab mafodotin	Timepoints not needed

Section # and Name	Description of Change	Brief Rationale
Protocol Clarification and Alignment		
Section 13.2	Revise QoL assessments to capture IL52 (symptom assessment) portion of EORTC QLQ-My20 and timepoints	Clarify assessments and timing
Section 13.2	Replace ophthalmologist and optometrist with eye-care specialist term and define same	Simplify and define provider terminology
Section 13.16	Modified text on contraception	Clarification on contraceptive requirements
Throughout	Asset numbers/abbreviations replaced with generic names except for laboratory sampling	Provide consistency throughout document
Editing, format, style changes		
Throughout	Correction of typos and technical document aspects	Minor changes; no impact on content

Protocol Amendment 2 (16 December 2019)

Protocol Amendment 2 Summary of Changes Specific to Sub-study 3

The protocol has been amended to introduce a new sub-study into Section 13 of the protocol.

- Introduction of Substudy 3- Belantamab Mafodotin and nirogacestat (Section 13)

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