Protocol Amendment 7

Study ID: 208887 Sub Study 2

Official Title of Sub Study 2: 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 2 – Belantamab Mafodotin and Feladilimab (GSK3359609) in Combination

NCT ID of Sub Study 2: NCT07217119

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TITLE PAGE

Protocol Title: A Phase I/II, Randomized, Open-label Platform Study Utilizing a Master Protocol to Study Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination with Anti-Cancer Treatments in Participants with Relapsed/Refractory Multiple Myeloma (RRMM)–DREAMM5 - Sub-study 2 – Belantamab Mafodotin and Feladilimab (GSK3359609) in Combination

Protocol Number: 208887 / Amendment 7 for Sub-study 2

Compound Number or Name: Belantamab mafodotin (GSK2857916), feladilimab (GSK3359609)

Study Phase: 1/2

Short Title: Sub-study of Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination with Feladilimab (GSK3359609) in Participants with RRMM

Acronym: DREAMM-5 Sub-study 2

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PROTOCOL AMENDMENT 7 SUB-STUDY 2 INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: 208887

AMENDMENT NUMBER: Protocol Amendment 7 for Sub-study 2

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 2 – Belantamab Mafodotin and Feladilimab (GSK3359609) 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 2)	03 Sep 2024	TMF-19486323
Amendment 6 (Sub-study 2)	10 July 2023	TMF-16095796
Amendment 5 (Sub-study 2)	21 January 2022	TMF-13841945
Amendment 4 (Sub-study 2)	14 December 2020	2020N453184_00
Amendment 3 (Sub-study 2)	08 July 2020	2017N352487_03
Amendment 2 (Sub-study 2)	16 December 2019	2017N352487_02
Amendment 1 (Sub-study 2)	24 June 2019	2017N352487_01
Original Protocol	12 March 2019	2017N352487_00

Amendment 7 (Sub-study 2): 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.	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 2 are in the subsections below in Table 1.

Table 1 Location of Sub-study 2 Specific Content

Section	Heading title	Brief description of content
1.3	Schedules of Activities	Comprehensive SoA tables specific for Sub-study 2
2.1	Rationale for combination of Belantamab Mafodotin with Feladilimab	Explanation why treatment with belantamab mafodotin and feladilimab is expected to be complementary
2.2	Background	Available data on clinical pharmacology, safety, clinical activity, and preclinical syngeneic model
2.3	Benefit/Risk Assessment	Risk assessments for feladilimab treatment; benefit assessment summary
4.1	Overall Design	Description of dose escalation design for the combination treatment
4.3	Justification for Dose	Data for the basis of the planned feladilimab dosing
5.2	Exclusion Criteria	Two additional exclusion criteria were defined for Sub-study 2
6.1	Study Treatment(s) Administered	Specifications for belantamab mafodotin and feladilimab investigational product
6.2	Administration of Belantamab Mafodotin and Feladilimab	Specifications for administration of belantamab mafodotin and feladilimab
6.6	Dose Modification	Detailed directions guidance for dose modifications of combination treatment
8.3.7	Management of Pregnancy	Timeframes for on data collection
8.3.10	Adverse Events of Special Interest	Information on feladilimab AESI
8.4	Treatment of Overdose	Guidance for potential drug overdose of feladilimab
8.8	Biomarkers	Summary of the biomarker research being conducted for Sub-study 2
12.13	Appendix 13: Protocol Amendment History	Summary of Changes Tables for Sub-study 2 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 2 – Belantamab Mafodotin and Feladilimab (GSK3359609) in Combination

Short Title: Platform Study of Belantamab Mafodotin (GSK2857916) in Combination with Feladilimab (GSK3359609) in Participants with RRMM

Rationale: Enhanced antigen presentation through ICD and resulting T-cell mediated durable immunity suggests that additional therapeutic benefit can be obtained from combination treatment of belantamab mafodotin with immune-enhancing agents, such as GSK3359609 (feladilimab; anti- ICOS). Belantamab mafodotin treatment induces ICD, which may lead to priming of new tumor specific T-cells, resulting in up-regulation of ICOS on CD4 and CD8 T-cells. Feladilimab, upon binding to ICOS on tumor specific T-cells, can induce their expansion, effector function and increased survival, as well as

re-activate tumor specific memory T-cells. Therefore, the complementary mechanisms of the combination may be expected to enhance anti-tumor activity.

The combination of belantamab mafodotin with an agonist ICOS mAb was tested in the EL4-hBCMA syngeneic model, with the anti-mouse ICOS dosed at 10 mg/kg alone and in combination with belantamab mafodotin at 10 mg/kg both given intraperitoneally 2 times a week over 3 weeks. The anti-mouse ICOS antibody in combination with belantamab mafodotin showed a trend of 10% to 20% survival advantage over anti-ICOS and belantamab mafodotin monotherapy treatments, although the differences were not statistically significant. The combination cohort showed 30% tumor-free mice compared to 20% and 10% tumor-free mice in the anti-ICOS and belantamab mafodotin monotherapy groups, respectively.

This is a randomized Phase 1/2, open-label, platform-design study of belantamab mafodotin in combination with feladilimab treatment compared to belantamab mafodotin monotherapy in participants with RRMM. Overall design is in relation to the dose exploration of combination treatment.

There will be a DE Phase which will evaluate the safety and tolerability profile of belantamab mafodotin when administered in combination with other anti-cancer treatments. The number of dose levels explored will vary per sub-study, and up to 10 participants per dose level will evaluated for safety and preliminary efficacy. An RP2D for each combination treatment will be identified based on the safety and preliminary efficacy in DE. This will be followed by a CE Phase which will evaluate the clinical activity of the combination treatment at the RP2D in comparison to monotherapy belantamab mafodotin in additional participants with RRMM.

A total of 5 dose levels can potentially be evaluated, so there could potentially be a maximum of 5 dosing cohorts in the DE Phase. The starting dose of belantamab mafodotin will be 1.9 mg/kg and the starting dose of feladilimab will be 8 mg Q3W. Please see 208887 MP Section 4.1.1 for details of decision making during the DE Phase.

1.2. Schema

Refer to the 208887 MP for the general design for the study.

1.3. Schedule of Activities

The timing and number of planned study assessments (including safety, PK, 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) to ensure appropriate monitoring.

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

Screening Study Assessments	Screening	Notes
Note: All Screening assessments must be performed within **30** days prior to C1D1 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 hematology/chemistry results are below eligibility threshold required, 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 C1D1 (see 208887 MP Section 8.2.7 for list of ophthalmic exam procedures). 2. Perform only in WOCBP. A pregnancy test must be performed at Screening. If the test is completed within 72 hrs prior to the first dose, this assessment need not be repeated on C1D1. 3. Refer to 208887 MP Appendix 2 for a comprehensive list of laboratory 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 laboratory (first void). 6. If a participant tested HBcAb positive, refer to Table 7 for additional procedures throughout the study. HCV RNA testing is optional, but it will be performed to determine participant eligibility if HCV antibody positive. If negative, participant is eligible (see exclusion criteria 12 for details). 7. Complete at Screening or within 12 weeks prior to C1D1. 8. Single ECG at Screening. 9. ECHO or MUGA scan for LVEF may be performed within 30 days prior to C1D1. 10. SPEP and UPEP will include M-protein levels. 11. Serum FLC assay will include kappa/lambda ratio and quantification of involved and uninvolved light chains. 12. IgD/IgE testing is only required for participants with IgD/IgE myeloma.
Demography	X	
Medical History (includes substance abuse)	X	
Full Physical Exam	X	
Throughout the study, participants are educated about in lifestyle considerations (208887 MP Section 5.3) for the study and the need of maintaining adequate urinary output (208887 MP Section 2.3.1).	X	
Inclusion/Exclusion criteria	X	
Past and current medical conditions	X	
Concomitant Medication review	X	
Screening Safety Assessments		
Ocular Exam	X[1]	
ECOG Performance Status	X	
Vital Signs (BP, HR, Body Temperature)	X	
Weight and Height	X	
Serum Pregnancy Test (WOCBP only)	X[2]	
Hematology (CBC)	X[3]	
Clinical chemistry	X[3]	
eGFR	X[4]	
Urinalysis (dipstick) or Spot Urine (albumin/creatinine ratio)	X[5]	
HBsAg[6], HbcAb[6], HCV[6] tests	X[7]	
12-lead ECG	X[8]	
ECHO or MUGA scan for LVEF	X[9]	

Screening Study Assessments	Screening	Notes
Note: All Screening assessments must be performed within **30** days prior to C1D1 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 hematology/chemistry results are below eligibility threshold required, Medical Director to be contacted for review prior to dosing**.		
Screening Disease Evaluation		13. 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 C1D1 may be used for Screening. Same modality used at Screening should be used throughout study. 14. 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 first dose. 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 PD. 15. Please refer to Table 6 for scheduled BM collection procedures to include aspirate and biopsy. 16. If FISH testing cannot be performed at a local laboratory the samples can be sent to the central laboratory.
Beta-2 microglobulin	X	
UPEP 24 hr urine collection	X[10]	
Urine immunofixation 24 hr urine collection	X	
SPEP	X[10]	
Serum immunofixation	X	
Serum FLC assay	X[11]	
IgG, IgM, IgA	X	
IgD or IgE, if applicable	X[12]	
Calcium corrected for albumin (serum)	X	
Skeletal survey	X[13]	
Extramedullary Plasmacytoma Assessment (by whole body CT or whole-body MRI or CT/PET)	X[14]	
BM Aspiration/Biopsy		
BM aspirate and/or core biopsy for local disease assessment	X[15]	
BM aspirate for FISH testing	X[15, 16]	

Table 3 SoA – Treatment Period for DE and CE Phases: Belantamab Mafodotin and Feladilimab Study Assessments to be Carried Out on Day 1 and Q3W Regardless of Whether Participant is Dosed

Study Assessments regardless of whether participant is dosed	Day 1 (Week 1)	Treatment Period: Q3W from Week 4 until EOT Visit	Notes
• All assessments will apply to the CE Phase unless otherwise specified. • Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. • 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 dosing may occur on different days.			
AEs/SAEs	Ongoing[1]		1. AEs/SAEs will be collected up to 70 days after the last dose of study treatment and immune-related AEs/SAEs will be collected up to 70 days post last dose. 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	Ongoing		
Throughout the study, participants are educated about in lifestyle considerations (208887 MP Section 5.3) for the study and the need of maintaining adequate urinary output (208887 MP Section 2.3.1).	X		
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	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.
Safety			
Ocular Exam		X[3]	
Hematology (CBC)	X[4]	X[4]	4. CBC and chemistry panel may be done more frequently as clinically indicated. Refer to 208887 MP Appendix 2 for comprehensive list of laboratory 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 laboratory (first void).
ECHO or MUGA scan for LVEF		X[7]	7. ECHOs or MUGA scans for LVEF to be done if clinically indicated. The same procedure used at Screening should be used throughout the study.

Study Assessments regardless of whether participant is dosed	Day 1 (Week 1)	Treatment Period: Q3W from Week 4 until EOT Visit	Notes
• All assessments will apply to the CE Phase unless otherwise specified. • Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. • 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 dosing may occur on different days.			
Disease Evaluation (Q3W even if a dose is delayed)			8. SPEP must be performed Q3W. UPEP will only be performed Q3W 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 or 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 Q3W. 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. Repeated as clinically indicated. Same modality used at Screening should be used throughout study. 13. Imaging is required for participants with extramedullary disease, as clinically indicated, 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 to confirm CR or sCR 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.
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]	
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]	
MRI, CT or PET/CT upon achieving CR or sCR		Once after CR or sCR[14]	
BM Aspiration/Biopsy			
BM aspirate and/or core biopsy for local Disease assessment		X[15]	
BM core biopsy to assess sCR (local)		X[15]	

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

Study Assessments	C1D1 (Week 1)	Cycle 1 Day 8 Day 15	Cycle 2 to EOT Visit	Notes
• All assessments will apply to the CE Phase unless otherwise specified. • 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. • **If C1D1 hematology/chemistry 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 minutes. For the first infusion, vital signs must be monitored for each study drug infusion at: predose (within 30 min prior to SOI); at the EOI (+ 0-10 min); and 1 hr post EOI (+ 0-10 min). For subsequent infusions, vital signs must be monitored for each study drug infusion: at predose (within 30 min prior to each SOI); and at each EOI (+ 0-10 min), and 30 min post each EOI (+ 0-10 min) and as clinically indicated. 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. See 208887 MP Section 8.2.7 for list of ophthalmic exam procedures and frequency of exams. 3. Perform only in women of childbearing potential. Pregnancy tests may be either predose serum or urine and should be performed within 72 hrs prior to dosing. 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 laboratory (first void). 5. If already completed within 72 hrs prior to dosing, this assessment does not need to be repeated on Day 1 of the cycle. CBC and chemistry panel may be done more frequently as clinically indicated. Refer to 208887 MP Appendix 2 for comprehensive list. 6. eGFR as calculated by MDRD formula (208887 MP Appendix 6).
Physical Exam (Full exam on treatment days Day 1 of each cycle, and Cycle 1 Day 8 only)	X	X	X	
Vital Signs (BP, HR, Body Temperature)	X[1]	X[1]	X[1]	
Ocular Exams	X[2]		X[2]	
Weight	X		X	
ECOG Performance Status	X		X	
Pregnancy Test	X[3]		X[3]	
Urinalysis (dipstick) or Spot Urine (albumin/creatinine ratio)	X[4]		X[4]	
Hematology (CBC)	X[5]	X[5]	X[5]	
Clinical chemistry	X[5]	X[5]	X[5]	
eGFR	X[6]	X[6]	X[6]	
Treatment with belantamab mafodotin				
Administration of belantamab mafodotin	X[7, 9]		X (Day 1 of each dose)[6, 8]	
Premedication if needed			X (at the start of each dose)[7]	
Treatment prophylaxis and management of preservative-free artificial tears and cooling masks	X[9]		X[9]	

Study Assessments	C1D1 (Week 1)	Cycle 1 Day 8 Day 15	Cycle 2 to EOT Visit	Notes
• All assessments will apply to the CE Phase unless otherwise specified. • 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. • **If C1D1 hematology/chemistry results are outside of the eligibility requirements, Medical Director to be contacted for review prior to dosing.**				
Treatment with feladilimab				7. Please refer to 208887 MP Section 6.6.3 for guidance on dose delays, reduction, and modification. 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. 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 208887 MP Section 6.2 and 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). 8. Premedication should be considered in any participant who experienced an IRR at first or any subsequent infusion with belantamab mafodotin or partner combination (see Section 6.2). 9. Supportive care information: a. Prophylactic preservative-free artificial tears should be administered in each eye at least 4-8 times daily beginning on Dose 1 Day 1 until EOT Visit. In the event of ocular symptoms (e.g., dry eyes), the use of artificial tears may be increased up to every 2 hrs as needed. Corticosteroid eye drops are not required but can be used if clinically indicated per the discretion of a qualified eye care specialist (see 208887 MP Appendix 10). Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops (if administered). b. At the start of each infusion, participants may apply cooling eye masks to their eyes for approximately 1 hr 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. 10. Administration to occur 1 hr after administration of belantamab mafodotin.
Administration of feladilimab	X[10]		X (Day 1 of each 21-day cycle)[10]	

Table 5 SoA – End of Treatment and Follow-Up for Sub-study 2: Belantamab Mafodotin and Feladilimab

Study Assessments	EOT Visit[1]	PFS Follow-up[2]	OS Follow-up[3]	Notes
All assessments will apply to both the DE and CE Phases unless stated otherwise.				
Physical Exam	X	X		1. EoT safety assessments to occur within 30 days from decision to discontinue treatment and at least prior to the new anti-MM treatment (whichever occurs first).
Vital Signs (BP, HR, Body Temperature)	X	X		2. PFS follow-up every 21 days (±7 days) for participants who discontinue investigational product 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.
AEs	X[4]	Related SAEs only[4]	Related SAEs only[4]	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 communication 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 EOT Visit.
Concomitant Medications	X	X		4. AEs/SAEs will be collected up to 70 days after the last dose of study treatment and immune-related AEs/SAEs will be collected up to 70 days post last dose. 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 Visit should be recorded when given for SAEs/AESIs as defined in 208887 MP Section 8.3.
Safety				
Ocular Exam	X[5,6]	X[6]	X[6]	5. EOT ophthalmic exam to be performed by a qualified eye care specialist. See 208887 MP Section 8.2.7 for list of exams.
ECOG Performance Status	X	X		6. Participants with a treatment-related corneal exam findings, ocular symptoms and/or change in vision at the 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 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.
Hematology (CBC)	X[7]	X[7]		7. CBC may be done more frequently as clinically indicated. Refer to 208887 MP Appendix 2 for comprehensive list of laboratory tests.
Clinical chemistry	X[7]	X[7]		8. Final pregnancy test (serum or urine) must be performed per 208887 MP Section 12.2. Follow-up pregnancy assessments should be performed per 208887 MP Section 12.7.3.
Pregnancy Test	X[8]	X[8]	X[8]	9. eGFR as calculated by MDRD formula (208887 MP Appendix 6).
eGFR	X[9]			
Urinalysis (dipstick) or Spot Urine (albumin/creatinine ratio)	X[10]			
ECG/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]		
Calcium corrected for albumin (serum)	X	X		
Skeletal survey	X[13,14]	X[13,14]		

Study Assessments	EOT Visit[1]	PFS Follow-up[2]	OS Follow-up[3]	Notes
All assessments will apply to both the DE and CE Phases unless stated otherwise.				
Imaging for Extramedullary Plasmacytoma Assessment (by whole body CT or whole-body MRI or CT/PET	X[14,15]	X[14,15]		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 laboratory (first void). 11. ECG/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/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 PD 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 participant 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). Selected target lesion needs to be measured 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.
BM Aspiration/Biopsy				
BM aspirate and/or core biopsy for Disease assessment	X[16]	X[16]		
BM core biopsy to assess sCR	X[16]	X[16]		

Table 6 SoA - Bone Marrow Aspiration/Biopsy Collection

Timepoint	BM aspirate for FISH testing[1,2]	BM (core biopsy and/or aspirate) for disease assessment[1]
Screening	X[3]	X[3]
Suspected CR/sCR	X[4]	X[4]
Suspected PD (only if PD not evident otherwise)		X[4]

1. These assessments will be performed at a local laboratory. For FISH testing, if testing cannot be performed at a local laboratory the samples can be sent to the central laboratory.
2. See Table 31 in 208887 MP for details on FISH.
3. 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.
4. 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.

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, Table 3, Table 4, Table 5, 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

Please refer to the 208887 MP for the overall Introduction to belantamab mafodotin for the study.

Information and details specific to Sub-study 2 are in Section 2.1, Section 2.2 and Section 2.3 below.

2.1. Rationale for Combination of Belantamab Mafodotin with Feladilimab

ICD is triggered by apoptotic cell death where DAMP molecules either released from the dying cell into the extracellular microenvironment or translocated from the endoplasmic reticulum to the cell surface, engage the adaptive immune response and activate antigen presenting cells, contributing to T cell-mediated anti-tumor activity and leading to durable immunity. Antibody drug conjugate-induced apoptosis by belantamab mafodotin produced DAMPs, including cell surface externalization of calreticulin and secretion of high mobility group box 1 protein and ATP. ICD induced by belantamab mafodotin resulted in activation of dendritic cells in vitro and in vivo. In vivo, studies using a syngeneic lymphoma mouse model engineered to express human BCMA (EL4-hBCMA) have demonstrated durable tumor regression, and resistance to rechallenge upon treatment with belantamab mafodotin [Montes De Oca, 2021]. Therefore, enhanced antigen presentation through ICD, and resulting T-cell mediated durable immunity suggests that additional therapeutic benefit can be obtained from combination treatment of belantamab mafodotin with immune-enhancing agents, such as GSK3359609 (feladilimab).

ICOS is a checkpoint co-stimulatory receptor expressed on cytotoxic CD8 and helper CD4 T-cells. As belantamab mafodotin and feladilimab have unique mechanisms of action, and while ICOS is not known to be expressed on myeloma plasma cells [Muccio, 2016], it is hypothesized that the combined effect of these 2 molecules will be complementary, and therefore, will allow for more effective targeting of immune resistance/tolerance mechanisms in MM. Agonist ICOS mAb 2C7 induced T-cell activation and also induced apoptosis of a MM cell line (XG2) which abnormally expressed ICOS [Deng, 2004]. Belantamab mafodotin treatment induces ICD, which may lead to priming of new tumor specific T-cells, resulting in up-regulation of ICOS on CD4 and CD8 T-cells. Feladilimab, upon binding to ICOS on tumor specific T-cells, can induce their expansion, effector function and increased survival, as well as re-activate tumor specific memory T-cells. Therefore, the complementary mechanisms of the combination may be expected to enhance anti-tumor activity.

The combination of belantamab mafodotin with an agonist ICOS mAb was tested in the EL4-hBCMA syngeneic model. The anti-mouse ICOS antibody (surrogate mouse antibody clone 7E.17G9 expressed on murine IgG1 isotype) was dosed at 10 mg/kg alone and in combination with belantamab mafodotin at 10 mg/kg both given intraperitoneally 2 times a week over 3 weeks (n=10 females/group). Relevant isotype controls were used. Treatments were well tolerated with no significant loss in body weight or adverse clinical observations. One mouse was found dead on Day 31 following treatment of GSK2857916 and mouse isotype control. All other mice in these cohorts were removed due to reaching tumor volume endpoint or were tumor-free at study end on Day 83. Thus, no pattern related to a dose or treatment was evident for the mouse death. Anti-ICOS antibody in combination with belantamab mafodotin showed a trend of 10% to 20% survival advantage over anti-ICOS and belantamab mafodotin monotherapy treatments, although the differences were not statistically significant. The combination cohort showed 30% tumor-free mice compared to 20% and 10% tumor-free mice in the anti-ICOS and belantamab mafodotin monotherapy groups, respectively.

Evidence to date does not indicate that overlapping toxicities would be expected between belantamab mafodotin and feladilimab.

2.2. Background for Feladilimab

Feladilimab is a humanized anti-ICOS mAb selected for its specific, high affinity binding to and agonist activity in ICOS-expressing CD4+ and CD8+ effector T-cells. Feladilimab is specifically engineered as an IgG4 hinge-stabilized isotype, IgG4PE, to markedly decrease binding affinity of the Fc region of the mAb to activating Fcγ receptors and C1q, and thereby diminish the cytotoxic potential of feladilimab that would result in depletion of ICOS-positive T-cells through antibody-dependent or complement-dependent cell mediated mechanisms, respectively. Moreover, the IgG4PE isotype retains functional binding to the Fcγ inhibitor receptor, FcγRIIb, a feature described as important for modulating antibody agonist activity [Li, 2011], which also may be essential for optimal ICOS agonist activity and its associated anti-tumor effects in humans.

The desired pharmacology of feladilimab is the expansion in the total number as well as an increase in the activity of tumor specific effector and memory CD4+ and CD8+ T-cell populations. Tumor specific T-cells must be primed and activated in order for the induction of ICOS expression to occur, and for feladilimab to bind and function. Therefore, the expectation is that feladilimab may be most active in settings where an anti-tumor immune response is primed by prior lines of anti-cancer therapy and/or in combination with agents that prime or modulate tumor immunity. Additional information on the effects of feladilimab can be found in the IB [GSK Document No. RPS-CLIN-040657, 2022].

2.2.1. Clinical Experience with Feladilimab

GSK initiated the clinical development of feladilimab in June 2016, with the FTIH study, 204691; this is the first clinical investigation of feladilimab initiated and remains an ongoing study as of the clinical cutoff date of 16 March 2020.

In addition, there are 3 ongoing studies of feladilimab: Study 205801 (Phase 2), Study 207871 (Phase 1/2), and Study 204686 (Phase 1), evaluating feladilimab in combination with immunotherapy agents in select solid tumor participant populations, details of which are outlined in the IB [GSK Document No. RPS-CLIN-0406577, 2022].

As of the data cutoff date of 16 March 2021, 290 participants received at least 1 dose of feladilimab in Part 1 of Study 204691, including the monotherapy dose escalation and expansion phases at the following dose levels: 0.001 mg/kg (n=1), 0.003 mg/kg (n=1), 0.01 mg/kg (n=2), 0.03 mg/kg (n=7), 0.10 mg/kg (n=24), 0.30 mg/kg (n=63), 1.0 mg/kg (n=127),3.0 mg/kg (n=27), 10.0 mg/kg (n=7), and 24 mg (n=31).

Of the 290 participants who received feladilimab alone (Part 1), 78 (27%) remain on the study either on study treatment (27 participants, 9%) or in follow-up for survival and the reporting of subsequent anti-cancer therapy (51 participants, 18%); of 215 (86%) participants who are no longer receiving study treatment, the majority (90%; 262 of 290 participants) discontinued study treatment due to PD (refer to the feladilimab IB for more details [GSK Document No. RPS-CLIN-0406577, 2022].

Emerging clinical data from studies 209227 and 209229 showed a lack of efficacy improvement in feladilimab plus pembrolizumab compared with pembrolizumab alone. Therefore, the benefit/risk of administering feladilimab was deemed unfavorable for first-line metastatic/recurrent head and neck squamous cell carcinoma population. These 2 studies were discontinued.

2.2.2. Pharmacokinetic and Pharmacodynamic Summary of Feladilimab

The PK of feladilimab was evaluated after 30 minutes of IV infusion at doses from 0.001 mg/kg to 10.0 mg/kg Q3W in participants with solid tumors in Study 204691. The plasma PK samples (received prior to the 2020 IB update cutoff date of 16 March 2020) were analyzed with a validated bioanalytical method with a lower limit of quantitation of 0.1 µg/mL. As of safety cutoff date of 16 March 2020, preliminary PK data in monotherapy cohorts were available in 1 participant at 0.003 mg/kg, 2 participants at 0.01 mg/kg, 7 participants at 0.03 mg/kg, 25 participants at 0.1 mg/kg, 52 participants at 0.3 mg/kg, 123 participants at 1.0 mg/kg, 23 participants at 3.0 mg/kg dose and 7 participants at 10.0 mg/kg dose.

Median feladilimab plasma PK profiles after dosing at 8, 24, and 80 mg fixed doses in combination with GSK3174998 or chemotherapy-containing regimens were superimposable to the median PK profiles observed with 0.1, 0.3, and 1.0 mg/kg doses. The preliminary plasma PK parameters (AUC, Cτ, and Cmax) calculated over the first dosing interval (up to 503 hrs) exhibit approximate dose proportional increases in feladilimab exposure over the range of 0.01 to 10.0 mg/kg doses. Preliminary population PK estimated geometric mean systemic t1/2 of feladilimab is approximately 19 days.

Based on the preliminary data, median CD4 and CD8 RO was maintained at or above 70% during the dosing interval of first cycle for feladilimab doses ≥0.3 mg/kg.

2.2.3. Safety for Feladilimab Monotherapy

Two hundred and thirty-one of 249 participants (93%) experienced at least 1 AE. Of the 249 participants treated in Part 1, 82 participants (33%) experienced at least 1 SAE, of which 7 (3%) experienced at least 1 SAE considered by the investigator as related to study treatment. Nine participants (4%) had AEs leading to permanent discontinuation of study treatment in Part 1. The most common AEs (occurring in ≥15% of participants overall regardless of dose level or relationship) were anemia (22%), asthenia (21%), nausea (19%), fatigue (18%), diarrhea (16%), and vomiting (15%).

Overall, in Part 1 (N=249), 98 of 249 participants (39%) experienced at least 1 AE of maximum Grade ≥3; most participants with at least 1 AE of maximum Grade ≥3 (82 out of 98 [84%]) experienced at least 1 AE of maximum Grade 3. Across feladilimab dose levels with >2 participants enrolled, the percentage of participants who experienced at least 1 Grade 3 AE is: 57% (4 of 7 participants) at 0.03 mg/kg; 28% (7 of 25 participants) at 0.1 mg/kg; 23% (13 of 56 participants) at 0.3 mg/kg; 37% (46 of 126 participants) at 1.0 mg/kg; 42% (10 of 24 participants) at 3.0 mg/kg; and 14% (1 of 7 participants) at 10.0 mg/kg. Overall, 9 participants (4%) experienced at least 1 AE of maximum Grade 4: (1 event of lipase increased in 1 participant at 0.1 mg/kg;1 event each of anemia, general physical health deterioration, blood bilirubin increased, performance status decreased, tumor hemorrhage, acute respiratory failure, septic shock, and 2 events of lipase increased at 1.0 mg/kg;1 event each of ALT increased, AST increased, blood ALP increased, and GGT increased at 3.0 mg/kg). Overall, 7 participants (3%) experienced at least 1 AE of maximum Grade 5 (1 event of tumor perforation at 0.1 mg/kg, and 1 event each of lower gastrointestinal hemorrhage, general physical health deterioration, PD, pleural effusion, and hepatic failure in 1 participant each, at 1.0 mg/kg, and 1 event of neoplasm progression at 3.0 mg/kg); none of the Grade 5 events were considered by the investigator as related to feladilimab monotherapy.

Of the 249 participants treated in Part 1, 82 participants (33%) experienced at least 1 SAE, of which 5 participants (2%) experienced at least 1 treatment-related SAE of maximum Grade ≥3. Across feladilimab dose levels, treatment-related SAEs are Grade 3: atrioventricular block complete at 0.3 mg/kg, hypopituitarism encephalitis and gastric hemorrhage at 1.0 mg/kg, and hepatic function abnormal at 3.0 mg/kg. No participant experienced at least 1 treatment-related SAE of maximum Grade 4 or Grade 5. SAEs reported in >1 participant each included pneumonia, dyspnea, device-related infection, abdominal pain, general physical health deterioration, pain, vomiting, back pain, pleural effusion, pulmonary embolism, pyrexia, acute kidney injury, neoplasm progression, troponin increased, tumor pain, and urinary tract infection.

Among the dose levels of feladilimab monotherapy investigated in the dose escalation phase of feladilimab monotherapy (from 0.001 mg/kg to 10.0 mg/kg), no participant had a DLT during the 28-day DLT observation period (i.e., time since the first dose of study drug). One of 19 DLT evaluable participants in the PK/pharmacodynamic cohort receiving feladilimab 3.0 mg/kg experienced a DLT of Grade 4 elevation in AST that occurred 24 days after the first dose of study treatment (i.e., during the 28-day observation period). Factors relevant in the assessment of these events include: the participant was receiving paracetamol as a concomitant treatment for pain and an ultrasound of the liver showed marked dilation of the biliary tract and the presence of liver lesion measuring 51 x 41 mm; the participant underwent biliary stent placement. The same participant experienced DLTs of elevations in Grade 3 or Grade 4 ALT, ALP, bilirubin, GGT, impaired liver function (serious), lipase, and Grade 1 amylase outside of the 28-day observation period while receiving feladilimab 3.0 mg/kg. All events are ongoing (except for elevated bilirubin), considered by the investigator as related to study treatment, and led to treatment discontinuation.

In order to elucidate the AESI profile of immune-mediated events, a very broad net of preferred terms was included in the various categories as these are potential terms that may be representative of signs/symptoms or conditions of the respective broader category (which are outlined below); not all terms reflect true cases of immune-mediated events and should not be construed as such.

In monotherapy, in the broad AESI category of Colitis, there were 39 (16%) cases of diarrhea, with 1 reported case of colitis (Grade 3) (<1%). In the broad category of Endocrinopathies, there was 1 (<1%) event of hypophysitis (Grade 3), 5 (2%) low grade events of hypothyroidism, and 1 low grade hyperthyroidism. In the broad category of Hepatitis, there were many terms included, including laboratory evaluations; no cases of hepatitis were reported, however there were laboratory elevations of 6%, 5%, and 3% of AST, ALT and blood bilirubin elevated (the majority of which were low grade), respectively. In the broad category of IRRs, 1 (<1%) Grade 3 IRR was reported. In the broad category of Myocarditis, no events of myocarditis or immune-mediated events were reported. In the broad category of Nephritis, no immune-mediated events were reported. In the broad category of Pneumonitis, no events of pneumonitis were reported. In the broad category of Skin Reactions, the highest reported event was pruritis at 20 (8%) events (all low grade); the remainder of the reported skin reactions were all low grade.

For more details on AEs of feladilimab, please refer to the IB [GSK Document No. RPS-CLIN-0406577, 2022].

2.2.4. Clinical Activity of Feladilimab

At a clinical efficacy data cutoff date of 26 July 2019, 17 participants with anti-PD-1/L1 treatment-experienced head and neck squamous cell carcinoma received at least 1 dose of 1 mg/kg feladilimab in the Part 1B cohort. In the treated population (n=17), the median age was 56 years (range: 41 to 73 years); 82% were male and 82% received ≥1 prior lines of systemic therapy in the advanced/metastatic setting. Sixteen of the 17 dosed participants were considered evaluable for efficacy analysis; the ORR in the evaluable population was 6% with 1 of the 16 participants achieving a PR.

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].

Belantamab mafodotin risk assessment and mitigation strategies are in the 208887 MP Section 2.3.1.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of feladilimab may be found in the IB [GSK Document No. RPS-CLIN-040657, 2022].

2.3.1. Risk Assessment

Table 8 outlines the risk assessment and mitigation strategy for feladilimab. Belantamab mafodotin risk assessment and mitigation strategies are in the 208887 MP (see Section 2.3.1).

Table 8 Potential Risks Related to Feladilimab

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risks related to feladilimab		
Immune-related AEs	• Inflammatory AEs such as diarrhea/colitis, pneumonitis, nephritis, and hepatotoxicity are well established as treatment emergent AEs with immune-modulating agents and are consistent with the immune-stimulatory mechanism of action of these agents. • Belantamab mafodotin preclinical data indicate a potential for systemic inflammation and may potentiate any immune or inflammatory related AEs in combination with feladilimab.	• Participants with the following medical history are ineligible for this study: ○ Toxicity (Grade ≥3) related to prior immunotherapy leading to study treatment discontinuation, ○ Active autoimmune disease, ○ Severe hypersensitivity to another mAb. • Established management algorithms for irAEs. • Refer to the 208887 MP Section 11 for further details on the identification, evaluation, and management of toxicities with a potential immune etiology.
Hypersensitivity reaction	• Risk for infusion reactions and hypersensitivity is inherent to many mAbs [Brennan, 2010].	• Participants with history of severe hypersensitivity to another mAb ineligible for this study. • Refer to the 208887 MP Section 11. For further details on management of infusion reactions.
Severe cytokine release syndrome	• ICOS is a co-stimulatory receptor that can stimulate proliferation and activation of T-cells. • Feladilimab is an ICOS agonist that can co-stimulate T-cell activation in the context of T-cell receptor signal. • No cytokine release syndrome events have been reported in clinical programs investigating feladilimab (refer to feladilimab IB; GSK3359609 IB V07, 2022).	• Refer to 208887 MP Section 11 for further details on management of cytokine release syndrome.
Immune complex disease	• Immune complex formation and deposition findings in nonclinical safety studies (refer to the feladilimab IB [GSK3359609 IB V07, 2022]).	• Clinical laboratory safety assessments and immunogenicity testing.

2.3.2. Benefit Assessment

Study participants may benefit from medical tests and Screening performed during the study. Any potential benefit of the addition of feladilimab to belantamab mafodotin is unknown. Data obtained in this study may help identify individuals more likely to benefit or have side-effects from feladilimab plus belantamab mafodotin.

Current data from feladilimab preclinical studies indicate a potential for immune-mediated anti-tumor activity through effects resulting from stimulation of ICOS.

2.3.3. Overall Benefit: Risk Conclusion

This is the first study testing the combination of feladilimab plus belantamab mafodotin in participants with RRMM that have been treated with standard therapies.

Considering the measures taken to minimize risks to participants in the Phase 1 clinical study, the potential risks identified in association with feladilimab as a monotherapy or combination therapy are justified by the anticipated benefits that may be afforded to participants with RRMM.

3. OBJECTIVES AND ENDPOINTS

The primary and secondary objectives, along with the corresponding endpoints for DE and the primary and secondary objectives and endpoints for CE are the same as the 208887 MP (see 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 2 are in Section 4.1 and Section 4.3 below.

4.1. Overall Design

Overall design is in relation to the dose exploration of combination treatment belantamab mafodotin co-administered with feladilimab being described in this Sub-study.

A total of 4 dose levels can potentially be evaluated (Table 9). Therefore, there could potentially be a maximum of 5 dosing cohorts running simultaneously in the DE Phase. At Dose Level 1, the starting dose of belantamab mafodotin will be 1.9 mg/kg and the starting dose of feladilimab will be 8 mg. The maximum dose of belantamab mafodotin will be 2.5 mg/kg (Dose Levels 2-4), and the maximum dose of feladilimab will be 80 mg (Dose Level 4). Sponsor may decide not to evaluate all dose levels based on data external to this study. Please see Section 4.1.1 in the 208887 MP for details of decision making during the DE Phase.

Table 9 Dose Exploration Schema Belantamab Mafodotin in Combination with Feladilimab

Dose level	Belantamab mafodotin dose	Feladilimab dose
1 (starting dose level)	1.9 mg/kg	8 mg
2	2.5 mg/kg	8 mg
3	2.5 mg/kg	24 mg
4	2.5 mg/kg	80 mg

4.2. Scientific Rationale for Study Design

4.3. Justification for Dose

Feladilimab is being currently investigated in the Phase 1 Study 204691 with doses ranging from 0.001 mg/kg (~0.08 mg) to 10 mg/kg (~800 mg) as monotherapy and from 0.01 mg/kg (~0.8 mg) to 3 mg/kg (~240 mg) in combination with a PD-1 inhibitor in participants with solid tumors. To date, no maximum tolerated dose has been established and no dose limiting toxicities have been observed in the dose escalation cohorts over this range of feladilimab dose levels. Preliminary exposure–safety analyses demonstrate Grade ≥2 AE incidence to be similarly flat among the clinically tested doses/exposures analyses, up to 3 mg/kg Q3W; a 10 mg/kg dose level of feladilimab has been evaluated in 7 participants as a dose escalation cohort, and current safety data support expansion of that dose level in the feladilimab monotherapy PK/pharmacodynamics cohort.

Pop PK analyses demonstrate that a fixed dose of 8 mg of feladilimab provides exposures comparable to 0.1 mg/kg, which is ~100-fold lower than the 10 mg/kg dose currently studied in solid tumors and the minimal dose where clinical activity has been observed in the monotherapy cohorts of 204691. Doses of >~0.1 mg/kg (~8 mg) also have adequately high peripheral RO levels on CD4+ and CD8+ T-cells over the first 21-day dosing cycle (>~70%). Quantitative immunofluorescent multi-analyte profiling of participant tumor biopsies indicates potentially favorable cytotoxic T-cell to regulatory T-cell ratios at concentrations ranging from 1000 to 10,000 ng/mL at Week 6, associated with end of Cycle 1 trough concentrations at dose levels of ranging from ~0.1 mg/kg to ~1 mg/kg (8 to 80 mg). No drug-drug interaction related changes are expected in feladilimab PK with belantamab mafodotin co-administration and there are no known overlapping toxicities.

Hence, collectively, these data support 8 mg Q3W as a conservative initial starting dose for feladilimab in combination with belantamab mafodotin in MM to characterize the safety and tolerability of the combination in the DE Phase. The feladilimab dose may be adjusted within the 8-80 mg range based on any emerging safety, exposure and/or pharmacodynamic data. Refer to feladilimab IB [GSK3359609 IB V07, 2022] for further details.

4.3.1. Feladilimab Dosing Frequency

The systemic $t_{1/2}$ of feladilimab is approximately 19 days based on the preliminary population PK analysis of exposure data from ongoing Study 204691. The existing feladilimab Q3W regimen in the ongoing clinical study is also consistent with the Q3W dosing regimen typical with IgG4 based mAb therapies. Thus, feladilimab will be dosed Q3W in combination with belantamab mafodotin.

4.3.2. Rationale for Fixed Dose

The preliminary population PK simulations using the data from the 204691 study indicated that using fixed dosing would result in a similar range of exposures as that of body weight-based dosing. Also, fixed dosing offers the advantage of reduced dosing errors, reduced drug wastage, shorten preparation time, and improved ease of administration. Thus, switching to a fixed dose based on a reference body weight of 80 kg is reasonable and appropriate.

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 208887 MP.

5. STUDY POPULATION

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

Information and details specific to Sub-study 2 are in Section 5.2 below.

Participants are eligible to be included in the study only if all of the criteria in Section 5.2, and in the 208887 MP Section 5.1 and Section 5.2 apply. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria for Participants

There are no additional inclusion criteria for Sub-study 2.

5.2. Exclusion Criteria

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

The exclusion criteria #27 and #28 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.

27. Autoimmune disease (current or history) or syndrome that required systemic treatment within the past 2 years. Replacement therapies which include, physiological doses of corticosteroids for treatment of endocrinopathies (for example, adrenal insufficiency) or treatment of hypothyroidism is allowed on study.
28. In addition, exclusion for a recent (within the past 6 months) history of symptomatic pericarditis.

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 sub-study.

Information and details specific to Sub-study 2 are in the Section 6.1, Section 6.2 and Section 6.6 below.

Study treatment is defined as belantamab mafodotin administered with feladilimab treatment and administered to a study participant according to the study protocol.

6.1. Study Treatments Administered

Specifications for belantamab mafodotin and feladilimab treatment in this study are given in Table 10.

Table 10 Belantamab Mafodotin and Feladilimab

Intervention label	Belantamab mafodotin	Feladilimab
Intervention name	GSK2857916 for injection, 100 mg	GSK3359609 injection, 10 mg
Intervention description	Belantamab mafodotin (GSK2857916) is a powder for solution for infusion	Feladilimab (GSK3359609) is a solution for infusion
Type	Drug	Drug
Dose Formulation	Lyophilized powder for solution for infusion	Aqueous solution
Unit Dose Strength(s)	100 mg/vial	10 mg/mL
Dosage Level(s)	2.5 mg/kg Q3W	8-80 mg Q3W
Route of Administration	Delivered as IV solution over 30-60 minutes	Delivered as IV solution over 30 minutes.
Use	IMP	IMP
Authorized AxMP / Unauthorized AxMP	Not applicable	Not applicable
Sourcing	GSK	GSK
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 vials. Each vial will be labeling as required per country requirement.
Current / former name(s) or alias(es)	Not applicable	Not applicable

6.2. Administration of Belantamab Mafodotin and Feladilimab

Belantamab mafodotin will be administered to participants IV as mg/kg calculated dose at the study site. The dose to be administered is based on actual body weight calculation and may be reduced for toxicity according to protocol guidelines.

Administration will be documented in the source documents (208887 MP Appendix 1, Section 12.1.8) and reported in the eCRF. The time of start and EOI 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 infusion unless deemed medically necessary by the investigator, in which case it should be administered according to institutional recommendations. In case of IRRs related to belantamab mafodotin the rules outlined in the 208887 MP Section 7.1.3 and Section 11 should be followed.

After the infusion of belantamab mafodotin has been completed, participants will be required to enter at least a 1-hour rest period before starting feladilimab infusion where appropriate.

The belantamab mafodotin starting dose will be 1.9 mg/kg. Belantamab mafodotin will be administered IV first, followed by IV administration of feladilimab.

- Belantamab mafodotin will be administered via IV infusion on Day 1 of each 21-day cycle (Q3W dosing schedule; each cycle is referred to as a dose throughout the protocol). Belantamab mafodotin is not to be given again any sooner than 21 days, with the exception of discussion with the Medical Director (208887 MP Section 6.1).
- Three dose levels of feladilimab will be investigated: 8 mg, 24 mg, 80 mg administered Q3W. Additional doses may be investigated following emerging data from the FTIH study (204691).
- Feladilimab will be administered via IV infusion on Day 1 of each 21-day cycle (once Q3W dosing schedule).

Table 11 Route of Administration and Dose Timing for Belantamab Mafodotin and Feladilimab in the DE Phase

	Dose and timing of belantamab mafodotin[a]	Dose and timing of feladilimab
Route of administration	Delivered as an IV infusion (see Section 6.1 for details)	Delivered as an IV infusion (see Section 4.3 for details)
Timing	Belantamab mafodotin is to be administered first	Start at 1 hr post EOI for belantamab mafodotin infusion

Participants enrolled in the DE Phase and CE Phase will be treated until PD, intolerable toxicity, informed consent withdrawal or death.

6.3. Preparation/Handling/Storage/Accountability

Please refer to the 208887 MP.

6.4. Measures to Minimize Bias: Randomization and Blinding

Please refer to the 208887 MP.

6.5. Concomitant Therapy

Please refer to the 208887 MP.

6.6. Dose Modification

6.6.1. Permitted Dose Reductions for Belantamab Mafodotin When in Combination with Feladilimab

For further details regarding dose modifications for belantamab mafodotin see 208887 MP Section 6.6 and 208887 MP Section 11.

Table 12 Permitted Dose Reductions of Belantamab Mafodotin When in Combination with Feladilimab

Belantamab mafodotin dose level	1st Dose reduction	2nd Dose reduction	3rd Dose reduction	4th Dose reduction	5th Dose reduction
2.5 mg/kg	1.9 mg/kg	1.4 mg/kg	1.0 mg/kg	0.75 mg/kg	0.5 mg/kg

- If the participant cannot tolerate belantamab mafodotin after the allowed dose reductions, he/she must be withdrawn from the study for lack of tolerability.

Resuming treatment with belantamab mafodotin will be possible with or without dose reduction after the toxicity has resolved to Grade 1 or less. Dose modification text and guidance for belantamab mafodotin is provided in this section. Also see 208887 MP Section 11 for guidance on guidelines for dose modification and management of events for belantamab mafodotin and other partner combination treatments.

6.6.2. Permitted Dose Reductions and Delays of Feladilimab When in Combination with Belantamab Mafodotin

- No dose reductions are permitted for feladilimab. Fixed (flat) dosing of feladilimab will be used during the study for all participants receiving feladilimab, regardless of participant weight.
- Delays will be allowed for feladilimab if needed, but this will not affect the dosing schedule for belantamab mafodotin, with the possibility of feladilimab administration 1 day later than belantamab mafodotin in the case of an IRR on the day of belantamab mafodotin infusion. Otherwise feladilimab would be re-introduced in line with the next dose of belantamab mafodotin.
- Feladilimab may only be administered with belantamab mafodotin. If belantamab mafodotin is delayed for any reason, then feladilimab will also be delayed. The maximum treatment delay for feladilimab is 12 weeks, therefore the maximum treatment delay for combination therapy is 12 weeks (+1 day).
- For participants with dosing delays of belantamab mafodotin-feladilimab combination therapy for whom continued/further benefit of combination therapy is anticipated, treatment with combination therapy beyond 12 weeks delay may be considered on a case-by-case basis after discussion with the treating investigator and approval from the Medical Director.
- If belantamab mafodotin is permanently withdrawn the participant will be withdrawn from all study treatment.

- If participants develop toxicity which would preclude additional dosing with feladilimab, they can continue with belantamab mafodotin only. For drug-related toxicities not listed in these tables, the general rule of withholding the dose for Grade ≥3 toxicity should be followed. Resuming treatment will be possible after the toxicity has resolved to Grade ≤1 and with agreement between the principal investigator and Medical Director.

Investigators must contact the Medical Director for all Grade ≥3 clinically significant non-hematological drug-related toxicities where interruption or permanent discontinuation of study treatment may be warranted according to the guidelines provided in the 208887 MP Section 11. Otherwise, investigators are encouraged to contact the Medical Director as needed to discuss any case that warrants separate discussion outside of the scope of current 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 2 are in the Section 8.3.7, Section 8.3.9 and Section 8.4 below.

8.1. Efficacy Assessments

Please refer to the 208887 MP.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA tables (Section 1.3).

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

Please refer to the 208887 MP.

Details of all pregnancies in female participants will be collected after the start of study treatment and for 4 months following last dose of belantamab mafodotin.

Details of all pregnancies for female partners of male participants will be collected after the start of study treatment and 6 months following last dose of belantamab mafodotin.

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 AESI are contained in the 208887 MP Section 8.3.10.

AESI for Feladilimab

The list of terms and reporting requirements for GSK AESI are provided below. These are selected non-serious AEs and SAEs that **must be reported to GSK** regardless of relationship to study treatment. Any event that meets the criteria described below must be reported regardless of investigator-determined relationship to study treatment or if considered immune-related (unless otherwise specified). Investigators/study coordinators/designated site personnel are required to record these experiences in the eCRF (as described in the eCRF completion guidance document) and to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event. Please note this table lists known AESI, additional events may be identified during the course of the study.

Table 13 Potential Immune-related AEs for Feladilimab Treatment

Pneumonitis (reported as AESI if Grade ≥2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as AESI if Grade ≥2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as AESI if Grade ≥3 or Grade ≥2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if Grade ≥3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as AESI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic (reported as AESI if Grade ≥3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic thrombocytopenic purpura
Idiopathic (or immune) Thrombocytopenia purpura	Disseminated intravascular coagulation	Hemolytic uremic syndrome
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as AESI if Grade ≥2, or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or AST)
Infusion Reactions (reported as AESI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	IRRs
Neurologic (reported as AESI for any grade)		
Autoimmune neuropathy	Guillain-Barré syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as AESI if Grade ≥2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as AESI if Grade ≥2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as AESI if Grade ≥3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as AESI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		

Skin (reported as AESI if Grade ≥3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as AESI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

8.4. Treatment of Overdose

Guidelines for management of belantamab mafodotin overdose are contained in the 208887 MP Section 8.4. There is no specific antidote for overdose with feladilimab. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care should be instituted, as dictated by the participant's clinical status. Obtain an additional plasma sample for PK analysis if requested by the Medical Director.

8.5. Pharmacokinetics

Not applicable.

8.6. Pharmacodynamics

Not applicable.

8.7. Genetics

Please refer to the 208887 MP.

8.8. Immunogenicity Assessments

Please refer to the 208887 MP.

8.9. Biomarkers

Not applicable.

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

Please refer to the 208887 MP.

9. STATISTICAL CONSIDERATIONS

Please refer to the 208887 MP for the overall Statistical Considerations for the study.

9.1. Statistical Hypotheses

Please refer to the 208887 MP.

9.2. Sample Size Determination

Please refer to the 208887 MP.

9.3. Populations for Analyses

Please refer to the 208887 MP.

9.4. Statistical Analyses

Please refer to the 208887 MP.

9.5. Interim Analyses

Please refer to the 208887 MP.

9.6. Sample Size Sensitivity

Please refer to the 208887 MP.

10. REFERENCES

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

Please refer to the 208887 MP for the overall guidelines for dose modification for the study.

12. APPENDICES: SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Please refer to the 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.

12.10. 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

AE	Adverse event
AESI	Adverse events of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine Triphosphate
AUC	Area under the concentration-time curve
BCMA	B-cell maturation antigen
BM	Bone marrow
BP	Blood pressure
C1D1	Cycle 1 Day 1
CBC	Complete blood count
CE	Cohort Expansion Phase
Cmax	Maximum plasma drug concentration
CMMC	Circulating multiple myeloma cells
CR	Complete response
CRP	C-reactive protein
CT	Computerized tomography
CTCAE	Common Toxicity Criteria for Adverse Events
$C\tau$	Concentration in a dosing interval
DAMP	Damage-Associated Molecular Pattern
DE	Dose Expansion Phase
DKA	Diabetic ketoacidosis
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOI	End of infusion
EORTC IL52	European Organisation for Research and Treatment of Cancer Item Library 52
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires 30-item Core module
EOT	End of treatment
Fc	Fragment crystallizable
FISH	Fluorescence in situ hybridization;
FLC	Free light chain
FTIH	First-time in human
GGT	Gamma-glutamyl transferase
GSK	GlaxoSmithKline Research & Development Limited
GSK2857916	GSK anti-BCMA antibody drug conjugate (CA8 J6M0 Potelligent MMAF)
HBcAb	Hepatitis B core antibody

hBCMA	Human BCMA
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HR	Heart rate
hr(s)	Hour(s)
IB	Investigator's Brochure
ICD	Immunogenic cell death
ICOS	Inducible T-cell co-stimulatory
Ig	Immunoglobulin
IHC	Immunohistochemistry
INR	International normalized ratio
IRR	Infusion-related reaction
IV	Intravenous(ly)
KVA	Keratopathy and visual acuity
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MDRD	Modified diet in renal disease
MM	Multiple myeloma
MP	Master Protocol
MRI	Magnetic resonance Imaging
MUGA	Multiple gated acquisition
NT-proBNP	N-terminal B-type natriuretic peptide
ORR	Overall response rate
OS	Overall survival
OSDI	Ocular Surface Disease Index
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease/Disease progression
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient reported outcome
Q3W	Every 3 weeks
Q4W	Every 4 weeks
QoL	Quality of life
RNA	Ribonucleic acid
RO	Receptor occupancy
RP2D	Recommended Phase 2 dose
RRMM	Relapsed/refractory multiple myeloma
SAE	Serious adverse event
sBCMA	Soluble B-cell maturation antigen
sCR	Stringent complete response
SoA	Schedule of Activities
SOI	Start of infusion
SPEP	Serum protein electrophoresis

t1/2	Half-life
UPEP	Urine protein electrophoresis
WOCBP	Women of childbearing potential

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.
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.

Term	Definition
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 Sub-study 2 Amendment 7 is located directly before the Table of Contents (TOC).

Amendment 6 (Sub-study 2): 10 July 2023

Overall Rationale for the Amendment:

The Sub-study 2 protocol has been amended to make corrections to typographical errors and inconsistencies, to add clarifications in line with program level changes, and to add administrative and safety updates, which are summarized in the table below.

Section # and Name	Description of Change	Brief Rationale
Throughout document	Changed all instances of Medical Monitor to consistently refer to the Medical Director, and updated medical director contact information	Correction of typographical or consistency error
Throughout document	Minor editorial and document formatting revisions, applied GSK style guide for abbreviations, date format, reference details, etc.	Correction of typographical or consistency errors
Throughout document	Updated amendment numbering in sub-study to be unique and not identical to MP	Correction of typographical or consistency error
Throughout document	The term GSK'916 (used for laboratory samples) was replaced by belantamab mafodotin. The term GSK'609 (used for laboratory samples) was replaced by feladilimab	Clarification of wording
Throughout document	Updated reference to GSK2857916/ belantamab mafodotin Investigator's Brochure	To refer to the most recent version of the IB
Throughout document	Added references to the MP where missing	Correction of typographical or consistency error
Throughout document	Updated cross-references to the relevant MP section	Correction of typographical or consistency error
Investigator Protocol Amendment Agreement Page	Added page and included sub-study title for consistency with title page	Correction of typographical or consistency error
1.3. Schedule of Activities	In Table 2 and Table 4, clarified that anytime C1D1 hematology/chemistry results are outside of eligibility requirements, Medical Director should be contacted prior to dosing. Removed "at Screening" for clarity	Clarification for study conduct
1.3. Schedule of Activities	Removed extraneous text from Table 2 (footnote 1)	Correction of typographical or consistency error
1.3. Schedule of Activities	In Table 2 (footnote 2), revised requirement of 2 pregnancy tests at Screening	Program level update
1.3. Schedule of Activities	Table 2 (footnote 6), clarified the HCV RNA testing will be performed to determine participant eligibility if HCV antibody is positive	Clarification of study conduct

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities	In Tables 2, 3, and 5, clarified that urine immunofixation should be done on 24 hr urine collection sample	Clarification for study conduct
1.3. Schedule of Activities	Updates to Table 3 (footnote 3) and Table 4 (footnote 2), clarifying timing of ocular exams in relation to dosing	Clarification for study conduct
1.3 Schedule of Activities	Clarified in Table 3 that if scheduled visits are 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	Clarification for study conduct
1.3. Schedule of Activities	Table 3 (footnote 8) and Table 5 (footnote 21), decreased frequency of UPEP assessments	Program level update
1.3. Schedule of Activities	Table 3 (footnote 9), modified footnote for urine and serum immunofixation to include "not quantifiable"	Clarification for study conduct
1.3. Schedule of Activities	Revised language related to imaging for Skeletal surveys and for participants with extramedullary disease in Table 3 (footnote 13)	Clarification for study conduct
1.3. Schedule of Activities	Revised footnote text in Table 4 (footnote 5) to clarify that chemistry panel can be done more frequently as clinically indicated	Clarification for study conduct
1.3. Schedule of Activities	Revised timing of EOT safety assessments in Table 5 (footnote 1)	Clarification for study conduct
1.3. Schedule of Activities	In Table 5 (footnote 8) referred to the Section 8.3.7 and MP Appendix 7 instead of repeating pregnancy test requirements	Clarification for study conduct
1.3. Schedule of Activities	Added that disease evaluation should occur Q3W or Q4W in Table 5	Clarification for study conduct
1.3 Schedule of Activities	Removed footnote 12 which was redundant with footnote 2	Correction of typographical or consistency error
1.3. Schedule of Activities	Revision to clarify timing of follow-up OSDI questionnaires following the EOT in Table 5, footnote 18	Clarification for study conduct
1.3. Schedule of Activities	Removed reference to footnotes 3 and 4 in the Table 6 column 1 heading because these footnotes do not apply to every timepoint in column 1	Clarification for study conduct
1.3 Schedule of Activities	In Table 6, the term “suspected VGPR, CR/sCR” was corrected to “suspected CR/sCR”.	Correction of typographical or consistency error
1.3 Schedule of Activities	Details regarding FISH testing were removed from Table 6 (footnote 2) and reference to Table 31 in the MP has been provided.	Clarification for study conduct
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 4.1 Overall Design	Corrected typo in the number of dose levels to potentially be evaluated and the typo for maximum dose of feladilimab.	Correction of typographical or consistency error

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria	Added note that numbering for exclusion criteria may not be sequential from the MP; for consistency with MP	Correction of typographical or consistency error
Section 6.1 Study Treatment(s) Administered	In Table 10, updated language concerning belantamab mafodotin formulation.	Clarification for study conduct
Section 6.6.1 Permitted Dose Reductions for Belantamab Mafodotin When in Combination with Feladilimab	Added new dose modification guidance for belantamab mafodotin in combination with feladilimab	To align dose modification guidelines in Sub-study 2 with those implemented in other sub-studies

Amendment 05 (Sub-study 2): 21 January 2022

Overall Rationale for the Amendment:

Changes listed in the table below are for the Sub-study 2 protocol only. Changes for Protocol Amendment 05 that are related to the 208887 MP 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 changes within the document
1.3. Schedule of Activities (SoA)	Added multiple gated acquisition (MUGA) scan Clarified text for the Treatment Period for belantamab mafodotin and feladilimab for DE and CE phase, for performing the same procedure (ECHOs or MUGA scans for LVEF) at screening to be throughout the study, and during end of treatment (EoT) and Follow-up	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. 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
	Removed the single vital signs assessment on Day 4 (Cycle 1 only), Day 8 (Cycles 1-6) and Day 15 (Cycles 1 and 2).	To reduce patient burden

Section # and Name	Description of Change	Brief Rationale
	Updated the schedule for bone marrow aspiration and sample collection, throughout the study	To reduce patient burden
	Added additional procedures for participants who were HBcAb positive during screening Added Table 7 for additional procedures for participants with a history of Hepatitis B	To align with the latest regulatory guidance
	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
	Removed biomarker assessments	To reduce patient burden
2.2.1. Clinical Experience with Feladilimab	Updated feladilimab related text to align with the latest clinical experience	To improve overall clarity and alignment with the most recent Investigator's Brochure
Section 10. Reference	New reference added – Montes, 2021	Updated with latest literature
Appendix 11 Decentralized and Remote Assessment Approaches	Updated the heading from 'Home Healthcare and Telemedicine Approaches'.	To align with Master protocol
Appendix 12. Abbreviations and Trademarks	Updated the new abbreviations used in the document.	To reflect new changes
Appendix 13: Protocol Amendment History	Addition of summary of changes from amendment 04 in the appendix as per the template requirement	Template alignment

Amendment 04 (Sub-study 2): 14 December 2020

Overall Rationale for the Amendment:

The 208887 protocol has been amended to convert to a modular document format with separate Master Protocol (MP) and sub-study modules. The organizational changes for Sub-study 2 are administrative and are mapped in the table below.

Section # for PA3 and Name		Section # for PA4 and Name	
12.1	Protocol Amendment 3 Summary of Changes Specific to Sub-study 2	12.13.1	Protocol Amendment 3
12.2	Schedule of Activities (SoA) for Belantamab mafodotin + GSK'609 (aICOS)	1.3	Schedule of Activities (SoA)
12.3	Background of GSK'609 (aICOS)	2.2	Background for feladilimab
12.4	Rationale for combination of Belantamab mafodotin with GSK'609 (aICOS)	2.1	Rationale for combination of Belantamab mafodotin with feladilimab
12.5	Belantamab mafodotin in combination with anti-ICOS agonist antibody in the EL4-hBCMA syngeneic model		
12.6	Dose justification for GSK'609 (aICOS) when in combination with Belantamab mafodotin	4.3	Justification for Dose
12.7	Study Interventions Administered	6.1	Study Intervention(s) Administered
12.8	Belantamab mafodotin and GSK '609 (aICOS) Dose Administration	6.2	Administration of Belantamab mafodotin and feladilimab
12.9	Preparation/Handling/Storage/Accountability	6.3	Preparation/Handling/Storage/Accountability – content deleted as was identical to the 208887 MP
12.10	Combination Treatment Belantamab mafodotin Co-Administered with GSK'609 (aICOS)	4.1	Overall Design
12.10.1	Treatment Durations of Belantamab mafodotin and GSK'609 (aICOS)	6.2	Administration of Belantamab mafodotin and feladilimab
12.10.2	Permitted Dose Reductions of Belantamab mafodotin when in combination with GSK'609 (aICOS)	6.6.1	Permitted Dose Reductions for Belantamab mafodotin When in Combination with feladilimab
12.10.3	Permitted Dose Reductions of GSK'609 (aICOS) when in combination with Belantamab mafodotin	6.6.2	Permitted Dose Reductions of feladilimab when in combination with Belantamab mafodotin
12.11	Adverse Events of Special Interest for GSK'609 (aICOS)	8.3.10	Adverse Events of Special Interest
12.12	Benefit/Risk	2.3	Benefit/Risk Assessment
12.13	Inclusion/Exclusion Criteria for Sub-study 2	5.1	Inclusion Criteria for Participants
		5.2	Exclusion Criteria
12.14	Specific GSK'609 (aICOS) - Related Dose Reduction and delays Criteria and Guidance	6.6.2	Permitted Dose Reductions of Feladilimab when in combination with Belantamab mafodotin
12.14.1	Management of Pregnancy	8.3.7	Management of Pregnancy
12.15	Protocol Amendment History for Changes Specific to Sub-study 2	12.13	Appendix 13: Protocol Amendment History

Changes listed in the table below are for the Sub-study 2 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
Changes in Assessments and SoAs		
1.3. Schedule of Activities	Clarified footnote on Single ECG at Screening (Table 3)	Clarified based on prior edits (Protocol Amendment 03)
	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
Safety		
6.6.2 Permitted Dose Reductions of feladilimab when in combination with belantamab mafodotin	Added clarifying language for treatment with combination therapy following a delay of more that 12 weeks with approval by the GSK Medical Director	To clarify language
Editing, format, style changes		
Throughout	Correction of typos and technical document aspects	Minor changes with no impact on content

Protocol Amendment 3: 08 July 2020

Protocol Amendment 03 Summary of Changes Specific to Sub-study 2

Section # and Name	Description of Change	Brief Rationale
Revised Study Design		
Section 12.10	Removal of 3.4 mg/kg dose from tables and text	See Lonial, 2020 reference for monotherapy recommended dose
Section 12.13.1	Added exclusion for recent symptomatic pericarditis	To better define appropriate study population
Safety Changes		
Section 12.2, Table 32 and 34	AEs/SAEs will be collected until at least 70 days post EOT	As per belantamab mafodotin program safety language
Section 12.2, Table 34	Change EoT pregnancy restriction from 9 months to 4 months	As per belantamab mafodotin program safety language
Section 12.3, Section 12.5 and Section 12.6	Updated clinical experience and safety information for GSK3359609 (aICOS)	As per current GSK3359609 Investigator's Brochure, v05, 2020
Section 12.8.1	Added section on overdose	To provide available guidance on overdose
Changes in Assessments and SoAs		
Section 12.2	Removal of post EOT ADA assessments for belantamab mafodotin	Not needed
Section 12.2	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 12.2	Added additional timepoints for cytokines, whole blood RNA, PBMCs and CMMC.	To provide consistency across sub-studies and a more comprehensive longitudinal analysis of these samples
Section 12.2	Revised assessments and descriptions, including: Urinalysis assessment and description Removal of post-baseline ECG assessments, 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, as with Master Protocol
Section 12.2	Added optional follow-up Qualitative phone interview	Clarified timepoint assessment for qualitative phone interview
Protocol Clarification and Alignment		
Section 12.2	Revisions to QoL assessments to include IL52 (symptom assessment) portion of EORTC QLQ-My20 and revised timepoints	Clarify assessments and timing
Section 12.2	Replace ophthalmologist and optometrist with eye-care specialist term and define same	Simplify and define provider terminology
Throughout	Asset numbers/abbreviations replaced with generic names except for laboratory sampling	For consistency throughout document
Editing, format, style changes		
Throughout	Correction of typos and technical document aspects	Minor changes with no impact on content

Protocol Amendment 2: 16 December 2019

Protocol Amendment 02 Summary of Changes Specific to Sub-study 2

Section # and Name	Description of Change	Brief Rationale
Revised Study Design		
Section 12.2, 12.14.1	Updated pregnancy wording: follow up timing and management of pregnancy.	Program level changes
Safety Changes		
Section 12.2	Ophthalmology wording updated throughout the protocol. Changes in the frequency of assessments. The GSK scale removed, steroid eye drops not mandatory and corneal images no longer required. Updated stopping criteria based on ocular examination findings	Updated in line with program level changes
Section 12.2	Updated timing of SAE assessments	Updated timing of SAE assessments in line with program
Changes in Assessments and SoAs		
Section 12.2, Table 31, Table 32	CRP assessment removed from SoA tables	
Section 12.2 Table 32	Removed physical exam and vital sign assessment from SoA for assessments to be done regardless of dosing (and updated footnote numbering)	These evaluations are done with dosing
Section 12.2, Table 33 and 34	Removed AESI assessment.	This is covered under AE's and SAEs. This is still being collected.
Section 12.2, Table 33	Clarification around timings for biomarker samples	Clarification
Protocol Clarification and Alignment		
Section 12.4	Clarification of preclinical data for belantamab mafodotin in combination with anti-ICOS agonist antibody.	Regulatory Agency request for clarified wording
Section 12.7 Table 35	Infusion timing of belantamab mafodotin and GSK'609 (aICOS) added	Regulatory Agency request. Infusion timings added
Section 12.10	Added wording that "Sponsor may decide not to evaluate all dose levels based on data external to this study…"	Clarity of wording around when a sub-study can be closed
Section 12.10.3	Clarification around dose delay timing.	Clarification of wording

Protocol Amendment 1: 24 June 2019

The protocol was amended in line with comments from the FDA, which included the following:

- More preclinical data included to provide the biological rationale for the use of belantamab mafodotin in combination with GSK'609 (aICOS).
- Lower starting doses for GSK'609 (aICOS).

Protocol Amendment 01 Summary of Changes Specific to Sub-study 2

Section # and Name	Description of Change	Brief Rationale
Revised Study Design		
Section 12.3 Rationale for combination of belantamab mafodotin with GSK'609 (aICOS)	Additional preclinical data added	Amended to include further details regarding the preclinical studies that were conducted to support the investigation of specific combinations in patients with multiple myeloma. As requested by the FDA.
Section 12.4 belantamab mafodotin in combination with anti-ICOS agonist antibody in the EL4-hBCMA syngeneic model	Text updated.	As requested by the FDA
Section 12.5 Dose justification for GSK'609 (aICOS)when in combination with belantamab mafodotin	Updated dose justification text	As requested by the FDA
Section 12.7 belantamab mafodotin and GSK'609 (aICOS)Dose Administration	Changes to the starting dose of belantamab mafodotin from 2.5 mg/kg to 1.9 mg/kg. An additional dose of 8 mg, administered every 3 weeks was added.	As requested by the FDA
Section 12.9 Combination Treatment belantamab mafodotin Co-Administered with GSK'609 (aICOS)	Dose exploration schema modified to add extra dose levels.	As requested by the FDA
Section 12.9.2 Permitted Dose Reductions of belantamab mafodotin when in combination with GSK'609 (aICOS)	Modified text and table wording around permitted dose reductions of belantamab mafodotin when in combination with GSK'609 (aICOS)	Clarification in line with FDA request
Section 12.9.4 Intrasubject dose escalation or de-escalation in DE	This section was deleted	Clarification in line with FDA request

Section # and Name	Description of Change	Brief Rationale
Changes in Assessments and SoAs		
Section 12.1 Table 29	Clarified timings Addition of Screening thyroid function tests	Clarification of wording and timings, and addition of missing tests
Section 12.1 Table 30	Clarified of timings/wording Clarified AE/SAE timings to agree with text in the protocol: "AEs will be assessed up to 45 days post the last dose. SAEs will be assessed up to 90 days post last dose, or 45 days post last dose if the participant initiates a new anti-cancer therapy (whichever is shorter). All related SAEs are to be collected from first dose through OS follow-up" Spot urine (albumin/creatinine ratio) removed.	Clarification of wording and timings and removal of tests
Section 12.1 Table 31	Clarified timings/wording of PK, ADA, sBCMA samples Day 4 Cycle 1 column added for clarity "Ocular Examination" removed (to avoid confusion, this is carried out every 3 weeks regardless of dosing). ECOG performance status added Deleted reference to EDTA tube & PAXgene tube	Clarification of wording and timings, removal/addition of tests and other edits for consistency between SoA tables

Signature Page for 208887 TMF-19486323 v2.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 03-Sep-2024 14:02:18 GMT+0000

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