Protocol Amendment 4

Study ID: 208887 Sub Study 1

Official Title of Sub Study 1: 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 1 - Belantamab Mafodotin and aOX40 (GSK3174998) in Combination

NCT ID of Sub Study 1: NCT06160609

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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 1 – Belantamab Mafodotin and aOX40 (GSK3174998) in Combination

Protocol Number: 208887 Sub-study 1 / Amendment 04

Compound Number or Name: Belantamab mafodotin (GSK2857916), GSK3174998

Short Title: Platform Sub-study of belantamab mafodotin (GSK2857916) in combination with aOX40 (GSK3174998) in participants with RRMM

Acronym: DREAMM-5 Sub-study 1

Study Phase: Phase I/II

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 4 (Sub-study 1)	*14-DEC-2020*	*2020N453267_00*
Amendment 3	*08-JUL-2020*	*2017N352487_03*
Amendment 2	*16-DEC-2019*	*2017N352487_02*
Amendment 1	*24-JUN-2019*	*2017N352487_01*
Original Protocol	*12-MAR-2019*	*2017N352487_00*

Amendment 04 (Sub-study 1) 14-DEC-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 1 are administrative and are mapped in the table below.

Section # for Prot-Amend 3 and Name		**Section # for Prot-Amend 4 and Name**	
11.1	Protocol Amendment 3 Summary of Changes Specific to Sub-study 1	12.13.1	Protocol Amendment 3
11.2	Schedule of Activities (SoA) for Belantamab mafodotin + GSK'998 (aOX40)	1.3	Schedule of Activities (SoA)
11.3	Background of GSK'998 (aOX40) (GSK3174998)	2.2	Background for GSK'998 (aOX40) (GSK3174998)
11.4	Rationale for combination of Belantamab mafodotin with GSK'998 (aOX40)	2.1	Rationale for combination of Belantamab mafodotin with GSK'998 (aOX40)
11.5	Dose justification for GSK'998 (aOX40)	4.3	Justification for Dose
11.6	Dose Exploration of Combination Treatment Belantamab mafodotin Co-Administered with GSK'998 (aOX40)	4.1	Overall Design
11.7	Study Interventions Administered	6.1	Study Intervention(s) Administered
11.8	Administration of Belantamab mafodotin and GSK'998 (aOX40)	6.2	Administration of Belantamab mafodotin and GSK'998
11.9	Preparation/Handling/Storage/Accountability	6.3	Preparation/Handling/Storage/Accountability – content deleted as it was identical to the 208887 MP
11.10	Adverse Events of Special Interest for GSK'998 (aOX40)	8.3.9	Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs
11.11	Benefit/Risk	2.3	Benefit/Risk Assessment
11.12	Additional Inclusion/Exclusion Criteria for Sub-study 1	5.1	Inclusion Criteria for Participants
		5.2	Exclusion Criteria
11.13	Specific GSK'998 (aOX40)-Related Dose Reduction and Delay Guidance	6.6	Dose Modification
11.13.1	Management of Pregnancy	8.3.7	Management of Pregnancy
11.14	Protocol Amendment History for Changes Specific to Sub-study 1	12.13	Appendix 13: Protocol Amendment History

Changes listed in the table below are for the Sub-study 1 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
Administrative Changes		
1.1 Synopsis	Added language to state that Sub-study 1 has been closed to enrollment	Due to current data (observed lack of efficacy); investigators and sites have already been notified
Changes in Assessments and SoAs		
1.3 Schedule of Activities	Clarified FISH assessments that are to be completed at Screening (Table 2) based on availability on previous results	In line with other protocols in the program.
	Clarified footnote on Single ECG at Screening (Table 3)	Clarified based on prior edits (Protocol Amendment 03)
	Clarified language on definition of resolution of ophthalmic findings (to baseline instead of Grade 1)	To align with GSK belantamab mafodotin program language
Protocol Clarification and Alignment		
Section 12.11. Appendix 11: Home Healthcare and Telemedicine Approaches	Heading added for this Appendix	Added to match new Appendix added to the 208887 Master Protocol
Editing, format, style changes		
Throughout	Correction of typos and technical document aspects	Minor changes with no impact on content

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1. PROTOCOL SUMMARY

Please refer to the 208887 Master Protocol (MP) for the overall Protocol Summary for the study.

Information and details specific to Sub-study 1 are in the subsections below. These are summarized in Table 1. Please refer to the 208887 MP for other sections and content.

Table 1 Location of Sub-study 1-specific Content

Section	Heading title	Brief description of content
1.3	Schedules of Activities	Comprehensive SoA tables specific for Sub-study 1
2.1	Rationale for combination of Belantamab mafodotin with GSK'998 (aOX40)	Explanation why treatment with belantamab mafodotin and aOX40 is expected to be complementary
2.2	Background for GSK'998 (aOX40) (GSK3174998)	Available data on clinical pharmacology, safety and clinical activity
2.3	Benefit/Risk Assessment	Risk assessments for aOX40 treatment; benefit assessment summary
4.1	Dose Exploration of Combination Treatment Belantamab mafodotin Co-Administered with GSK'998 (aOX40)	Description of dose escalation design for the combination treatment
4.3	Dose justification for GSK'998 (aOX40)	Data for the basis of the planned aOX40 dosing
5.2	Exclusion Criteria	Two additional exclusion criteria were defined for Sub-study 1
6.1	Study Intervention(s) Administered	Specifications for belantamab mafodotin and aOX40 IP
6.2	Administration of Belantamab mafodotin and aOX40	Specifications for administration of belantamab mafodotin and aOX40
6.6	Dose Modification for Belantamab Mafodotin When in Combination with GSK'998	Detailed directions guidance for dose modifications of combination treatment
8.3.7	Management of Pregnancy	Timeframes for on data collection
8.3.9	Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs	Information on aOX40 AESI
8.4	Treatment of Overdose of aOX40 (GSK3174998)	Guidance for potential drug overdose of aOX40
12.13	Appendix 13: Protocol Amendment History	Summary of Changes Tables for Sub-study 1 specific amendments

1.1. Synopsis

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 GSK'998 (aOX40). Murine aOX40 (OX86) in combination with belantamab mafodotin provided with survival benefit in mice over GSK'916 single agent activity, although, it did not reach statistical significance. In addition, the combination of OX86 at 0.2, 1 and 5 mg/kg with belantamab mafodotin resulted in 7, 4 and 5 (out of 10 mice) tumor free survivors.

This is a randomized Phase I/II, open-label, platform-design study of belantamab mafodotin in combination with GSK'998 (aOX40) 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 dose exploration (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. A recommended Phase 2 dose (RP2D) for each combination treatment will be identified based on the safety and preliminary efficacy in DE. This will be followed by a cohort expansion (CE) phase which will evaluate the clinical activity of the combination treatment in comparison to monotherapy belantamab mafodotin in additional participants with RRMM at the RP2D in sub-studies.

A total of 3 dose levels can be potentially evaluated, so there could potentially be a maximum of 3 dosing cohorts running simultaneously in the dose exploration (DE) phase. The starting dose of belantamab mafodotin will be 1.9 mg/kg and the starting dose of GSK'998 (aOX40) will be 8 mg every 3 weeks. Please see 208887 MP Section 4.1.1 for details of decision making during the DE phase.

Sub-study 1 has been closed to enrollment.

1.2. Schema

1.3. Schedule of Activities (SoA)

- The timing and number of planned study assessments, including [safety, pharmacokinetic, ADA, biomarker or others] 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.
- Note: belantamab mafodotin is referred to as GSK'916 only for the purposes of Laboratory assessments and samples.
- Note: GSK'998 (aOX40) is referred to as GSK'998 only for the purposes of Laboratory assessments and samples

Table 2 SoA – Screening for DE and CE Phases: Belantamab Mafodotin and GSK'988 (aOX40)

Screening Study Assessments	Screening	Notes
Note: All Screening assessments must be performed within **30** days prior to Cycle 1 Day 1 (C1D1) unless otherwise specified. Informed Consent must be signed before any study-specific assessments are performed. Screening Assessment do not need to be repeated on C1D1 unless otherwise specified. All other assessments can be done ≤3 days prior to treatment unless otherwise specified.		
Informed Consent	X	1. Screening/baseline ocular examination will be performed by a qualified eye-care specialist (ophthalmologist/optometrist) within 30 days prior to C1D1 (see 208887 MP Section 8.2.7 for list of ophthalmic exam procedures). Screening assessment does not need to be repeated on C1D1 unless otherwise specified. (see 208887 MP Section 8.2.7 for list of ophthalmic exam procedures). 2. Perform only in women of child-bearing potential. Two serum pregnancy tests should be performed at screening. The first test should be performed at least 10 days prior to C1D1 and the second test within 72 hours prior to administration of C1D1. 3. Refer to 208887 MP Appendix 2 for a comprehensive list of lab tests that must be collected for all participants. 4. TSH, free T3 and T4. 5. eGFR as calculated by Modified Diet in Renal Disease (MDRD) formula (208887 MP Appendix 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 ≥1+ at screening, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab.(first void). 7. Complete at screening or within 12 weeks prior to C1D1. 8. Hep C RNA testing is optional, but it may be performed to determine participant eligibility if Hep C antibody positive. If negative, patient is eligible (see exclusion criteria 12 for details). 9. Single ECG at Screening. 10. ECHO may be performed within 30 days C1D1. 11. SPEP and UPEP will include M protein calculations. 12. Serum Free Light Chain assay will include kappa/lambda ratio and quantification of involved and uninvolved light chains. 13. IgD/IgE testing is only required for patients with IgD/IgE myeloma. 14. Skeletal Survey: Imaging of bones for lytic lesions by a method aligned with the institutional guidance (X-ray, CT, or MRI). X-Ray is acceptable for lytic disease, but other methods are needed (CT, MRI, 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. 15. In participants with known or suspected extramedullary plasmacytoma, a whole-body scan (i.e., CT, MRI, or PET-CT) should be performed within 30 days prior to C1D1. The same method should be
Throughout the trial, participants are educated about in life style considerations (208887 MP Section 5.3) for the study and the need of maintaining adequate urinary output (208887 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]	
Thyroid Function Tests	X[4]	
Estimated Glomerular Filtration (eGFR)	X[5]	
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)	X[6]	
HBsAg, HBcAb, HCV[8] tests	X[7]	
12-lead ECG	X[9]	
ECHO LVEF	X[10]	
Screening Disease Evaluation		

Screening Study Assessments	Screening	Notes
Note: All Screening assessments must be performed within **30** days prior to Cycle 1 Day 1 (C1D1) unless otherwise specified. Informed Consent must be signed before any study-specific assessments are performed. Screening Assessment do not need to be repeated on C1D1 unless otherwise specified. All other assessments can be done ≤3 days prior to treatment unless otherwise specified.		
$Beta_2$ microglobulin	X	used throughout the study (i.e., if a PET-CT scan was used as baseline scan than participants needs to be followed by PET-CT scans). Selected target lesion needs to be measured and followed over time. Whole body MRI is also acceptable, as long as it is able to be repeated over the duration of the study until confirmed disease progression. Note: Germany: no PET/CT to confirm CR or sCR will be performed until approval by the German Federal Office for Radiation Protection.
UPEP 24 hr urine collection	X[11]	
Urine immunofixation	X[11]	
SPEP	X[11]	
Serum Immunofixation	X	
Serum FLC assay	X[12]	16. Immunohistochemistry (IHC) of bone marrow core biopsy is preferred for quantitative assessment of malignant plasma cells. However, bone marrow aspirate is acceptable and should be performed within 60 days of C1D1. Archival tissue from up to 60 days prior to C1D1 is acceptable.
IgG, IgM, IgA	X	
IgD or IgE, if applicable	X[13]	17. FISH testing at least for: t(4;14), t(14;16), amp(1q), del(1p), del(17p13).). If participant is known to have tested positive for t(4;14) or t(14/16) on previous tests, FISH for those translocations does not need to be repeated, but results from previous tests are acceptable regardless of when those tests were performed. For amp(1q), del(1p) and del(17p13), FISH results from samples taken within 60 days prior to C1D1 are acceptable.
Calcium corrected for albumin (serum)	X	
Skeletal Survey	X[14]	18. These assessments will be performed by a central laboratory.
Extramedullary Plasmacytoma Assessment (by whole body CT or whole body MRI or CT/PET)	X[15]	19. Minimal residual disease (MRD) testing to be performed by the central lab at screening, at the time of first achieving VGPR or CR. Repeat MRD testing every 6 months after achieving VGPR or CR (provided VGPR/CR is maintained).
Bone Marrow (BM) Aspiration/Biopsy		
BM (biopsy and/or aspirate) for local disease assessment	X[16]	
BM aspirate for local FISH testing	X[17]	
BM aspirate for BCMA expression and immune cell characterization/profiling	X[18]	
BM aspirate for MRD testing	X[18,19]	

ADA = Anti-drug Antibody; ALP = alkaline phosphatase; NT-proBNP = N-terminal pro B-type natriuretic peptide; D1 = Day 1, etc.; CBC Complete Blood Count, cfDNA = Circulating free DNA; CK = creatinine kinase; CT = computed tomography; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EM = extramedullary; EOI = End of Infusion; FISH = Fluorescence in situ hybridization; FLC = free light chain; IgD/IgE = Immunoglobulin D or E; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PET = positron emission tomography; PFS = progression-free survival; PD = progressive disease; PK = pharmacokinetics; SOI = start of infusion; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

Table 3 SoA – Treatment Period for DE and CE Phases: Belantamab mafodotin and GSK'988 (aOX40) Study Assessments to be carried every 3 weeks 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**	**Notes**
Note: All assessments will apply to both the DE and CE Phases unless stated otherwise. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. All assessments from Week 4 can be performed ≤3 days prior to the scheduled date unless otherwise specified.				
Adverse Events	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 90 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 AE's/SAE's will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost t follow-up. 2. Informed consent for optional sub studies (e.g. genetic research) must be obtained before collecting a sample. The sample will be collected on C1D1 prior to infusion. 3. On-study ocular exams to be performed by a qualified eye-care specialist Q3W prior to 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). See 208887 MP Section 8.2.7 for list of ophthalmic exam procedures. If there are no significant ocular examination findings, change in patient symptoms or vision at the time of the sixth dose exam, participants may have their ophthalmologic exams decreased to once every 3 months. If a participant subsequently develops vision changes or other ocular symptoms, the participant should be promptly evaluated by a qualified eye care specialist. In case of persistent ophthalmic exam findings, newly developed ocular symptoms or vision changes, the participants will have further ophthalmologic exams at least every cycle until resolution (to baseline), or more frequently as clinically indicated by the qualified eye care specialist. 4. If completed within 72 hrs prior to the dose, this assessment does not need to be repeated on Day 1 of Cycle 1. Day 8 Cycles 1-6 only and Day 15 Cycles 1 and 2 only. CBC may be done more frequently as clinically indicated. Refer to 208887 MP Appendix 2 for comprehensive list of lab tests. 5. eGFR every dose as calculated by Modified Diet in Renal Disease (MDRD) formula (208887 MP Appendix 6).
Concomitant Medications	Ongoing			
Throughout the trial, participants are educated about in life style considerations (208887 MP Section 5.3) for the study and the need of maintaining adequate urinary output (208887 MP Section 2.3.1).	X			
Genetics	X[2]			
ECOG Performance Status			X	
Safety				
Ocular Exam			X[3]	
Hematology (CBC)	X[4]		X[4]	
Clinical chemistry	X[4]		X[4]	
eGFR	X[5]		X[5]	
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)	X[6]		X[6]	
ECHO			X[7]	
Disease Evaluation (every 3 weeks even if a dose is delayed)				
UPEP 24 hr urine collection			X	

Study Assessments regardless of whether participant is dosed	**Day 1 (Week 1)**		**Treatment Period: Q3W from Week 4 until EoT**	**Notes**
Note: All assessments will apply to both the DE and CE Phases unless stated otherwise. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. All assessments from Week 4 can be performed ≤3 days prior to the scheduled date unless otherwise specified.				
Urine immunofixation			X[8]	6. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥2+, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab be performed (first void). 7. ECHOs to be done if clinically indicated. 8. At time of first achieving serum and urine M protein ~ 0g/dl (suspected CR) and until suspected PD after CR or sCR.
SPEP			X	
Serum Immunofixation			X[8]	
Serum FLC assay			X[9,10]	
IgG, IgM, IgA			X	9. Every 3 weeks and at time of sCR assessment. 10. Serum Free Light Chain assay will include kappa/lambda ratio and quantification of involved and uninvolved light chains. 11. IgD/IgE testing is only required for participants with IgD/IgE myeloma. 12. Skeletal Survey (at the time of suspected disease progression or as clinicall indicated): Imaging of bones for lytic lesions by a method aligned with the institutional guidance (X-ray, CT, or MRI). X-Ray is acceptable for lytic disease, but other methods are needed (CT, MRI, PET/CT) for assessment of extramedullary disease. Same modality used at Screening should be used throughout study. 13. As clinically indicated, or to confirm 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 lesion needs to be measured and followed over time (every 12 weeks). 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. Bone marrow aspirate sample should be collected at time of Progressive Disease. Central laboratory assessment. 16. Optional bone marrow aspirate samples to be collected at one of the following timepoints: C1D8 or C1D15 during any 3 week period for biomarker assessments and, if possible as part of the same BM draw whenever MRD is assessed. BM aspirate clot is preferred for BCMA assay. Central laboratory assessment.
IgD orIgE			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 sCRr			Once after CR or sCR[14]	
Bone Marrow (BM) Aspiration/Biopsy				
BM aspirate for BCMA expression and immune cell characterization/profiling			X[15,16]	
MRD testing bone marrow aspirate			X[17]	
BM aspirate/core biopsy for local Disease assessment			X[18]	

Study Assessments regardless of whether participant is dosed	**Day 1 (Week 1)**		**Treatment Period: Q3W from Week 4 until EoT**	**Notes**
Note: All assessments will apply to both the DE and CE Phases unless stated otherwise. Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. All assessments from Week 4 can be performed ≤3 days prior to the scheduled date unless otherwise specified.				
BM core biopsy to assess sCR (local)			X[18]	17. MRD testing to be performed by a central lab at the time of first achieving VGPR or CR. Repeat MRD testing every 6 months after achieving VGPR or CR (provided VGPR/CR is maintained). 18. At the time of suspected CR for confirmation of PC% <5% (always) or at time of suspected PD (only if not evident otherwise). IHC to confirm sCR on BM biopsy when CR is achieved. Absence of clonal cells in BM biopsy by IHC is required to determine sCR. 19. Assessed in CE Phase only. 20. OSDI will be performed at C1D1, C4D1 and EoT only. Additional assessments may be conducted for those participants who are experience a worsening in visual function. 21. Collected pre-dose every 6 weeks from Cycle1 until EoT.
Health Outcomes[19]				
PRO-CTCAE	X		X	
OSDI	X[20]		X[20]	
EORTC-QLQ-C30 and EORTC-QLQ-IL52	X[21]		X[21]	

ADA = Anti-drug Antibody; ALP = alkaline phosphatase; D1 = Day 1, etc.; cfDNA = Circulating free DNA; CK = creatinine kinase; CT = computed tomography; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EM = extramedullary; EOI = End of Infusion; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module; EORTC QLQ-IL52 = European Organisation for Research and Treatment of Cancer Item Library 52; FLC = free light chain; IgE/D = Immunoglobulin E/D; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; OSDI = Ocular Surface Disease Index; PET = positron emission tomography; PFS = progression-free survival; PRO-CTCAE = Patient Reported Outcome version of the Common Term Criteria for Adverse Events; PD = progressive disease; PK = pharmacokinetics; RRMM = relapsed/refractory MM; SOI = start of infusion; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis

Table 4 SoA – Treatment Period on Dosing Days or After Dosing Only: regarding Belantamab mafodotin and GSK'998 (aOX40)

Study Assessments	Cycle 1 Day 1 (Week 1)	Day 4 (±1 day) (Cycle 1)	Cycle 1 Day 8 (Cycles 1-6) Day 15 (Cycles1 & 2 only) (Week 2)	Day 1 of Cycle 2 – last Cycle/participant	Notes
All assessments will apply to both the DE and CE Phases unless stated otherwise. Assessments should be done prior to drug administration, unless otherwise specified. From Dose 2, assessments can be performed ≤3 days prior to the scheduled date unless otherwise specified.					
Safety					1. Vital signs must be assessed for each infusion belantamab mafodotin at: pre-dose (within 30 minutes prior to SOI); post each infusion (EOI); and 1 hour post EOI. Measured after resting for at least 5 minutes. For first infusion, must be monitored at pre-dose (within 30 minutes prior to start of each infusion), and at the end of each infusion, and 1 hour post end of infusions. For subsequent infusions, vital signs must be monitored at pre-dose (within 30 minutes prior to start of each infusion) and at the end of each infusion, and 30 min post the end of infusion. On dosing days with PK sampling time points, vital signs should be assessed prior to PK samples being drawn. Single vital sign assessment measured after resting for at least 5 minutes required on Day 8 (Dose1-6) and Day 15 (Doses 1&2). 2. Perform only in women of child-bearing potential. Pregnancy tests may be either pre-dose serum or urine and should be performed within 72 hours prior to each dose. 3. Only if clinically indicated, at the local lab (troponin I or T) and a central lab if required (troponin I). 4. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥2+, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab (first void). 5. If completed within 72 hours prior to the dose, this assessment does not need to be repeated on Day 1 of each Cycle. Day 8 Cycles1-6 only and Day 15 Cycles 1 and 2 only
Physical Exam (Full exam on treatment days Day 1 of each cycle, and D8 Cycle 1 only)	X		X	X	
Vital Signs (BP, HR, Body Temperature)	X[1]	X[1]	X[1]	X[1]	
Weight	X		X	X	
ECOG Performance Status	X			X	
Pregnancy Test	X[2]			X[2]	
Troponin				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]	

Study Assessments	Cycle 1 Day 1 (Week 1)	Day 4 (±1 day) (Cycle 1)	Cycle 1 Day 8 (Cycles 1-6) Day 15 (Cycles1 & 2 only) (Week 2)	Day 1 of Cycle 2 – last Cycle/participant	Notes
Thyroid Function Tests	X[7]			X[7]	CBC may be done more frequently as clinically indicated. Refer to Appendix 2 for comprehensive list. 6. eGFR as calculated by Modified Diet in Renal Disease (MDRD) formula (208887 MP Appendix 6). 7. Every 6 weeks while on GSK'998 therapy: TSH, free T3 and free T4. 8. PK samples to be taken in all participants for GSK'998: Dose1 D1 - predose anytime prior to GSK'916 SOI, GSK'998 EOI (0 – 5 min after EOI), 2-4 h after GSK'998 SOI, 24 hr (±2h) after SOI; Dose1 D4 – anytime; Dose1 D8 – anytime; Not required on Dose 1 Day 15; Dose2 D1 – predose anytime prior to GSK'916 SOI (or Dose1 D22 if Dose 2 is delayed) and GSK'998 EOI (0 – 5 min after EOI); Doses 4, 6, 9, and 12 - predose (prior to GSK'916 SOI) and GSK'998 EOI (0 – 5 min after EOI); every 6 doses thereafter - predose (prior to GSK'916 SOI). 9. ADA serum samples will be collected predose (within 30 min prior to GSK'916 SOI) at: Doses 1, 2, 4, 6, 9, 12 and every 6 does thereafter. 10. PK samples to be taken in all participants for GSK'916: Dose1 D1 - predose (within 30 minutes prior to GSK'916 SOI), EOI (0 – 5 min after GSK'916 EOI); at Dose 1 2 hours (±15 min) after GSK'916 SOI; Dose 1 24 hours (±2 hours) after GSK'916 SOI; Dose1 D4 - anytime, Dose1 D8 – anytime; Not required on Dose 1 Day 15; Dose 2 D1 – predose (within 30 min prior to GSK'916 or Dose1 D22 if Dose 2 is delayed); Dose 2 D1 EOI (0 – 5 min after GSK'916 EOI); Doses 4, 6, 9, and 12 - predose (within 30 minutes prior to GSK'916 SOI) and EOI (0 – 5 min after GSK'916 EOI); every 6 doses thereafter - predose (within 30 minutes prior to GSK'916 SOI).
PK and ADA					
Plasma PK for GSK'998	X[8]	X[8]	X[8]	X[8]	
Serum immunogenicity (ADA) for GSK'998	X[9]			X[9]	
Plasma PK GSK'916	X[10]	X[10]	X[10]	X[10]	
Serum Immunogenicity (ADA) for GSK'916	X[9]			X[9]	
Biomarkers					
Serum (soluble BCMA) for GSK'916	X[11]		X[11]	X[11]	
Plasma-cfDNA	X[12]				
Cytokines/chemokines	X[13]		X[13]	X[13]	

Study Assessments	Cycle 1 Day 1 (Week 1)	Day 4 (±1 day) (Cycle 1)	Cycle 1 Day 8 (Cycles 1-6) Day 15 (Cycles1 & 2 only) (Week 2)	Day 1 of Cycle 2 – last Cycle/participant	Notes
Whole blood RNA	X[14]		X[14]		11. Collect a sBCMA serum sample every time a GSK'916 PK sample is collected and at additional timepoints, as indicated: at Dose 1 D1 predose (within 30 minutes prior to GSK'916 SOI), EOI (0 – 5 min after GSK'916 EOI), at 2 hours (±15 min) and 24 hours (±2 hours) after GSK'916 SOI, Dose1 D4 – anytime, Dose 1 D8 – anytime, Dose 1 D15 - anytime, Dose 2 D1 – predose GSK'916 (within 30 minutes prior to SOI or Dose1 D22 if Dose 2 is delayed), Dose 2 D1 EOI (0 – 5 min after GSK'916 EOI); Doses 4, 6, 9, and 12 - predose (within 30 minutes prior to GSK'916 SOI) and EOI (0 – 5 min after GSK'916 EOI); every 6 doses thereafter predose (within 30 minutes prior to GSK'916 SOI). Also collect sBCMA at every MRD assessment and at EoT. 12. Plasma cfDNA samples should be collected prior to the first GSK'916 infusion, at Dose 1 D1, every 12 weeks thereafter, at the end of treatment, and at every MRD assessment timepoint, regardless of dosing. 13. To be collected at Dose 1 predose, Dose 1 - 4 hours (±30 min after EOI), Dose 1 - D8 anytime, Dose 1 Day 15 – anytime and Dose 2 and Dose 4 predose. 14. Relevant to GSK'916 and sub-study combination treatments. Collection (Pax gene tube) at Dose 1 Day 1 predose, Dose 1 Day 8 – anytime, Dose 1 Day 15 – anytime, and Dose 2 Day 1 and Dose 4 Day 1- predose. 15. Relevant to GSK'916 and sub-study combination treatments. Collection at Dose 1 Day 1 predose, Dose 1 - 4 hours (±30 min after EOI), Dose 1 Day 8 – anytime Dose 1 Day 15 – anytime, and Dose 2 Day 1 and Dose 4 Day 1 - predose. 16. Collect prior to GSK'916 infusion at Dose 1 D1, Dose 2 D1, Dose 3 D1, at first MRD assessment, and at EoT. 17. Please refer to 208887 MP Section 6.6.3 and Section 6.6 of the protocol for guidance on dose delays, reduction and modification. The next scheduled dose must be administered every 21 days (+3-day window) since last dose. If in the judgment of the investigator,
Cryopreserved PBMCs	X[15]		X[15]		
Peripheral blood for CMMC analysis	X[16]			X[16]	
Treatment with Belantamab mafodotin					
Administration of belantamab mafodotin	X			Day 1 of each dose[17]	

Study Assessments	Cycle 1 Day 1 (Week 1)	Day 4 (±1 day) (Cycle 1)	Cycle 1 Day 8 (Cycles 1-6) Day 15 (Cycles1 & 2 only) (Week 2)	Day 1 of Cycle 2 – last Cycle/participant	Notes
Premedication if needed	-			X (at the start of each dose)[18]	treatment needs to be initiated prior to the next planned scheduled dose, in cases where clinical toxicity has resolved, please discuss with the Medical Director. 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). 18. Premedication should be considered in any participant who experienced an infusion related reaction at first or any subsequent infusion with belantamab mafodotin or partner combination see relevant sub-study Section 6.2. 19. 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 end of treatment. In the event of ocular symptoms (e.g., dry eyes), the use of artificial tears may be increased up to every 2 hours as needed. Corticosteroid eye drops are not required but can be used if clinically indicted per the discretion of the eye-care specialist. 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 hour 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. 20. Administration to occur at least 1 hour after administration of belantamab mafodotin.
Treatment prophylaxis and management of preservative-free artificial tears and cooling masks	X[19]			X[19]	
Treatment with GSK'998 (aOX40)					
Administration of GSK'998 (aOX40)	X			Day 1 of each 21-day cycle[20]	

ADA = Anti-drug Antibody; ALP = alkaline phosphatase; D1 = Day 1, etc.; cfDNA = Circulating free DNA; CK = creatinine kinase; CT = computed tomography; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EM = extramedullary; EOI = End of Infusion; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module; EORTC IL52 = European Organisation for Research and Treatment of Cancer Item Library 52; FLC = free light chain; IgE/D = Immunoglobulin E/D; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; OSDI = Ocular Surface Disease Index; PET = positron emission

tomography; PFS = progression-free survival; PRO-CTCAE = Patient Reported Outcome version of the Common Term Criteria for Adverse Events; PD = progressive disease; PK = pharmacokinetics; QID = 4 times a day; RRMM = relapsed/refractory MM; SOI = start of infusion; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis

Table 5 SoA: End of Treatment (EoT) and Follow-up for Sub-study 1: Belantamab mafodotin and GSK'998 (aOX40)

Study Assessments	End of Treatment Visit[1]		PFS Follow-up[2]	OS Follow-up[3]	Notes
All assessments will apply to both the DE and CE Phases unless stated otherwise.					
Physical Exam	X		X		1. EoT visit safety assessments to occur within 30 days from the last dose, or prior to the new anti-MM treatment (whichever occurs first). 2. PFS follow-up every 21 days (±7 days) for participants who discontinue IP for a reason other than PD. Disease evaluations will continue until confirmed PD, death, start of a new anticancer treatment, withdrawal of consent, or end of the study whichever occurs first. Once participant progresses, move to OS Follow-up. 3. The survival for MM will be documented in medical charts. No visit necessary. Contacts will be made via phone calls, emails or other means of communications every 12 weeks (±14 days) until end of study. Participant does not need to come in for visit unless they are being followed for corneal signs that are present at the end of study treatment. 4. AEs/SAEs will be collected up to 70 days after the last dose of study treatment and immune-related AEs/SAEs will be collected up to 90 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 AE's/SAE's will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up. 5. End of treatment ophthalmic exam to be performed by a qualified eye-care specialist. See 208887 MP Section 8.2.7 for list of exams. 6. Participants with a treatment-related change in vision at the End of Treatment Visit will be followed every 6 weeks (±7 days) until return to baseline, deemed clinically stable by the eye-care specialist, or up to 12 months (whichever comes first). Clinically stable is defined as changes ≤Grade 1. See 208887 MP Section 8.2.7 for list of exams 7. CBC may be done more frequently as clinically indicated. Refer to 208887 MP Appendix 2 for comprehensive list of lab tests. 8. Final pregnancy test (serum or urine) must be performed in women of childbearing potential 90 days (±7 days) after last dose of study treatment. For
Vital Signs (BP, HR, Body Temperature)	X		X		
Adverse Events	X[4]		Related SAEs only[4]	Related SAEs only[4]	
Concomitant Medications	X		X		
Safety					
Ocular Exam	X[5]		X[6]	X[6]	
ECOG Performance Status	X		X		
Hematology (CBC)	X[7]		X[7]		
Clinical chemistry	X[7]		X[7]		
Pregnancy Test	X[8]		X[8]	X[8]	
eGFR	X[9]				
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)	X[10]				
ECHO	X[11]				
Disease Evaluation every 3 weeks					
UPEP 24 hr urine collection	X		X		
Urine immunofixation	X[12]		X[12]		
SPEP	X		X		
Serum Immunofixation	X[12]		X[12]		
Serum FLC assay	X		X		

Study Assessments	End of Treatment Visit[1]		PFS Follow-up[2]	OS Follow-up[3]	Notes
All assessments will apply to both the DE and CE Phases unless stated otherwise.					
IgG, IgM, IgA	X		X		questionable cases Follicle Stimulating Hormone (FSH) and estradiol (as needed in women of non-child bearing potential only). A follow up pregnancy assessment by telephone (for WOCBP only) should be performed 8 months after the last dose of study treatment.
IgD or IgE	X[13]		X[13]		9. eGFR as calculated by Modified Diet in Renal Disease (MDRD) formula (208887 MP Appendix 6).
Calcium corrected for albumin (serum)	X		X		10. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥2+, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab (first void).
Skeletal Survey	X[14,15]		X[14,15]		11. ECHO only done as clinically indicated. 12. At time of first achieving SPEP and UPEP M protein ~ 0g/dl (suspected CR) and until suspected PD after CR or sCR. 13. IgD/IgE testing is only required for patients with IgD or IgE myeloma. 14. 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. 15. At the time of suspected disease progression or as clinically indicated. Same modality used at Screening should be used throughout study.
Imaging for Extramedullary Plasmacytoma Assessment (by whole body CT or whole body MRI or CT/PET	X[15,16]		X[15,16]		16. 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 patients 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 and followed over time (every 12 weeks). 17. Collect one ADA at least 8 weeks post last dose. 18. Collect one PK at least 8 weeks post last dose. 19. MRD testing to be performed by a central lab at the time of first achieving VGPR or CR, repeat MRD testing every 6 after achieving VGPR or CR (provided VGPR/CR is maintained). 20. Only to confirm CR/sCR or suspected PD (if not shown by other methods) at this visit for plasma cell assessment by IHC or aspiration. For stringent CR in
PK and ADA					
Plasma PK for GSK'916	X				
Serum Immunogenicity (ADA) for GSK'916 and GSK'998.	X		X[17] for GSK'998 ONLY		
Plasma PK for GSK'998	X		X[18]		

Study Assessments	End of Treatment Visit[1]		PFS Follow-up[2]	OS Follow-up[3]	Notes
All assessments will apply to both the DE and CE Phases unless stated otherwise.					
Biomarkers					participants achieving a CR, bone marrow core biopsy is required to confirm sCR by IHC for light chain restriction (clonality). Only 1 marrow procedure required for CR and sCR assessment. 21. Optional bone marrow aspirate sample to be collected at one of the following timepoints: C1D8, C1D15 or during any 3 week period for biomarker assessments. If possible, whenever MRD is assessed a further BM aspirate sample may be taken as part of the same BM draw. Central laboratory assessment. 22. Assessed in CE Phase only. 23. Participants with ocular signs at the end of study treatment visit will have follow-up OSDI questionnaires every 3 months (±7 days) until resolution of ocular signs or up to 1 year post treatment discontinuation, whichever is soonest. 24. Must be conducted via telephone within approximately 21 days of the end of study visit. 25. Optional interview to be conducted via telephone approximately 6 months after EoT.
Serum (soluble BCMA)	X				
Plasma-cfDNA	X				
Peripheral blood for CMMC analysis	X				
Bone Marrow (BM) Aspiration/Biospy					
MRD testing bone marrow aspirate	X[19,21]		X[19]		
BM aspirate/core biopsy for Disease assessment	X[20]		X[20]		
BM core biopsy to assess sCR	X[20]		X[20]		
BM aspirate for BCMA expression and immune cell characterization/profiling	X[21]				
Health Outcomes					
PRO-CTCAE	X[22]				
OSDI	X[22,23]		X[22,23]	X[22,23]	
EORTC-QLQ-C30 and EORTC-IL52	X[22]				
Qualitative interview	X[22,24]		X[25]	X[25]	
Schedule survival Status phone call	X[3]			X[3]	

ADA = Anti-drug Antibody; BP = Blood pressure; cfDNA = Circulating free DNA; CR = Complete response; CT = Computed tomography; eGFR = Estimated glomerular filtration rate; ECG = Electrocardiogram; ECHO = Echocardiogram; EOI = End of Infusion; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module; EORTC-IL52 = European Organisation for Research and Treatment of Cancer Item Library 52; FLC = Free light chain; Ig = Immunoglobulin; IHC = Immunohistochemistry; HR = Heart rate; MRD = Minimal residual disease; MRI = Magnetic resonance imaging; OS = Overall survival; OSDI = Ocular Surface Disease Index; PBMC Periferal Blod Mononuclear Cells: PD = Progressive disease; PET = Positron emission tomography; PFS = Progression free survival; PK = Pharmacokinetics; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events;; sCR = Stringent complete response; SOI = start of infusion; SPEP = Serum protein electrophoresis; T3 = Triiodothyronine 3; T4 = Triiodothyronine 4; TSH = Thyroid Stimulating Hormone; UPEP = Urine protein electrophoresis; VGPR = Very good partial response

2. INTRODUCTION

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

Information and details specific to Sub-study 1 are in Section 2.1, Section 2.2 and Section 2.3 below.

2.1. Rationale for combination of Belantamab mafodotin with GSK'998

Immunogenic cell death (ICD) is triggered by apoptotic cell death, where Damage-Associated Molecular Pattern (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. ADC-induced apoptosis by belantamab mafodotin produced DAMPs, including cell surface externalization of calreticulin (CRT) and secretion of high mobility group box 1 protein (HMGB1) 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) demonstrated durable tumor regression, and resistance to re-challenge upon treatment with belantamab mafodotin. 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 GSK'998 (aOX40).

Pre-clinical studies in combination with belantamab mafodotin were not conducted with GSK'998 (aOX40) as this humanized IgG1 anti-OX40 agonistic monoclonal antibody does not cross-react with the mouse OX40 receptor. Therefore, a surrogate monoclonal antibody to murine OX40 (OX86) was used in combination with GSK'916 in non-clinical in vivo experiments. The experimental evidence from the combination of GSK'916 and OX86 in mice is described below.

Belantamab mafodotin at 10 mg/kg combined with an IgG2a isotype control at 5 mg/kg resulted in no tumor-free mice at end of study. OX86 (IgG2a) monotherapy at 1 and 5 mg/kg with an IgG1-MMAF control antibody resulted in 80% and 50% tumor-free mice, respectively. The change in durable tumor regressions in combination therapy compared to monotherapy were dependent upon the OX86 dose. In the combination cohorts, GSK'916 dosed at 10 mg/kg in combination with 1 mg/kg OX86 resulted in 50% tumor-free mice, a decrease from the 80% tumor-free mice observed with the 1 mg/kg OX86 alone, although this decrease was not statistically significant. Belantamab mafodotin in combination with 5 mg/kg OX86 resulted in 90% tumor-free mice, an increase from the 50% tumor-free mice observed with the 5 mg/kg OX86 alone, although this was also not statistically significant. In summary, OX86 in combination with belantamab mafodotin provided with survival benefit in mice over GSK'916 single agent activity; however, it did not reach statistical significance.

A second efficacy study was performed to verify the dose dependent effects of combining OX86 IgG2a (0.2, 1 or 5 mg/kg, biweekly x 3) with belantamab mafodotin (10 mg/kg, bi-weekly x 3), n=10 female tumor-bearing mice/group. In this study, the combination of belantamab mafodotin with OX86 at 0.2, 1 and 5 mg/kg provided additional benefit compared to each single agent, by significantly increasing survival and tumor growth inhibition or tumor growth delay. The combination of OX86 at 0.2, 1 and 5 mg/kg with belantamab mafodotin resulted in 7, 4 and 5 (out of 10 mice) tumor free survivors, respectively, at the end of the study (Day 60). In contrast, in the monotherapy groups, there were no tumor free mice treated with GSK'916 or 0.2 mg/kg OX86, and only one tumor free mouse in each of the 1 and 5 mg/kg anti-OX86 groups.

Changes in pharmacodynamic markers were analysed in EL4-hBCMA tumors following treatment with OX86 IgG2a (1 mg/kg or 5 mg/kg) and GSK'916 (10 mg/kg) dosed intraperitoneally biweekly x 3 in the EL4-hBCMA model. The dosing was started when the tumors were approximately 200 mm^3 and the tissues were harvested 48 hours following the first or second dose. Plasma was analysed for cytokine changes, draining lymph nodes and tumors were analysed for changes in pharmacodynamic markers following the treatments. Belantamab mafodotin alone and the combination treatment resulted in an increase in the proportion of dendritic cells (DC) compared to the isotype controls. There was also a significant increase in regulatory T cells following belantamab mafodotin treatment. Flow cytometric analysis was carried out on the tumors obtained after first dose. Belantamab mafodotin alone and the combination treatment with OX86 IgG2a resulted in an increase in the expression of the immunogenic cell death marker calreticulin in live tumor cells. An increase in a type I interferon gene signature was observed primarily in the group treated with belantamab mafodotin alone and in the combination with OX86 IgG2a (1 mg/kg) after one dose of treatment [GSK Internal Data].

Evidence to date does not indicate that overlapping toxicities would be expected between belantamab mafodotin and GSK'998 (aOX40).

2.2. Background for GSK'998 (GSK3174998)

GSK'998 (aOX40) is a humanized wild-type IgG1 anti-OX40 agonistic mAb. OX40 is a potent costimulatory receptor expressed primarily on activated CD4+ and CD8+ T-cells. OX40 signalling promotes effector T-cell activation and proliferation, while blocking the suppressive function of regulatory T cells (Tregs). A surrogate mAb to murine OX40 (OX86) has been shown to increase antitumor immunity and to improve tumor-free survival in nonclinical models. GSK'998 (aOX40) is currently under investigation in a FTIH study in solid tumors, in combination with pembrolizumab in participants in solid tumors (Study 201212; ENGAGE-1; NCT02528357) and in combination with TLR4 (Study 204686; NCT03447314). Additional information on the effects of GSK'998 (aOX40) can be found in the IB [GlaxoSmithKline Document Number 2014N212091_05, 2018].

2.2.1. Clinical pharmacology data with GSK'998

As of a clinical data cut-off date of 13 Aug 2017, a total of 82 participants with advanced solid tumors have been treated in the ongoing FTIH study 201212. Forty-five received monotherapy GSK'998 (aOX40) at doses between 0.003-10 mg/kg intravenously (IV) once every 3 weeks

In Study 201212, the PK of GSK'998 (aOX40) administered as single-agent monotherapy was evaluated after IV administration at doses of 0.003 mg/kg to 10 mg/kg every 3 weeks in patients with solid tumors.

The GSK'998 (aOX40) concentration-time profiles [GlaxoSmithKline Document Number 2014N212091_05, 2018] initially exhibited a bi-exponential decline typical for IV-administered mAbs. At lower GSK'998 (aOX40) concentrations, faster elimination and shorter half-lives were observed, indicating target-mediated disposition. Consequently, AUC and trough concentrations were increasing more than proportionally with dose. GSK'998 (aOX40) Cmax values normalized by dose for Cycle 1 indicated dose-proportionality for Cmax and Cmax values were typical for mAbs.

At a data cut-off date of 22 Jun 2017, 49% of participants with available post-treatment data tested positive for anti- GSK'998 (aOX40) anti-drug antibodies (ADA) across dose levels 0.003–10 mg/kg GSK'998 (aOX40) in Part 1A (monotherapy) and 0.003–0.1 mg/kg in Part 2A (combination therapy). Positive ADA titers were detectable as early as 3 weeks after the first dose of GSK'998 (aOX40). Of the 30 participants with positive ADA titres, two participants experienced infusion related reactions beginning with administration of the third dose of GSK'998 (aOX40); no other infusion reactions have been reported in the study to date.

Receptor occupancy (RO) was assessed for peripheral blood CD3+ T cells in study 201212. Preliminary data indicated that a high degree (≥80%) of receptor occupancy is achieved initially (≤1 day after dosing) even for the lowest dose of 0.003 mg/kg GSK'998 (aOX40). For doses of 0.1 mg/kg or smaller, receptor occupancy subsequently declines towards the end of the dosing cycle. At doses of GSK'998 (aOX40) 0.3 mg/kg or greater, continuously high receptor occupancy levels are observed over the whole 21-day dosing cycle.

2.2.2. Safety Data for GSK'998 (GSK3174998) monotherapy

No dose-limiting toxicities, or treatment-related Grade 4, or Grade 5 toxicities were reported for doses from 0.003mg/kg to 10mg/kg. One event of Grade 3 asthenia and lymphocytopenia were reported independently in a single patient and attributed to study treatment. A single event led to treatment discontinuation, Grade 5 stroke manifested as aphasia, attributed to disease progression.

The most common AEs reported with GSK'998 (aOX40) monotherapy included fatigue (11, 24%), back pain (9, 20%), diarrhea (9, 20%), nausea (9, 20%), asthenia (8, 18%), vomiting (8, 18%), anemia, (7, 16%), headache (6, 13%), dyspnoea (5, 11%), myalgia (5, 11%), pain in extremity (5, 11%), and pyrexia (5, 11%). The most common treatment

related AEs included diarrhea (5, 11%) and fatigue (5, 11%) [GlaxoSmithKline Document Number 2014N212091_05, 2018].

2.2.3. Clinical Activity of GSK'998 Monotherapy

At the time of the clinical data cut-off (13 Aug 2017), one confirmed PR was reported in a participant with soft tissue sarcoma (STS), who subsequently discontinued treatment for PD at Week 30. A second participant with NSCLC was reported to have SD for 24 weeks, and discontinued treatment with PD after 39 weeks. Both of these participants

received a GSK'998 dose of 0.3 mg/kg (equivalent to 24 mg) administered once every 3 weeks. An additional 5 participants were reported to have SD at Week 12, but subsequently discontinued treatment for PD prior the next imaging assessment.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK'998 may be found in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2014N212091_05, 2018]. .

2.3.1. Risk Assessment

Table 6 outlines the risk assessment and mitigation strategy for GSK'998 (aOX40). Belantamab mafodotin risk assessment and mitigation strategies are in the 208887 MP (see Section 2.3.1).

Table 6 Risks related to GSK'998 (aOX40)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risk related to GSK'998 (aOX40)		
Infusion-related reactions (IRRs) and hypersensitivity	Risk for IRRs and hypersensitivity is inherent to many mAbs [Brennan, 2010]. FTIH study of GSK'998 (aOX40) observed a 6% rate of IRR. Most IRRs observed in the clinic to date have been Grade 1 to 2, manageable with medical treatment.	Participants with history of severe hypersensitivity to another mAb ineligible for this study Refer to 208887 MP Section 11 for further details on management of infusion reactions.
Immune-related AEs	Monoclonal antibodies which affect the acquired immune system and promote the killing of tumor cells (e.g., ipiliumumab, pembrolizumab and nivolumab) have been associated with inflammatory AEs such as diarrhea/colitis, pneumonitis, nephritis, hypophysitis, adrenalitis, thyroiditis, severe skin reactions, uveiitis, myocarditis and hepatotoxicity. These are well established after treatment with checkpoint modulators, and are consistent with the immune-stimulatory mechanism of action of these agents. Currently, data are insufficient to fully appreciate the characteristics of GSK'998 (aOX40) in this regard; however, surveillance for events of this nature is warranted.	Participants with the following medical history are ineligible for this study o Toxicity (Grade ≥3) related to prior immunotherapy leading to study treatment discontinuation o Active autoimmune disease o Severe hypersensitivity to another mAb Established management algorithms for irAEs: Refer to 208887 MP Section 11 for further details on the identification, evaluation, and management of toxicities including cumulative effects, with a potential immune etiology.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Belantamab mafodotin preclinical data indicate a potential for systemic inflammation and may potentiate any immune or inflammatory related AEs in combination with OX40.	
Severe cytokine release syndrome (sCRS)	OX40 is a co-stimulatory receptor that can stimulate proliferation and activation of T-cells. GSK'998 (aOX40) is an OX40 agonist that can co-stimulate T-cell activation in the context of TCR signal and CD28 co-signal and could potentially cause severe cytokine release syndrome. No CRS has been observed in the clinic in the OX40 FTIH study as of the data cutoff.	Management guidelines have been included in 208887 MP Section 11.

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 GSK'998 (aOX40) to belantamab mafodotin is unknown. Data obtained in this study may help identify individuals more likely to benefit or have side-effects from GSK'998 (aOX40) plus belantamab mafodotin.

OX40 agonists have been shown to increase antitumor immunity and improve tumor-free survival in non-clinical models and OX40 agonist monoclonal antibodies (mAbs) are currently being evaluated in Phase I clinical trials.

2.3.3. Overall Benefit: Risk Conclusion

This is the first study testing the combination of GSK'998 (aOX40) plus belantamab mafodotin in participants with relapsed/refractory multiple myeloma that have been treated with standard therapies.

Considering the measures taken to minimize risks to subjects participating in the Phase I clinical trial, the potential risks identified in association with GSK'998 (aOX40) as a monotherapy or combination therapy are justified by the anticipated benefits that may be afforded to subjects with relapsed/refractory solid tumors.

3. OBJECTIVES AND ENDPOINTS

The primary, secondary and, exploratory objectives, along with the corresponding endpoints for both Dose Exploration and for Cohort Expansion are identical to those listed in the 208887 MP Section 3.

4. STUDY DESIGN

Please refer to the 208887 Master Protocol for the overall Study Design for the study.

Information and details specific to Sub-study 1 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 GSK'998 (aOX40) being described in this Sub-study.

A total of 3 dose levels can be potentially evaluated (Table 7). Therefore, in the aOX40 sub-study, there could potentially be a maximum of 3 dosing cohorts running simultaneously in the dose exploration (DE) phase. At Dose Level 1, the starting dose of belantamab mafodotin will be 1.9 mg/kg and the starting dose of GSK'998 (aOX40) will be 8 mg. From the emergent safety data at Dose Levels 1 and 2, the 8 mg dose of GSK'998 (aOX40) can be escalated to 24 mg in combination with 2.5 mg/kg belantamab mafodotin. At Dose Level 3, the maximum dose of belantamab mafodotin will be 2.5 mg/kg and the maximum dose of GSK'998 (aOX40) will be 24 mg. Sponsor may decide not to evaluate all dose levels based on data external to this study. Please see 208887 MP Section 4.1.1 for details of decision making during the DE phase.

Table 7 Dose Exploration Schema Belantamab mafodotin in combination with GSK'998 (aOX40)

Dose level	Belantamab mafodotin dose	GSK'998 (aOX40) 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. Scientific Rationale for Study Design

4.3. Justification for Dose

GSK'998 (aOX40) will initially be administered at a flat dose of 8 mg IV Q3W on Day 1 of each 21-day cycle after the infusion with belantamab mafodotin. Please refer to 208887 MP Section 4.3 for starting dose of belantamab mafodotin.

Previous clinical experience for GSK'998 (aOX40) in Study 201212 [NCT02528357] was based on weight-proportional dosing. The 8 mg dose to be tested in this study is considered equivalent to the 0.1 mg/kg dose in the ongoing FTIH trial [NCT02528357], assuming a median participant weight of 80 kg.

The 8-mg dose of GSK'998 (aOX40) is considered an appropriate dose for combination therapy with belantamab mafodotin based on the following: According to currently available data, the starting dose of 8 mg was well tolerated and did not result in excessive toxicity in advanced solid tumor patients. Doses up to 10 mg/kg (800 mg equivalent) GSK'998 (aOX40) monotherapy tested in the ongoing FTIH trial [NCT02528357] did not result in DLTs and an MTD was not established. To date, there is no apparent dose-toxicity response with GSK'998 monotherapy. The starting dose of 8 mg results in exposure approximately 100-fold lower than the 10 mg/kg dose.

In the ongoing FTIH trial in participants with advanced solid tumors [NCT02528357] the GSK'998 dose level of 0.1 mg/kg (equivalent to 8 mg) represents one dose level below the dose (0.3 mg/kg, equivalent to 24 mg) that demonstrated linear PK, saturation of peripheral OXO40 RO across the dosing interval, and clinical activity. No clinical activity was observed for GSK'998 monotherapy 0.1 mg/kg in participants with solid tumors; however, evidence of some pharmacological target engagement was observed, with ~30% RO by Week 3 post-dose compared ~85% RO for the 0.3 mg/kg dose level. GSK'998 0.1 mg/kg trough plasma concentrations dropped below the level of quantification by Week 3, whereas 0.3 mg/kg trough concentrations remained measurable. Thus, an 8 mg (0.1 mg/kg equivalent) dose of GSK'998 is considered to balance appropriate tolerability with the potential for exposing participants to subtherapeutic doses.

Based on the large capacity, non-specific clearance, and recycling mechanisms for mAbs, no DDI related to non-specific IgG turnover is expected between belantamab mafodotin and GSK'998 (aOX40) for the dose ranges considered.

Because the ligands of belantamab mafodotin and GSK3174998 are expressed on different target cell populations, no DDI related to target mediated disposition is expected between belantamab mafodotin and GSK'998 (aOX40).

The safety profiles of both antibodies currently do not suggest overlapping toxicity.

Therefore, a starting dose of 8 mg (0.1 mg/kg equivalent) IV Q3W is anticipated to be well tolerated without excessive, treatment-related toxicity in this RRMM participant population.

4.4. Participant Completion and End of Study Definition

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:

Sub-study completion: For the DE and CE phases, a sub-study is considered to have completed if all participants have been followed up for 36 months, withdrawn consent, are lost to follow up, or died. A sub-study may close after or during DE for safety or tolerability reasons or if an insufficient number of responders have been observed.

The end of study (EOS) is the last visit of the last participant in the last sub-study. This will occur when the last participant has been followed up for 36 months, died, withdrawn consent or is lost to follow-up. Any patient who has not reached PD at this time will be treated in a separate study roll over study or at the investigators' discretion.

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 1 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 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 1.

5.2. Exclusion Criteria

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

The exclusion criteria #26 and #27 below are in addition to the exclusion criteria already defined in 208887 MP Section 5.2.

26. 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.
27. In addition, exclusion for a recent (within the past 6 months) history of symptomatic pericarditis.

5.3. Lifestyle Considerations

5.4. Screen Failures

6. STUDY INTERVENTION

Please refer to the 208887 MP for the overall Study Intervention for the study.

Information and details specific to Sub-study 1 are in Section 6.1, Section 6.2 and Section 6.6 below.

Study intervention is defined as belantamab mafodotin administered with GSK'998 treatment and administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Specifications for belantamab mafodotin and GSK'998 IP in this study are given (Table 8).

Table 8 Belantamab mafodotin and GSK'998

Intervention Name	**Belantamab mafodotin**	**GSK'998 (OX40)**
Type	Drug	Drug
Dose Formulation	Powder for solution for infusion	Powder for solution for infusion
Unit Dose Strength(s)	100 mg/vial	40 mg/vial
Route of Administration	Delivered as IV solution, infused over 30-60 minutes	Delivered as IV solution over 30 minutes
IMP	GSK2857916 **(belantamab mafodotin)**	GSK3174998
Sourcing	GSK	GSK
Packaging and Labelling	Study Intervention will be provided in vials. Each vial will be labeled as required per country requirement.	Study Intervention will be provided in vials. Each vial will be labeled as required per country requirement.

6.2. Administration of Belantamab mafodotin and GSK'998

- Belantamab mafodotin will be administered before administration of GSK'998 (aOX40).
- GSK'998 (aOX40) will be administered via IV infusion on D1 of every 21 day cycle
- Belantamab mafodotin will be administered to subjects intravenously as mg/kg calculated dose at the study site. The dose to be administered is based on actual body weight calculation and may be reduced for toxicity according to protocol guidelines.
- Administration will be documented in the source documents (208887 MP Section 12.1.8) and reported in the eCRF. The time of start and end of infusion will be documented in eCRF.
- Belantamab mafodotin (Section 6.1) will be administered on Day 1 of each cycle at the assigned dose as an IV infusion. 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 infusion related reactions related to belantamab mafodotin the rules outlined in 208887 MP Section 7.1.6 and Section 11 should be followed.
- After the infusion of belantamab mafodotin has been completed subjects will be required to enter at least 1-hour rest period before starting GSK'998 (aOX40) infusion where appropriate.
- The intended cycle time of GSK'916 BCMA as a monotherapy is 21 days (+3-day window) and cannot occur more frequently than this.

Table 9 Route of Administration and Dose Timing for Belantamab mafodotin and GSK'998 in the DE phase

	Belantamab mafodotin	GSK'998 (aOX40)
Route of administration	IV infusion (see Section 6.1 for details)	IV infusion (see Section 4.1 for details)
Timing	Administer first, on day 1 of 21 day cycles	Start 1 h after belantamab mafodotin EOI on day 1 of 21 day cycles. For guidance about dosing if an infusion related reaction (IRR) occurs please see 208887 MP Section 11.

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

6.3. Preparation/Handling/Storage/Accountability

6.4. Measures to Minimize Bias: Randomization and Blinding

6.5. Concomitant Therapy

6.6. Dose Modification

Dose modification is for Belantamab Mafodotin when in Combination with GSK'998. For information related to overall dose modification refer to the 208887 Master Protocol. Also see 208887 MP Section 11 for guidelines on dose modification and management of events for belantamab mafodotin and other partner combination treatments.

6.6.1. Permitted Dose Reductions for Belantamab Mafodotin when in combination with GSK'998

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

Table 10 Permitted dose reductions for Belantamab mafodotin when in combination with GSK'998 (aOX40)

Belantamab mafodotin Dose Level	1st Dose Reduction
2.5 mg/kg	1.9 mg/kg
1.9 mg/kg	-

- The dose of GSK'998 (aOX40) will not be modified. Please refer to Section 2.3.
- If the participant cannot tolerate the drug after the allowed dose reductions, he or she must be withdrawn from the study for lack of tolerability.
- Only one dose reduction of belantamab mafodotin (to 1.9 mg/kg) is permitted from any 2.5 mg/kg belantamab mafodotin dose level in Table 10.

- No dose reduction of belantamab mafodotin is permitted from the starting dose level of 1.9 mg/kg as lower doses are likely to be inefficacious based on findings from Part 1 of the FTIH trial (GSK Study BMA117159).
- In case of full resolution of symptoms which lead to dose reduction, further treatment with belantamab mafodotin at the initially-assigned dose may be considered by the investigator.
- Resuming treatment with belantamab mafodotin may be possible after the toxicity has resolved to Grade 1 or less.
- If GSK'998 (aOX40) is permanently withdrawn the participant can remain on belantamab mafodotin, if belantamab mafodotin is permanently withdrawn the participant will be withdrawn from all study treatment.

6.6.2. Permitted Dose Modifications of GSK'998 when in combination with Belantamab mafodotin

There are no dose modifications allowed for GSK'998 (aOX40). Fixed (flat) dosing of GSK'998 (aOX40) will be used during the study for all participants receiving GSK'998 (aOX40), regardless of participant weight.

Dosing of GSK'998 (aOX40) may be delayed **if needed, but this will not affect the dosing schedule for belantamab mafodotin.** GSK'998 may only be administered with GSK'916 with the possibility of GSK'998 administration 1 day later than GSK'916 in the case of an IRR on the date of GSK'916 infusion. The maximum treatment delay to GSK'916 treatment is 16 weeks and therefore the maximum treatment delay to GSK'998 is 16 weeks +1 day, unless agreed in writing by the Medical Director. Please refer to 208887 MP Section 11 for details on management of adverse events requiring delay or discontinuation of GSK'998 (aOX40) dosing.

If belantamab mafodotin is delayed for any reason, then GSK'998 (aOX40) will also be delayed.

If participants develop toxicity which would preclude additional dosing with GSK'998 (aOX40), 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 with or without dose reduction after the toxicity has resolved to Grade ≤1 and with agreement between the principal investigator (PI) and GSK Medical Director.

Investigators must contact the GSK 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 208887 MP Section 11. Otherwise, investigators are encouraged to contact the GSK Medical Director as needed to discuss any case that warrants separate discussion outside of the scope of current guidelines.

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

Please refer to the 208887 MP for the information contained in the Level 2 headings below.

7.1. Discontinuation of Study Intervention

7.2. Participant Withdrawal from the Study

7.3. Lost to Follow Up

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

8.1. Efficacy Assessments

8.2. Safety Assessments

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

8.3. Adverse Events and Serious Adverse Events

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

8.3.2. Method of Recording AE and SAE Information

8.3.3. Method of Detecting AEs and SAEs

8.3.4. Follow-up of AEs and SAEs

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

8.3.6. Regulatory Reporting Requirements for SAEs

8.3.7. Management of Pregnancy

Details of all pregnancies in female participants will be collected after the start of study treatment and for 8 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 5 months following last dose of belantamab mafodotin.

8.3.8. Cardiovascular and Death Events

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

8.3.10. Adverse Events of Special Interest

Information on belantamab mafodotin AESI are contained in the 208887 MP Section 8.3.10.

Adverse Events of Special Interest for GSK'998

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. For participants who experience signs or symptoms that may be consistent with an AESI, sites are strongly encouraged to immediately notify the GSK Medical Director of the event via email and/or phone. Documentation of potential AESIs should occur after discussion between the investigator and the sponsor/Medical Director. Even events without clear confirmation of their immunologic etiology may qualify as AESIs. Many of these events may also qualify as SAEs. Details are available in the SRM. 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 11 Immune-related AEs for GSK'998 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 (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Hemolytic Uremic Syndrome (HUS)
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	Infusion-like reactions
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 GSK3174998 (aOX40). In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care should be instituted, as dictated by the subject's clinical status.

8.5. Pharmacokinetics

8.6. Genetics

8.7. Immunogenicity Assessments

8.8. Biomarkers

8.9. Health-Related Quality of Life

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

9.2. Sample Size Determination

9.3. Populations for Analyses

9.4. Statistical Analyses

9.5. Interim Analysis

9.6. Sample Size Sensitivity

10. REFERENCES

Brennan FR, Morton LD, Spindeldreher S, Kiessling A, Allenspach R, Hey A, et al. Safety and immunotoxicity assessment of immunomodulatory monoclonal antibodies. mAbs. 2010; 2:233-255.

GlaxoSmithKline Document Number 2014N212091_05 version 4. GSK3174998 Investigator's Brochure. Report Date 11 December 2018.

GSK Internal Data Report 2018N384579, IND119333 Sequence No. 0114.

11. GUIDELINES FOR DOSE MODIFICATION AND OTHER PARTNER COMBINATION TREATMENTS FOR ALL SUBSTUDIES

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

12. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

Any information and details specific to Sub-study 1 are in Section 12.12 and Section 12.13 below.

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

12.2. Appendix 2: Clinical Laboratory Tests

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

12.4. Appendix 4: ECOG Performance Status

12.5. Appendix 5: NYHA Functional Classification System

12.6. Appendix 6: Modified Diet in Renal Disease

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

12.8. Appendix 8: Genetics

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

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

12.11. Appendix 11: Home Healthcare and Telemedicine Approaches

12.12. Appendix 12: Abbreviations and Trademarks

ADA	Anti-drug antibody
ADC	Antibody drug conjugate
ADCC	Antibody dependent cellular cytotoxicity
AE	Adverse event
AESI	Adverse events of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BCMA	B cell maturation antigen
BCVA	Best corrected visual acuity
CBC	Complete blood count
CBR	Clinical benefit rate
CE	Cohort Expansion phase
cfDNA	Cell-free deoxyribonucleic acid
CI	Confidence interval
CK	Creatine kinase
CL	Clearance
Cmax	Maximum plasma drug concentration
CMMC	Circulating multiple myeloma cells
CPMS	Clinical Pharmacology Modeling and Simulation
CR	Complete response
CRP	C-reactive protein
CRT	Calreticulin
CT	Computer tomography
CTCAE	Common Toxicity Criteria for Adverse Events
Cys-mcMMAF	cys Monomethyl auristatin F
DAMP	Damage-Associated Molecular Pattern
DC	Dendritic cells
DE	Dose Exploration phase
DIC	Disseminated intravascular coagulation
DoR	Duration of response
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eGFR	Estimated Glomerular Filtration (eGFR)
EOI	End of infusion

EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires
FISH	Fluorescence in situ hybridization;
FLC	Free light chain
FSH	Follicle stimulating hormone
FTIH	First time in human
GFR	Glomerular filtration rate
GSK	GlaxoSmithKline
GSK2857914	GlaxoSmithKline anti-BCMA antibody (CA8 J6M0 Potelligent)
GSK2857916	GlaxoSmithKline anti-BCMA antibody drug conjugate (CA8 J6M0 Potelligent MMAF)
HBs-Ag	Hepatitis B surface antigen
HBc	Hepatitis B core
HbcAb	Hepatitis B core antibody
HBV	Hepatitis B
HCV	Hepatitis C
HMGB1	High mobility group box 1
ICD	Immunogenic cell death
ICF	Informed consent form
ICH	International Council on Harmonization
IEC	Institutional ethics committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMWG	International Myeloma Working Group
IP	Investigational Product
IRB	Institutional review board
IRR	Infusion-related reaction
ITT	Intent-to-treat
IV	Intravenous
LBCL	Large B-cell lymphoma
LFT	Liver function test
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MDRD	Modified diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MMAF	Monomethyl auristatin F
MoA	Mechanism of action
MP	Master Protocol
MR	Minimal response
MRD	Minimal residual disease
MRI	Magnetic resonance Imaging
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute – Common Toxicity Criteria for Adverse Events

NT-proBNP	N-terminal B-type natriuretic peptide
NK	Natural killer
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
OSDI	Ocular Surface Disease Index
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PET	Probability of early termination
PFS	Progression-free survival
PI	Proteasome inhibitor
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient reported outcome
Q3W	Every 3 week
QoL	Quality of life
RAP	Reporting and analysis plan
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
SD	Stable disease
SoA	Schedule of Activities
SoC	Standard of care
SOI	Start of infusion
SPEP	Serum protein electrophoresis
SRM	Study research manual
t½	Half-life
TTP	Time to progression
TTR	Time to response
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
VGPR	Very good partial response
WOCBP	Women of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current Amendment 04 is located directly before the Table of Contents (ToC).

Protocol Amendment 3 (08-JUL-2020)

Germany Participation

Sub-study 1 is not applicable for Germany at this time and centers in Germany will not participate in Sub-study 1.

Protocol Amendment 3 Summary of Changes Specific to Sub-study 1

The protocol has been amended to introduce a new sub-study into Section 14 of the protocol. In addition, changes were made in line with comments from regulators, program level changes and safety updates, which include the following:

- Removal of post-baseline ECG assessments
- Modifications to the Dose Escalation Plan (DEP)
- Revised guidance added for belantamab mafodotin overdose
- Revisions to statistical projections and analyses due to addition of Sub-study 4
- Replaced asset number or abbreviations with generic name belantamab mafodotin
- Included reference Lonial, 2020 to support 2.5 mg/kg starting dose and removal of references to 3.4 mg/kg dose
- Guidance on dose modifications modified to include/change management of IRRs, urine dipstick results, thrombocytopenia, neutropenia without fever, pneumonitis
- Modified text on Risk Assessment for thrombocytopenia, potential cardiotoxicity, immunosuppression
- Minor editorial and document formatting revisions

Section # and Name	Description of Change	Brief Rationale
Revised Study Design		
Section 11.6	Change from 4 to 3 dose levels	See Lonial, 2020 reference for monotherapy recommended dose
Section 11.12.1	Added exclusion for recent symptomatic pericarditis	To better define appropriate study population
Safety Changes		
Section 11.8.2	Change dose reduction table	As above, see Lonial, 2020 reference for monotherapy recommended dose.
Section 11.8.4	Added section on aOX40 overdose	To provide available guidance on overdose
Changes in Assessments and SoAs		
Section 11.2	Specified follow-up ADA assessment for aOX40	Clarified immunogenicity assessments

Section # and Name	Description of Change	Brief Rationale
Section 11.2	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	Provide clarifications and more specific guidance, as with Master Protocol
Section 11.2	Added optional follow-up Qualitative phone interview	Clarified timepoint assessment for qualitative phone interview
Protocol Clarification and Alignment		
Section 11.2	Replace ophthalmologist and optometrist with eye-care specialist term and define same	Simplify and define provider terminology
Section 11.2,	Revisions to QoL assessments to include IL52 (symptom assessment) portion of EORTC QLQ-My20 and revise timepoints	Clarify assessments and timingUpdated QoLassessment reflects disease symptom portion of
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-DEC-2019)

Protocol Amendment 2 Summary of Changes Specific to Sub-study 1

Section # and Name	Description of Change	Brief Rationale
Revised Study Design		
Section 11.2, 11.13.1	Updated pregnancy wording: follow up timing and management of pregnancy.	Program level changes
Safety Changes		
Section 11.2	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 11.2 SoA tables	Updated timing of SAE assessments.	Updated timing of SAE assessments in line with program.
Changes in Assessments and SoAs		
Section 11.2,Table 21, Table 22	CRP assessment removed from SoA tables	
Section 11.2	Removed physical exam and vital sign assessment from SoA table of assessments to be done regardless of dosing (and updated footnote numbering)	These evaluations are done with dosing
Section 11.2, Table 23 and 24	Removed AESI assessment.	This is covered under AE's and SAEs. This is still being collected.

Section # and Name	Description of Change	Brief Rationale
Section 11.2, Table 23	Clarification around timings for biomarker samples.	Clarifications
Protocol Clarification and Alignment		
Section 11.6	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 11.7, Table 26	Infusion timing of belantamab mafodotin and GSK'998 (OX40) added	Regulatory Agency request. Infusion timings added
Section 11.4	Rationale for combination of belantamab mafodotin with GSK'998 (aOX40) preclinical wording clarified	Regulatory Agency request for clarified wording
Section 11.13	Clarification around wording for the administration of GSK'998 only to be administered with GSK'916 with the possibility of GSK'998 administration 1 day later than GSK'916 in the case of an IRR on the date of GSK'916 infusion and the maximum treatment delay for GSK'998.	Regulatory Agency request for clarified wording

Protocol Amendment 1 (24-JUN-2019)

The protocol was amended in line with comments from the regulatory agency which included the following:

- More preclinical data included to provide the biological rationale for the use of belantamab mafodotin in combination GSK'988 (aOX40).
- Lower starting doses for GSK'988 (aOX40).
- Note: belantamab mafodotin is referred to as GSK'916 only for the purposes of Laboratory samples.
- Note: GSK'998 (aOX40) is referred to as GSK'998 only for the purposes of Laboratory samples.

Section # and Name	Description of Change	Brief Rationale
Revised Study Design		
Section 11. 3 Rationale for combination of belantamab mafodotin with GSK'998 (aOX40)	Additional pre-clinical data added, and wording clarified	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 11.4 Dose justification for GSK'998 (aOX40)	Starting dose of GSK'998 (aOX40) lowered from 24 mg IV to 8 mg IV Q3W considered equivalent to the 0.1 mg/kg dose in the ongoing FTIH trial [NCT02528357], assuming a median participant weight of 80 kg.	As requested by the FDA to include a lower starting dose
Section 11.4.1 Clinical Activity of GSK'998 (aOX40) monotherapy	Added dose of GSK'998 administered.	As requested by the FDA
Section 11.5 Dose Exploration of Combination Treatment belantamab mafodotin Co-Administered with GSK'998 (aOX40)	Updated the dose exploration schema for belantamab mafodotin in combination with GSK'998 (aOX40).	As requested by the FDA
Section 11.7.2 Permitted Dose Reductions for belantamab mafodotin when in combination with GSK'998 (aOX40)	Modified permitted dose reductions for belantamab mafodotin when in combination with GSK'998 (aOX40) in Table 26 and text.	Clarification in line with FDA request
11.7.3 Permitted Dose Modifications of GSK'998 (aOX40) when in combination with belantamab mafodotin	Revised text on permitted dose modifications.	Clarification
Changes in Assessments and SoAs		
Section 11.1 Table 19	Clarified timings Added screening thyroid function tests	Clarification of wording and timings, and addition of missing tests

Section # and Name	Description of Change	Brief Rationale
Section 11.1 Table 20	Clarified 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 anticancer 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 11.1 Table 21	Clarified timings/wording of PK, ADA, GSK'916, 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 the SoA tables