Protocol Amendment 5

Study ID: 208887 Sub Study 4

Official Title of Sub Study 4: 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 4 - Belantamab Mafodotin and Dostarlimab (GSK4057190) in Combination

NCT ID of Sub Study 4: NCT06655818

Date of Document: 21-Jan-2022

NCT ID of Master Protocol: NCT04126200

TITLE PAGE

Protocol Title: A Phase I/II, Randomized, Open-label Platform Study Utilizing a Master Protocol to Study Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination with Anti-Cancer Treatments in Participants with Relapsed/Refractory Multiple Myeloma (RRMM)–DREAMM5. Sub-study 4 – Belantamab mafodotin and Dostarlimab (GSK4057190) in Combination

Protocol Number: 208887 Sub-study 4 / Amendment 05

Compound Number or Name: Belantamab mafodotin (GSK2857916), dostarlimab (GSK4057190)

Study Phase: I/II

Brief Title: Sub-study of belantamab mafodotin (GSK2857916) as monotherapy and in combination with dostarlimab (GSK4057190) in participants with RRMM

Acronym: DREAMM 5 Sub-study 4

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SPONSOR SIGNATORY:

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 4 – Belantamab mafodotin and Dostarlimab (GSK4057190) in Combination

Protocol Number: 208887 Sub-study 4 / Amendment 05

Compound Number:	Belantamab mafodotin (GSK2857916)

Brandon Kremer, MD, PhD — **Date**

Clinical Development Leader

The signed page is a separate document.

Medical Monitor Name and Contact Information is provided on the protocol title page

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 05	*21-Jan-2022*	*TMF-13844075*
Amendment 04 (Sub-study 4)	*14-DEC-2020*	*2020N453224_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 05 (Sub-study 4): 21-Jan-2022

Overall Rationale for the Amendment:

Changes listed in the table below are for the Sub-study 4 protocol only. Changes for Protocol Amendment 5 that are related to the 208887 Master Protocol and specific sub-studies are tabulated at the beginning of each relevant Sub-study module.

Section # and Name	Description of Change	Brief Rationale
Throughout document	Updated reference to GSK2857916/ belantamab mafodotin Investigator's Brochure	To refer to the most recent version of the IB
	Minor editorial and document formatting revisions	To improve overall clarity and typographical corrections
	Renumbering of Tables and Footnotes	As a result of changes within the document
	For more information of certain sections mentioned the reference to master protocol	To align with program level updates and for clarity
1.3. Schedule of Activities (SoA)	Added multiple gated acquisition (MUGA) scan Clarified text for the Treatment Period for belantamab mafodotin and dostarlimab for DE and CE phase, for performing the same procedure (ECHOs or MUGA scans for LEVF) used at screening throughout the study, and during end of treatment (EoT) and Follow-up	Updated in line with cardiac monitoring requirements across belantamab mafodotin program, based on emerging safety data
	Updated guidance on bone marrow/core biopsy sample collection	To clarify language
	Updated text to reflect the serum protein electrophoresis (SPEP) to be performed at Q3W and the urine protein electrophoresis [UPEP]) to be performed to confirm objective response (PR or better) or if there is concern for disease progression, during the Treatment Period. Clarified the text suggesting the Serum Immunofixation to be perfumed when SPEP or UPEP are negative; and performed to confirm objective response (PR or better).	To clarify language
	Removed the single vital signs assessment on Day 4 (Cycle 1 only), Day 8 (Cycles 1-6) and Day 15 (Cycles 1 and 2).	To reduce patient burden
	Added additional procedures for participants who were HBcAb positive during screening Added Table 7 for additional procedures for participants with a history of Hepatitis B	To align with the latest regulatory guidance

Section # and Name	Description of Change	Brief Rationale
	Revised the ocular exam follow-up time period for participants with a treatment-related change in vision at the end of treatment visit from every 6 weeks to every 3 months	To align with program level updates
	Removed biomarker assessments	To reduce patient burden
	Removed PK and ADA assessments (Also removed previous Table 7 Pharmacokinetic and ADA- Belantamab mafodotin and Dostarlimab; sBCMA blood sampling times)	To reduce patient burden
Section 2.3. Benefit/Risk Assessment	For more information of benefit and risk of belantamab mentioned reference to IB and master protocol	To clarify language
Section 4.1 Overall Design	Removed Previous Table 9 “Dose Exploration Schema- Belantamab mafodotin in combination with Dostarlimab (GSK’190)”	To clarify language
Section 6.2 Administration of Belantamab mafodotin and Dostarlimab	Updated the text for belantamab mafodotin administration	To clarify language
Section 10 References	Some new references were added and some references were updated	Addition and update of references were because of changes in the main text.
Appendix 11 Decentralized and Remote Assessment Approaches	Updated the heading from ‘Home Healthcare and Telemedicine Approaches’.	To align with Master protocol
Appendix 12. Abbreviations and Trademarks	Updated the new abbreviations used in the document.	To reflect new changes
Appendix 13: Protocol Amendment History	Addition of summary of changes from amendment 04 in the appendix as per the template requirement	Template alignment

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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 4 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 4-specific Content

Section	Heading title	Brief description of content
1.3	Schedules of Activities	Comprehensive SoA tables specific for Sub-study 4
2.1	Rationale for Combination of Belantamab mafodotin with Dostarlimab (GSK4057190)	Explanation why treatment with belantamab mafodotin and dostarlimab is expected to be complementary
2.2	Background for Dostarlimab (GSK4057190)	Available data on clinical pharmacology, safety and clinical activity
2.3	Benefit/Risk Assessment	Risk assessments for dostarlimab treatment; benefit assessment summary
4.1	Overall Design	Description of dose escalation design for the combination treatment
4.3	Justification for Dose	Data for the basis of the planned dostarlimab dosing
5.2	Exclusion Criteria	Three additional exclusion criteria were defined for Sub-study 4
6.1	Study Intervention(s) Administered	Specifications for belantamab mafodotin and dostarlimab IP
6.2	Administration of Belantamab mafodotin and Dostarlimab	Specifications for administration of belantamab mafodotin and dostarlimab
6.6	Dose Modification	Detailed directions guidance for dose modifications of combination treatment
8.3.7	Management of Pregnancy	Timeframes for on data collection
8.3.10	Adverse Events of Special Interest	Information on dostarlimab AESI
8.4	Treatment of Overdose	Guidance for potential drug overdose for dostarlimab
8.8	Biomarkers	Summary of the biomarker research being conducted for sub-study 4
12.13	Appendix 13: Protocol Amendment History	Summary of Changes Tables for Sub-study 4 specific amendments

1.1. Synopsis

Protocol Title: A PhaseI/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 4 – Belantamab mafodotin and Dostarlimab (GSK4057190) in Combination

Belantamab mafodotin causes auristatin-induced immunogenic cell death (ICD) on target multiple myeloma (MM) tumor cells and therefore, belantamab mafodotin is a good candidate for combining with immune checkpoint inhibitors.

Many tumors, including MM, use various escape mechanisms to evade immune control and promote tumor growth. One of those mechanisms is the expression of PD-1 ligands (PD-L1). Recent advances in cancer treatment include successful checkpoint blockade by using antibodies binding to PD-1 or PD-L1. The anti-PD-1 and anti-PD-L1 antibodies have a favorable safety profile and have resulted in durable responses in a variety of cancers, including melanoma, kidney cancer, lung cancer, and Hodgkin lymphoma. The agents continue to be evaluated in various solid tumors and hematological malignancies, alone or in combination with other therapies. There is also a growing body of data demonstrating broad expression of PD-1 and its ligands in the microenvironment of MM, indicating an important role of the PD-1 pathway. Although thus far, anti-PD-1 treatment alone has not been effective in MM, there is a recent report of a stringent Complete Response (sCR; ongoing for 27 months at time of publication) achieved in a patient with high-risk smoldering MM following pembrolizumab monotherapy.

Based on the scientific rationale of checkpoint blockade combination with agents such as belantamab mafodotin, which leads to ICD, the GSK205207 combination clinical trial of belantamab mafodotin and pembrolizumab in patients with RRMM initiated enrollment and there have been no safety concerns towards pembrolizumab in 12 treated patients.

This Sub-study will evaluate the safety and anti-myeloma activity of belantamab mafodotin in combination with GSK's PD-1 inhibitor dostarlimab (GSK4057190). Evidence to date does not indicate that overlapping toxicities would be expected between belantamab mafodotin and dostarlimab.

The starting dose of belantamab mafodotin will be 1.9 mg/kg to be evaluated in Dose Level 1, with the highest dose of Belamaf of 2.5 mg/kg planned for dose level 2. The dose of dostarlimab will be identical across the dose level groups and will be 500 mg Q3W for 4 cycles followed by 1000 mg Q6W for subsequent cycles.

1.2. Schema

Please refer to the 208887 MP.

1.3. Schedule of Activities (SoA)

- The timing and number of planned study assessments (including safety, pharmacokinetic, biomarker or other assessments) may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations of study treatments administered) to ensure appropriate monitoring.
- Note: belantamab mafodotin is referred to as GSK'916 and dostarlimab is referred to as GSK'190 only for the purposes of Laboratory assessments and samples.

Table 2 SoA – Screening for Dose Expansion and Cohort Expansion Phases: Belantamab Mafodotin + Dostarlimab

Screening Study Assessments[1]	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 Assessments do not need to be repeated at C1D1 unless otherwise specified. All other assessments can be done ≤3 days prior to treatment unless otherwise specified. **If C1D1 Hem/Chem results are below eligibility threshold required at Screening, GSK Medical Director to be contacted for review prior to dosing.**		
Informed Consent	X	1. Screening/baseline ocular examination will be performed by a qualified eye-care specialist (ophthalmologist/optometrist, see 208887 MP Appendix 10) 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. 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 C1D1and the second test within 72 hours prior to administration of C1D1. 3. Refer to the 208887 MP Appendix 2 for a comprehensive list of lab tests that must be collected for all participants. 4. eGFR as calculated by MDRD formula (208887 MP Appendix 6) 5. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥1+ at screening, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab (first void). 6. Complete at screening or within 12 weeks prior to C1D1. 7. If a participant tested hepatitis B core antibody positive, refer to Table 7 for additional procedures throughout the study. Hep C RNA testing is optional, but it may be performed to determine participant eligibility if Hep C antibody positive. If negative, participant is eligible (see exclusion criteria 12) for details). 8. Single ECG at Screening. 9. ECHO or MUGA scan for LVEF may be performed at baseline or within 30 days of C1D1. 10. SPEP and UPEP will include M protein levels. 11. Serum Free Light Chain assay will include kappa/lambda ratio and quantification of involved and uninvolved light chains. 12. 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.
Demography	X	
Medical History (includes substance abuse)	X	
Full Physical Exam	X	
Throughout the trial, participants are educated about in life style considerations (208887 MP Section 5.3) for the study and the need for maintaining adequate urinary output (208887 MP Section 2.3.1).	X	
Inclusion/Exclusion criteria	X	
Past and current medical conditions	X	
Concomitant Medication review	X	
Screening Safety Assessments		
Ocular Exam	X[1]	
ECOG Performance Status	X	
Vital Signs (BP, HR, Body Temperature)	X	
Weight and Height	X	
Serum Pregnancy Test (WOCBP only)	X[2]	
Haematology	X[3]	
Clinical chemistry	X[3]	
Estimated Glomerular Filtration Rate (eGFR)	X[4]	
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)	X[5]	
HBsAg[7], HBcAb[7], HCV tests[7]	X[6,7]	
12 Lead ECG	X[8]	
ECHO or MUGA scan LVEF	X[9]	

Screening Study Assessments[1]	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 Assessments do not need to be repeated at C1D1 unless otherwise specified. All other assessments can be done ≤3 days prior to treatment unless otherwise specified. **If C1D1 Hem/Chem results are below eligibility threshold required at Screening, GSK Medical Director to be contacted for review prior to dosing.**		
Screening Disease Evaluation		13. In participants with known or suspected extramedullary plasmacytoma, a whole-body scan (i.e., CT, MRI, or PET-CT) may be performed within 30 days prior to C1D1. The same method should be used throughout the study (i.e., if a PET-CT scan was used as baseline scan then participant 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. 14. Only required for participants with IgD/IgE myeloma. 15. Please refer to Table 6 for scheduled BM collection procedures to include aspirate and biopsy. 16. If FISH testing cannot be performed at a local lab the samples can be sent to the central lab.
Beta-2 microglobulin	X	
UPEP 24 hr urine collection	X[10]	
Urine immunofixation	X	
SPEP	X[10]	
Serum Immunofixation	X	
Serum FLC assay	X[11]	
IgG, IgM, IgA	X	
IgD or IgE, if applicable	X[14]	
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]	
Bone Marrow (BM) Aspiration/Biopsy		
BM aspirate and/or core biopsy for local disease assessment	X[15]	
BM aspirate for FISH testing	X[16]	

ALP = alkaline phosphatase; BCVA = best corrected visual acuity; BNP = B-type natriuretic peptide; D1 = Day 1, etc.; CK = creatinine kinase; CRP = C-reactive protein; CT = computed tomography; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EM = extramedullary; EOI = End of Infusion; FLC = free light chain; IgD/IgE = Immunoglobulin D or E; LVEF = left ventricular ejection; MDRD = Modified Diet in Renal Disease; MP = Master Protocol; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition; PET = positron emission tomography; PFS = progression-free survival; PD = progressive disease; PK = pharmacokinetics; QID = 4 times a day; RRMM = relapsed/refractory MM; sBCMA = soluble B cell maturation antigen; SOI = start of infusion; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

Table 3 SoA – Treatment Period for DE and CE Phases Regardless of Dosing: Belantamab Mafodotin + Dostarlimab

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. • From Dose 2, assessments can be delayed or brought forward by a maximum of 5 days to be aligned with the next dosing date. If administration of study treatment is delayed ≤7 days, assessments indicated to occur at the dosing visit can be scheduled to occur when dosing occurs. If administration of study treatment is delayed >7 days, assessments indicated at the dosing visit are to be performed at the next expected weekly visit. • All assessments from Dose 2 can be performed ≤3 days prior to the scheduled date unless otherwise specified.			
Adverse Events[1]	Ongoing		1. AEs/SAEs will be collected up to 70 days after the last dose of study treatment and immune-related AEs/SAEs will be collected up to 70 days post last dose. All SAEs related to study participation (e.g., protocol mandated procedures, tests, or change in existing therapy) are to be collected from consent through OS follow-up. All AE's/SAE's will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to 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 C1D1prior to infusion. 3. On study ocular exams to be performed by a qualified eye-care specialist (see 208887 MP Appendix 10) 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 Section 208887 MP Section 8.2.7 for list of ophthalmic exam procedures. If there are no significant KVA Grade 2 or above) treatment related ocular examination findings ocular 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 h prior to the dose, this assessment does not need to be repeated on Day 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 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 ≥2+, or with positive protein if
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]	
Haematology (CBC)	X[4]	X[4]	
Clinical chemistry	X[4]	X[4]	
eGFR[5]	X	X	
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)	X[6]	X[6]	
ECHO or MUGA scan for LVEF		X[7]	
Disease Evaluation (every 3 weeks even if a dose is delayed)			
UPEP 24 hr urine collection		X[8]	

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. • From Dose 2, assessments can be delayed or brought forward by a maximum of 5 days to be aligned with the next dosing date. If administration of study treatment is delayed ≤7 days, assessments indicated to occur at the dosing visit can be scheduled to occur when dosing occurs. If administration of study treatment is delayed >7 days, assessments indicated at the dosing visit are to be performed at the next expected weekly visit. • All assessments from Dose 2 can be performed ≤3 days prior to the scheduled date unless otherwise specified.			
Urine immunofixation		X[9]	urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab (first void).
SPEP		X[8]	7. ECHOs or MUGA scans for LEVFto be done if clinically indicated. The same procedure used at screening should be used throughout the study.
Serum Immunofixation		X[9]	8. SPEP must be performed Q3W. UPEP must be performed to confirm objective response (PR or better) or if there is concern for disease progression.
Serum FLC assay		X[10]	9. To be performed when SPEP and UPEP are negative. Also to be performed to confirm objective response (PR or better).
IgG, IgM, IgA		X	10. Serum Free Light Chain assay will include kappa/lambda ratio and quantification of involved and uninvolved light chains; to be done every 3 weeks.
IgD or IgE		X[11]	11. Only required for participants with IgD/IgE myeloma
Calcium corrected for albumin (serum)		X	12. Skeletal Survey (at the time of suspected disease progression or as clinically indicated): Imaging of bones for lytic lesions by a method aligned with the institutional guidance (X-Ray, CT, or MRI). X-Ray is acceptable for lytic disease, but other methods are needed (CT, MRI, PET/CT) for assessment of extramedullary disease. Same modality used at Screening should be used throughout study.
Skeletal Survey		X[12]	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
Extramedullary Plasmacytoma Assessment (by whole body CT or whole body MRI or CT/PET)		X[13]	14. **Note:** Germany: no PET/CT to confirm CR or sCR will be performed until approval by the German Federal Office for Radiation Protection.
MRI, CT or PET/CT upon achieving CR or sCR		Once after CR or sCR[14]	15. Please refer to Table 6 for scheduled BM collection procedures to include aspirate and biopsy.
Bone Marrow (BM) Aspiration/Biopsy			16. Assessed in CE Phase only.
BM aspirate and/or core biopsy for local Disease assessment		X[15]	17. OSDI will be performed at C1D1, at or directly after C4D1 and at EOT only. Additional assessments may be conducted for those participants who are experience a worsening in visual function.
BM core biopsy to assess sCR (local)		X[15]	18. Collected pre-dose Q6W from Cycle 1 until EOT.
Health Outcomes[17]			
PRO-CTCAE	X	X	
OSDI	X[17]	X[17]	
EORTC QLQ-C30 and EORTC IL52	X[18]	X[18]	

AE = Adverse Event; ALP = alkaline phosphatase; BCVA = best corrected visual acuity; BNP = B-type natriuretic peptide; D1 = Day 1, etc.; CK = creatinine kinase; CRP = C-reactive protein; 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; MDRD = Modified Diet in Renal Disease; MP = Master Protocol; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition; NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire 25; 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; SAE = Serious Adverse Event; 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 + Dostarlimab

Study Assessments	Cycle 1 Day 1 (Week 1)	Cycle 1 Day 8 Day 15	Cycle 2 to EoT	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 dose unless otherwise specified. From Dose 2, assessments can be delayed or brought forward by a maximum of 5 days to be aligned with the next dosing date. If administration of study treatment is delayed ≤7 days, assessments indicated to occur at the dosing visit can be scheduled to occur when dosing occurs. If administration of study treatment is delayed >7 days, assessments indicated at the dosing visit are to be performed at the next expected weekly visit. **If C1D1 Hem/Chem results are below eligibility threshold required at Screening, GSK Medical Director to be contacted for review prior to dosing.**				
Safety				1. Measured after resting for at least 5 minutes. For the first infusion, vital signs must be monitored for each study drug infusion at: pre-dose (within 30 min prior to SOI); at the end of infusion (EOI) (+0-10 min); and 1 hr post EOI (+0-10 min). For subsequent infusions, vital signs must be monitored for each study drug infusion: at pre-dose (within 30 min prior to SOI); at EOI (+0-10 min), and 30 min post EOI (+0-10 min) and as clinically indicated. 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. 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). 4. If completed within 72 hours prior to the dose, this assessment does not need to be repeated on Day 1 of each Cycle. CBC may be done more frequently as clinically indicated. Refer to 208887 MP Appendix 2 for comprehensive list. 5. eGFR as calculated by MDRD formula (208887 MP Appendix 6). 6. Please refer to 208887 MP Section 6.6.3 of the protocol for guidance on dose delays, reduction and modification. <u>The next scheduled dose must be administered every 21 days (Q3W) or 42 days (Q6W) (+3-day window) since prior/last dose and cannot be given sooner/more frequently than</u>
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]	
Weight	X		X	
ECOG Performance Status	X		X	
Pregnancy Test	X[2]		X[2]	
Troponin			X	
Urinalysis (dipstick) OR Spot Urine (albumin / creatinine ratio)	X[3]		X[3]	
Hematology (CBC)	X[4]	X[4]	X[4]	
Clinical Chemistry	X[4]	X[4]	X[4]	
eGFR	X[5]	X[5]	X[5]	
Treatment with Belantamab Mafodotin				
Administration of belantamab mafodotin	X		Day 1 of each dose[6]	
Premedication if needed	X		X (at the start of each dose)[7]	
Treatment prophylaxis and management of	X[8]		X[8]	

preservative-free artificial tears and cooling masks				this. If in the judgment of the Investigator, treatment needs to be initiated prior to the next planned scheduled dose *following a dosing delay and where clinical toxicity has resolved*, please discuss with the Medical Director.Please see Section 6.2. All assessments should remain on schedule with the exception of those associated with dosing. Belantamab
Treatment with Dostarlimab				
Administration of dostarlimab[9]	X[10,11]		Day 1 of each dose[10,11]	

	mafodotin will be administered as an IV infusion (see Section 6.1 for details). 7. Premedication should be considered in any participant who experienced an infusion related reaction at first or any subsequent infusion with belantamab mafodotin or dostarlimab combination see relevant sub-study Section 6.2. 8. 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 indicated per the discretion of thea qualified eye-care specialist (see 208887 MP Appendix 10). Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops (if administered). b. At the start of each infusion, participants may apply cooling eye masks to their eyes for approximately 1 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. 9. Administration to occur minimum one hour after completion of infusion of belantamab mafodotin. Dostarlimab to be administered as IV infusion at prescribed flat dose over 30 minutes. A window of +3 days is acceptable for both for Q3W and Q6W dosing schedule. If in the judgment of the Investigator, belantamab mafodotin and dostarlimab combination treatment needs to be initiated prior to the next planned scheduled dose following a dosing delay and where clinical toxicity has resolved, please discuss with the Medical Director. 10. Note: If belantamab mafodotin is held or discontinued for any toxicity, dostarlimab is also to be held or discontinued. 11. Dosing Schedule (Section 6.2): 500 mg every 3 weeks for the first 4 doses, followed by then 1000 mg every 6 weeks

ALP = alkaline phosphatase; BCVA = best corrected visual acuity; BNP = B-type natriuretic peptide; D1 = Day 1, etc.; CK = creatinine kinase; CRP = C-reactive protein; 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; MDRD = Modified Diet in Renal Disease; MP = Master Protocol; MRI = magnetic resonance imaging; NEI-VFQ-25 = National Eye Institute Visual Functioning Questionnaire 25; 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: EoT and Follow-up for Belantamab Mafodotin + Dostarlimab Sub-Study

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 up to 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 for at least 70 days after the last dose of study treatment and immune-related AEs/SAEs will be collected up to 70 days post last dose. All SAEs related to study participation (e.g., protocol mandated procedures, tests, or change in existing therapy) are to be collected from consent through OS follow-up. All AE's/SAE's will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up. Concomitant medications administered after the EoT visit should be recorded when given for SAEs/AESIs as defined in Section 8.3 and 208887 MP Section 8.3. 5. End of treatment ophthalmic exam to be performed by an eye-care specialist. See 208887 MP Section 8.2.7 for list of exams. 6. Participants with a treatment-related corneal exam findings, ocular symptoms and/or change in vision at the End of Treatment Visit will be followed every 3 months (±7 days), or more frequently if clinically indicated, until return to baseline, deemed clinically stable by the qualified eye-care specialist (see Appendix 10 Section 12.10), or up to 12 months (whichever comes first). Clinically stable is defined as changes ≤Grade 1. See 208887 MP Section 8.2.7 for list of exams. 7. CBC may be done more frequently as clinically indicated. Refer to 208887 MP Appendix 2 for comprehensive list of lab tests 8. Pregnancy test (serum or urine) must be performed in women of childbearing potential at EoT and 90 days (±7 days) after last dose of study treatment. A follow up pregnancy assessment by telephone (for WOCBP only) should be performed 4 months after the last dose of study treatment 9. eGFR as calculated by MDRD formula (208887 MP Appendix 6).
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 or MUGA scan for LVEF	X[11]			
Disease Evaluation every 3 weeks[2]				
UPEP 24 hr urine collection	X	X[12]		
Urine immunofixation	X	X[12]		
SPEP	X	X[12]		
Serum Immunofixation	X	X[12]		
Serum FLC assay	X	X[12]		
IgG, IgM, IgA	X	X		
IgD or IgE	X[13]	X[13]		

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.				
Calcium corrected for albumin (serum)	X	X		10. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥2+, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab (first void). 11. ECHO or MUGA scan for LVEF only done as clinically indicated. The same procedure used at screening should be used throughout the study. 12. To be done every 3 weeks until suspected PD 13. IgD/IgE testing is only required for participants with IgD or IgE myeloma. 14. At the time of suspected disease progression or as clinically indicated. Same modality used at Screening should be used throughout study. 15. 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. 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 participants withdrew from study treatment. To be performed by the same method throughout the study as was done at baseline (i.e. if CT/PET scan was used as baseline, participant needs to be followed by CT/PET scans). Selected target lesion needs to be measured and followed over time (every 12 weeks). 17. Please refer to Table 6 for scheduled BM collection procedures to include aspirate and biopsy. 18. Assessed in CE Phase only 19. Participants with ocular signs at the end of study treatment visit will have follow-up questionnaires every 3 months (±7 days) until resolution of ocular signs or up to 1 year post treatment discontinuation, whichever is soonest. 20. Must be conducted via telephone within approximately 21 days of the end of study visit. 21. Optional interview to be conducted via telephone approximately 6 months after EOT.
Skeletal Survey[14,15]	X	X		
Imaging for Extramedullary Plasmacytoma Assessment (by whole body CT or whole body MRI or CT/PET	X[14,16]	X[14,16]		
Bone Marrow (BM) Aspiration/Biopsy				
BM aspirate and/or core biopsy for Disease assessment	X[17]	X[17]		
BM core biopsy to assess sCR	X[17]	X[17]		
Health Outcomes[18]				
PRO-CTCAE	X			
OSDI	X[19]	X[19]	X[19]	
EORTC-QLQ-C30 and EORTC-IL52	X			
Qualitative interview	X[20]	X[21]	X[21]	
Schedule Survival Status phone call	X[3]		X[3]	

AE = Adverse Event; BP = Blood pressure; BCVA = Best corrected visual acuity; BNP = B-type natriuretic peptide; CR = Complete response; CRP = C-reactive protein; 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; MDRD = Modified Diet in Renal Disease; MP = Master Protocol; MRD = Minimal residual disease; MRI = Magnetic resonance imaging; MUGA = multiple gated acquisition; NEI-VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; OS = Overall survival; OSDI = Ocular Surface Disease Index; PBMC Peripheral Blood 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; QID = 4 times a day; SAE =

Serious Adverse Event; 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

Table 6 Bone Marrow Aspiration/Biopsy Collection

Timepoint	BM aspirate for FISH testing[a,b,c,d]	BM (core biopsy and/or aspirate) for disease assessment[a,c,d]
Screening	X	X
Suspected CR/sCR	X	X
PD (only if PD not evident otherwise)		X

BCMA = B-cell maturation antigen; BM = bone marrow; EoT = end of treatment; FISH = fluorescence in situ hybridization; MRD = minimal residual disease; PFS = progression-free survival; Q3W = every 3 weeks; sCR = stringent complete response.

Note: Bone marrow assessment will be done approximately every 3 - 4 treatment cycles (~ every 9 - 12 weeks), in alignment with IMWG criteria/clinical practice guidelines for MM (208887 MP Section 8.1), and as needed based upon disease status/treatment response (ie, VGPR, CR) as outlined below.

a. These assessments will be performed at a local laboratory. For FISH testing, if testing cannot be performed at a local lab the samples can be sent to the central lab.

b. Screening- 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.

c. At Screening, immunohistochemistry (IHC) of bone marrow core biopsy is preferred for quantitative assessment of malignant plasma cells (PC). 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.

For participants who discontinue IP for reasons other than PD and have current disease response of PR or better, Notes f and g below are applicable:

d. At EoT or /PFS, only to confirm CR/sCR or suspected PD at this visit for plasma cell assessment by IHC or aspiration. For stringent CR in participants achieving a CR, bone marrow core biopsy is required to confirm sCR by IHC for absence of clonal cells. Only 1 marrow procedure required for CR and sCR assessment.

Table 7 SoA – Additional Procedures for Participants HBcAb Positive

The procedures listed in this table apply ONLY to participants in screening or who have been enrolled and who have positive HBcAb; all procedures must be done in addition to the required procedures for all participants detailed in Table 2 to Table 6				
HBV Study Assessments	During Screening / Prior to starting treatment	During Treatment	EOT	Notes
HBV-DNA testing	X	X	X	HBV-DNA testing prior to the start of belantamab mafodotin and subsequently every 3 months, or if liver function test elevations requiring increased monitoring or stopping criteria occur, or for any clinical suspicion of Hepatitis reactivation.

2. INTRODUCTION

2.1. Rationale for Combination of Belantamab mafodotin with Dostarlimab

Belantamab mafodotin causes auristatin-induced immunogenic cell death (ICD) on target MM tumor cells [Montes De Oca, 2019; Montes De Oca, 2021] and therefore, belantamab mafodotin is a good candidate for combining with immune checkpoint inhibitors. ICD is characterized by induction of the endoplasmic reticulum (ER) stress response and exposure of danger-associated molecular patterns (DAMPs), many of which are Toll-like receptor ligands. Exposure of dendritic cells to tumor cells undergoing ICD evokes an inflammatory phenotype (innate response) including an increase in co-stimulatory markers CD86 and MHC Class II antigens, and activation of NFκB, an intermediate of inflammatory signaling pathways. Mature dendritic cells (DCs) play key roles in priming robust immune responses in tumor-bearing hosts and ICD can induce an effective anti-tumor immune response through activation of DCs and consequent activation of specific T cell responses, by priming tumor antigen-specific T cells [Kroemer, 2013; Muller, 2014]. The T cell anti-tumor response can be further augmented by a PD-1 inhibitor, such as dostarlimab. Programmed cell death-1 (PD-1) expressed on T cells is a member of the CD28 superfamily that delivers negative signals upon interaction with its two ligands, programmed cell death ligand 1 (PD-L1) or programmed cell death ligand 2 (PD-L2). Physiologically, PD-1 and its ligands are broadly expressed and exert a wider range of immunoregulatory roles in T cell activation and tolerance. Recent studies show that PD-1/PD-L1 interaction regulates the induction and maintenance of peripheral tolerance and protects tissues from autoimmune attack. PD-1 and its ligands are also involved in attenuating tumor immunity and facilitating tumor progression.

Many tumors, including MM, use various escape mechanisms to evade immune control and promote tumor growth [McLaughlin, 2016]. One of those mechanisms is the expression of PD-1 ligands (PD-L1). Recent advances in cancer treatment include successful checkpoint blockade by using antibodies binding to PD-1 or PD-L1 (e.g., pembrolizumab, nivolumab). The anti-PD-1 and anti-PD-L1 antibodies have a favorable safety profile and have resulted in durable responses in a variety of cancers, including melanoma, kidney cancer, lung cancer, and Hodgkin lymphoma. The agents continue to be evaluated in various solid tumors and hematological malignancies, alone or in combination with other therapies [Dolan, 2014]. There is also a growing body of data demonstrating broad expression of PD-1 and its ligands in the microenvironment of MM, indicating an important role of the PD-1 pathway [Liu, 2011; Kuranda, 2010; Atanackovic, 2014; Benson, 2010]. Although thus far, anti-PD-1 treatment alone has not been effective in MM [Lesokhin, 2014; Suen, 2015], there is a recent report of a sCR (ongoing for 27 months at time of publication) achieved in a patient with high-risk smoldering MM following pembrolizumab monotherapy [Manasanch, 2019]. The KEYNOTE-023 study examined whether an anti-PD-1 treatment (Keytruda [pembrolizumab]) in combination with immunomodulatory agents, may create synergism, in this case with lenalidomide and dexamethasone. Lenalidomide doses of 10 mg and 25 mg were examined, with the 25 mg dose further explored. Of the participants evaluable for efficacy (N=40), 88% of participants had a decrease in M protein. The

ORR for this population was 50%, including a 38% ORR for participants who were lenalidomide refractory [Mateos, 2016]. Based on these findings, the KEYNOTE-183 and KEYNOTE-185 Phase 3 studies were initiated, exploring combinations of pembrolizumab with IMiDs.

Following review of both studies by data monitoring committees, KEYNOTE-183 and KEYNOTE-185 were placed on full clinical hold. In both studies, it was determined that the benefit-risk was unfavorable for the combination of pembrolizumab with IMiDs. The US FDA also placed Cohort 1 (combination with lenalidomide and dexamethasone) of KEYNOTE-023 on full clinical hold as a result of the data from KEYNOTE-183 and KEYNOTE-185.

Keynote-183 was a randomized trial which evaluated pomalidomide and low-dose dexamethasone with or without pembrolizumab in participants with relapsed and refractory multiple myeloma. The ORR was 34% in the pembrolizumab containing arm versus 40% in the control arm without pembrolizumab; however, there was no difference in time-to-progression between arms. There were 29 deaths in the pembrolizumab arm compared to 21 in the control arm, reflecting an overall survival hazard ratio of 1.61 (95% CI: 0.91, 2.85) [Krauss, 2018]. An analysis conducted with the removal of participants with high-risk disease characteristics (high-risk cytogenetics, plasmacytoma and quadruple refractory status) resulted in a similar number of deaths (n=13) in both arms [Mateos, 2018], suggesting perhaps an imbalance of patients with high risk disease between treatment arms.

Keynote-185 was a randomized trial which evaluated lenalidomide and dexamethasone with or without pembrolizumab in participants with newly diagnosed multiple myeloma. The ORR was 64% in the pembrolizumab containing arm versus 62% in the control arm without pembrolizumab; however, there was no difference in time-to-progression between arms. There were 19 deaths in the pembrolizumab arm compared to 9 in the control arm, reflecting an overall survival hazard ratio of 2.06 (95% CI: 0.93, 4.55) [Krauss, 2018].

There were no unifying causes of death or unique adverse event patterns in both studies that could explain the observed effects on overall survival [Gormley, 2018].

Enrollment was also halted (due to pembrolizumab findings cited above) on Checkmate 602, a randomized Phase 3 trial comparing the PD-1 inhibitor nivolumab plus pomalidomide–dexamethasone with pomalidomide–dexamethasone alone in patients with RRMM. The trial was re-opened for enrollment in May 2018 while a concurrent early futility analysis was performed at FDA request based on 170 of participants enrolled. Enrollment was subsequently stopped in September 2018 based on the results of this analysis, with a median f/u of 9.3 months and HR for PFS of 1.08 (95% CI: 0.68-1.70) and OS of 1.19 (95% CI: 0.64-2.2) were observed with nivolumab-Pd (NPd) when compared to Pd alone [Gormley, 2018; Lesokhin, 2019].

Researchers could again not find any unifying cause or distinct adverse events associated with the excess deaths, nor whether they are attributable solely to the PD-1 drug or to a drug interaction [Gormley, 2018].

The safety profiles for monotherapy of pembrolizumab and nivolumab in RRMM are consistent with its safety profile in other cancers. Nevertheless, the above mentioned findings along with results of other studies in this patient population suggest that the future of PD-1 inhibition, in combination with other agents as treatment for RRMM, should be carefully designed. Importantly, combinations other than those with immunomodulatory agents should be considered [Ribraq, 2019].

More recently, the Nivo-Dara study investigated efficacy and safety of nivolumab combined with daratumumab (ND), with or without low-dose cyclophosphamide (50 mg once daily) (NDc) in RRMM. Inclusion criteria included ≥2 prior therapies, lenalidomide-refractory disease, and prior treatment with a PI-containing regimen. With a median follow-up of 8.6 months, ORR (50%) and deaths due to progressive disease (25%) were similar in the treatment arms. As expected, the infection rate and the need for supportive care were higher in patients treated with NDc, the ND regimen was selected for further evaluation in the planned part B of the study [Verkleij, 2019].

In addition, currently ongoing studies in relapsed MM reflect use of combination strategies. Included among these active/recruiting trials are:

- A Study of Atezolizumab (Anti-Programmed Death-Ligand 1 [PD-L1] Antibody) Alone or in Combination with an Immunomodulatory Drug and/or Daratumumab in Participants with Multiple Myeloma (MM); Phase 1b, NCT02431208; Recruitment status: Active, not recruiting; First Posted April 30, 2015; Study start date July 22, 2015; Last Update Posted February 6, 2020
- NY-ESO-1^{c259}T Alone and in Combination with Pembrolizumab for Multiple Myeloma; Phase 2, NCT03168438; Recruitment Status :Recruiting; First Posted May 30, 2017; Study start date August 18, 2017; Last Update Posted : October 29, 2019
- Isatuximab in Combination with Cemiplimab in Relapsed/Refractory Multiple Myeloma (RRMM) Patients; Phase 1,2, NCT03194867; Recruitment Status: Active, not recruiting; First Posted: June 21, 2017; Study start date February 21, 2018; Last Update Posted: January 13, 2020 [ClinicalTrials, 2020]

Based on the scientific rationale of checkpoint blockade combination with agents such as belantamab mafodotin, which leads to ICD, the GSK205207 combination clinical trial of belantamab mafodotin and pembrolizumab in patients with RRMM initiated enrollment and there have been no safety concerns towards pembrolizumab in 12 treated patients.

This Sub-study will evaluate the safety and anti-myeloma activity of belantamab mafodotin in combination with GSK's PD-1 inhibitor dostarlimab. Evidence to date does not indicate that overlapping toxicities would be expected between belantamab mafodotin and dostarlimab.

Safety will be closely monitored with dose modification guidelines in Section 6.6, and GSK will also use an internal Safety Review Team (iSRT) as described in Section 1.1 of the 208887 Master Protocol (MP). We hypothesize that given the immunogenic properties induced by belantamab mafodotin-mediated cell death, an augmented anti-

tumor activity will be observed in MM participants when treated with the combination of belantamab mafodotin and dostarlimab.

2.2. Background for Dostarlimab

An overview of dostarlimab (GSK4057190; TSR-042) is provided below, a summary of all relevant data and information available as of 21 JAN 2020. Detailed information concerning the biology, pharmacology, PK, and safety characteristics can be found in the Investigator's Brochure (IB) for dostarlimab [Dostarlimab, 2021].

The broad spectrum of cancers amenable to PD-1 blockade supports the value of developing an antibody that targets PD-1 to utilize as a single agent and in combination with other therapeutic approaches. Dostarlimab (also known as TSR-042) is an IgG4κ humanized monoclonal antibody that binds with high affinity to PD-1 resulting in inhibition of binding to PD-L1 and PD-L2. This antibody was generated based on a proprietary platform that utilizes affinity maturation to select antibodies with desired functional characteristics. The functional antagonist activity of dostarlimab was confirmed in a mixed lymphocyte reaction (MLR) assay demonstrating enhanced interleukin-2 production upon addition of dostarlimab.

Dostarlimab has demonstrated an acceptable clinical and nonclinical safety profile based on human experience in participants with advanced or recurrent solid tumors and the nonclinical pharmacology and toxicology information. As of the data cutoff date, key toxicities in the observed safety profile are consistent with the safety experience of other approved mAb PD-1 inhibitors. Based on the observed anti-tumor activity of other antibodies in the same class, dostarlimab is expected to exhibit clinical activity in a broad spectrum of cancers.

2.2.1. Clinical Experience

As of the clinical cutoff date of 21 January 2020, there were 4 ongoing Phase 1 studies and 3 ongoing Phase 2 studies with dostarlimab. The summary of safety and efficacy data provided below is for dostarlimab monotherapy study 4040-01-001, as remaining ongoing trials are evaluations of combination therapies.

In addition, 2 double-blind Phase 3 studies with dostarlimab combination therapy are ongoing and, therefore, are not included in the evaluated safety population.

Dostarlimab Monotherapy Study 4010-01-001

Study 4010-01-001 is an ongoing, first-in-human Phase 1 study of dostarlimab to evaluate the safety and tolerability, PK, pharmacodynamics, and clinical activity of dostarlimab in participants with recurrent or advanced solid tumors.

A total of 21 participants were dosed in the dose escalation phase of the study (Part 1). Dose escalation continued to a maximally administered dose of 10 mg/kg every 2 weeks (Q2W) and a maximum tolerated dose was not identified. No dose limiting toxicities (DLTs) were observed. The PK of dostarlimab were dose proportional across the dose range tested. Receptor occupancy was measured by direct binding of dostarlimab to PD-

1 on T cells from participants in Part 1 and by the dostarlimab induced inhibition of IL-2 production after ex vivo stimulation of T cells from participants in Part 1. Maximal receptor occupancy was achieved at all doses tested (1, 3, and 10 mg/kg) down to dostarlimab plasma concentrations as low as 2.435 µg/mL and was maintained for approximately 29 days.

The pharmacokinetic/pharmacodynamic (PK/PD) data was used to determine the fixed dosing tested in Part 2A of the study. In this phase of the study, the safety and tolerability of dostarlimab were evaluated at 2 fixed dosing schedules: 500 mg every 3 weeks (Q3W) and 1,000 mg every 6 weeks (Q6W). The recommended therapeutic dose (RTD) regimen was determined to be 500 mg Q3W for 4 cycles followed by 1,000 mg Q6W for all cycles thereafter.

The RTD selection was based on a combination of results from a preliminary 2-compartment population PK model, receptor occupancy data from peripheral blood cells of participants in Part 1, and safety data from Part 2A, wherein the 500 mg Q3W and 1,000 mg Q6W regimens were found to have acceptable tolerability with no observed DLTs. In Part 2A, the PK and pharmacodynamic data confirmed that both dosing regimens provided sufficient and sustained drug concentrations to allow for maximal receptor occupancy throughout the dosing cycle.

The RTD is being evaluated in expansion cohorts for mismatch repair-deficient (dMMR)/microsatellite instability high (MSI H) and MMR proficient/microsatellite stable (MSS) endometrial cancer, non small cell lung cancer (NSCLC), and dMMR/MSI H and/or polymerase ε-mutated non endometrial cancer in Part 2B of study. The PK/PD profile of participants in Part 2B of the study was similar to that of participants in Part 2A of the study.

Overall, the safety and tolerability of dostarlimab has been evaluated in 535 participants with advanced or recurrent solid tumors who received at least one dose of dostarlimab monotherapy (500 mg Q3W for 4 doses followed by 1,000 mg Q6W thereafter) prior to the data cut-off date (January 21, 2020) in study 4010-01-001 (GARNET), the first-in-human Phase 1 study.

As of 10 August 2018, an irORR of 9.52% (2 of 21 participants) was observed with dostarlimab monotherapy in Part 1 of Study 4010-01-001. Based on Investigator's assessment using irRECIST, both participants achieved a partial response. No participant in Part 2A achieved a partial or complete response with dostarlimab monotherapy.

As of 08 July 2019, efficacy results for Part 2B of the study are available for the following 2 cohorts: Cohort A1 (dMMR/MSI-H endometrial cancer) and Cohort F (dMMR/MSI-H and/or polymerase ε-mutated non-endometrial cancer). Based on blinded independent central review assessments using RECIST v1.1, ORRs of 43.1% and 44.0% were observed for the 2 cohorts respectively.

Given this encouraging clinical activity in heavily pretreated patients with diverse tumor types, and the manageable safety profile of dostarlimab, the benefit-risk profile for use of dostarlimab for treatment of patients with advanced cancers appears positive.

2.2.2. Pharmacokinetic Summary

The PK of dostarlimab is being evaluated in Study 4010-01-001. In Parts 1 and 2A of the study, 34 participants were dosed with dostarlimab and included in the PK analysis. Part 1 included 6 participants dosed with 1 mg/kg, 3 participants dosed with 3 mg/kg, and 12 participants dosed with 10 mg/kg of dostarlimab. In Part 2A, 6 participants received dostarlimab 500 mg Q3W and 7 participants received dostarlimab 1,000 mg Q6W. In Part 2B, 443 participants received the RTD and had PK data available for the analysis as of the data cutoff date of 08 July 2019: 267 participants diagnosed with endometrial cancer, 67 participants diagnosed with NSCLC, and 109 participants diagnosed with dMMR/MSI-H and/or polymerase ε-mutated non-endometrial cancer. Based on noncompartmental data, dostarlimab exhibited dose proportional PK over the dose range and dose regimens tested. Dostarlimab was cleared slowly with a terminal elimination half-life ranging from approximately10 to 20 days. Body weight (range 45.6 to 145.6 kg) was not a significant covariant for dostarlimab clearance. Dostarlimab PK continues to be evaluated in Part 2B of Study 4010 01 001 through sparse sampling for all participants upon administration of first, fourth, fifth, eighth, and twelfth doses at predose and 0.5 and 1.5 hours postdose. For the first 4 doses, participants received dostarlimab at 500 mg with a 21-day cycle (Q3W). Starting at dose 5, participants received dostarlimab at 1,000 mg with a 42-day cycle (Q6W). Following 4 cycles of dostarlimab 500 mg Q3W, steady state was reached, with comparable trough concentrations at the end of Cycles 3 and 4. An increase in dose from 500 mg Q3W to 1,000 mg Q6W resulted in an approximately 1.7-fold increase in postdose concentrations (Cmax of Cycle 4 compared to Cycle 5). Similar mean trough concentrations were observed for 500 mg Q3W (mean predose Cycles 4 and 5: 72.85 and 82.86 µg/mL, respectively) and 1,000 mg Q6W (mean predose Cycles 8 and 12: 85.29 and 77.68 µg/mL, respectively). When dosed at the RTD regimen, dostarlimab showed an approximate 2-fold accumulation (Cycle 4 through Cycle 12 based on Cmin compared to single-dose data), consistent with the terminal-phase elimination half-life.

A population PK model was developed using concentration-time data from 477 participants who had at least 2 postdose evaluable concentrations, with a total of 4,308 evaluable observations. The model was used to simulate concentrations to evaluate dostarlimab Cmax, Cavg, and Cmin after 500 mg Q3W and 1,000 mg Q6W following a single dose and at steady state.

A 2-compartment model with nonlinear, time-dependent elimination, and weight as an allometric factor on CL and central volume of distribution fit the data well. Generally, the estimated model parameters were comparable to published data of anti PD-1 mAb [Ahamadi, 2017; Liu, 2017] with mean steady-state clearance (CLss) of 0.00742 L/hr, a Vss of 5.34 L, and a terminal half-life of 25.4 days. The population clearance estimate was approximately 15.5% lower at steady state when compared to single dose due to time-dependent changes in this parameter. Based on model simulations of exposure parameters following either 500 mg Q3W or 1,000 mg Q6W dosing, both Cmin and Cavg were similar for the 2 dose regimens. In particular, the comparability of dostarlimab steady-state Cavg suggests a similar overall dostarlimab exposure following either the 500 mg Q3W or 1,000 mg Q6W dosing regimen.

2.2.2.1. Pharmacodynamics

Dostarlimab administration resulted in maximal PD-1 occupancy on T cells in peripheral blood of participants at all dostarlimab dose levels tested, including with the RTD regimen. Maximal receptor occupancy, as measured by direct PD-1 binding and alleviation of inhibition of IL 2 production, was maintained throughout the dosing period for all doses and dose regimens tested [Dostarlimab, 2021].

2.2.2.2. Fixed dose selection for dostarlimab monotherapy

The RTD (500 mg Q3W for 4 cycles, followed by 1,000 mg Q6W for all subsequent cycles) selection was based on a combination of results from a preliminary 2-compartment population PK model, receptor occupancy data from peripheral blood cells of participants in Part 1, and safety data from Part 2A, wherein the 500 mg Q3W and 1,000 mg Q6W regimens were found to have acceptable tolerability with no observed DLTs. In Part 2A, the PK and pharmacodynamic data confirmed that both dosing regimens provided sufficient and sustained drug concentrations to allow for maximal receptor occupancy throughout the dosing cycle [Dostarlimab, 2021].

2.2.3. Safety

As of 21 January 2020, 535 participants with heavily pretreated advanced solid tumors have been treated with dostarlimab monotherapy in Study 4010-01-001: 21 participants in Part 1 and 514 participants in Parts 2A and 2B. As of the data cutoff date, 527 participants (98.5%) reported at least 1 treatment-emergent adverse event (TEAE), with events of fatigue (25.6%), nausea (24.9%), anaemia (23.6%), and diarrhoea (21.5%) being the most frequently reported (>20%). TEAEs that were ≥Grade 3 were reported in 256 participants (47.9%), and were considered as study drug-related in 70 participants (13.1%). The majority of the ≥Grade 3 events TEAEs occurred in 2% of participants or less each, with the exception of anaemia (8.6%), dyspnoea (3.7%), abdominal pain (3.4%), fatigue (2.8%), hyponatraemia (2.8%), and pulmonary embolism (2.4%). Serious adverse events (SAEs) occurred in 205 participants (38.3%); 39 participants (7.3%) had SAEs considered study drug-related. Forty-eight participants (9.0%) had a TEAE leading to study drug discontinuation. Twenty-five participants (4.7%) had a TEAE leading to study drug discontinuation that was considered study drug-related. Sixteen participants (3.0%) developed a TEAE not related to study drug that led to death. No study drug related TEAE leading to death was reported.

The safety profile of monotherapy dostarlimab in participants with advanced or recurrent solid tumors was generally similar to the reported safety profiles of other mAbs blocking the PD-1 interactions [KEYTRUDA PI, 2019; OPDIVO PI, 2019; LIBTAYO PI, 2019].

Please see the dostarlimab IB v5 [Dostarlimab, 2021] for additional details.

2.2.3.1. Potential for Drug-Drug Interactions (DDIs) between Belantamab Mafodotin and Dostarlimab

Elimination pathways for belantamab mafodotin and cys-mcMMAF have not been characterized in humans. Cys-mcMMAF was not an inhibitor, an inducer, or a good

substrate of cytochrome P450 enzymes in vitro. In addition, cys-mcMMAF was shown to be a substrate of P-glycoprotein (P-gp). It is unlikely that belantamab mafodotin or cys-mcMMAF would impact the PK of dostarlimab.

No DDI studies have been conducted for dostarlimab. Monoclonal antibodies (mAbs) such as dostarlimab are not substrates for cytochrome P450 or drug transporters. Dostarlimab is not a cytokine and it is unlikely to be a cytokine modulator. Additionally, PK DDI of dostarlimab with small molecule drugs are not expected [Silva, 2015; Wang, 2014; ICH, 2011; Varga, 2015]. There is no evidence of DDI mediated by non-specific CL of lysosome degradation for antibodies [Silva, 2015].

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of belantamab mafodotin may be found in the IB [GSK Document Number RPS-CLIN-004867, GSK2857916 Investigator's Brochure V09, 2021].

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

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of dostarlimab may be found in the IB [Dostarlimab, 2021].

2.3.1. Risk Assessment

Table 8 outlines the risk assessment and mitigation strategy for dostarlimab. Belantamab mafodotin risk assessment and mitigation strategies are in the master protocol (MP; see Section 2.3.1).

Table 8 Potential Risks Related to Dostarlimab

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risk related to dostarlimab		
Infusion-related reactions (IRRs)	Risk for IRRs and hypersensitivity is inherent to many mAbs [Brennan, 2010]. Infusion-related reactions, which may be severe, have been reported in association with dostarlimab.	Participants will be closely monitored for signs of IRR. Premedication prior to first infusion of belantamab mafodotin is not mandatory but may be considered based on investigator judgement. If an IRR occurs during belantamab mafodotin administration, management may follow guidance in the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		208887 MP Section 11 or local standard of care. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions associated with dostarlimab, stop infusion and permanently discontinue.
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. Immune-related AEs have been reported in association with dostarlimab.	Participants with the following medical history are ineligible for this study: o Active autoimmune disease o Severe hypersensitivity to another mAb Established management algorithms for irAEs: Refer to the 208887 MP Section 11 for further details on the identification, evaluation, and management of toxicities including cumulative effects, with a potential immune etiology.
Embryo-Fetal Toxicity	There are no available data on the use of dostarlimab in pregnant women. Animal reproduction studies have not been conducted with dostarlimab to evaluate its effect on reproduction and fetal development. Based on its mechanism of action, dostarlimab can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy	Pregnancy testing outlined in the SoA. Contraception requirements are detailed in the 208887 MP Section 12.7.2

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	through induction of maternal immune tolerance to fetal tissue.	

2.3.2. Benefit Assessment

Although there is limited human experience with belantamab mafodotin, and no clinical experience with the combination of belantamab mafodotin with dostarlimab, given the currently available safety data and the low likelihood of drug-drug interactions between belantamab mafodotin and dostarlimab, combination therapy may have an acceptable safety profile. Additionally, the combination may provide anti-tumor effect in participants with MM.

The safety profile of dostarlimab is similar to the safety profiles of anti-PD1 drugs [Dostarlimab, 2021].

2.3.3. Overall Benefit: Risk Conclusion

This is the first study testing the combination of dostarlimab plus belantamab in participants with relapsed/refractory multiple myeloma that have been treated with standard therapies. Study participants may benefit from medical tests and screening performed during the study. Any potential benefit of the addition of dostarlimab to belantamab mafodotin is unknown. Data obtained in this study may help identify individuals more likely to benefit or have side-effects from dostarlimab plus belantamab mafodotin.

Based on current data from the dostarlimab development program and the observed anti-tumor activity of other antibodies in the same class, dostarlimab is expected to exhibit clinical activity in a broad spectrum of cancers.

The current nonclinical and clinical safety information for both belantamab mafodotin and dostarlimab, used as single agents, provide support for their use in combination in the target patient population. Based on the mechanism of action of belantamab mafodotin following engagement with both target and the FcγRIIIA, leading to ADCC and the potential for cytokine release as a result of inflammation secondary to non-specific cytotoxicity. Dostarlimab is unlikely to independently induce cytokine release, as incubation of dostarlimab with donor PBMCs in vitro did not induce significant stimulation of interferon (IFN)-γ, tumor necrosis factor (TNF)-α, IL-2, IL-4, IL-6, and IL-10. Dostarlimab is not expected to induce antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). The potential risk for cytokine release when these agents are administered in combination is considered to be low. To ensure the safety of participants, a careful dose escalation of belantamab mafodotin will be implemented where no more than one participant will be dosed per day.

In addition, the starting dose of belantamab mafodotin in this combination regimen has been selected to be 2 dose levels below a dose that has been shown to be well tolerated

during the belantamab mafodotin monotherapy dose escalation and should provide a sufficient safety margin when dostarlimab is added with starting dose of 500 mg. In addition, close clinical monitoring will be implemented.

Considering the measures taken to minimize risks to participants in the Phase I clinical trial, the potential risks identified in association with dostarlimab as a monotherapy or combination therapy are justified by the anticipated benefits that may be afforded to participants with relapsed/refractory multiple myeloma.

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 4 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 dostarlimab being described in this Sub-study.

The starting dose of belantamab mafodotin will be 1.9 mg/kg to be evaluated in Dose Level 1, with the highest dose of belantamab mafodotin of 2.5 mg/kg planned for Dose Level 2.

The dose of dostarlimab will be identical across the dose level groups and will be 500 mg Q3W for 4 cycles followed by 1000 mg Q6W for subsequent cycles.

Please see 208887 MP Section 4.1.1 for details of decision making during the DE phase.

4.2. Scientific Rationale for Study Design

Please refer to the 208887 MP.

4.3. Justification for Dose

There is no clinical experience with dostarlimab in patients with multiple myeloma.

The RTD regimen of dostarlimab is 500 mg Q3W for 4 cycles followed by 1000 mg Q6W in patients with solid tumor. This regimen was determined from the results of the Phase 1/2 study 4010-01-001, where the PK, efficacy and safety were evaluated over 3 parts:

- Part 1 (dose escalation): Q2W at doses of 1, 3 and 10 mg/kg

- Part 2A (Fixed-dose Safety Run-in): 1000 mg Q6W and 500◦mg Q3W
- Part 2B (expansion): 500 mg Q3W for the first 4 cycles followed by 1000 mg Q6W

The combination of meaningful efficacy responses in mismatch repair deficient endometrial cancer patients and overall manageable safety profile of dostarlimab supports this therapeutic dose and regimen

A starting dose of 500 mg Q3W for 4 cycles followed by 1000 mg Q6W is considered an appropriate dose for combination therapy with belantamab mafodotin (GSK'916) based on the following:

- 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 dostarlimab for the dose ranges considered.
- Because the ligands of belantamab mafodotin and dostarlimab are expressed on different target cell populations, no DDI related to target mediated disposition is expected between belantamab mafodotin and dostarlimab (GSK'190).
- According to currently available data, the flat dose of 500 mg IV Q3W was well tolerated and did not result in excessive toxicity in solid tumor patients. The highest tested flat dose was 1000 mg IV Q6W in the Phase 1 4010-01-001 (GARNET) trial; this dosing also did not result in excessive toxicity in solid tumor patients.

4.4. Participant Completion and End of Study Definitions

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

4.4.1. Participant Completion Definitions:

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

4.4.2. Study Completion:

Please refer to the 208887 MP.

5. STUDY POPULATION

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

Information and details specific to Sub-study 4 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 4.

5.2. Exclusion Criteria

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

The exclusion criteria #36-38 below are in addition to the exclusion criteria already defined in 208887 MP Section 5.2.

36. Patient has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs).
37. Patients who have received prior therapy with an anti-programmed death-1 (anti-PD-1), anti-PD-1-ligand-1 (anti-PD-L1), or anti-PD-1 ligand-2 (anti-PD-L2) agent.
38. Patient has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. Use of inhaled steroids, local injection of steroids, and steroid eye drops are allowed.

5.3. Lifestyle Considerations

Please refer to the 208887 MP.

5.4. Screen Failures

Please refer to the 208887 MP.

6. STUDY INTERVENTION

Study intervention is defined as belantamab mafodotin administered with the sub-study-specific anti-cancer combination partner treatment and administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Specifications for belantamab mafodotin and dostarlimab IP in this study are given (Table 9).

Dostarlimab kits will be supplied as a single vial in a carton, open label and non-patient specific. IP will be provided in a single-use vial as 50 mg/mL, 10.0 mL volume (500 mg) vial. Expiration date is printed on the product label. The product should be stored between 2°C and 8°C, and in accordance with the Pharmacy Manual.

Refer to the Pharmacy Manual for additional details on study drug preparation, administration, handling, storage, accountability and disposal and/or return of unused study treatment(s).

Table 9 Belantamab Mafodotin and Dostarlimab Investigational Product

Intervention Name	Belantamab Mafodotin	Dostarlimab
Type	Drug	Drug
Dose Formulation	Lyophilized powder	50 mg/ml solution
Unit Dose Strength(s)	100 mg/vial in single-use vial for reconstitution	10 ml (50 mg/ml) single-use vial
Route of Administration	Delivered as IV solution over 30-60 minutes (see SRM for details)	Delivered as IV solution over 30 minutes (see Pharmacy Manual for details)
IP	Belantamab mafodotin	Dostarlimab
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 Dostarlimab

Belantamab mafodotin and dostarlimab will be administered as per instructions below, and participants enrolled in 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.

Belantamab mafodotin

- Belantamab mafodotin will be administered before administration of dostarlimab.
- Belantamab mafodotin will be administered to participants intravenously as mg/kg calculated dose at the study site. The dose to be administered is based on actual body weight calculation and may be reduced for toxicity according to protocol guidelines.
- Administration will be documented in the source documents and reported in the eCRF. The time of start and end of infusion will be documented in eCRF.
- Belantamab mafodotin will be administered on Day 1 of each cycle at the assigned dose as an IV infusion (see Section 6.1 and Section 6.2 for details). Premedication is not required prior to infusion unless deemed medically necessary by the investigator, in which case it should be administered according to institutional recommendations. In case of infusion related reactions related to belantamab mafodotin the rules outlined in the 208887 MP Section 7.1.6 and in 208887 MP Section 11 should be followed.

- After the infusion of belantamab mafodotin has been completed participant will be required to enter at least 1 hour rest period before start of dostarlimab infusion. In case of IRR during belantamab mafodotin infusion, participant needs to recover to Grade 1 or less in order to be able to receive dostarlimab infusion.

The intended cycle time of belantamab mafodotin is 21 days (+ 3-day window) for Q3W administration or 42 days (+3-day window) for Q6W administration and cannot occur more frequently than this.

Dostarlimab

- Participants will receive dostarlimab starting C1D1 and will be treated until disease progression, intolerable toxicity, informed consent withdrawal, the end of the sub-study, study or death. There is no pre-specified duration of therapy after which administration must be stopped.
- Dostarlimab will be administered using IV infusion on Day 1 of each treatment cycle after all procedures and assessments have been completed.
- Dostarlimab will be administered at flat prescribed dose (outlined below) over 30 min IV infusion time after at least 1 hour rest period after completion of belantamab mafodotin infusion. Premedication is not required prior to infusion unless deemed medically necessary, in which case it should be administered according to institutional guidelines/recommendations.
    - 500 mg every 3 weeks for the first 4 doses, followed by
    - 1000 mg every 6 weeks.
- Visit window for treatment of dostarlimab allowed by the protocol is ± 3 days for both Q3W and Q6W schedule. However, it is recommended that sites try to keep participants on the original dosing schedule based on C1D1 and maintain the dosing intervals as closely as possible to the Q3W and Q6W schedule, respectively. If in the judgment of the Investigator, belantamab mafodotin and dostarlimab combination treatment needs to be initiated prior to the next planned scheduled dose *following a dosing delay and where clinical toxicity has resolved*, please discuss with the Medical Director.
- In case of IRR during or after preceding belantamab mafodotin infusion, the administration of dostarlimab will be delayed to allow for recovery to Grade 1 or less. In total, the infusion of dostarlimab may be delayed for up to the allowed +3-day window from the scheduled dose date to allow for recovery, and to accommodate scheduling conflicts in a given cycle. If the participant does not recover from IRR to Grade 1 or less within the +3 day window, the dosing of dostarlimab will be skipped in a given cycle, and may be resumed in the next cycle.
- All participants are required to remain under observation at the study site for at least three hours post-infusion of the last study drug administered for the first two study treatment dosing visits. At subsequent study treatment dosing visits, for participants who experience infusion-related reactions, the post-infusion observation time should remain as at least three hours; for participants who do not experience infusion reactions, these participants should remain under observation for a time period not

shorter than one hour (or longer as per the judgement of the investigator or as per institutional guidelines).

- In case of IRR during dostarlimab administration –please refer to the 208887 MP Section 11.1.1 for management guidelines.

6.3. Preparation/Handling/Storage/Accountability

Please refer to the 208887 MP.

6.4. Measures to Minimize Bias: Randomization and Blinding

Please refer to the 208887 MP.

6.5. Concomitant Therapy

Please refer to the 208887 MP.

6.6. Dose Modification

Dose modification is for belantamab mafodotin when in combination with dostarlimab. For information related to overall dose modification refer to the 208887 MP. Also see 208887 MP Section 11 for guidelines on dose modification and management of events for belantamab mafodotin and other partner combination treatments.

Table 10 Permitted Dose Reductions for Belantamab Mafodotin when in Combination with Dostarlimab

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

- If the participant cannot tolerate belantamab mafodotin after the allowed dose reductions, he or she must be withdrawn from study treatment for lack of tolerability.
- Resuming treatment with belantamab mafodotin may be considered after the toxicity has resolved to Grade 1 or less.
- For further details regarding dose modifications see 208887 MP Section 11.

No dose reductions are allowed for dostarlimab.

Dose Modification Guidelines for immune related Adverse Events are listed in the 208887 MP Section 11. For immune related encephalitis event of any Grade, dostarlimab should be discontinued.

If belantamab mafodotin is held or discontinued for any toxicity, dostarlimab is also to be held or discontinued.

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

Please refer to the 208887 MP.

7.1. Discontinuation of Study Intervention

Please refer to the 208887 MP.

7.2. Participant Withdrawal from the Study

Please refer to the 208887 MP.

7.3. Lost to Follow Up

Please refer to the 208887 MP.

8. STUDY ASSESSMENTS AND PROCEDURES

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

Information and details specific to Sub-study 4 are in Section 8.3.7, Section 8.3.10 and Section 8.4 below.

8.1. Efficacy Assessments

Please refer to the 208887 MP.

8.2. Safety Assessments

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

8.3. Adverse Events and Serious Adverse Events

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

Please refer to the 208887 MP.

8.3.2. Method of recording AE and SAE information

Please refer to the 208887 MP.

8.3.3. Method of Detecting AEs and SAEs

Please refer to the 208887 MP.

8.3.4. Follow-up of AEs and SAEs

Please refer to the 208887 MP.

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

Please refer to the 208887 MP.

8.3.6. Regulatory Reporting Requirements for SAEs

Please refer to the 208887 MP.

8.3.7. Management of Pregnancy

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

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

8.3.8. Cardiovascular and Death Events

Please refer to the 208887 MP.

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

Please refer to the 208887 MP.

8.3.10. Adverse Events of Special Interest

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

Immune-related TEAEs for dostarlimab are summarized in Section 5.4.6 of Dostarlimab IB v5 [Dostarlimab, 2021].

8.4. Treatment of Overdose

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

An overdose of dostarlimab is defined as any dose that is ≥ 20% than the intended dostarlimab dose. For fixed doses, an overdose of dostarlimab is defined as any dose that is ≥20% than 1000 mg Q6W. All overdoses, regardless of associated AE/SAE are to be reported as described for SAEs and as per the SAE form completion guidelines. Obtain an additional plasma sample for PK analysis if requested by the GSK Medical Director.

8.5. Pharmacokinetics

Not applicable.

8.6. Genetics

Please refer to the 208887 MP.

8.7. Immunogenicity Assesments

Please refer to the 208887 MP.

8.8. Biomarkers

Not applicable

8.9. Health-Related Quality of Life

Please refer to the 208887 MP.

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

Please refer to the 208887 MP.

9.2. Sample Size Determination

Please refer to the 208887 MP.

9.3. Populations for Analyses

Please refer to the 208887 MP.

9.4. Statistical Analyses

Please refer to the 208887 MP.

9.5. Interim Analysis

Please refer to the 208887 MP.

9.6. Sample Size Sensitivity

Please refer to the 208887 MP.

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

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

Additional guidelines specific to Sub-study 4 are provided in Table 11.

Table 11 Guidelines for Treatment and Management of Immune-Related Adverse Events of Interest- Dostarlimab

Toxicity	Grade/description of toxicity	Recommendations
Immune-related Encephalitis	Any grade	Permanently discontinue

12. APPENDICES: SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

Please refer to the 208887 MP.

12.2. Appendix 2: Clinical Laboratory Tests

Please refer to the 208887 MP.

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

Please refer to the 208887 MP.

12.4. Appendix 4: ECOG Performance Status

Please refer to the 208887 MP.

12.5. Appendix 5: NYHA Functional Classification System

Please refer to the 208887 MP.

12.6. Appendix 6: Modified Diet in Renal Disease

Please refer to the 208887 MP.

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

Please refer to the 208887 MP.

12.8. Appendix 8: Genetics

Please refer to the 208887 MP.

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

Please refer to the 208887 MP.

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

Please refer to the 208887 MP.

12.11. Appendix 11: Decentralized and Remote Assessment Approaches

Please refer to the 208887 MP.

12.12. Appendix 12: Abbreviations and Trademarks

ABC	Airway breathing and circulation
ADC	Antibody drug conjugate
ADCC	Antibody dependent cellular cytotoxicity
AE	Adverse event
AESI	Adverse events of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APRIL	A proliferation-inducing ligand
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC (0-∞)	Area under the concentration-time curve to infinity
AUC (0-τ)	Area under the concentration time curve over the dosing interval
AV	Atrioventricular
BAFF/BlyS	B-cell activating factor/B-lymphocyte stimulator
BAL	Bronchoaveolar lavage
BCMA	B cell maturation antigen
BCRP	Breast cancer resistant protein
BCVA	Best corrected visual acuity
BED	Biologically Effective Dose
BIW	Twice a week
BLRM	Bayesian logistic regression modelling
BM	Bone Marrow
BSA	Body surface area
BWT	Body weight
CA	Competent Authority
Car-T	Chimeric Antigen T cell therapy
CBC	Complete blood count
CBR	Clinical benefit rate
CDISC	Clinical Data Interchange Standards Consortium
CE	Cohort Expansion phase
CI	Confidence interval
CK	Creatine kinase
CK-MB	Creatine kinase MB-isoenzyme
CL	Clearance
CLL	Chronic lymphocytic leukemia
Cmax	Maximum plasma drug concentration
CMMC	Circulating multiple myeloma cells
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPMS	Clinical Pharmacology Modeling and Simulation
CPR	Cardio-pulmonary resuscitation
CR	Complete response
CRM	Continual Reassessment Method
CRP	C-reactive protein

CRT	Calreticulin
CT	Computer tomography
CTCAE	Common Toxicity Criteria for Adverse Events
cTn	Cardiac troponin
Ctrough	Trough plasma concentration
CYP	Cytochrome P450
CV%	Coefficient of variation percent
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
DMPK	Drug metabolism and pharmacokinetics
DNA	Deoxyribonucleic acid
EC	Ethics committee
EC50	Concentration associated with 50% maximal effect
ECG	Electrocardiogram
ECHO	Echocardiogram
ECL	Electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eGFR	Estimated Glomerular Filtration Rate
EM	Extramedullary
EOI	End of infusion
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires
FACTS	Fixed and adapted clinical trials simulator
FISH	Fluorescence in situ hybridization
FLC	Free light chain
FSH	Follicle stimulating hormone
FTIH	First time in human
G-CSF	Granulocyte colony stimulating factor
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLDH	Glutamate dehydrogenase
GLP	Good laboratory practice
GM-CSF	Granulocyte macrophage colony stimulating factor
GSI	Gamma secretase inhibitor
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
HIPAA	Health Insurance Portability and Accountability Act
HMGB1	High mobility group box 1
HNSTD	Highest non-severely toxic dose
HPLC	High performance liquid chromatography
HRT	Hormone replacement therapy
HSCT	Hematopoietic stem cell transplant
IB	Investigator's Brochure
IC50	Concentration associated with 50% inhibition of maximal effect
ICD	Immunogenic cell death
ICF	Informed consent form
ICH	International Council on Harmonization
IDSL	Integrated Data Standards Library
IEC	Institutional ethics committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMIDs	Immunomodulators
IMWG	International Myeloma Working Group
INR	International normalized ratio
IP	Intraperitoneal
IRB	Institutional review board
IRC	Independent review committee
IRR	Infusion-related reaction
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVRS	Integrated voice response system
KIM-1	Kidney injury molecule-1
LBCL	Large B-cell lymphoma
LDH	Lactate dehydrogenase
LFT	Liver function test
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MABEL	Minimum anticipated biological effect level
mAb	Monoclonal antibody
Mc	Maleimidocaproyl
MDRD	Modified diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MM	Multiple Myeloma
mm^3	Millimeter cube
MMAF	Monomethyl auristatin F

MoA	Mechanism of action
MP	Master Protocol
MR	Minimal response
MRD	Minimal residual disease
MRI	Magnetic resonance Imaging
MSDS	Material safety data sheet
MTD	Maximum Tolerated Dose
mTNBC	Metastatic triple negative breast cancer
mTPI	Modified toxicity probability interval
MUGA	Multiple gated acquisition
NAG	N-Acetyl-β-D-glucosaminase
NCI-CTCAE	National Cancer Institute – Common Toxicity Criteria for Adverse Events
N-CRM	A modification of the Continual Reassessment Method (CRM) proposed by Neuenschwander et al.
NHV	Normal healthy volunteers
NICD	NOTCH intracellular domain
NF-κB	Nuclear factor kappa light-chain enhancer of activated B cells
NT-proBNP	N-terminal B-type natriuretic peptide
NK	Natural killer
NONMEM	Non linear mixed effects modelling
NYHA	New York Heart Association
OAT	Organic anion transporter
OATP	Organic anion transporter polypeptide
ORR	Overall response rate
OS	Overall survival
OSDI	Ocular Surface Disease Index
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PFT	Pulmonary function test
Pgp	P-glycoprotein
PI	Proteasome inhibitor
PK	Pharmacokinetic(s)
PK/PD	Pharmacokinetic(s)/Pharmacodynamic(s)
PR	Partial response
PRO	Patient reported outcome
PT	Prothrombin time
PTS	Platform technologies and sciences
PTT	Partial thromboplastin time
Q3W	Every 3 week
QID	4 times a day
QoL	Quality of life

RAP	Reporting and analysis plan
RAMOS	Registration and medication ordering system
REML	Restricted maximum likelihood
RIBA	Recombinant immunoblot assay
RNA	Ribonucleic acid
Ro	Observed accumulation ratio
RO	Receptor occupancy
RPA-1	Renal papillary antigen-1
RP2D	Recommended Phase 2 dose
RRMM	Relapsed/refractory multiple myeloma
RT-qPCR	Reverse transcription quantitative polymerase chain reation
RTD	Recommended therapeutic dose
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 reference manual
SRT	Safety Review Team
SPR	Surface plasmon resonance
t½	Half-life
TALL	T-cell acute lymphoblastic leukemia
TBNK	T-cell, B-cell and Natural Killer cells
TEAE	Treatment emergent adverse event
T_{last}	Time of last quantifiable concentration
TLS	Tumor lysis syndrome
Tmax	Time to maximum drug concentration
TNBC	Triple negative breast cancer
TTP	Time to progression
TTR	Time to response
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
VGPR	Very good partial response
Vd	Volume of distribution
Vss	Volume of distribution at steady state
WM	Waldenstrom's macroglobulinemia
WOCBP	Women of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
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LIBTAYO
OPDIVO

12.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of changes Table for the current Amendment 05 is located directly before the Table of Contents (TOC).

Amendment 04 (Sub-study 4) 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 4 are administrative and are mapped in the table below.

Section # for PA3 and Name		Section # for PA4 and Name	
14.1	Schedule of Activities Tables	1.3	Schedule of Activities (SoA)
14.2	Background of Dostarlimab	2.2	Background for Dostarlimab
14.2.1	Clinical Experience with Dostarlimab	2.2.1	Clinical Experience
14.2.2	Pharmacokinetic Summary of Dostarlimab	2.2.2	Pharmacokinetic Summary
14.2.3	Safety for Dostarlimab	2.2.3	Safety
		8.3.10	Adverse Events of Special Interest
14.3.1	Rationale for the Combination	2.1	Rationale for combination of Belantamab mafodotin with Dostarlimab
14.3.2	Dose justification for Dostarlimab when in combination with Belantamab Mafodotin	4.3	Justification for Dose
14.3.3	Potential for Drug-Drug Interactions (DDIs) between Belantamab Mafodotin and Dostarlimab	2.2.3.1	Potential for Drug-Drug Interactions (DDIs) between Belantamab Mafodotin and Dostarlimab
14.3.4	Benefit/Risk	2.3	Benefit/Risk Assessment
14.4	Study Design Details	6.2	Administration of Belantamab mafodotin and Dostarlimab
14.4.1	Dostarlimab Dosing Frequency		
14.4.2	Study Intervention(s) Administered - Belantamab Mafodotin and Dostarlimab		
14.4.2.2	Treatment of Overdose	8.4	Treatment of Overdose
14.4.3	Study Intervention Product and Accountability	6.3	Preparation/Handling/Storage/Accountability – content deleted as it was identical to the 208887 MP
14.4.4	Combination Treatment Belantamab Mafodotin (GSK'916) Co-Administered with Dostarlimab (GSK'190)	4.1	Overall Design
14.4.5	Treatment Duration of Dostarlimab	6.2	Administration of Belantamab mafodotin and Dostarlimab
14.4.6	Dose modification for Belantamab Mafodotin when in combination with Dostarlimab	6.6	Dose Modification
14.4.7	Inclusion/Exclusion Criteria for Dostarlimab Sub-study	5.1	Inclusion Criteria for Participants
		5.2	Exclusion Criteria
14.4.8	Management of Pregnancy	8.3.7	Management of Pregnancy
14.5	References	10	References
14.6	Appendices	11	Guidelines for dose modification and other partner combination treatments for all substudies

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

Section # and Name	Description of Change	Brief Rationale
Changes in Assessments and SoAs		
1.3. Schedule of Activities	Clarified footnote on Single ECG at Screening (Table 3)	Clarified based on prior edits (Protocol Amendment 03)
	Extraction of information regarding BM Assessments in a separate table (current Table 6)	To clarify assessments
	Clarified FISH assessments that are to be completed at Screening (Table 6) based on availability on previous results	In line with other protocols in the program.
	Added footnote 20c for supportive care information (Table 4)	To align with belantamab mafodotin program guidelines
	Added language on biomarker assessments for PD-L1 expression (Table 6)	To clarify biomarker assessments for the Sub-study 4 combination
	Clarified language on definition of resolution of ophthalmic findings (to baseline instead of Grade 1)	To align with GSK belantamab mafodotin program language
8.8 Biomarkers	Addition of language for prospective evaluation of PD-L1	To clarify assessments for the Sub-study 4 combination
Editing, format, style changes		
Throughout	Correction of typos and technical document aspects	Minor changes; no impact on content

Protocol Amendment 3 (08-JUL-2020)

Protocol Amendment 03 Summary of Changes Specific to Sub-study 4

The protocol has been amended to introduce a new sub-study into Section 14 of the protocol.

- Introduction of Substudy 4- Belantamab Mafodotin and dostarlimab (Section 14)

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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 21-Jan-2022 23:03:29 GMT+0000

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