Protocol Amendment 3

Study ID: 208887 Sub Study 5

Official Title of Sub Study 5: 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 5 - Belantamab Mafodotin and Isatuximab in Combination

NCT ID of Sub Study 5: NCT07217184

Date of Document: 03-Sep-2024

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 5 – Belantamab Mafodotin and Isatuximab in Combination

Protocol Number: 208887 / Amendment 3 for Sub-study 5

Compound Number or Name: Belantamab Mafodotin (GSK2857916), Isatuximab (SAR650984)

Study Phase: 1/2

Short Title: Platform Study of Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination with Isatuximab in Participants with RRMM

Acronym: DREAMM-5 Sub-study 5

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PROTOCOL AMENDMENT 3 SUB-STUDY 5 INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: 208887

AMENDMENT NUMBER: Protocol Amendment 3 for Sub-study 5

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 5 – Belantamab Mafodotin and Isatuximab in Combination

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

Investigator Name:

_____

Investigator Address:

_____

_____

_____ _____

Investigator Signature Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 3 (Sub-study 5)	03 Sep 2024	TMF-19536835
Amendment 2 (Sub-study 5)	10 July 2023	TMF-15016831
Amendment 1 (Sub-study 5)	21 January 2022	TMF-13844205
Original Sub-study 5 Protocol	14 December 2020	2020N453220_00

Amendment 03 (Sub-study 5): 03 Sep 2024

Overall Rationale for the Amendment:

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

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities	Tables 3 & 5: Procedures related to health outcomes evaluation were removed. Tables 3 & 6: A note to specify that MRD testing will be done via NGS method was added. Tables 3, 5 & 8: Sampling for interference assay for Isatuximab was removed. Tables 4 & 5: A note to stop plasma PK sampling once enough data have been collected was added. Table 6: A note to stop sampling for MRD and biomarker research once enough data have been collected was added. Tables 4, 5 & 8: Sampling for sBCMA and CMMC analyses was removed.	To update the study procedures in line with project-level updates.
Section 2.2.3. Clinical Activity / Efficacy of Isatuximab Monotherapy	Clinical data related to Isatuximab were updated.	To add the recent clinical experience with Isatuximab.
Section 6.1. Study Treatment(s) Administered	The information regarding study treatments was updated.	To comply with the latest regulatory requirements.
Section 8.10. Health-related Quality of Life	Wording related to health outcomes evaluation was removed.	To align with the updates in study procedures.
Section 12.13. Appendix 13: Abbreviations, Trademarks, and Definitions of Terms	A list of definitions was included.	To define the terms used throughout the document.

Section # and Name	Description of Change	Brief Rationale
Throughout the document	Editorial and wording updates.	Updates in wording were added to align with the new Sponsor's standard protocol template and ways of working.

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1. PROTOCOL SUMMARY

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

Information and details specific to Sub-study 5 are included 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 5-Specific Content

Section	Heading title	Brief description of content
1.3	Schedules of Activities	Comprehensive SoA tables specific for Sub-study 5
2.1	Rationale for combination of Belantamab Mafodotin with Isatuximab	Explanation of why treatment with belantamab mafodotin and isatuximab is expected to be complementary
2.2	Background for Isatuximab	Available data on clinical pharmacology, safety and clinical activity
2.3	Benefit/Risk Assessment	Risk assessment for isatuximab treatment; benefit assessment summary
4.1	Dose Exploration of Combination Treatment Belantamab Mafodotin Co-Administered with Isatuximab	Description of dose escalation design for the combination treatment
4.3	Dose Justification	Data for the basis of the planned isatuximab dosing
5.2	Exclusion Criteria	Three additional exclusion criteria were defined for Sub-study 5
6.1	Study Treatment(s) Administered	Specifications for belantamab mafodotin and isatuximab IP
6.2	Administration of Belantamab Mafodotin and Isatuximab	Specifications for administration of belantamab mafodotin and isatuximab
6.3	Preparation/Handling/Storage/Accountability	Information on isatuximab kits
6.6	Dose Modification for Belantamab Mafodotin and Isatuximab in Combination	Detailed directions and guidance for dose modification/delay of combination treatment
8.3.7	Management of Pregnancy and Contraception	Detailed directions for management of pregnancy and guidance on contraception specific to Sub-study 5
8.3.10	Adverse Events of Special Interest for Isatuximab	Information on isatuximab AESI
8.4	Treatment of Overdose of Isatuximab	Guidance for potential drug overdose of isatuximab
8.8	Biomarkers	Information on biomarkers for belantamab mafodotin and/or specific to the combination with isatuximab

1.1. Synopsis

Protocol Title: A Phase I/II, Randomized, Open-label Platform Study Utilizing a Master Protocol to Study Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination with Anti-Cancer Treatments in Participants with Relapsed/Refractory Multiple Myeloma (RRMM)–DREAMM5- Sub-study 5 – Belantamab Mafodotin and Isatuximab in Combination

Short Title: Platform Study of Belantamab Mafodotin (GSK2857916) as monotherapy and in combination with Isatuximab in Participants with RRMM

Rationale: Enhanced antigen presentation through belantamab mafodotin-mediated immunogenic cell death (ICD), and the resulting T cell-mediated durable immunity suggests that additional therapeutic benefit may be obtained from combination treatment of belantamab mafodotin with immune-enhancing agents, such as isatuximab. Isatuximab is an IgG1-derived monoclonal antibody that binds to a specific extracellular epitope of the cluster of differentiation (CD) 38 receptor, a transmembrane glycoprotein that is expressed on plasma cells and other lymphoid and myeloid cell populations. Since its expression is very high and uniform on myeloma cells, CD38 is a good target for novel therapeutic strategies, and isatuximab has been shown to have clinical activity in RRMM.

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

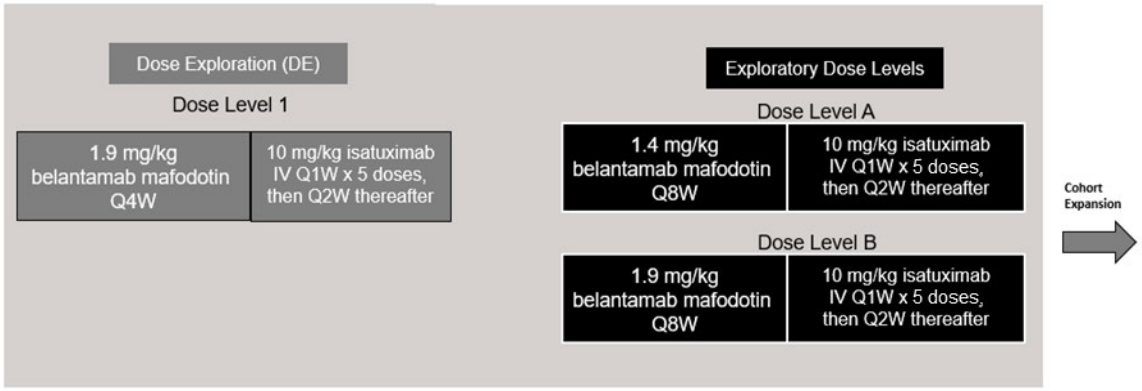
This study will evaluate the safety, tolerability and preliminary efficacy of belantamab mafodotin in combination with isatuximab in adult participants with RRMM, who have been previously treated with at least 3 prior lines of therapy that include the following: an immunomodulatory agent, a proteasome inhibitor (PI) and an anti-CD38 monoclonal antibody (mAb) treatment.

The dose level of 1.9 mg/kg every 4 weeks (Q4W) of belantamab mafodotin will be evaluated as a starting dose. Isatuximab dosing will be 10 mg/kg weekly for the first 5 doses, followed by every 2 weeks thereafter (in combination with belantamab mafodotin). A total of 2 dose levels of belantamab mafodotin (1.4 mg/kg and 1.9 mg/kg) every 8 weeks (Q8W) may be evaluated as exploratory dose levels. The sponsor may decide not to evaluate all dose levels based on data external to this study.

Cycle for dose level 1 is Q4W. DLT evaluation period for Cycle 1 will be 28 days. Cycle for Dose level A and B will be Q8W. DLT evaluation period for Cycle 1 will be 56 days.

1.2. Schema

Figure 1 Dose exploration schema – belantamab mafodotin in combination with isatuximab



1.3. Schedule of Activities (SoA)

The timing and number of planned study assessments (including safety, PK, ADA, biomarker or other assessments) may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations of study treatments administered) to ensure appropriate monitoring.

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

Screening Study Assessments	Screening	Notes
Note: All Screening assessments must be performed within **30** days prior to Cycle 1 Day 1 (C1D1) unless otherwise specified. Informed Consent must be signed before any study-specific assessments are performed. Screening assessments do not need to be repeated on C1D1 unless otherwise specified. All other assessments can be done ≤3 days prior to treatment unless otherwise specified. **If C1D1 Hem/Chem results are outside of the eligibility requirements, Medical Director to be contacted for review prior to dosing.**		
Informed Consent	X	1. Screening/baseline ocular examination will be performed by a qualified eye care specialist (ophthalmologist/optometrist 208887 MP Appendix 10) within 30 days prior to C1D1 (see 208887 MP Section 8.2.7 for list of ophthalmic exam procedures).
Demography	X	
Medical History (includes substance abuse)	X	
Full Physical Exam	X	2. Perform only in WOCBP. A pregnancy test must be performed at Screening. If the test is completed within 72 hours prior to the first dose, this assessment needs not to be repeated on C1D1.
Throughout the study, participants are educated about lifestyle considerations (208887 MP Section 5.3) for the study and the need of maintaining adequate urinary output (208887 MP Section 2.3.1).	X	3. Refer to 208887 MP Appendix 2 for a comprehensive list of lab tests that must be collected for all participants. Indirect antiglobulin test (indirect Coombs test), blood type and screen to be done at Screening in addition to those in the MP.
Inclusion/Exclusion criteria	X	4. eGFR as calculated by MDRD formula (208887 MP Appendix 6).
Past and current medical conditions	X	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).
Concomitant Medication review	X	
Screening Safety Assessments		
Ocular Exam	X[1]	6. Complete at Screening or within 12 weeks prior to C1D1.
ECOG Performance Status	X	
Vital Signs (BP, HR, Body Temperature)	X	7. If a participant tested hepatitis B core antibody positive, refer to Table 9 for additional procedures throughout the study. Hep C RNA testing is optional, but it will be performed to determine participant eligibility if Hep C antibody positive. If negative, participant is eligible (see exclusion criteria 12 for details).
Weight and Height	X	
Serum Pregnancy Test (WOCBP only)	X[2]	
Hematology (CBC)	X[3]	8. For participants who have been previously exposed to HIV, HIV viral load must be <400 copies/mL and CD4+ T-cell (CD4+) counts ≥350 cells/uL
Indirect antiglobulin test (indirect Coombs test)	X[3]	
Blood type and screen	X[3]	9. Single ECG at Screening.
Clinical chemistry	X[3]	10. ECHO or MUGA scan for LVEF may be performed within 30 days prior to C1D1.
Estimated Glomerular Filtration Rate (eGFR)	X[4]	11. SPEP and UPEP will include M-protein calculations.
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)	X[5]	12. Serum Free Light Chain assay will include kappa/lambda ratio and quantification of involved and uninvolved light chains.
HbsAg[7], HbcAb[7], HCV[7] tests	X[6]	13. IgD/IgE testing is only required for participants with IgD/IgE myeloma.
HIV viral load and CD4+ count	X[8]	14. Skeletal survey: Imaging of bones for lytic lesions by a method aligned with the institutional guidance (X-ray, CT, or MRI). X-ray is acceptable for lytic disease, but other methods are needed (CT, MRI, PET/CT) for assessment of extramedullary disease. Skeletal survey results within 30 days prior to
12-lead ECG	X[9]	
ECHO or MUGA scan for LVEF	X[10]	

Screening Study Assessments	Screening	Notes
Screening Disease Evaluation		C1D1 may be used for Screening. Same modality used at Screening should be used throughout study. 15. In participants with known or suspected extramedullary plasmacytoma, a whole body scan (i.e., CT, MRI, or PET-CT) should be performed within 30 days prior to C1D1. The same method should be used throughout the study (i.e., if a PET-CT scan was used as baseline scan, then the participants need to be followed by PET-CT scans). Selected target lesions need to be measured and followed over time. Whole body MRI is also acceptable, as long as it can be repeated over the duration of the study until confirmed disease progression. 16. Please refer to Table 6 for scheduled BM collection procedures to include aspirate and biopsy.
$Beta_2$ microglobulin	X	
UPEP 24 hr urine collection	X[11]	
Urine immunofixation 24 hr urine collection	X	
SPEP	X[11]	
Serum immunofixation	X	
Serum FLC assay	X[12]	
IgG, IgM, IgA	X	
IgD or IgE, if applicable	X[13]	
Calcium corrected for albumin (serum)	X	
Skeletal survey	X[14]	
Extramedullary Plasmacytoma Assessment (by whole body CT or whole body MRI or CT/PET)	X[15]	
BM Aspiration/Biopsy		
BM aspirate and/or core biopsy for Disease assessment	X[16]	
BM aspirate for FISH testing	X[16]	
BM aspirate for BCMA and/or CD38 expression and biomarker research	X[16]	
BM aspirate for MRD testing	X[16]	

Table 3 SoA – Treatment Period for DE and CE Phases: Belantamab Mafodotin and Isatuximab. Study assessments to be carried every 4 weeks regardless of whether participant is dosed

Study Assessments regardless of whether participant is dosed	Day 1 (Week 1)	Treatment Period: Q4W from Week 5 until EOT	Notes
• All assessments will apply to both the DE and CE Phases unless otherwise specified. • Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. • Scheduled visit dates during the treatment period can be delayed or brought forward by a maximum of 5 days to be aligned with the next dosing date. If administration of study treatment is delayed ≤7 days, assessments indicated to occur at the dosing visit can be scheduled to occur when dosing occurs (every effort should be made to realign subsequent weekly visits with dosing visits). If administration of study treatment is delayed >7 days, dosing and weekly assessments may occur on different days.			
AEs	Ongoing[1]		1. AEs/SAEs will be collected until at least 70 days post last dose of study treatment and immune-related AEs/SAEs will be collected up to 90 days post last dose. All SAEs related to study participation (e.g., protocol mandated procedures, tests, or change in existing therapy) are to be collected from consent through OS follow-up. All AEs/SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.
Concomitant Medications	Ongoing		
Throughout the study, participants are educated about in lifestyle considerations (208887 MP Section 5.3) for the study and the need of maintaining adequate urinary output (208887 MP Section 2.3.1).	X		
Genetics	X[2]		2. Informed consent for genetic research must be obtained before collecting a sample. The sample will be collected on C1D1 prior to infusion.
ECOG Performance Status		X	3. On-study ocular exams to be performed by a qualified eye care specialist (see 208887 MP Appendix 10) for scheduled visits regardless of dosing, up to the sixth dose of belantamab mafodotin (assessment window up to 5 days prior to scheduled visit date, but all effort should be made to schedule as close to belantamab mafodotin dosing as possible). If there are no significant KVA Grade 2 or above treatment-related ocular examination findings, change in participant symptoms or vision at the time of the sixth dose exam, participants may have their ophthalmologic exams decreased to once every 3 months. See 208887 MP Section 8.2.7 for list of ophthalmic exam procedures and frequency of exams.
Safety			
Ocular Exam		X[3]	
Hematology (CBC)	X[4]	X[4]	
Clinical chemistry	X[4]	X[4]	
eGFR	X[5]	X[5]	
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)	X[6]	X[6]	
ECHO or MUGA scan for LVEF		X[7]	4. <u>If C1D1 Hem/Chem results are below eligibility threshold required, Medical Director to be contacted for review prior to dosing.</u> Hem/Chem panels may be done more frequently as clinically indicated. Refer to 208887 MP Appendix 2 for comprehensive list of lab tests.
Disease Evaluation (every 4 weeks even if a dose is delayed)			
UPEP 24 hr urine collection		X[8]	
Urine immunofixation 24 hr urine collection		X[9]	5. eGFR as calculated by MDRD formula (208887 MP Appendix 6).
SPEP		X[8]	6. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥2+, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab be performed (first void).
Serum immunofixation		X[9]	
Serum FLC assay		X[10]	
IgG, IgM, IgA		X	

Study Assessments regardless of whether participant is dosed	Day 1 (Week 1)	Treatment Period: Q4W from Week 5 until EOT	Notes
• All assessments will apply to both the DE and CE Phases unless otherwise specified. • Assessments scheduled on days of dosing should be done prior to drug administration, unless otherwise specified. • Scheduled visit dates during the treatment period can be delayed or brought forward by a maximum of 5 days to be aligned with the next dosing date. If administration of study treatment is delayed ≤7 days, assessments indicated to occur at the dosing visit can be scheduled to occur when dosing occurs (every effort should be made to realign subsequent weekly visits with dosing visits). If administration of study treatment is delayed >7 days, dosing and weekly assessments may occur on different days.			
IgD or IgE		X[11]	7. ECHOs or MUGA scans for LVEF to be done if clinically indicated. The same procedure used at Screening should be used throughout the study. 8. SPEP must be performed Q4W. UPEP will only be performed Q4W for participants who had detectable M-protein only in the urine at screening. For all other participants, UPEP will be performed only after a tumor response based on SPEP protein during treatment is observed, where UPEP on 24 hours urine sample is required to confirm the response per IMWG criteria 9. To be performed when SPEP and UPEP are negative or not quantifiable. Also, to be performed to confirm objective response (PR or better). 10. Serum Free Light Chain assay will include kappa/lambda ratio and quantification of involved and uninvolved light chains, to be done every 4 weeks. 11. IgD/IgE testing is only required for participants with IgD/IgE myeloma. 12. Skeletal survey (as clinically indicated): Imaging of bones for lytic lesions by a method aligned with the institutional guidance (X-ray, CT, or MRI). X-ray is acceptable for lytic disease, but other methods are needed (CT, MRI, PET/CT) for assessment of extramedullary disease. Same modality used at Screening should be used throughout study. 13. Imaging is required for participants with extramedullary disease, as clinically indicated, to document disease response PR or better, or to confirm PD. Imaging is also required when there is a suspected appearance of a new lesion (for confirmation of PD).To be performed by the same method throughout the study as was done at baseline (i.e., if CT/PET scan was used as baseline, participant needs to be followed by CT/PET scans). Selected target lesions need to be measured. 14. **Note**: Germany: no PET/CT to confirm CR or sCR will be performed until approval by the German Federal Office for Radiation Protection. 15. Please refer to Table 6 for scheduled BM collection procedures to include aspirate and biopsy. 16. MRD testing by NGS method.
Calcium corrected for albumin (serum)		X	
Skeletal survey		X[12]	
Extramedullary Plasmacytoma Assessment (by whole body CT or whole body MRI or CT/PET)		X[13]	
MRI, CT or PET/CT upon achieving CR or sCR		Once after CR or sCR[14]	
Bone Marrow (BM) Aspiration/Biopsy			
BM aspirate for BCMA and/or CD38 expression and biomarker research		X[15]	
BM aspirate for MRD testing		X[15, 16]	
BM aspirate and/or core biopsy for Disease assessment		X[15]	
BM core biopsy to assess sCR		X[15]	

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

Study Assessments	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 1 Day 22	Cycle 2 to EOT	Notes
• All assessments will apply to both the DE and CE Phases unless otherwise specified. • Assessments should be done prior to drug administration, unless otherwise specified. • From Dose 2, assessments can be performed ≤ 3 days prior to the scheduled date unless otherwise specified. • If Hematology/Clinical Chemistry completed within 72 hr prior to the Day 1 dose, this assessment does not need to be repeated on C1D1 and C2D1 on. **If C1D1 Hem/Chem results are below eligibility threshold required, Medical Director to be contacted for review prior to dosing.**						
Safety						1. Measured after resting for at least 5 minutes. For the first infusion, vital signs must be monitored for each study drug infusion at: predose (within 30 min prior to SOI); at the 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 predose (within 30 min prior to SOI); at EOI (+0-10 min), and 30 min post EOI (+0-10 min) and as clinically indicated. On days with PK sampling time points, if vital signs assessments are conducted, they should be assessed prior to PK samples being drawn. The timing of the assessments should allow the blood draw to occur at the exact nominal time. 2. On-study ocular exams to be performed by a qualified eye care specialist (see 208887 MP Appendix 10) regardless of dosing up to the sixth dose of belantamab mafodotin (assessment window up to 5 days prior to dosing, but all effort should be made to schedule as close to belantamab mafodotin dosing as possible). If there are no significant KVA Grade 2 or above treatment-related ocular examination findings, change in participant symptoms or vision at the time of the sixth dose exam, participants may have their ophthalmologic exams decreased to once every 3 months. See 208887 MP Section 8.2.7 for list of ophthalmic exam procedures and frequency of exams. 3. Perform only in WOCBP. Pregnancy tests may be either predose serum or urine and should be performed within 72 hours prior dosing. 4. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥2+, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab (first void). 5. Hematology/Clinical Chemistry to be done prior to isatuximab dosing for Cycle 1. Hematology/Clinical Chemistry to be done on Day 1 and prior to isatuximab dosing
Physical Exam (Full exam on treatment days Day 1 of each cycle, and C1D8 only)	X	X			X	
Vital Signs (BP, HR, Body Temperature)	X[1]	X[1]	X[1]	X[1]	X[1]	
Ocular Exam	X[2]				X[2]	
Weight	X				X	
ECOG Performance Status	X				X	
Pregnancy Test	X[3]				X[3]	
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)	X[4]				X[4]	
Hematology (CBC)	X[5]	X[5]	X[5]	X[5]	X[5]	
Indirect antiglobulin test (indirect Coombs test)	X[6]				X[6]	
Clinical chemistry	X[5]	X[5]	X[5]	X[5]	X[5]	
eGFR	X[7]	X[7]			X[7]	

Study Assessments	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 1 Day 22	Cycle 2 to EOT	Notes
• All assessments will apply to both the DE and CE Phases unless otherwise specified. • Assessments should be done prior to drug administration, unless otherwise specified. • From Dose 2, assessments can be performed ≤ 3 days prior to the scheduled date unless otherwise specified. • If Hematology/Clinical Chemistry completed within 72 hr prior to the Day 1 dose, this assessment does not need to be repeated on C1D1 and C2D1 on. **If C1D1 Hem/Chem results are below eligibility threshold required, Medical Director to be contacted for review prior to dosing.**						
PK and ADA						
Plasma PK for isatuximab	X[8]	X[8]	X[8]	X[8]	X[8]	
Serum immunogenicity (ADA) for isatuximab	X[8]				X[8]	
Plasma PK for belantamab mafodotin	X[8]	X[8]	X[8]	X[8]	X[8]	
Serum Immunogenicity (ADA) for belantamab mafodotin	X[8]				X[8]	
Biomarkers						
Hematology (TBNK and/or enhanced TBNK cell activation panel)	X[9]				X[9]	

Q2W from Cycle 2 on. Hematology and Chemistry may be done more frequently, as clinically indicated. Refer to 208887 MP Appendix 2 for comprehensive list.

6. On C1D1 indirect antiglobulin testing (indirect Coombs testing) to be done only if results from Screening are not available. From Cycle 2 to EOT indirect antiglobulin testing (indirect Coombs testing) to be done only if a participant has a blood transfusion. To be performed prior to the blood transfusion.
7. eGFR as calculated by MDRD formula (208887 MP Appendix 6).
8. Please refer to Table 7 for scheduled belantamab mafodotin and isatuximab PK and ADA collections by timepoint. Samples to be taken for all participants. Vital signs should be assessed prior to PK samples being drawn. Pharmacokinetic and accompanying sBCMA sample collection may be terminated when sufficient data have been collected.
9. Please refer to Table 8 for scheduled biomarker sample collection.
10. Please refer to 208887 MP Section 6.6.3 and Section 6.6 for guidance on dose delays, reduction and modification. The next scheduled dose must be administered every 28 days (+3-day window) (Q4W) or 56 days (+3-day window) (Q8W) since last dose. If in the judgment of the investigator, treatment needs to be initiated prior to the next planned scheduled dose, in cases where clinical toxicity has resolved, please discuss with the Medical Director. All assessments should remain on schedule with the exception of those associated with dosing. Belantamab mafodotin will be administered as an IV infusion (see Section 6.1 for details).

Study Assessments	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 1 Day 22	Cycle 2 to EOT	Notes
• All assessments will apply to both the DE and CE Phases unless otherwise specified. • Assessments should be done prior to drug administration, unless otherwise specified. • From Dose 2, assessments can be performed ≤ 3 days prior to the scheduled date unless otherwise specified. • If Hematology/Clinical Chemistry completed within 72 hr prior to the Day 1 dose, this assessment does not need to be repeated on C1D1 and C2D1 on. **If C1D1 Hem/Chem results are below eligibility threshold required, Medical Director to be contacted for review prior to dosing.**						
Treatment with Belantamab Mafodotin						11. Premedication should be considered in any participant who experienced an infusion-related reaction at first or any subsequent infusion with belantamab mafodotin or partner combination (see relevant sub-study protocol section). 12. 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 the eye care specialist. Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops (if administered). b. At the start of each infusion, participants may apply cooling eye masks to their eyes for approximately 1 hour or as long as tolerated. c. For participants with history of dry eyes, or participants who develop dry eye during study treatment, the eye care specialist should consider use of additional products/treatments as per local institutional guidance. 13. Premedication required prior to isatuximab infusion to be given 15 mins following belantamab mafodotin infusion completion and 15-60 mins before isatuximab- infusion start see Section 6.2.1. 14. Administration to occur at least 1 hour after administration of belantamab mafodotin. IV Q1W X 5 doses, then Q2W thereafter. Within a cycle, an isatuximab administration can be delayed for up to 1 day in case of weekly administration or 2 days for every 2 weeks administration. If the dose cannot be administered within 3 days, the isatuximab dose will be omitted. Further omissions must be discussed on a case-by-case basis with the Medical Director.
Administration of belantamab mafodotin	X				Day 1 of each 28 day or 56 day cycle[10]	
Premedication if needed					X (at the start of each dose)[11]	
Treatment prophylaxis and management of preservative-free artificial tears and cooling masks	X[12]				X[12]	
Treatment with Isatuximab						
Premedication for Isatuximab[13]	X	X	X	X	X	
Administration of Isatuximab[14]	X	X	X	X	After 5 weekly doses beginning C1D1, then Q2W thereafter	

Table 5 SoA: End of Treatment (EOT) and Follow-Up for Sub-study 5: Belantamab Mafodotin and Isatuximab

Study Assessments	End of Treatment Visit[1]	PFS Follow-up[2]	OS Follow-up[3]	Notes
Note: All assessments will apply to both the DE and CE Phases unless otherwise specified.				
Physical Exam	X	X		1. EOT safety assessments to occur within 30 days from when decision made to discontinue treatment and prior to the new anti-MM treatment (whichever occurs first). 2. PFS follow-up every 28 days (±7 days) for participants who discontinue IP for a reason other than PD. Disease evaluations will continue until confirmed PD, death, start of a new anti-cancer treatment, withdrawal of consent, or end of the study whichever occurs first. Once participant progresses, move to OS follow-up. 3. The survival for MM will be documented in medical charts. No visit necessary. Contacts will be made via phone calls, emails or other means of communications every 12 weeks (±14 days) until end of study. Participant does not need to come in for visit unless they are being followed for corneal signs that are present at the end of study treatment. 4. AEs/SAEs will be collected until at least 70 days post last dose of study treatment and immune-related AEs/SAEs will be collected up to 90 days post last dose. All SAEs related to study participation (e.g., protocol mandated procedures, tests, or change in existing therapy) are to be collected from consent through OS follow-up. All AE's/SAE's will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up. 5. End of treatment ophthalmic exam to be performed by a qualified eye care specialist. See 208887 MP Section 8.2.7 for list of exams. 6. Participants with treatment-related corneal exam findings, ocular symptoms and/or change in vision at EOT will be followed every 3 months (±7 days), or more frequently if clinically indicated, until return to baseline, deemed clinically stable by the qualified eye care specialist (see 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.
Vital Signs (BP, HR, Body Temperature)	X	X		
AEs	X[4]	Related SAEs only[4]	Related SAEs only[4]	
Concomitant Medications	X	X		
Safety				
Ocular Exam	X[5]	X[6]	X[6]	
ECOG Performance Status	X	X		
Hematology (CBC)	X[7]	X[7]		
Clinical chemistry	X[7]	X[7]		
Pregnancy Test	X[8]	X[8]	X[8]	
eGFR	X[9]			
Urinalysis (dipstick) OR Spot Urine (albumin/creatinine ratio)	X[10]			
ECHO or MUGA scan for LVEF	X[11]			
Disease Evaluation				
UPEP 24 hr urine collection	X[20]	X[20]		
Urine immunofixation 24 hr urine collection	X	X		
SPEP	X	X		
Serum immunofixation	X	X		
Serum FLC assay	X	X		
IgG, IgM, IgA	X	X		
IgD or IgE	X[12]	X[12]		

Study Assessments	End of Treatment Visit[1]	PFS Follow-up[2]	OS Follow-up[3]	Notes
Note: All assessments will apply to both the DE and CE Phases unless otherwise specified.				
Calcium corrected for albumin (serum)	X	X		7. CBC may be done more frequently as clinically indicated. Refer to 208887 MP Appendix 2 for comprehensive list of lab tests. 8. Final pregnancy test (serum or urine) must be performed per 208887 MP Section 12.2. Follow-up pregnancy assessments should be performed per 208887 MP Section 12.7.3. 9. eGFR as calculated by MDRD formula (208887 MP Appendix 6). 10. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥2+, or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab (first void). 11. ECHO or MUGA scan for LVEF only done as clinically indicated. The same procedure used at Screening should be used throughout the study. 12. IgD/IgE testing is only required for participants with IgD or IgE myeloma. 13. 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
Skeletal survey	X[13,14]	X[13,14]		
Imaging for Extramedullary Plasmacytoma Assessment (by whole body CT or whole body MRI or CT/PET)	X[14,15]	X[14,15]		
PK and ADA				
Plasma PK for belantamab mafodotin	X[17]			
Serum Immunogenicity (ADA) for belantamab mafodotin	X			
Serum Immunogenicity (ADA) for isatuximab	X	X[16]		
Plasma PK for isatuximab	X[17]	X[17]		
Biomarkers				
Hematology (TBNK and/or enhanced TBNK cell activation panel)	X[18]	X[18]		
BM Aspiration/Biopsy				
BM aspirate for MRD testing		X[19]		
BM aspirate and/or core biopsy for local Disease assessment	X[19]	X[19]		
BM core biopsy to assess sCR (local)	X[19]	X[19]		

Study Assessments	End of Treatment Visit[1]	PFS Follow-up[2]	OS Follow-up[3]	Notes
Note: All assessments will apply to both the DE and CE Phases unless otherwise specified.				
BM aspirate for BCMA and/or CD38 expression and biomarker research	X[19]			30 days prior to C1D1 may be used for Screening. Same modality used at Screening should be used throughout study. 14. At the time of suspected disease progression or as clinically indicated. Same modality used at Screening should be used throughout study. 15. In participants with extramedullary MM, if the last radiographic assessment occurred ≥8 weeks prior withdrawal from study treatment, and PD has NOT been documented otherwise, a new assessment should be obtained at the time the participants withdrew from study treatment. To be performed by the same method throughout the study as was done at baseline (i.e., if CT/PET scan was used as baseline, participant needs to be followed by CT/PET scans). Selected target lesions need to be measured 16. Collect ADA sample ONLY for isatuximab 90 days post last dose (±14 days). 17. Collect PK sample ONLY for isatuximab 90 days post last dose (±14 days). Pharmacokinetic and accompanying sBCMA sample collection may be terminated when sufficient data have been collected. 18. Please refer to Table 8 for scheduled biomarker sample collection. 19. Please refer to Table 6 for scheduled BM collection procedures to include aspirate and biopsy. 20. UPEP will only be performed for participants who had detectable M-protein only in the urine at screening. For all other participants, UPEP will be performed only after a tumor response based on SPEP protein during treatment is observed, where UPEP on 24 hours urine sample is required to confirm the response per IMWG criteria.

Table 6 SoA – Bone Marrow Aspirate/Biopsy Collection

Timepoint	BM aspirate for FISH testing[1,3]	BM (core biopsy and/or aspirate) for disease assessment[1]	BM aspirate for MRD testing for disease assessment[2, 6]	BM aspirate for BCMA and/or CD38 expression and biomarker research[2]
Screening	X	X [4]	X	X
VGPR or suspected CR/sCR	X	X[5]	X	
EOT	X	X		
Suspected PD (only if PD not evident otherwise)		X[5]		
At PD				X[7]

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

2 These assessments will be performed at a central laboratory.

3 See Table 31 in 208887 MP for details on FISH.

4 At Screening, IHC of bone marrow core biopsy is preferred for quantitative assessment of malignant 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.

5 At EOT or PFS follow-up, only to confirm CR/sCR or suspected PD (if not shown by other methods) for plasma cell assessment by IHC from aspirate. 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 bone marrow procedure required for CR and sCR assessment.

6 MRD samples to be collected at Screening, and at the time of first achieving VGPR or better. Thereafter, MRD testing must be repeated every 6 months (±1 month) until PD. This also applies to participants who discontinue IP for reasons other than PD and have current disease response of VGPR or better. In case of deepening of response from VGPR to CR, or achieving CR without prior VGPR, MRD testing must be performed at the time of achieving suspected CR and repeated every 6 months (±1 month) until PD. Sample collection may be terminated when sufficient data have been collected, and this applies across all sub-studies. Note that MRD testing will be done by NGS method.

7 **Optional BM consent required.** Additional BM aspirate samples may be collected at any time during the study for biomarker research and if possible, as part of the same BM collection for disease assessments including MRD. Sample collection may be terminated when sufficient data have been collected.

Table 7 Pharmacokinetic and ADA (Belantamab Mafodotin and Isatuximab) and sBCMA Biomarker Blood Sampling Collection

Note that the sample collection as presented below may be terminated when sufficient data have been collected.

Cycle Day[2]	Sampling Times	Belantamab Mafodotin PK	sBCMA	Belantamab Mafodotin ADA	Isatuximab PK	Isatuximab ADA	Sampling window
C1D1	Predose belantamab mafodotin	X	X	X			Within 30 min prior to start of infusion
	EOI belantamab mafodotin	X	X				0–10 min **after** EOI
	Predose Isatuximab[1]				X	X	Draw along with predose belantamab mafodotin sample
	EOI Isatuximab [1]				X		0–10 min after EOI
	EOI+1h Isatuximab[1]				X		±10 min
	2 hr after SOI belantamab mafodotin	X	X				±15 min
	24 hr after SOI belantamab mafodotin (DE only)	X	X				±2 hr
C1D8	Predose Isatuximab[1]	X	X		X		Predose
C1D15	Predose Isatuximab[1]	X	X		X		Predose
C1D22	Predose Isatuximab[1]	X	X		X		Predose
C2D1	Predose belantamab mafodotin	X	X	X			Within 30 min prior to start of infusion (if belantamab mafodotin dosing at C2D1 is delayed, pre-dose isatuximab PK sample still to be collected)
	EOI belantamab mafodotin	X	X				Within 5 min (0 – 10 min) **after** EOI

Cycle Day[2]	Sampling Times	Belantamab Mafodotin PK	sBCMA	Belantamab Mafodotin ADA	Isatuximab PK	Isatuximab ADA	Sampling window
	Pre-dose Isatuximab[1]				X	X	Draw along with pre-dose belantamab mafodotin sample
	EOI Isatuximab[1]				X		±10 min
C2D15	**Pre-dose Isatuximab[1]**				X		Pre-dose
C3D1	**Pre-dose Isatuximab[1]**				X	X	Pre-dose
C3D15	**Pre-dose Isatuximab[1]**				X		Pre-dose
C4D1	**Pre-dose belantamab mafodotin**	X	X	X			Within 30 min prior to start of infusion
	EOI belantamab mafodotin	X	X				Within 5 min (0 – 10 min) **after** EOI
	Pre-dose Isatuximab[1]				X	X	Draw along with pre-dose belantamab mafodotin sample
	EOI Isatuximab[1]				X		±10 min
	EOI+1h Isatuximab[1]				X		±10 min
C4D15	**Pre-dose Isatuximab[1]**				X		Pre-dose
C5D1	**Pre-dose Isatuximab[1]**				X	X	Pre-dose
C6D1	**Pre-dose belantamab mafodotin**	X	X	X			Within 30 min prior to start of infusion
	EOI belantamab mafodotin	X	X				Within 5 min (0 – 10 min) **after** EOI
	Pre-dose Isatuximab[1]				X	X	Draw along with pre-dose belantamab mafodotin sample
C7D1	**Pre-dose Isatuximab[1]**				X	X	Pre-dose
C8D1	**Pre-dose Isatuximab[1]**				X	X	Pre-dose

Cycle Day[2]	Sampling Times	Belantamab Mafodotin PK	sBCMA	Belantamab Mafodotin ADA	Isatuximab PK	Isatuximab ADA	Sampling window
C9D1	**Pre-dose belantamab mafodotin**	X	X	X			Within 30 min prior to start of infusion
	EOI belantamab mafodotin	X	X				Within 5 min (0 – 10 min) **after** EOI
	Pre-dose Isatuximab[1]				X	X	Draw along with pre-dose belantamab mafodotin sample
C10D1	**Pre-dose Isatuximab[1]**				X	X	Pre-dose
C12D1	**Pre-dose belantamab mafodotin**	X	X	X			Within 30 min prior to start of infusion
	EOI belantamab mafodotin	X	X				Within 5 min (0 – 10 min) **after** EOI
C18D1	**Pre-dose belantamab mafodotin**	X	X	X			Within 30 min prior to start of infusion
With every MRD assessment			X				
EOT		X	X	X	X	X	
90 Days post last dose					X	X	

1. To be obtained irrespective of any belantamab mafodotin dose delay.
2. Sampling will be stopped at the primary cutoff date or closure of sub-study by sponsor, whichever comes first.

Table 8 Biomarker Sample Collection

Cycle/Dose and Day	Sampling window	Hematology (TBNK and/or enhanced TBNK activation panel)[1]
C1D1	Pre-dose belantamab mafodotin	X
C2D1	Pre-dose belantamab mafodotin	X
C3D1	Pre-dose belantamab mafodotin	X
C4D1	Pre-dose belantamab mafodotin	
C6D1	Pre-dose belantamab mafodotin	
With every MRD assessment	Anytime	
Q4W regardless of dosing	Anytime	
EOT	Anytime	
PD	Anytime	X

1. Samples will be used to characterize NK cells as part of or independently from immunophenotyping.

Table 9 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 8.

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

2. INTRODUCTION

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

Information and details specific to Sub-study 5 are in Section 2.1, Section 2.2, and Section 2.3 below.

2.1. Rationale for Combination of Belantamab Mafodotin with Isatuximab

Belantamab mafodotin employs distinct mechanisms of action for its anti-tumor activity including ADC and antibody-dependent cellular cytotoxicity and phagocytosis ADCC/ADCP. These mechanisms of action are designed to enable anti-tumor activity against non-dividing (ADCC) as well as dividing (ADC) cells. Moreover, ADC-induced cell death by belantamab mafodotin was recently shown to be immunogenic as measured by cell surface externalization of calreticulin and secretion of high mobility group box 1

and adenosine triphosphate. ICD induced by belantamab mafodotin resulted in activation of dendritic cells in vitro and in vivo and is believed to contribute to T cell-mediated anti-tumor responses and durable immunity. In vivo, induction of ICD correlated with an adaptive immune response and long-term tumor regression in immune-competent murine allograft models [Montes De Oca, 2021]. Therefore, enhanced antigen presentation through belantamab mafodotin-mediated ICD, and the resulting T cell-mediated durable immunity suggests that additional therapeutic benefit may be obtained from combination treatment of belantamab mafodotin with immune-enhancing agents, such as isatuximab.

Isatuximab (SARCLISA) is an IgG1-derived monoclonal antibody that binds to a specific extracellular epitope of the CD38 receptor, a transmembrane glycoprotein that is expressed on plasma cells and other lymphoid and myeloid cell populations. Since its expression is very high and uniform on myeloma cells, CD38 is a good target for novel therapeutic strategies. Isatuximab, once bound to a CD38-expressing cell, promotes tumor cell destruction via multiple mechanisms, including: ADCC, ADCP, complement-dependent cytotoxicity, and direct apoptosis. Also, isatuximab has been shown to inhibit suppressive activity of Tregs (which display higher CD38 levels vs conventional T cells in MM patients) by decreasing their number, reducing immune inhibitory cytokines and impeding their trafficking. In addition, it enhances CD8+ T effector and NK cell-mediated anti-tumor activity immune response [Feng, 2017].

Isatuximab in combination with pomalidomide and dexamethasone (pom/dex) was approved by the FDA and EMA for patients with relapsed/refractory multiple myeloma (RRMM) who have received at least 2 prior lines of therapy, including lenalidomide and a proteasome inhibitor. The approval was granted based on the data from the Phase 3 ICARIA-MM (NCT02990338) study, which showed improved ORR and PFS with isatuximab plus pom-dex as compared to pom-dex alone (ORR 60% vs 35%, p <0.0001; median PFS 11.5 months (95% CI 8·9–13·9) vs 6.5 months (4·5–8·3), HR 0.596, 95% CI, 0.44–0.81, p = 0.0010) [Attal, 2019].

Given recent experience with monoclonal antibodies which has expanded the treatment option landscape in MM and the demonstrated clinical activity of each as single-agent therapy in RRMM, the combination therapy of belantamab mafodotin with isatuximab is an attractive, potentially beneficial treatment option for exploration. Due to complementary mechanisms of action, the combination of belantamab mafodotin with isatuximab may have additive or perhaps synergistic effects and further enhance clinical benefits for MM patients. Additionally, based on the multi-modal mechanisms of action of both belantamab mafodotin and isatuximab, the proposed combination could potentially also further capitalize on augmentation of NK cell-mediated ADCC, facilitation of ADCP, and/or enhancement of ICD and immune-modulation of T cells (through further increase of CD4+, CD25- T cells and decrease of CD4+CD25+Foxp3+ Tregs).

This study will evaluate the safety, tolerability and preliminary efficacy of belantamab mafodotin in combination with isatuximab in adult participants with RRMM, who have been previously treated with at least 3 prior lines of therapy that include the following: an immunomodulatory agent, a proteasome inhibitor (PI) and an anti-CD38 monoclonal antibody (mAb) treatment.

2.2. Background for Isatuximab

An overview of isatuximab is provided below, a summary of relevant data and information available for Isatuximab IV as of 05 January 2020. Detailed information concerning the biology and mechanisms of action, PK/pharmacodynamics (PK/PD), safety and efficacy of isatuximab may be found in the current IB [Isatuximab, 2024].

Isatuximab is an immunoglobulin (Ig) G1 mAb that selectively binds to the human cell surface antigen molecule classified as CD38. The CD38 antigen is expressed in a number of hematological cells and malignancies from B-lymphocyte, T-lymphocyte, and myeloid origin. Therefore, isatuximab has the potential to be a therapeutic agent for a number of hematological malignancies, including multiple myeloma.

Primary Pharmacology

The biological mechanisms by which isatuximab can induce the killing of CD38-positive tumors that have been demonstrated in tumor cell lines are:

1. ADCC
2. ADCP
3. Complement-dependent cytotoxicity
4. Induction of apoptosis (pro-apoptosis)
5. Activation of NK cells

Secondary Pharmacology

No significant cytokine release, cellular activation, or depletion was induced by isatuximab in in vitro assays with normal human PBMC, despite some induction of apoptosis in purified NK cells.

Pre/Nonclinical Data

In vivo anti-tumor activity of isatuximab was demonstrated in several SC or IV implanted hematological tumor models. As a single agent, anti-tumor activity was observed in MM, non-Hodgkin's lymphoma, and acute lymphocytic leukemia tumor models.

In ex vivo primary patient tumor samples, isatuximab has demonstrated a direct proapoptotic effect in MM samples and acute myeloid leukemia samples.

In Good Laboratory Practice cross-reactivity studies with normal human tissues, isatuximab was bound specifically to lymphoid tissues (spleen, thymus, lymph node, and tonsil), bone marrow, pituitary gland (endothelial cells), prostate gland (glandular epithelial cells), and infiltrating or resident round cells (macrophages and/or lymphocytes) of the innate immune system including Kupffer cells in the liver. In preliminary non- Good Laboratory Practice tissue cross-reactivity studies using a different isatuximab batch and different mAb concentrations, additional staining was also observed in the brain (astrocytes) and lung (bronchial epithelium). Staining of all nonlymphoid tissue elements was interpreted as evidence of cross-reactivity, indicating potential unintended off-target sites.

Isatuximab is specific for human CD38 protein. In the absence of a relevant animal species for toxicity testing, a repeat-dose IV (once weekly for 3 weeks) study was conducted in cynomolgus monkeys (a non-pharmacologically-relevant species) with isatuximab IV in its clinical formulation in order to evaluate potential non-targeted and nonspecific general toxicity. In this cynomolgus monkey toxicity study, no compound-related changes were noted in any parameters evaluated, and the no-observed adverse effect level was 100 mg/kg/week (highest dose tested). In rabbits (a non-pharmacologically-relevant species), isatuximab in its clinical formulation was well tolerated locally after IV (clinical route of administration), IM, intra-arterial, SC, or paravenous injection (routes by which it might be administered by accident or accidental extravasations) at concentrations up to 5 mg/mL. In addition, isatuximab IV in its clinical formulation did not produce compound-related macroscopic or microscopic changes at the injection sites following QW IV infusion for 3 weeks in cynomolgus monkeys up to 20 mg/mL (the maximum concentration tested).

Plasma compatibility and the hemolytic potential of isatuximab IV in its clinical formulation in human whole blood were tested in vitro at concentrations up to 2.5 mg/mL. No hemolytic effect or plasma incompatibility was observed.

Above Background summary text excerpted from Isatuximab IB, Section 2 [Isatuximab, 2024].

2.2.1. Isatuximab Pharmacokinetics and Pharmacodynamics

Isatuximab displays nonlinear PK with target mediated drug disposition. Following IV infusion, isatuximab exhibits a low volume of distribution (8.75 L), which indicates it is primarily distributed into the circulatory system and undergoes elimination by parallel linear and nonlinear pathways. At 10 mg/kg QW/Q2W dose and schedule, the CL is the predominant elimination pathway, indicative of the saturation of the target. Additionally, as the linear CL is time dependent, a decrease by 50% from its initial value over the first 8 weeks of treatment is predicted for a typical patient based on population PK analysis. The typical half -life at steady-state associated with the linear CL is 28 days.

Isatuximab exposure increases in a greater than dose proportional manner from 1 to 20 mg/kg following Q2W schedule, while no deviation to the dose proportionality is observed between 5 mg/kg and 20 mg/kg QW. The median time to reach steady state was 8 weeks with a 3.1-fold accumulation.

The main source of intrinsic PK variability identified in patients based on population PK analysis is Ig myeloma type (IgG vs non-IgG), β2 microglobulin, and body weight. Myeloma type had the greatest impact with a 2-fold lower steady-state exposure in IgG patients compared to non-IgG patients. In addition, the impact of weight is already integrated by weight-based dosing of isatuximab. The other demographic characteristics (age, race, or gender) had no to limited effect on the PK of isatuximab. Mild to severe renal impairment or mild hepatic impairment do not have impact on the PK of isatuximab, based on population PK analysis. Overall, no dose adjustments of isatuximab are recommended based on demographic or disease characteristics.

Concomitant administration of IPd, ILd, and ICBd did not appear to alter isatuximab exposure or vice versa. Clinical data from the Phase 3 study confirmed the efficacy and safety of this dosing regimen and PK/PD analyses showed a positive association of isatuximab exposure and the probability of ORR and PFS. These results support the recommended 10 mg/kg QW/Q2W dose of isatuximab in combination therapy.

Overall, the clinical pharmacology data support the proposed dose regimen of 10 mg/kg QW for 4 weeks followed by Q2W when given in combination with pom/dex in MM patients.

Above PK/PD summary text excerpted from Isatuximab IB, Section 6.1.9 [Isatuximab, 2024].

2.2.2. Safety Data for Isatuximab Monotherapy

The overall safety profile of isatuximab, well characterized within its clinical studies, is predictable and manageable.

At the cutoff date of 05 January 2020, an estimated 1652 participants have been exposed to isatuximab through Phase 1, 2 and 3 studies in the clinical development program as monotherapy or in combination with other agents. The total number of participants exposed to isatuximab monotherapy is estimated to be 458. Twelve studies overall have been conducted in RRMM, 5 with single agent/monotherapy administration of isatuximab for which 4 studies are complete and 1 remains ongoing. An overview of all completed and ongoing clinical studies with isatuximab is available in Table 80 and Table 81 of the IB [Isatuximab, 2024].

Pooled safety analysis of completed monotherapy studies [TED10893 (Phase 1 and Phase 2 Stage 1) and TED14154 (Part A)] are summarized in more detail in Section 6.2.2.3.2 of the IB, excerpts follow:

The most common TEAEs- excluding IRRs and hematological TEAEs- were fatigue (35%), nausea (34%), cough (26%), upper respiratory tract infection (25%) diarrhea (24%) and headache (23%).

The most frequent Grade 3/4 hematologic laboratory abnormalities during treatment were lymphopenia (33%), leukopenia (11%), anemia (21%), thrombocytopenia (15%), and neutropenia (17%); the frequency of these abnormalities did not appear to be dose-dependent. Grade 3 and higher hematologic TEAEs for 10 mg/kg dosing in ≥5% of participants were anemia (18%), thrombocytopenia (5%).

Infusion reactions/IRRs have been reported as the most common adverse reactions consequent to the administration of isatuximab (whether administered as single agent or in combination with other anti-cancer agents). All IRRs started during the first isatuximab infusion and resolved on the same day in 98% of the cases. The most common (≥5%) symptoms of an infusion-related reaction included dyspnea, cough, chills, nausea, chest discomfort and coughing. The most common (≥1%) severe signs and symptoms included bronchospasm, hypertension and dyspnea.

Analysis of the IRRs reported in the 212 participants treated in the completed monotherapy studies [TED10893 (Phase 1 and Phase 2 Stage 1) and TED14154 (Part A)] showed:

- 51.9% of participants had an IRR, almost all Grade 1-2 (0.5% Grade 3, 1.4% Grade 4).
- Nearly 50% of the participants had IRRs upon the first administration of isatuximab, and 7.1% of the participants had IRRs during their second or subsequent infusions: 59.1% of all the IRRs resolved on the day of the infusion.
- The incidence of IRRs (all Grades) was higher at doses ≥10 mg/kg (56.8% of participants) than at doses <10 mg/kg (35.4% participants).
- There was no IRR reported after the first day of infusion.

For more details on clinical safety of isatuximab, please refer to the Isatuximab IB [Isatuximab, 2024].

2.2.3. Clinical Activity/Efficacy of Isatuximab Monotherapy

Efficacy results of completed monotherapy studies in participants with CD38+ hematologic malignancies [TED10893 (Phase 1 and Phase 2 Stage 1)] and RRMM [TED14154 (Part A)] are presented below. Data were collected for overall response rate by dose group for the pool of TED10893 Phase 1 and 2 Stage 1 and TED14154 Part A participants. All participants were evaluable for response. The overall response rate for isatuximab monotherapy in advanced RRMM is similar between 10 mg/kg QW/Q2W (N = 111) and 20 mg/kg QW/Q2W (N = 53) with 24.3% and 22.6% of patients, respectively.

Study TED10893 Phase 2 Stage 2 was conducted to evaluate the ORR of isatuximab at the monotherapy recommended dose and schedule as a single agent and in combination with dexamethasone; the final analysis confirms the efficacy of isatuximab monotherapy in heavily pre-treated participants with RRMM.

Twenty-six participants in the Isatuximab arm achieved a response and were evaluated for DoR- the median DoR was 8 months (1-21 months min/max). The median time to first response was 1.0 month (min: max of 1-9 months) and the median time to best response was 2.0 months (min: max of 2-10 months) for Isatuximab arm.

For more details on clinical efficacy of isatuximab monotherapy, please refer to the IB [Isatuximab, 2024].

2.3. Benefit:Risk Assessment

2.3.1. Risk Assessment

Table 10 outlines the risk assessment and mitigation strategy for Isatuximab. Belantamab mafodotin risk assessment and mitigation strategies are in the 208887 MP (see Section 2.3.1).

Table 10 Risks Related to Isatuximab

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Risk related to Isatuximab	
Infusion-Related Reactions (IRRs) and Hypersensitivity	Risk for IRRs and hypersensitivity is inherent to many mAbs [Brennan, 2010]. IRRs have been reported as the most common adverse reactions consequent to the administration of isatuximab (whether administered as single agent or in combination with other anti-cancer agents). IRRs associated with isatuximab are seen most commonly with first administration, not dose- dependent, and participants do not appear to sustain sequelae. Infusion reactions generally do not cause therapy discontinuation and tend not to recur at subsequent administrations. Occasionally, these reactions may be serious and systemic (as with anaphylactic reactions, which have been reported in 5 participants throughout the isatuximab program, corresponding to an incidence of 0.3%). Others have been referred to as Cytokine Release Syndrome. While no association between transient cytokine increases and the occurrence of IRRs has been demonstrated in participants, administration of isatuximab in the clinical setting has been correlated with a case of Grade 2 cytokine release syndrome in study TED10893 reported as a medical diagnosis in a participant who subsequently received further administrations of single-agent isatuximab without recurrence of symptoms suggestive of cytokine release syndrome. In addition, 2 cases of Grade 2 cytokine release	Participants with history of severe hypersensitivity to another mAb are ineligible for this study. Refer to Table 13 for further details on management of IRRs with isatuximab. CRS Management Guidelines have been included in 208887 MP Section 11.1.2, Table 23.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	syndrome were reported in study EFC14335 (ICARIA), isatuximab in combination with pomalidomide and low dose dexamethasone.	
Neutropenia and Potential Increased Risk of Infections	Potential isatuximab modulation of cell survival and differentiation of both lymphoid and myeloid cells due to CD38 presence on normal immune cells could increase risk of infections. For single-agent isatuximab there were no SAEs of neutropenia and 2 (0.4%) SAEs of febrile neutropenia. Grade 3/4 neutropenic events during monotherapy occurred in 17% of participants.	Management guidance as per Table 15 in the 208887 MP. CBC with differential per SoA; or more frequently per local guidance Participants with neutropenia to be monitored for s/s infection. Prophylactic antibiotics, per physician discretion and local institutional guidance. Antifungal and antiviral prophylaxis may be considered. Dose delays and use of colony stimulating factors (CSFs) may be considered to allow improvement in neutrophil count, except in during Cycle 1.
Thrombocytopenia	Grade 3/4 hematologic laboratory abnormalities during isatuximab monotherapy treatment included thrombocytopenia (15%); frequency of these hematologic abnormalities did not appear to be dose-dependent. Grade 3 and higher hematologic TEAEs for 10 mg/kg dosing in ≥5% of participants included thrombocytopenia (5%).	Management guidance as per Table 15 in the 208887 MP. CBC with differential per SoA; or more frequently per local guidance. Monitoring for signs/symptoms of bleeding as per local standard medical practice.
Interference with Response Assessment	Isatuximab is an IgG kappa monoclonal antibody that can be incidentally detected on both SPE and immunofixation assays used for the clinical monitoring of endogenous M-protein of participants with multiple myeloma. This interference can impact the accuracy of the determination of CR in some participants with IgG kappa myeloma protein, with incidence of CR being potentially underestimated.	All required elements of MM disease assessment- including serum, urine, bone marrow assessments and imaging for extramedullary disease- will be performed per protocol. Interference assay to be utilized.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Viral Reactivation-Hepatitis	Participants with MM undergoing immunosuppressive drug therapy are at high risk of hepatitis reactivation.	Participants with evidence of infection with hepatitis B and/or C are excluded. Exclusion Criteria in the 208887 MP: 11. Presence of HbsAg or HbcAb at Screening or within 3 months prior to first dose of study treatment 12. Positive Hepatitis C antibody test result or positive Hepatitis C RNA test result at Screening or within 3 months prior to first dose of study treatment. Note: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained. Hepatitis RNA testing is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.
Potential Interference with Blood Bank Serologic Testing	Based on information published in relation to a drug of the same class as isatuximab (daratumumab), the CD38 protein is weakly expressed on the surface of red blood cells. Because of this, anti-CD38 antibodies in patients' plasma can lead to pan-reactivity and thus interfere with various blood bank serologic tests. For example, plasma samples from daratumumab-treated patients showed positive reactions in indirect antiglobulin tests, antibody detection (Screening) tests, antibody identification panels, and antihuman globulin crossmatches. ABO/RhD typing is not affected by anti-CD38 antibody. To avoid potential problems with blood transfusion, the American Association of Blood Banks recommends that patients being treated with anti-CD38 antibodies have blood type and antibody screen test (indirect antiglobulin test [indirect Coombs test]) performed at baseline. After treatment, and each time before blood transfusion, the antibody screen test (indirect antiglobulin test [indirect Coombs test]) should be performed.	1) Blood type and screen to be performed at Screening. Consider full blood phenotyping pre-treatment, depending on local lab availability. 2) Indirect antiglobulin test (indirect Coombs test) to be performed at Screening or prior to first study treatment administration at C1D1, if results are not already available, as well as prior to blood transfusions post Screening/on study. See Section 8.2.1.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential Embryo-Fetal Toxicity	The effects of isatuximab on reproductive toxicity, pregnancy and lactation have not been investigated in formal toxicity studies. Therefore, the effects of isatuximab on reproductive organs in males and females are unknown.	Management of Pregnancy and Contraception as outlined in the 208887 MP Section 8.3.7, 208887 MP Appendix 7 and required testing/follow-up per SoAs.
Tumor Lysis Syndrome (potential risk)	Tumor Lysis Syndrome occurs due to the rapid destruction of tumor cells with massive release of cell contents including uric acid, phosphorus, and potassium. Uric acid levels may be increased due to the breakdown of DNA and lead to acute renal failure. Hyperphosphatemia may cause secondary hypocalcemia. TLS is more typically seen in rapidly proliferating hematologic malignancies, but may occur in MM. The incidence of TLS was 0.4% based on an assessment of the isatuximab clinical database with data cutoff of 07 February 2020 prepared for the label update after the first analysis of the IKEMA study.	Management is described in Section 6.6.3.

Overlapping Toxicities

Safety data for single-agent belantamab mafodotin is outlined in the 208887 MP Section 2.2.4.

Based upon observed AEs/AESI for each agent, there is the potential for overlapping risks for IRRs, thrombocytopenia and neutropenia.

Summary safety data for belantamab mafodotin for these risks are listed below.

- In clinical studies, the incidence of IRRs with belantamab mafodotin 2.5 mg/kg was 21%, and most (90%) occurred during the first infusion. Most IRRs were reported as Grade 1 (6%) and Grade 2 (12%) while 3% experienced Grade 3 IRRs. Serious IRRs were reported by 4% of participants and included symptoms of pyrexia and lethargy. Median time to onset and the median duration of the first occurrence of an IRR was 1 day. One participant (1%) discontinued treatment due to IRRs, experiencing Grade 3 IRRs at first and second infusion. No Grade 4 or 5 IRRs were reported.
- Thrombocytopenic events, (thrombocytopenia and platelet count decreased) occurred in 38% of participants. Grade 2 thrombocytopenic events occurred in 3% of participants, Grade 3 in 9%, and Grade 4 in 13%. Grade 3 bleeding events occurred in 2% of participants and no Grade 4 or 5 events were reported. Belantamab mafodotin has demonstrated a maximal effect on platelets at around Days 8-11 in a 3-week dosing cycle that typically resolves by the beginning of the next cycle, although in some cases, dose reductions or delays have been implemented to manage.
- 15% of participants experienced neutropenic events, with 9% experiencing Grade 3/4 in severity, all of which were deemed treatment-related. None of the Grade 3/4 events was associated with a concomitant report of Grade ≥2 infection or sepsis. None of these events were reported as SAEs and none resulted in a change in treatment. The incidence was considered low and not elevated compared to reported rates in the populations of RRMM patients. [GSK Document No. RPS-CLIN-105644, 2024].

Mitigation strategies for these risks may be found in Table 15 of the 208887 MP for belantamab mafodotin and Table 10 of this protocol for isatuximab, as well as in Section 6.6 of this protocol.

2.3.2. Benefit Assessment

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

Both isatuximab and belantamab mafodotin have demonstrated clinically meaningful efficacy in the treatment of patients with RRMM. Based on current data from the isatuximab development program and the observed anti-tumor activity of other anti-CD38 mAbs in the same class, isatuximab is expected to exhibit clinical activity in the target relapsed/refractory multiple myeloma patient population, potentially further enhanced in combination with belantamab mafodotin.

2.3.3. Overall Benefit: Risk Conclusion

Detailed information regarding the known and expected benefits and risks, AESI and exploration/selection of dose levels for belantamab mafodotin may be found in 208887 MP Section 2.2.4 and the IB [GSK Document No. RPS-CLIN-105644, 2024].

This is the first study testing the combination of isatuximab plus belantamab mafodotin in participants with relapsed/refractory multiple myeloma that have been treated with standard therapies. The current nonclinical and clinical safety information for both belantamab mafodotin and isatuximab used as single agents provide support for their use in combination in the target RRMM patient population.

Safety data for isatuximab is briefly summarized in Section 2.2.2, with detailed information available in the Isatuximab IB [Isatuximab, 2024]. The most frequent Grade 3/4 hematologic laboratory abnormalities during treatment were lymphopenia (33%), leukopenia (11%), anemia (21%), thrombocytopenia (15%), and neutropenia (17%); the frequency of these abnormalities did not appear to be dose-dependent. Grade 3 and higher hematologic TEAEs for 10 mg/kg dosing in ≥5% of participants were anemia (18%), thrombocytopenia (5%). There is additionally a potential for isatuximab modulation of cell survival and differentiation of both lymphoid and myeloid cells due to CD38 presence on normal immune cells, which could increase risk of infections.

Due to complementary mechanisms of action and potentially overlapping side effects of IRRs, thrombocytopenia and neutropenia, there is the potential for increased risk of these events or other unknown AEs when these 2 agents are given in combination.

To ensure the safety of participants, a careful dose escalation of belantamab mafodotin will be implemented where no more than 1 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 3.4 mg/kg dose that has been shown to be well tolerated during the belantamab mafodotin monotherapy dose escalation and should provide a sufficient safety margin when isatuximab is added with starting fixed dose of 10 mg/kg. Further, close clinical monitoring will be implemented as per SoAs and supportive management guidance for IRRs are included in the 208887 MP Section 11 and Section 6.2.2 of this protocol. Further guidance for hematologic events, including neutropenia, is included in Table 15 of the 208887 MP – Dose Modification Guidelines for Belantamab Mafodotin-Related Adverse Events and Section 6.2 of this protocol.

Considering the mitigation strategies outlined to minimize risks to participants participating in this combination sub-study, the benefit:risk ratio is favorable given this potential benefit of additive/possibly synergistic anti-tumor activity of isatuximab in combination therapy with belantamab mafodotin in participants with RRMM.

3. OBJECTIVES AND ENDPOINTS

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

4. STUDY DESIGN

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

Information and details specific to Sub-study 5 are in Section 4.1 and Section 4.3 below.

4.1. Dose Exploration of Combination Treatment Belantamab Mafodotin Co-Administered with Isatuximab

The dose level of 1.9 mg/kg Q4W of belantamab mafodotin will be evaluated as the starting dose (Figure 1). Isatuximab dosing will be 10 mg/kg weekly for the first 5 doses, followed by every 2 weeks thereafter (in combination at both dose levels 1 and 2 for belantamab mafodotin). Two exploratory dose levels may also be evaluated (Figure 1). The sponsor may decide not to evaluate all dose levels based on data external to this study. Please see 208887 MP Section 4.1.1 for details of decision making during the DE Phase.

Cycle for dose level 1 will be Q4W. DLT evaluation period for Cycle 1 will be 28 days. Cycle for Dose level A and B will be Q8W. DLT evaluation period for Cycle 1 will be 56 days.

At least 3 participants will be enrolled at the starting dose (Dose Level 1). If the safety profile in the first 3 participants is deemed to be favorable by the SRT as per modified toxicity probability interval, then up to 7 additional participants will be enrolled at Dose Level 1, and Dose Level B can be initiated without requiring sentinel participants.

Dose Level A can be initiated at the same time as Dose Level 1 because belantamab mafodotin dose is lower and the dosing schedule is less frequent. At least 3 participants will be enrolled first at Dose Level A. If the safety profile in the first 3 participants is deemed to be favorable by the SRT as per modified toxicity probability interval, then up to 7 participants will be enrolled. The 3 sentinel participants requirement for Dose Level A may be removed if the data of the first 3 participants in Dose Level 1 become available and the safety profile is deemed favorable by the SRT.

4.2. Scientific Rationale for Study Design

Please refer to the 208887 MP.

4.3. Dose Justification

Clinical data from the Phase 3 study of isatuximab in combination with pomalidomide and dexamethasone confirmed the efficacy and safety of this dosing regimen and PK/PD analyses showed a positive association of isatuximab exposure and the probability of ORR and PFS. These results support the recommended 10 mg/kg QW/Q2W dose of isatuximab in combination therapy. See Section 2.2.1 and Isatuximab IB [Isatuximab, 2024] for further details.

Therefore, a dose of 10 mg/kg IV Q1W x 5 doses followed by Q2W thereafter is anticipated to be well tolerated without excessive, treatment-related toxicity in combination with belantamab mafodotin for this RRMM sub-study population.

The belantamab mafodotin cycle length was extended from Q3W to Q4W dosing to account for the isatuximab schedule of administration. With the 28-day cycle belantamab mafodotin is expected to be tolerated as well or better than with a 21-day cycle. A cycle length of 28 days is deemed appropriate with regard to efficacy, given the belantamab mafodotin mechanism of action, durable monotherapy responses despite dose delays observed in Study 205678, and the enhanced efficacy expected from co-administration of isatuximab.

Belantamab mafodotin at dose intensities lower than the starting regimen of 1.9 mg/kg Q3W has the potential in combination with isatuximab to provide similar efficacy with a more tolerable safety profile, particularly in terms of corneal toxicities. Therefore, Q8W dose intervals at doses of 1.4 and 1.9 mg/kg will be tested in combination with isatuximab in this sub-study to evaluate if these dosing regimens provide a better benefit-risk profile and improvements in participants' quality of life compared to higher belantamab mafodotin dose intensities.

4.4. Participant Completion and End of Study Definition

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

4.4.1. Participant Completion Definitions

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

4.4.2. Study Completion

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 5 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 5.

5.2. Exclusion Criteria

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

The exclusion criteria #39-41 below are in addition to the Exclusion Criteria already defined in 208887 MP Section 5.2. Please note: The numbering in the criteria may not be sequential from the MP.

39. Severe hypersensitivity to Isatuximab-irfc or to any of its excipients.
40. Prior treatment with other anti-CD38 monoclonal antibody within 6 months of the first dose of study drug treatment.
41. Known intolerance or hypersensitivity to infused proteins products, sucrose, histidine, and polysorbate 80.

5.3. Lifestyle Considerations

Please refer to the 208887 MP.

5.4. Screen Failures

Please refer to the 208887 MP.

6. STUDY TREATMENT

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

Information and details specific to Sub-study 5 are in Section 6.1, Section 6.2, Section 6.3 and Section 6.6 below.

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

6.1. Study Treatment(s) Administered

Specifications for belantamab mafodotin and Isatuximab in this study are outlined in Table 11.

Table 11 Belantamab Mafodotin and Isatuximab

Intervention Label	Belantamab mafodotin	Isatuximab
Intervention Name	GSK2857916 for Injection, 100mg	Isatuximab
Intervention Description	Belantamab mafodotin (GSK2857916) is a powder for solution for infusion	Concentrate for solution for IV infusion
Type	Drug	Drug
Dose Formulation	Lyophilized powder for solution for infusion	Concentrate for solution for IV infusion
Unit Dose Strength(s)	100 mg/vial	20 mg/mL (500 mg/25 mL and 100 mg/5 mL)
Dosage Level(s)	2.5 mg/kg Q3W	10 mg/kg QW/Q2W
Route of Administration	Delivered as IV solution and infused over 30-60 minutes	Delivered as IV solution as per instructions outlined below, Section 6.2.1.3.
Dosing instructions	Reconstitute belantamab mafodotin for Injection, 100 mg with 2.0 mL of sterile WFI, dilute with saline before use. Dilute GSK2857916 in normal 0.9% saline to the appropriate concentration for the dose. Doses of GSK2857916 are to be administrated as an IV infusion via an infusion pump. See Investigator's Brochure for compatible administration materials GSK2857916 IB [GSK Document No. RPS-CLIN-105644, 2024].	Please refer to Pharmacy Manual
Use	IMP	IMP
Authorized AxMP / Unauthorized AxMP	Not applicable	Not applicable
Sourcing	GSK	Sanofi
Packaging and Labeling	Study Treatment will be provided in vials. Each vial will be labeled as required per country requirement.	Study Treatment will be provided in vials. Each vial will be labeled as required per country requirement.
Current / former name(s) or alias(es)	Not applicable	Not applicable

6.2. Administration of Belantamab Mafodotin and Isatuximab

- Belantamab mafodotin will be administered before administration of isatuximab.
- Belantamab mafodotin will be administered to participants IV as mg/kg calculated dose at the study site. The dose to be administered is based on actual body weight calculation and may be reduced for toxicity according to protocol guidelines.
- Administration will be documented in the source documents (208887 MP Section 12.1.8) and reported in the eCRF. The time of start and end of infusion will be documented in the eCRF.
- Belantamab mafodotin will be administered on Day 1 of each cycle at the assigned dose as an IV infusion (see Section 6.1 for details). Premedication is not required prior to infusion unless deemed medically necessary by the investigator, in which

case it should be administered according to institutional recommendations. In case of IRRs related to belantamab mafodotin the rules outlined in the 208887 MP Section 7.1.4 and in 208887 MP Section 11 should be followed.

- After the infusion of belantamab mafodotin has been completed, participants will be required to enter at least 1-hour rest period before starting isatuximab infusion where appropriate. Participants are to be premedicated 15 minutes following belantamab mafodotin infusion completion and prior to start of isatuximab infusion (see Section 6.2.1.1).
- The intended cycle time of belantamab mafodotin is 28 days (+3-day window) (Q4W) or 56 days (+3-day window) (Q8W) and cannot occur sooner/more frequently than this.
- Isatuximab will be administered via IV infusion Q1W x 5 doses, followed by Q2W thereafter. **Premedication is required prior to administration of isatuximab, see Section 6.2.1**.
- Isatuximab is to be administered as IV infusion at prescribed dosing at least 1 hour following completion of belantamab mafodotin infusion, see instructions for rate of administration in Section 6.2.1.3.

Table 12 Route of Administration and Dose Timing for Belantamab Mafodotin and Isatuximab in the DE Phase

	Belantamab Mafodotin	Isatuximab
Route of administration	IV infusion (see Section 6.1 for details)	IV infusion (see Section 4.1 for details)
Timing	Administer first, on Day 1 of each cycle	Start 1 h after belantamab mafodotin EOI on Day 1 dosing days where both combination agents to be given. Isatuximab dosing is Q1W x 5 doses and Q2W thereafter[1]. Premedication is required 15--60 mins prior to starting isatuximab infusion (see Section 6.2.1). For guidance about management/subsequent dosing if an infusion-related reaction (IRR) occurs please see Table 13.

1. Within a cycle, an isatuximab administration can be delayed for up to 1 day in case of weekly administration or 2 days for every 2 weeks administration. If the dose cannot be administered within 3 days, the isatuximab dose will be omitted. Only 1 omission per cycle is permitted. Further omissions must be discussed on a case-by-case basis with the sponsor.

Participants enrolled in the DE Phase and the CE Phase will be treated until disease progression, intolerable toxicity, informed consent withdrawal, the end of the sub-study, study or death (see exceptions below for permanent discontinuation of either belantamab mafodotin or isatuximab, Section 6.6.2).

6.2.1. Premedication and Rate of Isatuximab Infusion

6.2.1.1. Premedication for Isatuximab Administered in Combination with Belantamab Mafodotin

Required 15 minutes following belantamab mafodotin infusion completion (Section 6.2) and 15-60 minutes prior to starting isatuximab infusion:

- Dexamethasone 40 mg IV (or equivalent) (or 20 mg IV for participants ≥75 years of age)
- Acetaminophen 650 mg to 1000 mg orally (or equivalent)
- H_2 antagonists, selection at investigator's discretion, unless participant is already receiving H_2 antagonists/protein pump inhibitors for gastrointestinal prophylaxis
- Diphenhydramine 25 mg to 50 mg orally or IV (or equivalent). The IV route is preferred for at least the first 4 infusions.

Required 120 minutes prior to starting isatuximab infusion

Montelukast 10 mg orally (or equivalent).

Participants who do not experience an IR during the first 4 isatuximab infusions may have their need for subsequent premedication reconsidered at the investigator discretion, in consultation with the sponsor, to avoid unnecessary sedation.

6.2.1.2. Premedication for Isatuximab Administered as a Single Agent

Required 15-60 minutes prior to starting isatuximab infusion:

- Dexamethasone 40 mg IV (or equivalent) (or 20 mg IV for participants ≥75 years of age)
- Acetaminophen 650 mg to 1000 mg orally (or equivalent)
- H_2 antagonists, selection at investigator's discretion
- Diphenhydramine 25 mg to 50 mg orally or IV (or equivalent). The IV route is preferred for at least the first 4 infusions.

Required 120 minutes prior to starting isatuximab infusion

Montelukast 10 mg orally (or equivalent).

Patients who do not experience an IR during the first 4 isatuximab infusions may have their need for subsequent premedication reconsidered at the investigator discretion, in consultation with the sponsor, to avoid unnecessary sedation.

6.2.1.3. Rate

Isatuximab is to be administered as IV infusion at prescribed dosing following completion of belantamab mafodotin infusion on Day 1 of cycles and as per schedule below.

- Refer to the treatment schema (Figure 1) for cycle duration
- Dose regimen (Week 1 to 4): Isatuximab will be administered at the dose of 10 mg/kg IV weekly.
- Dose regimen (Week 5 and onwards): Isatuximab will be administered at the dose of 10 mg/kg every 2 weeks.

See Table 13 and detailed instructions for infusion rate/increase below:

- Do not administer isatuximab infusion solution concomitantly in the same IV line with other agents.

Infusion Rates

Following dilution, administer the isatuximab infusion solution IV at the infusion rates presented in Table 13.

Table 13 Infusion Rates for Isatuximab

	Dilution Volume	Initial Rate	Absence of IRR	Rate Increment	Maximum Rate
First infusion	250 mL	25 mL/hr	For 60 min	25 mL/hr every 30 min	150 mL/hr
Second infusion	250 mL	50 mL/hr	For 30 min	50 mL/hr every 30 min then increase by 100 mL/hr every 30 min	200 mL/hr
Third and subsequent infusions	250 mL	200 mL/hr	-	-	200 mL/hr

- **First infusion**: Infusion to be initiated at the rate of 25 mL/hr. In the absence of IRR after 60 minutes of infusion, the infusion rate to be increased by 25 mL/hr increments every 30 minutes, to a maximum of 150 mL/hr. In the event of Grade 2 IRRs during the first infusion, the infusion is to be interrupted and then restarted at one-half (12.5 mL/hr) of the initial infusion rate after the IRR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate to be increased in 25 mL/hr increments every 30 minutes, until the total volume is infused.
- **Second infusion**: Infusion to be initiated at 50 mL/hr. In the absence of Grade 2 IRR after 30 minutes of infusion, the rate is to be increased to 100 mL/hr for 30 minutes, then increased to 200 mL/hr for 30 minutes, then continue at 200 mL/hr until the total volume is infused. In case of Grade 2 IRR during the second infusion, the infusion is to be restarted at one-half (25 mL/hr) of the initial infusion rate once the IRR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate is to be increased in 50 mL/hr increments every 30 minutes, until the total volume is infused.

- **Third and subsequent infusions**: Infusion to be initiated at a fixed infusion rate of 200 mL/hr until the total volume is infused. In case of Grade 2 IRR during the third infusion, the infusion is to be restarted at one-half (100 mL/hr) of the infusion rate when the IRR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate is to be increased in 50 mL/hr increments every 30 minutes, until the total volume is infused.

Participants who do not experience an infusion reaction during the first 4 isatuximab infusions may have their premedication regimen modified with subsequent infusions (including dose reduction of dexamethasone or alternative administration of methylprednisolone) at the investigator's discretion and in consultation with the Medical Director.

One or several doses of dexamethasone can be decreased as per reduction levels below (Table 14) at the investigator's discretion and in consultation with the Medical Director.

Table 14 Dose Levels for Dexamethasone (PO/IV) Dose Reduction

Starting dose (PO/IV[1])	Dose Level -1	Dose Level -2	Dose Level -3	Dose Level -4
40 mg	20 mg	12 mg	8 mg	4 mg
20 mg (Participants ≥75 years of age[2])	12 mg	8 mg	4 mg	

1. Dexamethasone dosing should be administered IV for first 4 infusions of isatuximab.
2. All participants age ≥75 years will start dexamethasone dosing at 20 mg.

6.2.2. Management of Infusion-Related Reactions for Isatuximab

Table 15 Infusion-Related Reactions for Isatuximab

Symptom Severity NCI-CTCAE (Version 5.0)	Recommended Treatment
Mild (Grade 1): Infusion interruption or intervention not indicated	Continuation of isatuximab infusion per the judgment of the investigator following close direct monitoring of the participant's clinical status. Isatuximab infusion may be stopped at any time if deemed necessary. If stopped, IRR will be classified as Grade 2 as per NCI-CTCAE.
Moderate (Grade 2): Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hr	Stop isatuximab infusion. Give additional medication with diphenhydramine 25 mg IV (or equivalent) and/or methylprednisolone 100 mg IV (or equivalent) as needed. Isatuximab may be resumed only after participant recovery, at half the infusion rate before the interruption and with close monitoring, and may be increased subsequently at the investigator's discretion.
Severe or life-threatening (Grade 3 or 4): Grade 3: prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae Grade 4: life-threatening consequences; urgent intervention indicated	Stop the isatuximab infusion. Give additional medication with diphenhydramine 25 mg IV (or equivalent) and/or methylprednisolone 100 mg IV (or equivalent) and/or epinephrine as needed until the resolution of the AE or until the AE improves to Grade 1. Only then, if previous Grade 3, the infusion may be restarted at the investigator's discretion; if so, the infusion rate should be half of the initial infusion rate and may be increased subsequently at the investigator's discretion. If the severity of an infusion-related AE returns to Grade 3 after the restart of the infusion, the same procedure described above may be repeated at the investigator's discretion. If a Grade 3 infusion-related AE occurs

Symptom Severity NCI-CTCAE (Version 5.0)	Recommended Treatment
	for a third time, treatment with isatuximab will be definitively discontinued for that participant. In case of Grade 4, isatuximab will be permanently discontinued.

For IRRs that occur following and within 24 hours of isatuximab administration on Cycle 1 Day 1:

- Administration of belantamab mafodotin and isatuximab will be separated by 1 day at Cycle 2 (belantamab mafodotin to be given on Day 1 with premedication as outlined in 208887 MP Section 11.1.1, Table 22, and isatuximab to be given on Day 2 with premedication as outlined in Section 6.2.1.1).
- Evaluation of dosing and sequence of belantamab mafodotin and isatuximab for subsequent cycles following Cycle 2 to be determined in discussion between investigator and Medical Director.

6.3. Preparation/Handling/Storage/Accountability

Isatuximab kits will be supplied as a single vial in a carton, open-label and non-patient specific. Investigational product will be provided in a single-use vial as 20 mg/mL, 500 mg/25 mL and 100 mg/5 mL vials. 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 isatuximab preparation, administration, handling, storage, accountability and disposal and/or return of unused study treatment(s).

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 for Belantamab Mafodotin and Isatuximab in Combination

6.6.1. Permitted Dose Reductions for Belantamab Mafodotin when in Combination with Isatuximab

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

Table 16 Permitted dose reductions for Belantamab Mafodotin when in combination with Isatuximab

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

- If the participant cannot tolerate belantamab mafodotin after the allowed dose reductions, he/she must be withdrawn from belantamab mafodotin treatment for lack of tolerability.
- No dose reduction of belantamab mafodotin is permitted from dose level of 0.5 mg/kg in this sub-study.
- In case of full resolution of symptoms which lead to dose reduction, further treatment with belantamab mafodotin at the initially assigned dose may be considered by the investigator.
- Resuming treatment with belantamab mafodotin may be possible after the toxicity has resolved to Grade 1 or less.
- If isatuximab is permanently withdrawn the participant can remain on belantamab mafodotin; if belantamab mafodotin is permanently withdrawn the participant may continue on isatuximab, this latter continued treatment plan to be confirmed between GSK and Sanofi.

6.6.2. Permitted Dose Modifications of Isatuximab when in Combination with Belantamab Mafodotin

For further details regarding dose modifications see 208887 MP Section 6.6.3 Table 15 including management guidance for neutropenia and thrombocytopenia.

There are no dose modifications allowed for isatuximab. Fixed, weight-based dosing of isatuximab will be used during the study for all participants receiving isatuximab.

Dosing of isatuximab may be delayed if needed, but this will not affect the dosing schedule for belantamab mafodotin. Isatuximab may only be administered with belantamab mafodotin with the exception/possibility of isatuximab administration 1 day later than belantamab mafodotin in the case of an IRR on the date of belantamab mafodotin infusion, and select circumstances noted below. The maximum treatment delay to belantamab mafodotin treatment is 16 weeks and therefore the maximum treatment delay to isatuximab is 16 weeks +1 day, unless otherwise agreed in writing by the Medical Director. Please refer to 208887 MP Section 11 for details on management of AEs requiring delay or discontinuation of belantamab mafodotin dosing.

If belantamab mafodotin is delayed, then isatuximab will also be delayed *except in the following circumstances:*

- If belantamab mafodotin is delayed **due to ocular toxicity only**, isatuximab may continue to be administered as per scheduled dosing.
- If Grade≥3 hematologic toxicity (anemia, thrombocytopenia and neutropenia) that occurred on Day 1 improves to Grade ≤2 on Days 8, 15 and 22 of Cycle 1 or Day 15 of subsequent cycles (with CBC results obtained prior to dosing for isatuximab as per protocol), isatuximab may be administered.

For drug-related toxicities not listed in these tables, the general rule of withholding the dose for Grade ≥3 toxicity should be followed for both belantamab mafodotin and isatuximab. Resuming treatment will be possible with or without dose reduction after the toxicity has resolved to Grade ≤1 and with agreement between the Principal Investigator and Medical Director.

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

6.6.3. Tumor Lysis Syndrome Management

The participants at greatest risk of TLS are those with high tumor burden prior to treatment. These participants should be monitored closely and appropriate precautions should be taken (such as hydration, use of prophylactic uric acid lowering agents [e.g., allopurinol or rasburicase], regular measurement of electrolytes).

Tumor lysis syndrome has to be managed according to site usual practice. In the absence of local TLS guidelines, Table 17 provides some suggested parameters to be checked in case of TLS suspicion and high-level suggested recommendations for TLS management. Abnormalities listed in Table 17 do not support exclusively TLS diagnosis and any differential diagnosis also needs to be assessed if appropriate. After recovery, study treatment can be re-administered as planned at the same dose.

Suggested guidelines for the management of TLS are provided in Table 17.

Table 17 Management of Tumor Lysis Syndrome

TLS diagnosis	Recommended action
Laboratory TLS: ≥2 simultaneous abnormalities within 3 days prior to and up to 7 days after treatment start: • Uric acid >8 mg/dL (>475.8 µmol/L). • Potassium >6.0 mmol/L. • Phosphorus >4.5 mg/dL (>1.5 mmol/L). • Corrected calcium <7.0 mg/dL (<1.75 mmol/L), ionized calcium <1.12 mg/dL (<0.3 mmol/L)[1].	Omit study treatment until all serum/plasma chemistries have resolved. Ensure normal hydration; correct laboratory abnormalities, fluid

TLS diagnosis	Recommended action
Clinical TLS: laboratory TLS in addition to 1 of the following complications • Acute kidney injury: increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/L) or the presence of oliguria, defined as an average urine output of <0.5 mL/kg/hour for 6 hours. • Seizures, cardiac dysrhythmia, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign. • Dysrhythmias probably or definitely caused by hyperkalemia.	overload, electrolyte or acid-base deviation. Monitor TLS complications including renal functions. Reinstitute study treatment at full dose after resolution.

1. The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4 - albumin in g/dL).

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

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

7.1. Discontinuation of Study Treatment

Please refer to the 208887 MP.

7.2. Participant Withdrawal from the Study

Please refer to the 208887 MP.

7.3. Lost to Follow-Up

Please refer to the 208887 MP.

8. STUDY ASSESSMENTS AND PROCEDURES

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

Information and details specific to Sub-study 5 are in Section 8.3.7, Section 8.3.10, Section 8.4 and Section 8.9 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). Additional safety assessments for Sub-study 5 are listed below.

8.2.1. Blood type and Antibody Screening

Blood typing (A, B, O, and Rh), complete blood phenotyping (C,c; E,e; Kell; Kidd; Duffy; S,s) is recommended, if this typing is available, following site standard/institutional practice. Antibody screening (indirect antiglobulin test [indirect Coombs test]) to be drawn at Screening or prior to first study treatment administration at C1D1 if results are not already available.

Blood type information should be kept by the participant on or along with the study card. All blood transfusions are to be recorded in the eCRF. The blood bank needs to be informed that the participant is receiving treatment with an anti-CD38 therapy and a potential interference with indirect antiglobulin testing (indirect Coombs testing) is possible.

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 Medical Director

Please refer to the 208887 MP.

8.3.6. Regulatory Reporting Requirements for SAEs

Please refer to the 208887 MP.

8.3.7. Management of Pregnancy and Contraception

Please refer to the 208887 MP.

The effects of isatuximab on reproductive toxicity, pregnancy and lactation have not been investigated in formal toxicity studies. Therefore, the effects of isatuximab on reproductive organs in males and females are unknown.

Female participants

Female participants of childbearing potential shall be required to use highly effective contraceptive methods (a failure of <1% per year when used consistently and correctly) starting 2 weeks before first dose of combination study treatment, while on therapy, and for **5 months** following the last dose of combination study treatment.

Details of all pregnancies in female participants of childbearing potential will be collected after the start of study treatment and for **5 months** following last dose of combination study treatment.

For female participants of childbearing potential who stop isatuximab but continue with belantamab mafodotin treatment alone, these participants shall be required to use highly effective contraceptive methods and details of all pregnancies will be collected for **4 months** following last dose of belantamab mafodotin.

Male participants

Male participants with female partners of childbearing potential shall be required to use highly effective contraceptive methods (a failure of <1% per year when used consistently and correctly) starting 2 weeks before first dose of combination study treatment, while on therapy and for **6 months** following the last dose of combination study treatment.

Details of all pregnancies in male participants with female partners of childbearing potential will be collected after the start of study treatment and for **6 months** following last dose of combination study treatment.

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 for Isatuximab

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

The list of terms and reporting requirements for isatuximab AESI are provided below. These are selected non-serious AEs and SAEs that **must be reported to GSK** regardless of relationship to study treatment. For participants who experience signs or symptoms that may be consistent with an AESI, sites are strongly encouraged to immediately notify the Medical Director of the event via email and/or phone. Documentation of potential AESIs should occur after discussion between the investigator and the sponsor/Medical Director. Even events without clear confirmation of their immunologic etiology may qualify as AESIs. Many of these events may also qualify as SAEs. Details are available in the SRM. Any event that meets the criteria described below must be reported regardless of investigator-determined relationship to study treatment or if considered immune-related (unless otherwise specified). Investigators/study coordinators/designated site personnel are required to record these experiences in the eCRF (as described in the eCRF completion guidance document) and to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event. Please note this table lists known AESIs, additional events may be identified during the course of the study.

AESIs for Isatuximab:

- DLTs in Cycle 1 (including IRRs ≥Grade 3)
- IRRs ≥Grade 3
- Symptomatic Overdose
- Secondary primary malignancies

See 208887 MP Section 4.1.1.1, as DLTs in Cycle 1 and IRRs may be potentially overlapping events for belantamab mafodotin and isatuximab.

8.4. Treatment of Overdose of Isatuximab

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

There is no specific antidote for overdose with isatuximab. In the event of a suspected overdose (at least 30% above the intended administered dose at each cycle), it is recommended that the appropriate supportive clinical care should be instituted, as dictated by the participant's clinical status. In addition, the event, even if not fulfilling a seriousness criterion, is to be reported to the sponsor immediately (within 24 hours).

8.5. Pharmacokinetics

Please refer to the 208887 MP.

8.6. Pharmacodynamics

Please refer to the 208887 MP.

8.7. Genetics

Please refer to the 208887 MP.

8.8. Immunogenicity Assessments

Please refer to the 208887 MP.

8.9. Biomarkers

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

CD38 is expressed at high levels on myeloma cells and, to a lesser extent, on several immune effector cells, including natural killer (NK) cells. Treatment with anti-CD38 monoclonal antibodies such as daratumumab and isatuximab depletes CD38+expressing immune cells. Myeloid-derived suppressor cells, regulatory B cells, and a subset of regulatory T cells also express CD38 and are susceptible to anti-CD38-mediated lysis.

In patients treated with daratumumab, significantly higher CD38 expression levels on MM cells at baseline were found on responders (≥PR) compared with non-responders (<PR); implying that CD38 expression may be a predictive factor of clinical response. Further, CD38 expression levels were reduced in both bone marrow-localized and circulating MM cells, following the first daratumumab infusion, and this expression increased following daratumumab discontinuation (~6 months after the last daratumumab infusion) [Nijhof, 2016]. Similarly, decreases in NK cell (CD16+CD56+) populations from peripheral blood and in the bone marrow were also observed in daratumumab-treated participants, which recovered 3-6 months after treatment. The non-depleted NK cells seemed to retain functionality and therefore may have contributed to clinical activity [Casneuf, 2017].

We propose to explore the expression of CD38 and/or pharmacodynamic effects in plasma / myeloma cells and other immune cell populations at baseline (particularly as our patient population will be anti-CD38 treatment exposed) and after treatment with the belantamab mafodotin plus isatuximab combination. These analyses would support evaluation of mechanistic effects of the combination and/or association to patient responses. To this end, bone marrow samples will be collected during this study, at the time points indicated in the SoA (Section 1.3 and Table 6), and will be analyzed by flow cytometry. Evaluations may also include IHC or related technologies for expression of CD38, BCMA, or relevant biomarkers on tumor cells and/or phenotypic and functional markers on immune cell populations. Samples may also be evaluated for gene expression by DNA or RNA sequencing or related technologies, at baseline and after combination treatment, to explore expression changes in the tumor and/or immune cells and/or the tumor microenvironment. Whenever possible, similar analyses will be performed on tumor tissue obtained upon response or after disease progression, to identify biomarkers associated with clinical response or resistance, respectively. These studies may be complemented by parallel blood (and its derivatives) analyses that may evaluate effects on NK or other immune cell populations. If biomarkers potentially predictive of response

or associated with AEs are identified in samples, they may be used for the development of additional validated assays and/or diagnostic tests.

Details of sample preparation, storage and analysis will be provided in the SRM.

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

Please refer to the 208887 MP.

9. STATISTICAL CONSIDERATIONS

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

This sub-study follows the statistical design as described in the 208887 MP.

If this sub-study transitions through the DE Phase, participants will be randomized in the CE Phase to the recommended Phase 2 dose combination of belantamab mafodotin with isatuximab or to the control arm of belantamab mafodotin 2.5 mg/kg Q3W monotherapy. The dose/regimen of belantamab mafodotin for the control arm is based results from DREAMM-2 [Lonial, 2020]. Data from the control arm may be shared across concurrent sub-studies in the master study via adaptive randomization (208887 MP Section 4.1).

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 SUB-STUDIES

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

12. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

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: Third Parties and Subcontractors

Please refer to the 208887 MP.

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

ADA	Anti-drug antibody
ADC	Antibody drug conjugate
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody dependent cellular phagocytosis
AE	Adverse event(s)
AESI	Adverse event(s) of Special Interest
BCMA	B-cell maturation antigen
BM	Bone marrow
BP	Blood pressure
C	Cycle
CBC	Complete blood count
CD	Cluster of differentiation
CE	Cohort Expansion (Phase)
CI	Confidence interval
CL	Clearance
CMMC	Circulating multiple myeloma cells
CR	Complete response
CT	Computer tomography
CTCAE	Common Toxicity Criteria for Adverse Events

D	Day
DE	Dose Exploration (Phase)
DLT	Dose limiting toxicity
DoR	Duration of response
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EOI	End of infusion
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires 30-item Core Module
EOT	End of treatment
FDA	Food & Drug Administration
FISH	Fluorescence in situ hybridization
FLC	Free light chain
GSK	GlaxoSmithKline
GSK2857916	GSK anti-BCMA antibody drug conjugate (CA8 J6M0 Potelligent MMAF)
HBsAg	Hepatitis B surface antigen
HBc	Hepatitis B core
HBcAb	Hepatitis B core antibody
HBV	Hepatitis B
HCV	Hepatitis C
IB	Investigator's Brochure
ICBd	Isatuximab in combination with cyclophosphamide, bortezomib, and dexamethasone
ICD	Immunogenic cell death
Ig	Immunoglobulin
IHC	Immunohistochemistry
ILd	Isatuximab in combination with lenalidomide and dexamethasone
IP	Investigational Product
IPd	Isatuximab in combination with pomalidomide and dexamethasone
IR	Infusion reaction
IRR	Infusion-related reaction
IV	Intravenous(ly)
KVA	Keratopathy Visual Acuity
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MDRD	Modified diet in renal disease
MM	Multiple Myeloma
MP	Master Protocol
MRD	Minimal residual disease
MRI	Magnetic resonance Imaging
MUGA	Multiple gated acquisition

NCI-CTCAE	National Cancer Institute – Common Toxicity Criteria for Adverse Events
NK	Natural killer
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
OSDI	Ocular Surface Disease Index
PBMC	Peripheral blood mononuclear cells
PC	Plasma cells
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PI	Proteasome inhibitor
PK	Pharmacokinetic(s)
PK/PD	Pharmacokinetic(s)/pharmacodynamic(s)
PR	Partial response
QW	Every week
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
RNA	Ribonucleic acid
RRMM	Relapsed/refractory multiple myeloma
SAE	Serious adverse event(s)
sBCMA	Soluble B-cell maturation antigen
SC	Subcutaneous(ly)
sCR	Stringent complete response
SoA	Schedule of Activities
SOI	Start of infusion
SPEP	Serum protein electrophoresis
SRM	Study research manual
SRT	Safety Review Team
t½	Half-life
TBNK	T-cell, B-cell and Natural Killer cell
TEAE	Treatment-emergent adverse event(s)
TLS	tumor lysis syndrome
UPEP	Urine protein electrophoresis
VGPR	Very good partial response
WOCBP	Women of childbearing potential
WHI	Water for injection

Trademarks of the GSK group of companies	**Trademarks not owned by the GSK group of companies**
None	SARCLISA

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

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

12.14. Appendix 14: Country Specific Requirements

Please refer to the 208887 MP.

12.15. Appendix 15: Protocol Amendment History

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

Amendment 2 (Sub-study 5): 10 July 2023

Overall Rationale for the Amendment:

The Sub-study 5 protocol has been amended to make corrections to typographical errors and inconsistencies, to add clarifications in line with program level changes, and to add administrative and safety updates, which are summarized in the table below.

Section # and Name	Description of Change	Brief Rationale
Throughout document	Changed all instances of Medical Monitor to consistently refer to the Medical Director, and updated medical director contact information	Correction of typographical or consistency error
Throughout document	Minor editorial and document formatting and stylistic revisions; applied GSK style guide for abbreviations, date format, etc.	Correction of typographical or consistency errors
Throughout document	The term GSK'916 (used for laboratory samples) was replaced by belantamab mafodotin	Clarification of wording
Throughout document	Updated amendment numbering in SS to be unique and not identical to MP	Correction of typographical or consistency error
Throughout document	Updated reference to GSK2857916/ belantamab mafodotin Investigator's Brochure	To refer to the most recent version of the IB
Sponsor Signatory Page and Investigator Protocol Amendment Agreement Page	Included sub-study title for consistency with title page	Correction of typographical or consistency error
Section 1.1	Added protocol title, short title and rationale heading for consistency between sub-studies	Correction of typographical or consistency error
Section 1.3 Schedule of Assessments	Removed extraneous text from Table 2 footnote 1	Correction of typographical or consistency error
Section 1.3 Schedule of Assessments	Added HIV testing at screening to Table 2 footnote 8 to conform with FDA guideline for inclusion of patients with previous exposure to HIV.	Program level changes
Section 1.3 Schedule of Activities	Clarified guidance regarding realignment of scheduled weekly visits and dosing visits in Table 3	Clarification for study conduct

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	In Table 2 and Table 4, clarified that anytime C1D1 Hem/Chem results are outside of eligibility requirements, MD should be contacted prior to dosing. Removed "at Screening" for clarity.	Clarification for study conduct
Section 1.3 Schedule of Assessments	Updates to Table 3, footnote 3 and Table 4, footnote 2 to clarify timing of ocular exams in relation to dosing.	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 3 (footnote 8) and Table 5 (footnote 25), decreased frequency of UPEP assessments	Program level updates
Section 1.3 Schedule of Activities	Removed references to dosing in Table 3 footnote 4. Table 3 is not the dosing table.	Correction of typographical or consistency errors
Section 1.3 Schedule of Activities	Revised language related to imaging for Skeletal surveys and for participants with extramedullary disease in Table 3, footnotes 12 and 13	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 3, modified footnote for urine and serum immunofixation to include "not quantifiable"	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 4, physical exams on C1D15 and C1D22 were removed to reduce number of assessments required and are not required for Isatuximab dosing. Clarification for study conduct	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarified that on PK sampling visits, if vital signs assessments are conducted, they should be assessed prior to PK samples being drawn in Table 4, footnote 1	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarified timing of hematology and clinical chemistry prior to isatuximab dosing in Table 4, footnote 5.	Clarification for study conduct
Section 1.3 Schedule of Activities	Added guidance regarding isatuximab administration in Table 4 and Table 4, footnote 15	Clarification for study conduct
Section 1.3 Schedule of Activities	Created separate rows in Table 5 for serum immunogenicity (ADA) for belantamab and ADA for Isatuximab	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Revision to indicate change in timing of EOT to within 30 days from when decision to discontinue treatment in Table 5, footnote 1	Clarification for study conduct

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Belantamab mafodotin program safety language to be used throughout protocols. AE/SAEs will be collected until at least 70 days post last dose (Table 5)	Clarification of study conduct
Section 1.3 Schedule of Assessments	In Table 5 deleted footnote 12 to avoid repetition of information included in footnote 2	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Aligned row heading of hematology (enhanced TBNK panel) with 208887 MP in Table 5 and Table 8	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Updated guidance on pregnancy testing and collection of pregnancy information, Table 2 footnote 2 Table 5, footnote 8	Clarification for study conduct
Section 1.3 Schedule of Activities	Table 5 footnote 13 was missing text. Last sentence read "X-ray is acceptable for lytic disease" and updated to “X-ray is acceptable for lytic disease, but other methods are needed (CT, MRI, PET/CT) for assessment of extramedullary disease.”	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Revision to clarify timing of follow-up OSDI questionnaires following the end of treatment in Table 5, footnote 22	Clarification for study conduct
Section 1.3 Schedule of Activities	Corrected the term in the Schedule of Activities to refer to the “end of treatment” instead of ‘end of study’ in Table 5, footnote 23	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Aligned row heading of hematology (enhanced TBNK panel) with 208887 MP	Correction of typographical or consistency error
Section 1.3 Schedule of Activities	Added missing “x” related to bone marrow sampling for disease assessment for very good partial response/ suspected complete response/stringent response and bone marrow aspirate for FISH testing at end of treatment in Table 6	Clarification for study conduct
Section 1.3 Schedule of Activities	Updates to MRD, biomarker assessments, and optional bone marrow research in Table 6	Clarification for study conduct
Section 1.3 Schedule of Activities	Re-aligned language/table regarding BM collection samples in Table 6. Changes include: the term“suspected VGPR, CR/sCR” was corrected to “VGPR or suspected CR/sCR; separate rows were created for PD and Suspected PD, Cycle 2 Day 15 BM sample collection removed, and corresponding assessments; details regarding FISH testing were removed from Table 6 footnote 3 and reference to Table 31 has been provided.	Clarification for study conduct

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Revised window for PK sampling to 0-10 minutes to align with vital sign window in Table 7	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarified timing of PK, sBCMA, anti-drug antibody sampling for PD or end of treatment in Table 7	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarified Cycle 1 Day 2 predose sampling for PK, anti-drug antibodies, and soluble B cell maturation antigen in Table 7, footnote 1	Clarification for study conduct
Section 1.3 Schedule of Activities	In Table 2 and Table 7 sampling window for C2D1, clarified if belantamab mafodotin dosing at C2D1 is delayed, nirogacestat PK samples should still be collected and Bela PK sample dose not need to be collected	Clarification for study conduct
Section 1.3 Schedule of Activities	Consistency across MP and sub-studies regarding the timing of TBNK sample collection in Table 8	Clarification of study conduct
Section 1.3 Schedule of Activities	Clarified the timing of HBV-DNA testing to allow for grouping with the closest study visit in Table 9	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarified when the sample is collected for urine immunofixation in Table 2, Table 3, Table 5	Clarification of study conduct
Section 1.3 Schedule of Activities	Updates related to biomarker assessments Table 2, Table 3 (remove core biopsy), and Table 8	Clarification for study conduct
Section 1.3 Schedule of Activities	Removed Bone Marrow and/or Aspirate sample on Cycle 2 Day 15 and deleted Cycle 2 Day 15 column from Table 3	Clarification for study conduct
Section 1.3 Schedule of Activities	Clarified indirect Coombs testing should be performed by local laboratories (Table 4, footnote 6). Removed Coombs testing during Q4W visits (Table 3).	Clarification for study conduct
Section 1.3 Schedule of Assessments	Revised reference to Coombs testing in Table 2 and Table 4 to indirect antiglobulin testing (indirect Coombs testing)	Clarification for study conduct
Section 1.3 Schedule of Activities	Removed the need for bone marrow aspiration at end of study visit for MRD assessment in Table 5. Clarified conditions for MRD testing at screen and during study. Added a ±1 month window for follow-up MRD testing in Table 6.	Clarification for study conduct

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Assessments	Samples for serum cytokine/chemokines and cryopreserved PBMC analyses will no longer be collected (Table 8)	Update of study conduct
Section 1.3 Schedule of Activities, Section 2.3.1 Risk Assessment	Clarified that indirect antiglobulin test (indirect Coombs test) should be conducted at Screening (Table 2), Cycle 1 Day 1 (Table 4), and per Table 10	Clarification for study conduct
Section 2.3.1 Risk Assessment	In Table 10, added Tumor Lysis Syndrome as a risk related to Isatuximab	Clarification for study conduct
Section 2.3.3 Overall Benefit: Risk Conclusion Section 9 Statistical Considerations	Removed reference to EU approval	Correction of typographical or consistency error
Section 3 Objectives and Endpoints	Clarified the primary and secondary objectives and corresponding endpoints are the same as those listed for the MP; removed exploratory objectives	Correction of typographical or consistency error
Section 5.2 Exclusion Criteria	A note was added for consistency between sub-studies that states “The numbering in the criteria may not be sequential from the MP.”	Correction of typographical or consistency error
Section 6.1 Study Treatment(s) Administered	In Table 11, updated language concerning belantamab mafodotin dose formulation.	Clarification for study conduct
Section 6.2 Administration of Belantamab Mafodotin and Isatuximab	Added guidance regarding isatuximab administration in Table 12 footnote	Clarification for study conduct
Section 1.1 Synopsis, Section 4.1 Dose Exploration of Combination Treatment Belantamab Mafodotin Co-Administered with Isatuximab, Section 6.2 Administration of Belantamab Mafodotin and Isatuximab	Corrected the number of Isatuximab doses from 4 to 5 doses in Section 6.2 and Table 12	Correction of typographical or consistency error
Section 6.2.1 Premedication and Rate of Isatuximab Infusion	Updated guidance regarding pre-medication of isatuximab	Clarification for study conduct
Section 6.2.2 Management of Infusion-Related Reactions for Isatuximab	Updated guidance on recommended treatment for infusion-related reactions for isatuximab	Clarification for study conduct
Section 6.6.3 Tumor lysis syndrome management	Added new section on management of tumor lysis sydrome	Program level updates

Section # and Name	Description of Change	Brief Rationale
Section 8.2.1 Blood type and Antibody Screening	Clarified the types of tests to be performed for antibody screening and removed reference to the SRM	Clarification for study conduct
Section 8.3.7 Management of Pregnancy and Contraception	Clarified duration for use of approved methods of contraception after last dose of study treatment (90 days [7 days] after last dose of study treatment)	Clarification for study conduct
Section 10 References	Added references; applied GSK style guide for references	Correction of typographical or consistency errors
Section 12 Supporting Documentation and Operational Considerations	Added single statement in beginning of appendix 12 to "Please refer to the 208887 MP for the overall supporting documentation and operational considerations for the study."	Correction of typographical or consistency error
Section 12.12 – Appendix 12	Listing of all third parties and subcontractors who are supporting this study was deleted from sub-study and made available in MP.	Program level update

Amendment 01 (Sub-study 5): 21 January 2022

Overall Rationale for the Amendment:

The protocol has been amended to reflect an updated study design, which includes 2 new exploratory dose levels (belantamab mafodotin 1.4 mg/kg every 8 weeks (Q8W) + isatuximab 10 mg/kg weekly for the first 4 doses, followed by every 2 weeks thereafter and belantamab mafodotin 1.9 mg/kg every 8 weeks (Q8W) + isatuximab 10 mg/kg weekly for the first 4 doses, followed by every 2 weeks thereafter). Additionally, the protocol has been amended to reflect new dose modification guidance for belantamab mafodotin.

Changes listed in the table below are for the Sub-study 5 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 protocol.

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

Section # and Name	Description of Change	Brief Rationale
	For more information of certain sections mentioned the reference to master protocol	To align with program level updates and for clarity
1.2 Schema	Schema updated to reflect new study design, moved from Section 4.1 to Section 1.2 Added 2 exploratory doses to schema for belantamab mafodotin in combination with Isatuximab.	To explore new lower dose level and dose schedules to optimize safety and efficacy of the study treatment
1.3. Schedule of Activities (SoA)	Added the option to perform multiple gated acquisition (MUGA) scan in place of ECHO.	Updated in line with cardiac monitoring requirements across belantamab mafodotin program, based on emerging safety data
	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 (Partial 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
	Revised the study assessments timepoints from Cycle 2 Day 1 – End of Treatment (EoT), during the belantamab mafodotin and Isatuximab treatment period. Applicable changes in PK assessments were made accordingly.	To reduce collection of blood samples and reduce patient burden
	Removed plasma circulating free DNA sample	To reduce collection of blood samples and reduce patient burden
	Removed whole blood RNA sample	To reduce collection of blood samples and reduce patient burden

Section # and Name	Description of Change	Brief Rationale
	Added additional procedures for participants who were HBcAb positive during screening Added Table 9 for additional procedures for participants with a history of Hepatitis B	To align with program level updates
	Vital signs will also be collected as clinically indicated	To align with program level updates
	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
4.1. Dose Exploration of Combination Treatment Belantamab Mafodotin Co-Administered with Isatuximab	Added 2 exploratory doses to schema for belantamab mafodotin in combination with Isatuximab. Table "Dose Exploration Schema Belantamab Mafodotin in combination with Isatuximab" deleted Schema moved to Section 1.2	To explore new lower dose level and dose schedules to optimize safety and efficacy of the study treatment
4.3. Justification for Dose	Justification for lower dose of belantamab mafodotin added	To reflect new dose modification guidance for belantamab mafodotin, aligned with program level updates
4.4.2. Study Completion	Delete wording for study completion and mentioned reference of master protocol for further details	To align with program level updates
6.1 Study Intervention(s) Administered	Updated dosing instructions for Study Intervention	To reflect new dosing instruction guidance
6.2.1 Premedication and Rate of Isatuximab Infusion	Revised requirements for premedication with montelukast for isatuximab infusion	To align with isatuximab IB updates
6.6. Dose Modification for Belantamab Mafodotin and Isatuximab in combination	Revised to reflect new permitted dose reductions for belantamab mafodotin when give in combination with Isatuximab	To reflect new dose modification guidance for belantamab mafodotin, aligned with program level updates

Section # and Name	Description of Change	Brief Rationale
Section 10 References	Updated the new references used in the document.	To reflect new changes
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 as per the template requirement	Template alignment

Original (Sub-study 5) 14 December 2020

Overall Rationale for the Amendment:

The 208887 protocol has been amended to introduce a new sub-study (Sub-study 5) and to convert to a modular document format with separate Master Protocol (MP) and Sub-study modules.

Signature Page for 208887 TMF-19536835 v2.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 03-Sep-2024 14:32:23 GMT+0000

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