PROTOCOL

Study ID: 214098

Official Title of Study: Characterization of Corneal Epithelial Changes in Participants Treated with Belantamab Mafodotin (GSK2857916)

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TITLE PAGE

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Protocol Number: 214098

Protocol Amendment: 02

Compound Number or Name: GSK2857916 (Belantamab Mafodotin)

Brief Title: Characterization of Corneal Epithelial Changes in Participants Treated with Belantamab Mafodotin (GSK2857916)

Study Phase: IIIB

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

IND: 119333

EudraCT: n/a

NCT:

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SPONSOR SIGNATORY:

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Roxanne Cacioppo, PhD Global Medical Lead, Belantamab Mafodotin	**Date**

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document Type	**Document Number**	**Date**
Amendment 2	TMF-11824254	04-FEB-2021
Amendment 1.	2020N434638_01	28-JUL-2020
Original Protocol-	2020N434638_00	20-May-2020

Amendment 2: 04-FEB-2021
Overall Rationale for the Amendment:

The protocol has been amended to allow the inclusion of patients receiving belantamab mafodotin through a Physician prescription.

Section # and Name	**Description of Change**	**Brief Rationale**
Title Page	Deleted "companion" study from protocol title	This protocol has been amended to allow both trial participants and patients on commercial prescriptions. It is no longer exclusively a companion study.
1.1 Synopsis	Objectives and Endpoints: updated Exploratory endpoint Overall Design: Allow Inclusion of patients receiving belantamab mafodotin through a Physician prescription Brief Summary: Clarification of steroid treatment	Clarification Expand pool of eligible patients Clarification
1.2 Schema	Updated to remove symptom requirement	Clarification
1.3 Schedule of Activities	Added data collection, clarified procedural footnotes	Clarification
2.2 Background	Clarification of steroid treatment Reference to inclusion of patients receiving belantamab mafodotin through a Physician prescription	Clarification
3 Objectives and Endpoints	Updated Exploratory endpoint	Clarification
4.1 Overall Design	Allow Inclusion of patients receiving belantamab mafodotin through a Physician prescription Updated design criteria	Expand pool of eligible patients Clarification

Section # and Name	Description of Change	Brief Rationale
4.2 Study Procedures	Clarified that the target eye for the procedure is the one with the greater number of MECs	Clarification
5.1 Inclusion Criteria	Patients with superficial punctate keratopathy and no evidence of MEC's are not eligible Deleted reference to Grade 2 or 3 CTCAE v 5.0	Clarification
5.2 Exclusion Criteria	Added restriction on concurrent medication that might affect the cornea Added exclusion for any patient with decreased corneal sensation	Safety Safety
6.2 Patient Selection Considerations	Added Section on patient selection criteria	Safety
6.4 Superficial Keratectomy procedure	Clarification of steroid treatment	Clarification
6.9 Imaging Procedures	Added Section to clarify imaging procedures	Clarification
6.10 Concomitant Therapy	Added restriction on concurrent medication that might affect the cornea	Safety
8.1.3 Time Period and Frequency for Collecting AE and SAE Information	Clarification of AE/SAE collection, collect related AE/SAE only	Clarification
8.1.5 Follow-up of Aes and SAEs	Clarification of AE/SAE collection, collect related AE/SAE only	Clarification
8.3 Data Collection	Added section on data collection	Clarification
10.2.5 Reporting of SAEs to GSK	Added contact email	Clarification
Whole Document	Removed any instance of "companion" or "companion study"	This protocol has been amended to allow both trial participants and patients on commercial prescriptions. It is no longer exclusively a companion study.

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1 PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

Characterization of Corneal Epithelial Changes in Participants Treated with Belantamab Mafodotin (GSK2857916)

Brief Title:

Characterization of Corneal Epithelial Changes in Participants Treated with Belantamab Mafodotin (GSK2857916)

Rationale:

Multiple myeloma (MM) is an incurable hematologic malignancy, and despite advances in treatment, there remains a high unmet need to find effective novel therapies to treat this devastating disease. Belantamab mafodotin is a first-in-class immunoconjugate that targets B cell maturation antigen (BCMA), which is highly expressed on malignant plasma cells. Belantamab mafodotin comprises a humanized IgG antibody conjugated to the microtubule-disrupting agent monomethyl auristatin F (MMAF). Belantamab mafodotin has demonstrated clinically meaningful single-agent activity (overall response rate [ORR] 31% at the 2.5 mg/kg dose and median duration of response [DOR] not reached at a median follow-up of 6.3 months) in patients who are refractory to anti-CD38 monoclonal antibody, an immunomodulatory drug (IMiD), and proteasome inhibitor.

Patients who receive belantamab mafodotin often display corneal changes, which are associated with subjective and objective changes in vision. On slit-lamp exam, these changes appear as microcyst-like epithelial changes (MECs), . These adverse events (AEs) have been reported with other MMAF-containing antibody therapies, including SGN-75, SGN-CD19A, and ABT-414 The exact mechanism has not been confirmed, but a toxic effect mediated through MMAF's inhibition of tubulin polymerization within basal epithelial cells is thought to play a major role. Similar corneal findings by slit-lamp examination have been described in patients treated with high-dose cytarabine, although these are thought to represent actual microcysts. Confirmatory corneal histology is lacking to support and confirm a working explanatory theory for the belantamab mafodotin–related corneal AEs.

DREAMM-2 is an ongoing phase 2, open-label, two-arm clinical trial investigating two doses of belantamab mafodotin (2.5 mg/kg, n=97, and 3.4 mg/kg, n=99, every 3 weeks), in which 2.5 mg/kg was recommended to be the effective dose as the monotherapy dose for future use in patients with RRMM. Keratopathy of any grade (defined as changes to the corneal epithelium) was reported in 75% of patients. Furthermore, 22% experienced blurred vision (defined as blurred vision, including diplopia, decreased visual acuity, and vision impairment) and 14% experienced dry eye symptoms (defined as dry eye, ocular discomfort, eye pruritis, and foreign body sensation in the eyes) in the 2.5 mg/kg cohort. Grade 1 or 2 keratopathy occurred in 41 (43%), while Grade 3 keratopathy occurred in 26 (27%), Grade 1 or 2 blurred vision occurred in 17 (18%), and Grade 3 blurred vision in 4

(4%) patients. These events led to dose reductions in 22 (23%) patients and delays in 45 (47%) patients. Of the 45 patients with treatment delays due to keratopathy, 31 (69%) reinitiated treatment, with a median time to treatment reinitiation of 83 days (range 28–146). Higher belantamab mafodotin Ctau was associated with probability of developing keratopathy and OEF (ocular eye findings) and inversely correlated to time of onset. Grading of corneal events was performed using the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 as well as the GSK Grading Scale.

The mechanism of corneal events in patients treated with belantamab mafodotin is thought to be related to MMAF uptake into the transient amplifying cells in the basal epithelium. These cells have mitotic activity, and, furthermore, daughter cells migrate anteriorly as they differentiate into wing cells and terminal superficial epithelial cells. These processes are microtubule dependent and can be disrupted by potent tubulin inhibitors such as MMAF. We further hypothesize the following: these damaged cells then eventually undergo apoptosis and become pyknotic, which may appear as MECs in a pre-apoptotic state; they are eventually extruded from the epithelium; the corneal surface is secondarily affected both by these anatomic abnormalities and alterations in superficial in the epithelial cell replenishment.

The current management guidelines for belantamab mafodotin–related corneal events include the use of preservative-free lubricant eye drops, dose reductions, and dose delays. The efficacy of steroid eye drops was systematically evaluated in a randomized ocular substudy in the DREAMM-2 study, and the results revealed that empiric topical corticosteroid therapy conferred no benefit as prophylaxis for corneal events. A more complete understanding of the pathophysiology of the corneal events seen in these patients could help confirm the current hypothesis and inform management of these AEs. The direct analysis of corneal epithelial cells in affected patients is paramount to furthering this understanding.

In order to perform a direct analysis of affected corneal epithelial cells, we will collect corneal tissue specimens using either of the following procedures: impression cytology (IC) or superficial keratectomy (SK). Patients with epithelial corneal microcyst like changes, meeting study entry criteria, will be enrolled in this study to collect corneal epithelium tissue for analysis. Imaging of the corneal epithelial lesions will be obtained from slit-lamp examination and/or confocal microscopy, and the grade, and appearance will be correlated with the pathologic samples.

Objectives and Endpoints:

Objectives	Endpoints
Primary: To characterize corneal epithelial changes in participants treated with belantamab mafodotin	**Primary:** Pathologic characteristics and composition of corneal epithelial changes obtained by impression cytology (IC) or SK in participants treated with belantamab mafodotin
Secondary: • To correlate clinical data, including visual acuity and symptoms, as well as grade and appearance of corneal changes on imaging, with histopathologic findings • Safety profile of the IC or SK procedure	**Secondary:** • Results of analysis of clinical/imaging data with histopathologic findings • AEs associated with the IC or SK procedure
CCI [redacted]	

Overall Design:

This study will be available to any participant who has received or is currently receiving belantamab mafodotin treatment through either a clinical trial, (including an investigator-sponsored study [ISS], or an access program) or a Physician prescription; patients do not need to be on active treatment as long as they meet inclusion criteria.

Brief Summary:

The purpose of this study is to characterize corneal epithelial changes in participants with RRMM treated with belantamab mafodotin. Study details include:

- Study Duration: approximately 4 weeks
- Visit Frequency: each patient will have a total of 5 visits. Additional followup visits may be required in the event of delay in healing from the ocular procedures.

Impression cytology will be performed on some patients who received or are receiving treatment with belantamab mafodotin for relapsed/refractory MM (RRMM) and have objective evidence of keratopathy with corneal MECs on slit-lamp and/or confocal microscopy examination. Participants with Grade 2 or 3 CTCAE corneal symptoms, in addition to evidence of corneal deposits, will have the option to undergo SK instead of impression cytology as a potential means to reduce their symptoms. All participants enrolled are eligible for impression cytology. Those who are symptomatic may choose to undergo SK only. Each participant will only have one corneal procedure (impression cytology or SK). CCI [redacted]

Impression cytology is a minimally invasive procedure that involves the application of cellulose acetate filter paper to the ocular surface to collect superficial cell layers for histologic, immunohistologic, or molecular analysis. The procedure is performed by a trained ophthalmologist or ocular pathologist in the eye clinic with or without topical anesthesia, and multiple samples can be obtained in one sitting.

The study eye will be the one that appears to have a greater number of MECs. If both eyes appear equal in terms of epithelial changes, the eye with the worse visual acuity will be selected; if both eyes have the same visual acuity, then the investigator can select either eye. Following topical anesthesia, an eyelid speculum, will be placed. Next, the filter paper will be pressed to a preidentified region on the corneal surface of the study eye with a glass rod (or similar instrument) for 5–10 seconds. The filter papers obtained from the procedure will contain epithelial layers from areas of the cornea with microcyst-like changes and will be analyzed through histologic techniques. The filter paper will be placed on a glass slide and cover slip placed on top. The eye speculum will be removed and a topical antibiotic drop (e.g. polytrim) will be prescribed for participant use for 7 days.

Superficial keratectomy is a method to remove an area of full-thickness corneal epithelium. The procedure is performed by an ophthalmologist, takes 15–30 minutes to complete, and may be conducted in the eye clinic. While in some cases this procedure is performed in an operating room, only participants who are able to undergo the procedure in the clinic should be selected for it.

The study eye will be selected using the criteria described above. Following topical anesthesia (such as proparacaine hydrochloride 0.5%) and a drop of povidone iodine 5% for antisepsis, an eyelid speculum will be placed. The eye will then be visualized using a slit-lamp or operating microscope in a procedure room. The corneal epithelium of interest (the region that contains the MECs) will be carefully removed using either a Weck-Cel/dry cellulose sponge or small blade; Jeweler or 0.12 forceps may be required in some cases. The tissue will be submitted in formalin for histologic analysis. Care should be taken to minimize crush artefact to the epithelium and to avoid damage to Bowman layer.

Post procedure, another drop of povidone iodine 5% will be placed, followed by a drop of balanced salt solution or topical anesthetic (to wash out any residual povidone-iodine). A bandage contact lens will be placed. It is recommended that a topical antibiotic and a topical steroid (or a fixed combination of both) is prescribed 4 times per day, each, for at least one week (or longer), until the epithelial defect is documented as healed and the

bandage contact lens is no longer required in the assessment of treating Ophthalmologist. The topical antibiotic may be discontinued once the epithelial defect has healed. The topical steroid should be tapered off over the following two weeks.

The expected time for corneal re-epithelialization is 7–10 days. The procedure can cause some pain to the participant but is generally safe and well tolerated. Pain, if any, can be managed by the use of artificial tears, acetaminophen, and narcotics, if needed. The bandage contact lens should be helpful in reducing the need for pain medication. In participants with symptomatic blurred vision, the procedure may result in temporary visual improvement. The procedure may also be complicated by an infection or worsening vision. An ocular pathologist will be consulted to determine the appropriate testing of tissue sample.

Non-invasive pre-procedure imaging will also be obtained for all participants, regardless of procedure cohort. Anterior segment slit-lamp photography will be obtained, as will confocal microscopy (if available), prior to impression cytology or SK.

Only areas with microcyst-like changes should be sampled. All effort should be made to avoid or minimize intrusion into the limbus, if possible. The tissue derived from SK sampling should be placed in a formalin solution for transfer to the pathology laboratory. An ocular pathologist should examine the specimen to determine the composition of the deposits.

CCI

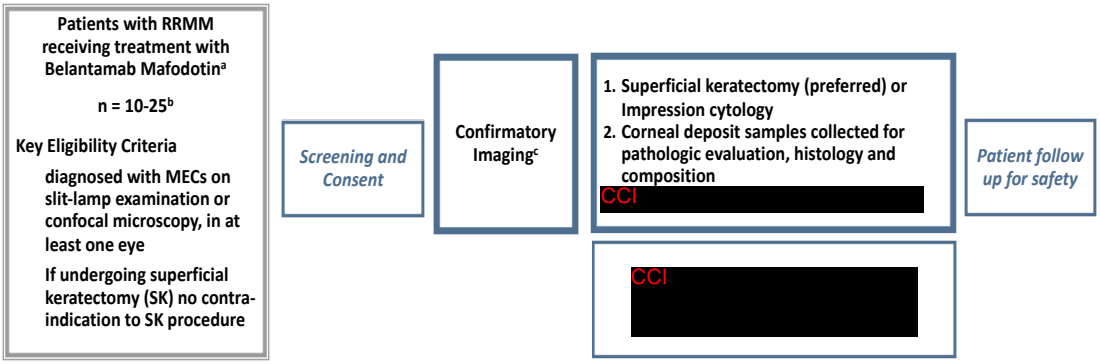
[redacted]

Number of Participants:

In this study up to 25 participants with MECs on slit-lamp and/or confocal microscopy examination resulting from belantamab mafodotin treatment of RRMM will be enrolled. Participants may be enrolled from any active research or access program, or Physician prescription, and do not need to be on active treatment. Participants will be identified by the treating MM physician and referred to an ophthalmologist, who will perform the SK or IC procedure. Once a total of 5 participant samples from the superficial keratectomy procedure have yielded evaluable material for pathologic examination and composition analysis of the corneal epithelial changes, further enrollment will cease.

Data Monitoring/Other Committee: No

1.2. Schema



[a] Patients on a DREAMM clinical trial, the compassionate use program, or a Physician Prescription are eligible.
[b] Up to 25 patients will be enrolled. The goal is to obtain 5 evaluable SK pathologic samples. Once 5 evaluable SK samples are obtained, enrollment will cease.
[c] An ophthalmic examination that includes best-corrected visual acuity, slit-lamp examination, and confocal microscopy (if available) must be performed prior to the impression cytology or keratectomy procedure to document site and size of corneal epithelial changes and to correlate imaging with pathologic findings. The slit-lamp examination must include orbit/lid/adnexa, conjunctiva, sclera, cornea, anterior chamber, iris, lens, and anterior vitreous. Confirmatory anterior segment photography is also required unless acceptable corneal images are available from an examination performed <14 days prior to impression cytology or SK.
CCI

1.3. Schedule of Activities (SoA)

Procedure	Screening	Pre–IC or SK procedure	IC or SK procedure (day of procedure)	Post–IC or SK procedure[e]	Safety follow-up (up to 1 week after SK procedure)	Safety follow-up (2 weeks after SK procedure)[f]	Additional follow-up at ophthalmologist's discretion[g]
Informed consent	X						
Eligibility criteria	X						
Slit-lamp examination and confocal microscopy (if available)[a] with imaging		X			X[d]		
Snellen eye test [a]			X		X	X	
CCI [redacted]							
Corneal tissue sampling[c]			X				
Pathology review of corneal sample				X			
Ophthalmology post-procedure checkup							X
Vital signs (pulse and blood pressure)			X				
AEs/SAEs			X	X	X	X	
Data Collection[h]	X	X	X	X	X	X	X
CCI [redacted]							
Blood Collection[j]			X				

AE, adverse event; CCI [redacted] IC, impression cytology; SAE, serious adverse event; SK, superficial keratectomy.

[a]An ophthalmic examination that includes best-corrected visual acuity, slit-lamp examination, and confocal microscopy (if available) must be performed prior to the impression cytology or keratectomy procedure to document site and size of corneal epithelial changes and to correlate imaging with pathologic findings. The slit-lamp examination must include orbit/lid/adnexa, conjunctiva, sclera, cornea, anterior chamber, iris, lens, and anterior vitreous. Confirmatory anterior segment photography is also required unless acceptable corneal images are available from an examination performed <14 days prior to impression cytology or SK. It is recommended that the imaging examination be performed at least 24 hrs prior to the procedure.

CCI [redacted]

[c]GSK may store samples for up to 3 years after the end of the study to achieve study objectives. Additionally, with participants' consent, samples may be used for further research by GSK or others such as universities or other companies to contribute to the understanding of the pathophysiology of belantamab mafodotin–associated keratopathy, the development of related or new treatments, or research methods.

[d]Preferred timing for follow-up slit-lamp examination is 24–48 hours post SK procedure but must be performed within 1 week after SK procedure. Safety follow-up after impression cytology is not required unless the participant is experiencing discomfort or an AE.

[e]The AE/SAE followup immediately after the Post–IC or SK procedure can by done by phone, in the 24-48 hours post-procedure.

[f]The participant should be reexamined 2 weeks after the SK procedure if the epithelial defect does not heal completely in the first follow-up. Otherwise, this follow-up is not required.

[g]In the event the cornea has not healed at 2 weeks, additional follow-up should be conducted at the ophthalmologist's discretion until healing is confirmed.

[h]Minimal additional data will be collected to adequately characterize the development of the corneal epithelial changes in participating patients See Section 8.3.

CCI [redacted]

2. INTRODUCTION

2.1. Study Rationale

The majority of patients who receive belantamab mafodotin display microcyst-like epithelial changes (MECs) on slit-lamp examination and/or experience symptoms including blurred vision and dry eye, which are recognized AEs associated with MMAF-containing antibody therapies, including SGN-75 [Tannir, 2014], SGN-CD19A, and ABT-414 [Reardon, 2017], but the exact mechanism has not been fully elucidated. Similar corneal findings by slit-lamp examination have been described in patients treated with high-dose cytarabine [Guthoff, 2010]. The specific corneal AE (microcyst-like epithelial changes) seen with belantamab mafodotin therapy has not been replicated in preclinical models, and confirmatory corneal histology is lacking to support and confirm the working explanatory theory for this corneal toxicity.

The purpose of this study is to gain a more complete understanding of the pathophysiology of the corneal events seen in some patients treated with belantamab mafodotin. To do this, impression cytology or SK will be employed in this study to collect corneal epithelium with epithelial changes for pathologic examination and composition analysis.

CCI [redacted]

2.2. Background

MM is an incurable malignancy that accounts for 1% of all cancers and 10% of all hematologic malignancies. Worldwide, approximately 103,000 new cases are diagnosed annually, and in the USA, 32,270 new cases and 12,830 deaths are estimated to occur in 2020 [Siegel, 2016]. Despite significant advances in treatment options, including hematopoietic stem cell transplant, and novel therapies like second- and (third-generation proteasome inhibitors, (IMiDs), and the recent addition of monoclonal antibodies, most patients with MM will ultimately develop resistance to existing therapies and relapse [Kumar, 2004][Rajkumar, 2016]. Each relapse requires salvage therapy, and there is often a decreasing response duration with each subsequent line of salvage therapy, and ultimately patients become resistant to or ineligible for available treatment regimens. Therefore, there is an urgent need to develop alternative treatments with novel mechanisms of action that provide a sustained response in patients with resistance to existing therapies [Anderson, 2016].

Belantamab mafodotin is a novel, humanized (IgG1) antibody-drug conjugate that is being developed for the treatment of MM. The parent anti-BCMA antibody is conjugated to the microtubule inhibitor, MMAF. Belantamab mafodotin binds to BCMA, a target widely expressed on malignant plasma cells in MM. The normal function of BCMA is to promote cell survival by transduction of signals from two known ligands: B cell activating factor from the tumor necrosis factor family (BAFF/BLyS) and APRIL, a proliferation-inducing ligand. Belantamab mafodotin binds to BCMA, is internalized, and

releases free cys-MMAF, which disrupts the microtubule network, leading to cell cycle arrest and apoptosis. Belantamab mafodotin also mediates antibody-dependent cell-mediated cytotoxicity effector function directed toward BCMA-expressing cells.

Clinical data from the phase 1, first-in-human trial, Study BMA117159 (DREAMM-1) in patients with RRMM (Part 2, n=35 patients treated at the 3.4 mg/kg starting dose) has demonstrated an ORR of 60% (95% confidence interval [CI] 42.1%–76.1%), with:

- 5 (15%) patients achieving a stringent complete response (sCR) or a complete response (CR);
- 14 (40%) achieving a very good partial response (VGPR);
- 2 (6%) achieving a partial response (PR).

The median time to first response was 1.2 months (95% CI 0.7–1.4); responses were maintained and generally deepened over time. The median progression-free survival (PFS) was 12.0 months (95% CI 3.1–not estimable) and the median DOR was 14.3 months (95% CI 10.6–not estimable). In patients refractory to both immunomodulators and proteasome inhibitors, median PFS was 7.9 months (95% CI 2.3–not estimable); in patients without prior daratumumab treatment, median PFS was 15.7 months (95% CI 2.3–not estimable). Overall, belantamab mafodotin was well tolerated and the AEs were manageable [Trudel, 2019]. All patients experienced at least one AE, most commonly thrombocytopenia (22/35; 63%), blurred vision (18/35; 51%), and cough (14/35; 40%). Grade 3 or 4 AEs were reported in 29 (83%) patients, the most common of which were thrombocytopenia (Grade 3, 9/35 [26%]; Grade 4, 3/35 [9%]) and anemia (Grade 3, 6/35 [17%]); no Grade 5 AEs were reported. Serious AEs (SAEs) were reported in 17/35 (49%) patients, most commonly pneumonia (3/35; 9%), lung infection (2/35; 6%), and infusion-related reactions (2/35; 6%). Seven (20%) patients experienced SAEs related to study treatment, most commonly infusion-related reactions (2/35; 6%). Four patients died during the study, all due to progression of MM. Four (11%) patients had AEs that led to permanent discontinuation of study treatment, each due to thrombocytopenia; keratopathy; fatigue and cough; and increased alanine aminotransferase (ALT), aspartate aminotransferase, and blood creatine phosphokinase. These results suggested that belantamab mafodotin demonstrated a manageable safety profile and positive clinical activity in patients with heavily pretreated RRMM. GSK has initiated (or plans to initiate) further clinical studies to evaluate belantamab mafodotin as monotherapy or in combination in participants with relapsed/refractory or newly diagnosed MM.

In the phase 2 pivotal study 205678 (NCT03525678, DREAMM-2), belantamab mafodotin was further evaluated as monotherapy in patients with RRMM at doses of 2.5 mg/kg and 3.4 mg/kg Q3W. This was a two-arm, randomized study in patients who had failed at least three prior lines of antimyeloma therapy, including an anti-CD38 antibody, and who were refractory to an IMiD and a proteasome inhibitor (n=97 in the 2.5 mg/kg cohort and n=99 in the 3.4 mg/kg cohort) [Lonial, 2020]. As of June 21, 2019 (the primary analysis data cutoff date), 30/97 patients (31%; 97.5% CI 20.8–42.6) in the 2.5 mg/kg cohort and 34/99 patients (34%; 97.5% CI 23.9–46.0) in the 3.4 mg/kg cohort

achieved an overall response. At the 2.5 mg/kg dose, median duration of response [DOR] not reached at a median follow-up of 6.3 months).

The most common Grade 3–4 AEs in the safety population were keratopathy (in 26/95 [27%] patients in the 2.5 mg/kg cohort and 21/99 [21%] patients in the 3.4 mg/kg cohort), thrombocytopenia (19 [20%] and 33 [33%]), and anemia (19 [20%] and 25 [25%]). A total of 38/95 (40%) patients in the 2.5 mg/kg cohort and 47/99 (47%) patients in the 3.4 mg/kg cohort reported SAEs. Two deaths were potentially treatment related (one case of sepsis in the 2.5 mg/kg cohort and one case of hemophagocytic lymphohistiocytosis in the 3.4 mg/kg cohort). Overall, both dose levels, 2.5 mg/kg and 3.4 mg/kg, have a positive benefit/risk profile. The dose of 2.5 mg/kg had a lower incidence of AEs, less frequent dose delays and reductions, and similar efficacy as the 3.4 mg/kg dose as measured by ORR. Based on benefit/risk assessment, a dose of 2.5 mg/kg Q3W has been recommended as the monotherapy dose of belantamab mafodotin for patients with RRMM in fourth-line or higher settings.

Keratopathy of any grade (defined as changes to the corneal epithelium documented by slit-lamp examination and/or confocal microscopy) was reported in 75% of patients. Furthermore, 22% experienced blurred vision (defined as blurred vision, including diplopia, decreased visual acuity, and vision impairment) and 14% experienced dry eye (defined as dry eye, ocular discomfort, eye pruritis, and foreign body sensation in the eyes) in the 2.5 mg/kg cohort. Grade 1 or 2 keratopathy occurred in 41 (43%), Grade 3 keratopathy in 26 (27%), Grade 1 or 2 blurred vision in 17 (18%), and Grade 3 blurred vision in 4 (4%) patients. These events led to dose reductions in 22 (23%) patients and delays in 45 (47%) patients. Dose reductions started at week 13 while dose delays started at week 4 for keratopathy. Of the 45 patients with treatment delays due to keratopathy, 31 (69%) reinitiated treatment, with a median time to treatment reinitiation of 83 days (range 28–146). Higher belantamab mafodotin Ctau was associated with probability of developing keratopathy and OEF and inversely correlated to time of onset. Grading of corneal events was performed using the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 as well as the GSK Grading Scale.

The mechanism of corneal events in patients treated with belantamab mafodotin is likely related to MMAF uptake into the corneal epithelial cells and eventual exposure to the basal epithelial stem cells that are located in the basal epithelial layer of the cornea [Donaghy, 2016]. These cells have mitotic activity, and, furthermore, daughter cells migrate anteriorly as they differentiate into wing cells and terminal superficial epithelial cells. Both processes are microtubule dependent and can be disrupted by potent tubulin inhibitors such as MMAF. The most affected basal epithelial cells die and fail to transition into functional wing cells. These damaged cells eventually undergo apoptosis and become pyknotic. They are extruded from the epithelium, and in that process, they appear microcyst-like on examination. The superficial corneal surface is secondarily affected both by these anatomic abnormalities and alterations in superficial corneal cell replenishment and tear film stability.

The current management guidelines for belantamab mafodotin-related corneal events include the use of preservative-free lubricant eye drops, dose reductions, and dose delays. The efficacy of steroid eye drops was systematically evaluated in a randomized ocular

substudy in the DREAMM-2 study, and the results revealed that empiric topical corticosteroid therapy conferred no benefit as prophylaxis for corneal events.

Corneal histopathologic samples in patients treated with belantamab mafodotin with this epitheliopathy are lacking, therefore, data is unavailable to support and confirm a working explanatory theory for the belantamab mafodotin–related corneal AEs. (Refer to the Investigator Brochure for pre-clinical findings regarding corneal events) [Investigator's brochure V8.0, GSK Version Number 8, Document Number 2013N175128_08]. A more complete understanding of the pathophysiology of the corneal events seen in these patients is needed. To do this, superficial keratectomy or impression cytology for any patients meeting study entry criteria, will be employed in this study to collect corneal epithelium with epithelial changes documented by slit-lamp examination and/or confocal microscopy for analysis. Images from slit-lamp examination and/or confocal microscopy at the time of patient enrollment will be obtained. Pathologic results will be correlated with the images to describe size, location, grade, and appearance of the epithelial lesions.

The study eye will be the one that that appears have a greater number of MECs. If both eyes appear equal in terms of epithelial changes, the eye with the worse visual acuity will be selected; if both eyes have the same visual acuity, then the investigator can select either eye.

Impression cytology is a technique used to diagnose a variety of ocular surface disorders and involves the application of cellulose acetate filter paper to collect superficial layers of the ocular surface for analysis. The procedure is performed by a trained ophthalmologist in the eye clinic with or without topical anesthesia and multiple samples can be obtained in one sitting.

Following topical anesthesia, an eyelid speculum, will be placed. Next, the filter paper will be pressed to a preidentified region on the corneal surface of the study eye with a glass rod (or similar instrument) for 5–10 seconds. The filter papers obtained from the procedure will contain epithelial layers from areas of the cornea with microcyst-like changes and will be analyzed through histologic techniques. The filter paper will be placed on a glass slide and cover slip placed on top. The eye speculum will be removed and a topical antibiotic drop (e.g. polytrim) will be prescribed for 4 times a day for 7 days.

Superficial keratectomy is a method to remove an area of full-thickness corneal epithelium. The procedure is performed by an ophthalmologist, takes 15–30 minutes to complete, and may be conducted in the eye clinic. While in some cases this procedure is performed in an operating room, only patients who are able to undergo the procedure in the clinic should be selected for it.

The study eye will be selected using the criteria described above. Following topical anesthesia (such as proparacaine hydrochloride 0.5%) and a drop of povidone iodine 5% for antisepsis, an eyelid speculum will placed. The eye will then be visualized using a slit-lamp or operating microscope in a procedure room. The corneal epithelium of interest (the region that contains the MECs) will be carefully removed using either a Weck-Cel/dry cellulose sponge or small blade; Jeweler or 0.12 forceps may be required in some

cases. The tissue will be submitted in formalin for histologic analysis. Care should be taken to minimize crush artefact to the epithelium and to avoid damage to Bowman layer.

Post procedure, another drop of povidone iodine 5% will be placed, followed by a drop of balanced salt solution or topical anesthetic (to wash out any residual povidone-iodine). A bandage contact lens will be placed. It is recommended that a topical antibiotic and a topical steroid (or a fixed combination of both) is prescribed 4 times per day, each, for at least one week (or longer), until the epithelial defect is documented as healed and the bandage contact lens is no longer required in the assessment of treating Ophthalmologist. The topical antibiotic may be discontinued once the epithelial defect has healed. The topical steroid should be tapered off over the following two weeks.

The expected time for corneal re-epithelialization is 7–10 days [Ashby, 2014]. The procedure can cause some pain to the patient but is generally safe and well tolerated. Pain, if any, can be managed effectively by the use of artificial tears, acetaminophen, and narcotics, if needed. The bandage contact lens should be helpful in reducing the need for pain medication. In patients with symptomatic blurred vision, the procedure may result in temporary visual improvement. The procedure may also be complicated by an infection or worsening vision. An ocular pathologist will be consulted to determine the appropriate testing of tissue sample.

It is common to experience varying degrees of discomfort beginning 30–90 minutes following the surgery as the topical anesthesia drops begin to wear off. Many patients describe this sensation as feeling like an eyelash is in the eye or lodged beneath the contact lens. This rarely lasts more than a few days and is a normal part of the healing process. Watery eyes, a runny nose, light sensitivity, and eye redness may occur during the early postoperative period. This is normal and is caused by the postsurgical eye irritation.

For both the impression cytology and SK cohorts, non-invasive imaging including anterior segment slit-lamp photography and confocal microscopy (if available) will be obtained prior to the procedure to correlate imaging and pathological findings. Confirmatory anterior segment photography is also required unless acceptable corneal images are available from an examination performed <14 days prior to impression cytology or SK.

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This study will be available to any patient who has received or is currently receiving belantamab mafodotin treatment through either a clinical trial (including an investigator-

sponsored study [ISS], or an access program) or a Physician prescription; they do not need to be on active treatment as long as they meet inclusion criteria.

2.3. Benefits and Risks

CCI

[redacted]

Pain:

The SK procedure can cause pain to the participant but is generally safe and well tolerated. Pain can be managed by the use of artificial tears or a bandage contact lens

Infection:

The SK procedure carries a risk of infection and requires prophylactic antibiotics. Infectious keratitis occurs in 2% of patients [Vo, 2015]. These data are from patients who underwent epithelial debridement and diamond burr polishing of the Bowman's membrane (n=91 eyes).

Delayed Healing:

In this study, it is anticipated that SK-induced epithelial defect will heal within 7 days with the use of a bandage contact lens.

Typically, healing occurs in 2 days for a 3–4 mm central epithelial debridement [Sta Iglesia, 2000] [Wilson, 2004] [Park, 2019]. Temporary scarring/subepithelial haze can occur in 21% of eyes at 1 month post procedure and in 9% of eyes at last follow-up and is not visually significant. No complications resulting in impaired vision at final follow-up have been reported [Vo, 2015] [Murueta-Goyena, 2018].

Comorbidities such as diabetes and dry eye can significantly delay the healing process and may require adjuvant therapy (e.g., bandage contact lens).

2.3.1. Benefit Assessment

In participants with central corneal deposits, the SK procedure may or may not be therapeutic. Any improvement in visual acuity will be documented via a Snellen eye test pre- and post-procedure as detailed in the SoA. Although this procedure is being performed primarily for diagnostic purposes, an improvement in vision, at least

temporarily, is a potential benefit. For any given patient it is not possible to predict whether an improvement in vision will occur or not.

2.3.2. Overall Benefit/Risk Conclusion

Approaches to minimize risk include supportive care with the performance of the SK, utilization of a post-procedure bandage contact lens along with topical antibiotics and a steroid, and close monitoring.

The scientific data that will be obtained from this study will provide critical information on the pathologic nature of the corneal epithelial changes, which may inform potential mitigating treatments for participants suffering from corneal symptoms while receiving treatment for RRMM with belantamab mafodotin.

3. OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**
Primary: To characterize corneal epitheliopathy in participants treated with belantamab mafodotin	**Primary:** Pathologic characteristics and composition of corneal epithelial changes obtained by impression cytology (IC) or SK in participants treated with belantamab mafodotin
Secondary: • To correlate clinical data, including visual acuity and symptoms, as well as grade and appearance of corneal changes on imaging, with histopathologic findings • Safety profile of the impression cytology or SK procedure	**Secondary:** • Results of analysis of clinical/imaging data with histopathologic findings • AEs associated with the impression cytology or SK procedure
CCI [redacted]	

4. STUDY DESIGN

4.1. Overall Design

- This study is available to any participant who has received or is currently receiving belantamab mafodotin treatment through a clinical trial (including an ISS, or an access program) or a Physician prescription; they do not need to be on active treatment as long as they meet inclusion criteria specified below.
- Up to 25 participants will complete the procedure. Once a total of 5 participant samples from SK procedure has yielded evaluable material for pathologic examination and composition analysis of the corneal epithelial changes, further enrollment will cease.
- Each patient will have a total of 3 (IC) to 6 (SK) visits. Additional followup visits may be required in the event of delay in healing from the ocular procedures.
- One eye will be the study eye. The study eye will be the eye most affected with the corneal epithelial changes. If both eyes are equally affected, the poorer-seeing eye will be selected.
- Each participant will only have one corneal procedure (impression cytology or SK). All participants will be asked to participate in the CCI [redacted] CCI [redacted]

4.2. Study Procedures

- Corneal epithelial tissue will be obtained by IC or SK from the study eye showing the greater number of MECs. Removal of the limbal tissue should be avoided during the SK procedure, if possible. The sample material will be processed and transferred to the central laboratory.
- Assessments of the epithelial changes will be made, including but not limited to histology, electron microscopy, and immunohistochemistry. See table below for methods to investigate the corneal epithelium.
- Anterior segment slit-lamp photography of both eyes.
- Confocal microscopy, if available, in the study eye.
- CCI [redacted]

Name of analysis[a]	**How should the sample be fixed/prepared?**	**Description of test**	**References**
Microscopic evaluation/ histopathology	Tissue fixed in 10% neutral buffered formalin and embedded in paraffin. 5 µm sections examined microscopically	Histologic characterization – description of cells in the epithelium; will show apoptotic cells	[Lee, 2018] [Stiefel, 2019]
		Hematoxylin-eosin (H&E) stain: hematoxylin is used to illustrate nuclear detail (color is related to the amount of DNA); eosin is used to stain cytoplasm	[Sampias, 2019]
		Periodic acid-Schiff (PAS) stain: used for structures with a high proportion of carbohydrates (e.g., glycogen, glycoproteins, proteoglycans) typically found in connective tissues, mucus, and basement membranes	[Anderson, 2020]
		Congo red stain: used for amyloid epithelial changes	[Byrwa-Neff, 2020]
		Masson's trichome stain: used for collagenous connective tissue fibers; differentiates collagen and smooth muscle; used in the detection of diseases or changes in connective/muscle tissue	[Anderson, 2020]
Immunohisto-chemistry (IHC) for IgG	Tissue samples examined by IHC; performed with primary antibodies	Will identify IgG-positive intracytoplasmic granules in the epithelium; because belantamab mafodotin is an IgG1, it could show if belantamab mafodotin itself is deposited in the epithelium	[Lee, 2018] [Stiefel, 2019]
Electron microscopy	Samples for transmission electron microscopy will be processed using standard techniques: tissues will be epoxy embedded in standard fashion without post fixation. Ultrathin sections measuring 80 nm will be stained with uranyl acetate and lead citrate and examined in a Zeiss EM900 transmission electron microscope at 80 kV	Used for high-resolution images of detailed structures such as tissues, cells, organelles, and macromolecular complexes	[Electron Microscopy, 2020] [Stiefel, 2019]

Name of analysis[a]	How should the sample be fixed/prepared?	Description of test	References
Mass spectrometry (nanoscale liquid chromatography coupled to tandem mass spectrometry [nano LC-MS/MS])	For comprehensive methods, see [Karring, 2012]	Analysis of peptide mixtures in sample-limited situations Can be used to identify in-gel digested protein spots Has been utilized to determine the composition of corneal epithelial changes associated with mutations in *TGFBI* gene	[Karring, 2012] [Gaspari, 2011]

[a]Histologic characterization, H&E, and PAS are required; all other stains and techniques are at the investigator's discretion.

Participants who receive belantamab mafodotin consistently display microcyst-like epithelial changes on slit-lamp examination and/or experience symptoms including changes in visual acuity, blurred vision, and dry eye, which are recognized AEs associated with MMAF-containing antibody therapies, including SGN-75 [Tannir, 2014], SGN-CD19A, and ABT-414 [Reardon, 2017], but the exact mechanism is unknown. The corneal findings by slit-lamp examination have been described in participants treated with high-dose cytarabine [Guthoff, 2010]. The specific corneal AE seen with belantamab mafodotin therapy has not been replicated in preclinical models, and confirmatory corneal histology is lacking to support and confirm the working explanatory theory for this corneal toxicity.

The mechanism of corneal events in participants treated with belantamab mafodotin is unknown, but it is likely related to MMAF uptake into the corneal basal epithelial stem cells that are located in the basal epithelial layer of the cornea [Donaghy, 2016]. These cells have mitotic activity, and, furthermore, daughter cells migrate anteriorly as they differentiate into wing cells and terminal superficial epithelial cells. Both processes are microtubule dependent and can be disrupted by potent tubulin inhibitors such as MMAF. The leading hypothesis is that the most affected basal epithelial cells die and fail to transition into functional wing cells. These damaged cells eventually undergo apoptosis and become pyknotic. They are extruded from the epithelium, and in that process, they appear microcyst-like on examination. The superficial corneal surface is secondarily affected both by these anatomic abnormalities and alterations in superficial corneal cell replenishment and tear film stability.

The current management guidelines for belantamab mafodotin-related corneal events include the use of preservative-free lubricant eye drops, dose reductions, and dose delays. The efficacy of steroid eye drops was systematically evaluated in a randomized ocular substudy in the DREAMM-2 study, and the results revealed that empiric topical corticosteroid therapy conferred no benefit. Corneal histopathologic samples in participants treated with belantamab mafodotin with this epitheliopathy are lacking. A more complete understanding of the pathophysiology of the corneal events seen in these participants could help confirm current hypotheses and inform management of these AEs. To do this, impression cytology or SK will be employed in this study to collect corneal epithelium with deposits for analysis. Advice from a council of corneal ophthalmology experts has been sought, and it is recommended that a total of 5 samples with sufficient

material for examination will provide confirmatory diagnosis of the underlying pathology and composition of these deposits. At least one highly experienced ophthalmic pathologist and laboratory will be utilized for tissue analysis.

4.3. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit, as specified in the SoA.

5. STUDY POPULATION

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Male or female, aged 18 years or older (at the time consent is obtained).
2. Capable of providing signed written informed consent, which includes compliance with the requirements and restrictions listed on the consent form.
3. Participants with RRMM who have received or are currently receiving treatment with belantamab mafodotin AND diagnosed with MECs on slit-lamp examination or confocal microscopy, with or without symptoms, in at least one eye.
    a. If patient only had superficial punctate keratopathy with no evidence of MEC's they are not eligible.
4. If undergoing SK procedure, treating provider has determined there is no excessive risk to the participant (see Section 6.2).

5.2. Exclusion Criteria

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

1. Any serious and or/unstable medical or psychiatric disorder, or other conditions that could interfere with the participant's safety.
2. Any excess risk of delayed wound healing (e.g., diabetes mellitus).
3. Do not meet criteria specified by the study or program through which they would receive belantamab mafodotin.
4. Any patient taking concurrent medication that may affect the cornea (i.e. amiodarone, some chloroquines).
5. Any patient with decreased corneal sensation.
6. Eye infections, including infectious keratopathy, stye, blepharitis, and conjunctivitis.
7. An active uveitis including anterior, posterior, or panuveitis in either eye.
8. Permanent legal blindness in the fellow (non-study) eye.

Note: If the participant's eyes are equally affected with the MECs, the study eye will be the one with lesser visual acuity.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

Impression cytology is a technique used to collect superficial layers from the ocular surface through the application of cellulose acetate filter paper. The procedure is performed with or without topical anesthesia by an ophthalmologist or ocular pathologist.

SK is a method to remove a small region of the corneal epithelium down to but not including the level of the Bowman's membrane. This procedure will be performed by an ophthalmologist and will be conducted in the eye clinic or hospital under local anesthesia with appropriate antisepsis.

In this study, impression cytology or SK will be employed to collect corneal epithelium with epithelial changes for analysis.

6.2. Patient Selection Considerations

6.2.1. Selection of Right or Left eye for the procedure

The study eye will be the one that appears to have a greater number of MECs. If both eyes appear equal in terms of epithelial changes, the eye with the worse visual acuity will be selected; if both eyes have the same visual acuity, then the investigator can select either eye.

6.2.2. Selection of SK or IC procedure

The following guidance should be considered before deciding which procedure (IC or SK) to perform:

1) Patients should be assessed carefully for participation in either procedure. Patient eligibility factors to be considered include but are not limited to: excessive risk of delayed wound healing, history of concerning ocular or systemic infections, ocular condition that may place the patient at increased risk for recovery, social or medical circumstances that would make the risk of increased recovery time too high
2) Corneal sensation is checked at the screening visit for this study, and any eyes with reduced sensation should be considered ineligible for SK.
3) For SK, a higher keratopathy disease burden, greater predominance of MECs and central corneal location of MECs is preferred.

6.3. Impression Cytology Procedure

The study eye will be selected using the criteria described above. Following topical anesthesia, an eyelid speculum, will be placed. Next, the filter paper will be pressed to a preidentified region on the corneal surface of the study eye with a glass rod (or similar instrument) for 5–10 seconds. The filter papers obtained from the procedure will contain epithelial layers from areas of the cornea with microcyst-like changes and will be analyzed through histologic techniques. The filter paper will be placed on a glass slide and cover slip placed on top. The eye speculum will be removed and a topical antibiotic drop (e.g. polytrim) will be prescribed for 4 times a day for 7 days.

6.4. Superficial Keratectomy Procedure

The study eye will be selected using the criteria described above. Following topical anesthesia (such as proparacaine hydrochloride 0.5%) and a drop of povidone iodine 5% for antisepsis, an eyelid speculum will placed. The eye will then be visualized using a slit-lamp or operating microscope in a procedure room. The corneal epithelium of interest (the region that contains the MECs) will be carefully removed using either a Weck-Cel/dry cellulose sponge or small blade; Jeweler or 0.12 forceps may be required in some cases. The tissue will be submitted in formalin for histologic analysis. Care should be taken to minimize crush artefact to the epithelium and to avoid damage to Bowman layer.

Post procedure, another drop of povidone iodine 5% will be placed, followed by a drop of balanced salt solution or topical anesthetic (to wash out any residual povidone-iodine). A bandage contact lens will be placed.

It is recommended that a topical antibiotic and a topical steroid (or a fixed combination of both) is prescribed 4 times per day, each, for at least one week (or longer), until the epithelial defect is documented as healed and the bandage contact lens is no longer required in the assessment of treating Ophthalmologist. The topical antibiotic may be discontinued once the epithelial defect has healed. The topical steroid should be tapered off over the following two weeks.

The expected time for corneal re-epithelialization is 7–10 days [Ashby, 2014]. The procedure can cause some pain to the participant but is generally safe and well tolerated. Pain, if any, can be managed by the use of artificial tears. A bandage contact lens should be helpful in reducing the need for pain medication. In participants with symptomatic blurred vision, the procedure may result in temporary visual improvement. The procedure may also be complicated by an infection or worsening vision. An ocular pathologist will be consulted to determine the appropriate testing of tissue sample.

If the epithelial defect has not healed completely at the day 7 visit, the bandage contact lens should be left in place and both the steroid and antibiotic continued. The participant should be examined again in approximately 1 week.

The participant should be re-examined 2 weeks after the SK procedure if the epithelial defect does not heal completely in the first follow-up. Otherwise, this follow-up is not required. In the event the cornea has not healed at 2 weeks, additional follow-up should be conducted at the ophthalmologist's discretion until healing is confirmed.

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6.8. sBCMA Sample Collection and Analysis

The BCMA receptor undergoes gamma-secretase mediated cleavage, leading to release of the BCMA extracellular domain as soluble BCMA (sBCMA) into the circulation [Laurent, 2015].

Samples will be collected to measure concentrations of sBCMA at a single timepoint, prior to IC or SK procedure. Serum analysis for sBCMA will be performed under control of GSK (further details are included in the SRM). Raw data will be archived at the bioanalytical site (detailed in the SRM).

The actual date and time of each blood sample collection will be recorded. Details on sBCMA blood sample collection including blood volumes, processing, storage, and shipping procedures are provided in the SRM.

6.9. Imaging Procedures

Slit-lamp examination, and confocal microscopy (if available) must be performed prior to the impression cytology or superficial keratectomy procedure to document site and size of corneal epithelial changes and to correlate imaging with pathologic findings. The slit-lamp examination must include orbit/lid/adnexa, conjunctiva, sclera, cornea, anterior chamber, iris, lens, and anterior vitreous. Full anterior segment (slit lamp) examination including fluorescein staining of the cornea.

It is recommended that the imaging examination be performed at least 24 hrs prior to the procedure.

Confirmatory anterior segment photography is also recommended, if available. Anterior segment exam includes:, conjunctiva, sclera, cornea, lens and anterior vitreous. If anterior segment photography of the cornea is available, representative images will be collected and stored centrally.

6.10. Concomitant Therapy

Any patient taking concurrent medication that may affect the cornea (i.e. amiodarone, some chloroquines) should not be enrolled.

Concomitant use of ophthalmic medications related to allowable underlying ophthalmic conditions is permitted. Any medication (including over-the-counter prescription medications, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment, at time of study procedure, and post procedure must be recorded along with:

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/ WITHDRAWAL

7.1. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- The participant will be permanently discontinued both from the study intervention and from the study at that time.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2. Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, [3] telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or the study as a whole is handled as part of Appendix 1. Discontinuation in this study does not mean the participant has discontinued from the associated treatment protocol.

8. STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form (ICF) must be obtained from the participant prior to any study-specific procedures or assessments being performed. The timing of each assessment is listed in the SoA.

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

8.1. Safety Assessments

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

8.1.1. Vital Signs

Vital signs will consist of 1 pulse and 1 blood pressure measurement.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones)

8.1.2. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 2.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up all AEs related to the study intervention.

The methods of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2 .

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

- All SAEs related to the IC or SK procedure only will be collected from the start of intervention until the last follow-up visit at the time points specified in the SoA. However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests) will be recorded from the time a participant consents to participate in the study.

- AEs related to the IC or SK procedure only will be collected from the start of intervention until the last follow-up visit at the time points specified in the SoA (Section 1.3).

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will not be collected.

- SAEs related to the IC and SK procedure will be recorded and reported to the sponsor or designee immediately, and under no circumstance should this exceed 24 hours, as indicated in Appendix 2 . The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

- Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.1.4. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.1.5. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. Related SAEs will be followed until the event is resolved, stabilized, or otherwise explained, and the epithelial defect is healed, or the

participant is lost to follow-up (as defined in Section 7.2). Further information on follow-up procedures is given in Appendix 2 .

8.1.6. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure (IB) and will notify the IRB/IEC, if appropriate, according to local requirements.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.1.7. Cardiovascular and Death Events

For any cardiovascular (CV) events detailed in Appendix 2 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the Case Report Form (CRF) will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific CV section of the CRF within 1 week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported.

8.2. Biomarkers

Cornea tissue samples will be collected to evaluate the composition of microcyst-like epithelial changes observed in participants treated with belantamab mafodotin. Samples will be collected according to the schedule described in the SoA and, as detailed in the laboratory manual, provided separately to sites.

GSK may store samples for up to 3 years after the end of the study to achieve study objectives. Additionally, with participants' consent, samples may be used for further research by GSK or others such as universities or other companies to contribute to the

understanding of the pathophysiology of belantamab mafodotin–associated keratopathy, the development of related or new treatments, or research methods.

8.3. Data Collection

Minimal additional data will be collected to adequately characterize the development of the corneal epithelial changes in participating patients.

a. Patient Demographics & Disease characteristics
b. Limited Medical History and prior cancer treatment
c. Belantamab mafodotin treatment Exposure
d. Ocular History including the time of development of keratopathy, and the grade.

9. STATISTICAL CONSIDERATIONS

This is an exploratory study, and only descriptive statistics apply.

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the safety data is outlined below.

9.1. Participant Information

All-treated population is defined as all participants who are enrolled. All analyses will be based on this population.

9.2. Sample Size Determination

No statistical hypotheses will be tested as part of this protocol. The primary objective of this protocol will be assessed through a qualitative evaluation of pathology results.

A total of 5 evaluable participants should provide sufficient information to make a qualitative assessment.

9.3. Analysis Methods

No formal statistical tests of hypothesis will be performed. All participants who have SK in this program will be included in the safety analysis.

Demographic characteristics and dosing level and duration will be summarized using descriptive statistics (i.e., categorical variables will be described by absolute and relative frequencies), while continuous variables will be summarized by mean, standard deviation, quartiles, minimum, and maximum. The available information on all nonserious AEs leading to discontinuation, SAEs, and all other AEs (including AEs of special interest) will also be summarized using descriptive statistics.

All available demographic and safety data will be included in the data listings and tabulations. No imputation of values for missing data will be performed. Participants who

are lost to follow-up will be included in the statistical analysis to the point of their last examination. All data will be examined using standard data management operating procedures.

Changes in corneal epithelial findings from pre to post procedure, pathological and [redacted] results in safety population will be tabulated in a descriptive manner.

10. APPENDICES

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
  - Applicable ICH Good Clinical Practice (GCP) Guidelines;
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

- A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

GSK (alone or working with others) may use a participant's coded study data and samples and other information to carry out this study, understand the results of this study, learn more about belantamab mafodotin–associated keratopathy, and publish the results of these research efforts.

The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorized designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant, who will be required to give consent for their data to be used as described in the ICF.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report (CSR). The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.

- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators which treatment their patients received. The investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.

- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve participant care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.

- Study details will be made available on www.clinicaltrials.gov prior to, during, and after the conduct of the study.

- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.

- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF (eCRF) unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- Guidance on completion of CRFs will be provided in the Study Reference Manual.

- Quality tolerance limits (QTLs) will be predefined in the Monitoring Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during and at the

end of the study, and all deviations from the QTLs and remedial actions taken will be summarized in the CSR.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator.
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission to the scientific meeting or peer-reviewed journal. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Definition of Unsolicited and Solicited AE
• An unsolicited AE is an AE that was not solicited using a Participant Diary and that is communicated by a participant who has signed the ICF. Unsolicited AEs include serious and nonserious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The participant will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during interviews with the participants and by review of available medical records at the next visit. • Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and that are noted by the participant in his/her diary.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiography [ECG], radiologic scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected intervention–intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it was more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Possible Hy's law case: ALT ≥3×ULN AND total bilirubin ≥2×ULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as an SAE.
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.2.3. Definition of Cardiovascular Events

Cardiovascular (CV) Events Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

10.2.4. Recording and Follow-up of AEs and SAEs

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, and laboratory and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK-required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.
- An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.2.5. Reporting of SAEs to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAEs to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as they become available. • The investigator or medically qualified subinvestigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to study intervention/study participation (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in the Study Reference Manual. Complete the SAE form and email it to the GSK Case Management Group (CMG) group mailbox: uk.gsk-rd-gcsp-ctsm-admin@gsk.com.

SAE Reporting to GSK via Paper Data Collection Tool
• Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the **medical monitor or the SAE coordinator**. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the Study Reference Manual. Complete the SAE form and email it to the GSK CMG group mailbox: uk.gsk-rd-gcsp-ctsm-admin@gsk.com.

Assessment of Intensity
• The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe. • An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe. • Other measures to evaluate AEs and SAEs may be utilized (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the IB or Product Information, for marketed products in his/her assessment. • For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to GSK. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3. Appendix 3: History of protocol changes

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

Amendment 1: 28-JUL-2020

Overall Rationale for the Amendment:

The protocol has been amended to update tear fluid specimen collection process and add a blood sample assessment at baseline.

Section # and Name	Description of Change	Brief Rationale
Objectives and Endpoints, Synopsis	Added Blood Sample Analysis	Add Analysis of blood BCMA levels
Multiple sections	Updated to include blood sample collection	Add Analysis of blood BCMA levels
1.3 Schedule of Assessments	Added Blood Sample Collection	Add Analysis of blood BCMA levels
3.0 Objectives and Endpoints	Added Blood Sample Analysis	Add Analysis of blood BCMA levels
4.2 Study Procedures	Added Tear Fluid & Blood Sample Analysis	Clarification
CCI [redacted]		
6.6 Belantamab Mafodotin PK Sample Analysis	Added Section	Clarification
6.7 sBCMA Sample Collection and Analysis	Added Section	Clarification of specific lab testing

10.4. Appendix 4: Abbreviations and Trademarks

ADC	Antibody-drug conjugate
AE	Adverse event
ALT	Alanine aminotransferase
APRIL	A proliferation-inducing ligand
BAFF	B-cell activating factor family
BCMA	B-cell maturation antigen
BIB	Bioanalysis Immunogenicity and Biomarkers
BLys	B lymphocyte stimulator
CD38	Cluster of differentiation 38
CFR	Code of Federal Register
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLW	Central Laboratory Worksheet
CMG	Case Management Group
CRF	Case Report Form
CSR	Clinical study report
CCI [redacted]	
CV	Cardiovascular
DOR	Duration of Response
DREAMM	Driving Excellence in Approaches to Multiple Myeloma
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
H&E	Hematoxylin-eosin
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IC	Impression Cytology
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IHC	Immunohistochemistry
IMiD	Immunomodulatory drugs
ISS	Investigator Sponsored Study
kg	kilogram
MECs	Microcyst-like epithelial changes
mg	milligram
MM	Multiple myeloma
MMAF	Monomethyl auristatin-F
NCI	National Cancer Institute
OEF	Ocular eye findings
ORR	Overall Response Rate

PAS	Periodic acid-Schiff
PFS	Progression-free Survival
PR	Partial Response
QTL	Quality Tolerance Limit
Q3W	Every three weeks
RRMM	Relapsed/Refractory multiple myeloma
SAE	Serious adverse event
sCR	Stringent Complete Response
CCI	[redacted]
SoA	Schedule of activities
SRM	Study Reference Manual
ULN	Upper limit of normal
VGPR	Very Good Partial Response

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Cytarabine
Polytrim

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