TITLE PAGE

Division: Pharma Research and Development
Information Type: Epidemiology PASS Protocol

Title:	**B**LENREP **E**ffectiveness **a**nd Safety in **M**ultiple **M**yeloma (BEaMM) – Real-World Evidence on Patients Taking Belantamab Mafodotin in Europe.

Compound Number:	GSK2857916
Development Phase	IV
Effective Date:	21 Apr 2022
Subject:	Real-world use, safety and effectiveness
Author(s):	PPD ; GlaxoSmithKline (GSK) PPD ; Syneos Health
Indication Studied:	Adults with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody

PASS INFORMATION

Title	**B**LENREP **E**ffectiveness **a**nd Safety in **M**ultiple **M**yeloma (BEaMM) – Real-World Evidence on Patients Taking Belantamab Mafodotin in Europe.
Protocol version identifier	Protocol amendment 1
Date of last version of protocol	21 Apr 2022
EU PAS (ENCEPP) register number	Study not registered yet.
Active substance	Belantamab mafodotin - L01XC39
Medicinal product	BLENREP
Product reference	EU/1/20/1474/001
Procedure number	EMEA/H/C/004935
Marketing authorisation holder(s)	GlaxoSmithKline (Ireland) Limited
Joint PASS	No
Research question and objectives	The purpose of this study is to collect real-world data on the use, safety and effectiveness of belantamab mafodotin in RRMM patients in Europe.
Country(-ies) of study	Patients will be included from sites in selected countries across Europe.
Authors	PPD PPD, Oncology Epidemiology GlaxoSmithKline plc 1250 S Collegeville Rd, Collegeville, PA 19426 PPD, PhD PPD, Epidemiology Syneos Health De Entrée 99-197, 14th floor 1101 HE Amsterdam, The Netherlands

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	GlaxoSmithKline (Ireland) Limited 12 Riverwalk Citywest Business Campus Dublin 24 Ireland
MAH contact person	PPD Oncology Therapeutic Group, Global Regulatory Affairs GlaxoSmithKline Research & Development Limited 980 Great West Road, Brentford, Middlesex, TW8 9GS United Kingdom

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1. LIST OF ABBREVIATIONS

ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ATU	Authorization for use
BCVA	Best Corrected Visual Acuity
BMI	Body mass index
CI	Confidence interval
CR	Complete response
DoR	Duration of response
DoT	Duration of treatment
EAP	Early access program
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EHA	European Hematology Association
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EP	Enrolled population
ESMO	European Society for Medical Oncology
EU	European Union
GCP	Good clinical practice
GSK	GlaxoSmithKline
GVP	Good Pharmaco Vigilance Practice
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
Ig	Immunoglobulin
IMWG	International Myeloma Working Group
IRB	Institutional review board
ISS	International Staging System
kg/m2	Kilogram per meter square
KM	Kaplan-Meier
KVA	Keratopathy and Visual Acuity
mAB	Monoclonal antibody
MEC	Microcystic-like epithelial changes
MedDRA	Medical Dictionary for Regulatory Activities
mg/kg	Milligram per kilogram
MM	Multiple myeloma
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

NPP	Named Patient Program
ORR	Overall response rate
OS	Overall survival
PASS	Post-authorisation safety study
PD	Progressive disease
PFS	Progression-free survival
PI	Proteasome inhibitor
PR	Partial response
PT	Preferred term
RMP	Risk management plan
RRMM	Relapsed or refractory MM
rwPFS	Real-world progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
sCR	Stringent complete response
SMA	Site management associate
SMP	Safety management plan
SmPC	Summary of product characteristics
SOC	System organ class
SP	Safety population
US	United States
USPI	US prescribing information
VEO	Value, Evidence and Outcomes
VGPR	Very good partial response
WHO	World Health Organization

TRADEMARK INFORMATION

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EU PAS
SAS

2. RESPONSIBLE PARTIES

Principal Investigator	PPD PPD, Oncology Epidemiology GlaxoSmithKline plc PPD
Drug Safety & Pharmacovigilance Lead	PPD PPD GlaxoSmithKline plc PPD

Contact details of all Investigators participating in the study and the Study Advisory Committee will be kept in stand-alone documents listed in ANNEX 1.

SPONSOR SIGNATORY

Title:	**B**LENREP **E**ffectiveness **a**nd Safety in **M**ultiple **M**yeloma (BEaMM) – Real-World Evidence on Patients Taking Belantamab Mafodotin in Europe.

Compound Number: GSK2857916

Linda V. Kalilani
Senior Director and Head, Oncology Epidemiology

Date

Julie Byrne
Safety Evaluation and Risk Management Director

Date

SPONSOR INFORMATION PAGE

Study ID: 217240

Sponsor Legal Registered Address:

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

Sponsor Medical Monitor Contact Information:

Dr. PPD, MD
Global Medical Affairs Lead-Hematology
GlaxoSmithKline plc
Poststrasse 6
6300 Zug
Switzerland
PPD

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol (protocol amendment 1).
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described health research study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

_____ _____

Investigator Signature Date

3. ABSTRACT

3.1. Title

BLENREP™ **E**ffectiveness **a**nd Safety in **M**ultiple **M**yeloma (BEaMM) – Real-World Evidence on Patients Taking Belantamab Mafodotin in Europe

Version 1.921 Apr 2022, PPD , GlaxoSmithKline & PPD , Syneos Health

3.2. Rationale and background

Multiple myeloma (MM) is a rare and incurable haematological malignancy which typically affects adults 60 years of age and older. Current MM therapies include glucocorticoids, chemotherapy, proteasome inhibitors (PIs), immunomodulatory agents and monoclonal antibodies (mAbs, e.g., daratumumab). Since the approval of daratumumab, MM patients have emerged who are refractory to at least one proteasome inhibitor (PI), one immunomodulatory agent and one anti-CD38 monoclonal antibody (mAb). There is a clear unmet medical need for new therapies among patients with relapsed or refractory MM (RRMM) as current treatment options are very limited with a median overall survival (OS) of approximately 7 to 10 months (Gandhi, 2019).

Belantamab mafodotin (BLENREP™) is a first in-class anti-B-cell maturation antigen therapy approved for use in the United States (US) and European Union (EU) based on data from the pivotal Phase II DREAMM-2 study (Study 205678) (Lonial, 2020; Lonial, 2021a).

In the EU, belantamab mafodotin was granted a Conditional Marketing Authorisation on 25 August 2020 for the treatment of MM in adult patients who have received at least four prior therapies and whose disease is refractory to at least one PI, one immunomodulatory agent, and an anti-CD38 mAB, and who have demonstrated disease progression on the last therapy. Because of the risk of ocular toxicity, the European Medicines Agency (EMA) required additional monitoring and additional risk minimisation measures in the form of educational materials for prescribers and patients as detailed in the Risk Management Plan (RMP) (Summary RMP, 2021). The goal of the EU RMP is to mitigate the risk of ocular toxicity of belantamab mafodotin by educating prescribers and patients. The EU Summary of Product Characteristics (SmPC) states ophthalmic examinations should be performed at baseline, before initiation of each of the subsequent 3 treatment cycles, and during treatment as clinically indicated (BLENREP SmPC, 2021).

To better understand the real-world management of RRMM patients exposed to belantamab mafodotin and the occurrence of ocular toxicity in routine clinical practice, this study aims to evaluate the real-world use, safety and effectiveness of belantamab mafodotin in RRMM patients in Europe.

3.3. Research question and Objective(s)

The purpose of this study is to collect real-world data on the use, safety and effectiveness of belantamab mafodotin in RRMM patients in Europe.

Objectives	**Description**
Primary Objective	Characterize RRMM patients treated with belantamab mafodotin per routine clinical care in terms of demographics, disease status, clinical characteristics and treatment history overall and by line of treatment)
Key Secondary Objectives	• Characterize patients with ocular AEs of special interest (AESIs) by belantamab mafodotin treatment, ophthalmic disease history and ocular AESI type, duration and severity (overall and by line of treatment • Describe frequency and timing of ophthalmic monitoring visits relative to belantamab mafodotin administration (for each cycle; overall and by line of treatment, occurrence of ocular AESIs as well as treatment dose and frequency)
Other Secondary Objectives	• Assess the incidence of ocular AESIs (overall and by line of treatment) and their impact on treatment discontinuation, interruption/delay, or dose modifications (overall and by line of treatment, comorbidity, ocular AESI type and severity as well as treatment dose and frequency) • Evaluate persistence and adherence with belantamab mafodotin • Describe reasons for treatment discontinuation • Describe the duration and reasons of treatment interruptions/ delays, or dose modifications • Evaluate effectiveness in terms of disease response to treatment, duration of response (DoR), duration of treatment (DoT), real-world progression-free survival (rwPFS) and overall survival (OS)

3.4. Study Design

This multinational, multisite, non-interventional study aims to collect real-world data on the use, safety and effectiveness of belantamab mafodotin in RRMM patients from Europe. Background data at the time of the first dose of belantamab mafodotin (i.e., demographics, disease status, clinical characteristics and treatment history) will be collected to characterize RRMM patients treated with belantamab mafodotin per routine clinical care. In addition, data will be collected on the occurrence, duration and management of ocular AESIs, the frequency and timing of ophthalmic examinations, persistence and adherence with belantamab mafodotin, treatment discontinuations, interruptions/delays and decreased dosing, and effectiveness in terms of treatment response and survival.

Data will be analysed from approximately 150 RRMM patients from sites in selected countries in Europe. Eligible RRMM patients from EU sites who are due to receive their first dose of belantamab mafodotin will be consecutively invited for study enrolment by haematologists and/or oncologists affiliated with investigator sites participating in this study. In the event the enrolment rate after study start is too low to meet the expected 150 RRMM patients within the planned enrolment timeframe, eligible RRMM patients from sites who received their first belantamab mafodotin dose before study enrolment will be

invited for study participation.. As the study is non-interventional, the decision to treat patients with belantamab mafodotin will be made prior to and independent from the decision to enrol patients into the study, and baseline and follow-up assessments will be in accordance with local standard medical care.

After obtaining informed consent, data will be collected into an electronic case report form (eCRF) directly during prospective follow-up or will be collected retrospectively from medical records, where applicable, from the time of the first dose of belantamab mafodotin to the end of follow-up at 15 months, study discontinuation for any reason, informed consent withdrawal or death; whichever comes first. The Investigator will follow ocular AESIs until resolved or until the last study visit of the patient.

The total study duration is estimated to be a maximum of two years and three months per site based on an estimated study enrolment period of 12 months and a follow-up period of 15 months.

3.5. Population

It is planned to include approximately 150 RRMM patients from sites in selected countries across Europe, from patients who are due to receive belantamab mafodotin as part of routine clinical care after study enrolment.

Inclusion Criteria:

A patient who meets **all** of the following criteria is eligible for inclusion:

- Written informed consent
- Male or female, ≥18 years of age at the start of belantamab mafodotin treatment
- Confirmed diagnosis of RRMM
- Received (first dose up to three months before study enrolment; if deemed required based on enrolment rate) or due to receive belantamab mafodotin treatment per routine clinical care by an oncologist or haematologist consistent with the approved labelling

Exclusion Criteria:

A patient who meets **any** of the following criteria is not eligible for inclusion:

- Concurrent enrolment in an interventional clinical trial involving either an investigational medicinal product (including belantamab mafodotin) or medical device
- Concurrent enrolment in a belantamab mafodotin early access program (EAP), Named Patient Program (NPP) or temporary authorization for use (ATU) program

3.6. Variables

- Demographics, disease status, clinical characteristics and treatment history data
- Belantamab mafodotin treatment details including dose, duration, discontinuations, interruptions/delays and dose changes
- Ophthalmic examination details (e.g. type, frequency, date) and results

- Information on all ocular AESIs, including severity, seriousness, duration, relationship to and impact on daily living, belantamab mafodotin treatment and actions taken
- Treatment effectiveness data including survival status, progression and tumour response according to International Myeloma Working Group (IMWG) criteria if feasible or to local standard practice

3.7. Data sources

Data will be collected by Investigators or their designees (i.e., haematologists, oncologists and ophthalmologists) directly into the eCRF during prospective follow-up from patients enrolled into this study from sites selected countries across Europe. Countries and sites in Europe will be included based on the expected belantamab mafodotin market uptake and site availability. In addition, data will be collected retrospectively from medical records from patients enrolled into this study who received their first belantamab mafodotin dose up to three months before study enrolment, if necessary.

3.8. Study size

A sample size of 150 evaluable RRMM patients is planned for this study.

3.9. Data analysis

Analysis populations:

Two analysis populations will be defined:

- Enrolled Population (EP) - All patients for whom written informed consent has been obtained
- Safety Population (SP) - All patients in the EP who received at least one dose of belantamab mafodotin. The SP will be used for descriptive, safety and effectiveness analyses

Statistical Methods:

For the primary objective, characteristics of RRMM patients treated with belantamab mafodotin per routine clinical care will be described for the SP (overall and by line of treatment). Characteristics to be described include demographics, disease status, clinical characteristics and treatment history collected before or at the time of the first dose.

For the secondary objectives, the following will be described for the SP (overall and by line of treatment):

- Treatment dose, duration, persistence and adherence
- Ocular AESIs during the study period:
- Number, proportions, co-occurrence, time to (specific) ocular AESIs and incidence rate (at the patient and event level); overall and by System Organ Class (SOC) and Preferred Term (PT) terms (Medical Dictionary for Regulatory Activities [MedDRA] classification) and according to severity, grade, seriousness, action taken, duration, impact on daily living and relationship to treatment as well as treatment dose and frequency

- Number, proportion, severity, grade, seriousness and duration of ocular AESIs by ophthalmic monitoring frequency, type(s) and timing relative to administration
- Severity, grade, seriousness and duration of ocular AESIs by their treatment impact (e.g., dose changes, duration of interruptions/delays, discontinuation), use of artificial tears and dry eye comorbidity
- Number and proportions of patients with dose reductions, interruptions/delays or discontinuing treatment due to an ocular AESI during the study period: overall and by comorbidity. This will include the description of the timing and dose of treatment re-introductions and the duration of dose reductions and interruptions/delays
- Treatment response (e.g., complete response [CR], very good partial response [VGPR]; partial response [PR]; according to IMWG criteria if feasible or to local standard practice) and time to events (i.e., death, progression, discontinuation)

Continuous variables will be described (distribution) by their mean, standard deviation, median, first and third quartile (Q1 and Q3), extreme values (minimum and maximum) and the number of non-missing and missing data. Categorical variables will be described using frequency counts and percentages.

Data analysis:

The following measures will be reported:

- Exposure-adjusted incidence and event rates with 95% confidence intervals of ocular AESIs (i.e., at the patient level and the event level): overall and by SOC and PT terms (MedDRA classification).
- Median, 95% confidence intervals (CIs) and 25th and 75th percentiles using the Kaplan-Meier (KM) method for time to event outcomes (i.e., OS, rwPFS, DoR, time to discontinuation, time to first [specific] ocular AESI)
- OS rates with 95% CIs at specified time points, including 12- and 15-months of follow-up
- Overall response rate (ORR) with 95% CIs calculated based on the exact binomial distribution (Clopper-Pearson method).

Additional subgroup analyses will be conducted for primary and secondary outcomes by key patient characteristics (e.g., Eastern Cooperative Oncology Group [ECOG] performance status, age groups at the index date, MM subtype, retrospective vs prospective data, and presence or absence of ocular AESIs) when deemed applicable and feasible, as described in the Statistical Analysis Plan (SAP).

Details of interim analyses will be described in the SAP.

3.10. Milestones

This study is projected to begin study enrolment in April 2022 and end in June 2024. The final study report is planned to be completed in Q2 2025.

4. AMENDMENTS AND UPDATES

During feasibility to assess site interest and potential number of patients that would be enrolled in the study, it was clear that there would not be enough sites in the US willing to participate to reach our enrolment target of 250 patients. Feasibility conducted in EU sites showed that patient enrolment targets could be reached, and therefore only the EU component of the study will continue.

As only patients from EU sites will be enrolled in the study, the total enrolment decreases to 150 patients from 400 patients. The analyses of the primary and secondary objectives are descriptively only and was never intended to be pooled for US and EU patients. Therefore, removal of US patients does not change the analysis plan for the EU patients. Additionally, a precision estimate was calculated for sample sizes of 400 and 150 patients (see calculations below). The widths of 95% CI for N=400 are decreased by approximately 38% compared to the widths of 95% CI for N=150.

PRECISION ESTIMATE CALCULATION

Total Sample size	Proportion (p1)	Width (UpperCL - LowerCL)	LowerCL	UpperCL
150	0.01	0.07	0.015	0.085
	0.05	0.096	0.052	0.148
	0.1	0.0881	0.062	0.15
	0.2	0.128	0.136	0.264
	0.3	0.147	0.227	0.373
	0.4	0.157	0.322	0.478
	0.5	0.16	0.42	0.58
	0.6	0.157	0.522	0.678
	0.7	0.147	0.627	0.773
	0.8	0.128	0.736	0.864
	0.95	0.096	0.852	0.948
	0.99	0.07	0.915	0.985
400	0.01	0.0227	0.003	0.025
	0.05	0.0454	0.031	0.076
	0.1	0.0613	0.072	0.134
	0.2	0.0807	0.162	0.243
	0.3	0.0921	0.255	0.348
	0.4	0.0982	0.352	0.45
	0.5	0.1002	0.45	0.55

Total Sample size	Proportion (p1)	Width (UpperCL - LowerCL)	LowerCL	UpperCL
	0.6	0.0982	0.55	0.648
	0.7	0.0921	0.652	0.745
	0.8	0.0807	0.757	0.838
	0.9	0.0613	0.866	0.928
	0.95	0.0454	0.924	0.969
	0.99	0.0227	0.975	0.997

REVISION CHRONOLOGY

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
2 1	April 21, 2022 April 01, 2022	Sections 8.6, 8.8.1 Sections 5, 6, 7, 8.1., 8.2., 8.2.1., 8.2.3., 8.3.7., 8.4., 8.5., 8.7.2.2., 8.7.2.3, 8.7.2.4., 8.7.2.5., 8.9.1. 8.9.2., Table 8, Annex 3	EDC text updated. Text regarding US sites and patients have been removed	EDC platform changed. After feasibility of patient enrolment in the US was conducted, it was clear that the enrolment target of 250 patients would not be met. As a result, a separate, retrospective study will be conducted using EHR data from the Flatiron database and the EU study will continue, unchanged.
		Sections 5, 6, 8.1., 8.2., 8.5.	The number of patients expected in the study has been reduced to 150 from 400	With a removal of the US sites, only patients in the EU will be enrolled, with an expected number of 150 patients. The analysis of the study objectives

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
				does not change despite the reduction in sample size, as all endpoints were always intended to be analyzed separately for the EU and US.
		Figure 1	The diagram showing US sites was removed	The study design figure was updated to show EU sites only
		Section 8.2.3.	The table comparing EU and US sites was removed	As US sites are no longer included in the study, the section was removed
		Section 8.9.2.	The text around retrospective data collection was specified to include the examples of the type of retrospective data that may be collected, “multiple myeloma history and treatment history”	To clarify the type of data that may be collected retrospectively
		Sections 3.4, 8.1 and 8.2	The following sentence was added, “In the event the enrolment rate after study start is too low to meet the expected 150 RRMM patients within the planned enrolment timeframe, eligible RRMM patients from sites who received their first	If there are difficulties in enrolment of patients, the option to collect retrospective data from EU sites is maintained. The additional sentence was included in Sections 3.4, 8.1 and 8.2 for clarity and consistency with the text in

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			belantamab mafodotin dose before study enrolment will be invited for study participation.	section 8.5
		Section 3.3	Text regarding US patients has been removed from the Key Secondary objectives description in the Table	
		Table 3 and Section 8.7.2.2.	Collection of race/ethnicity data has been removed	Race/ethnicity data was largely applicable to US data. In Germany, Austria and Italy, this data cannot be collected so the decision was made to remove this data element.

5. MILESTONES

Data collection will start at the time of study enrolment of the first patient into the study in April 2022. Data will be captured prospectively for a maximum of 15 months follow-up counting from the first dose of belantamab mafodotin.

Patients treated with belantamab mafodotin for a diagnosis of RRMM usually visit the clinic every 3 weeks. Thus, data will be collected from medical charts every 3 weeks until the end of follow-up at 15 months, study discontinuation for any reason, informed consent withdrawal or death; whichever comes first.

Study end: Data collection will continue until target enrolment is achieved of approximately 150 evaluable RRMM patients as well as a maximum of 15 months of follow-up. This is expected to be achieved by June 2024.

Table 1 Detailed Study Milestones

Milestone	Planned date
Start of data collection	April 2022
End of data collection	June 2024
Registration in the EU PAS register	Q4 2021 – Q2 2022
Final report of study results	Q2 2025

6. RATIONALE AND BACKGROUND

6.1. Background

Multiple myeloma (MM) is a rare and incurable haematological malignancy which typically affects adults 60 years of age and older. It is the second most common haematological malignancy (after non-Hodgkin's lymphoma), representing 1% of all cancers and 2% of all cancer deaths. In 2020, the estimated annual, age-standardised, worldwide MM incidence rate was 1.8 per 100,000 (GLOBOCAN, 2020).

Current MM therapies include glucocorticoids (e.g., dexamethasone), chemotherapy, proteasome inhibitors (PIs, e.g., bortezomib), immunomodulatory agents (e.g., thalidomide, lenalidomide and pomalidomide), monoclonal antibodies (mAbs, e.g., daratumumab, isatuximab and elotuzumab) and the histone deacetylase inhibitor panobinostat. Since the approval of daratumumab, MM patients have emerged who are refractory to at least one PI, one immunomodulatory agent and one anti-CD38 mAb. There is a clear unmet medical need for new therapies among patients with relapsed or refractory MM (RRMM) as current treatment options are very limited with a median overall survival (OS) of approximately 7 to 10 months (Gandhi, 2019).

Belantamab mafodotin (BLENREP^{TM}) is a first in-class anti-B-cell maturation antigen therapy approved for use in the United States (US) and European Union (EU) based on data from the pivotal Phase II DREAMM-2 study (Study 205678) (Lonial, 2020; Lonial, 2021a). DREAMM-2 is a phase II, open label, randomized, two-arm study investigating the efficacy and safety of two doses of belantamab mafodotin (3.4 mg/kg vs. 2.5 mg/kg) in participants with MM who had ≥3 prior lines of treatment, were refractory to a proteasome inhibitor and an immunomodulatory agent and had failed an anti-CD38 antibody (Lonial, 2020; Lonial, 2021a). DREAMM-2 results after 13-month follow-up showed an overall response rate (ORR) for the 97 patients who received the registration dose (i.e., 2.5 mg/kg) of 32% (97.5% confidence interval [CI], 21.7-43.6) with 58% of responders achieving a very good partial response (VGPR) or better, including 2 stringent complete responses (sCRs) and 5 CRs (Lonial, 2021a). Median estimated duration of response (DoR), OS, and progression-free survival (PFS) were 11.0 months (95% CI, 4.2 months to not reached), 13.7 months (95% CI, 9.9 months to not reached), and 2.8 months (95% CI, 1.6-3.6 months), respectively (Lonial, 2021a). The most frequent adverse reactions (≥30%) reported from 95 patients in DREAMM-2 who received belantamab mafodotin 2.5 mg/kg were keratopathy (71%) and thrombocytopenia (38%). The most commonly reported serious adverse reactions were pneumonia (7%), pyrexia (7%) and infusion-related reactions (3%). Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received belantamab mafodotin with 3% related to ocular adverse reactions.

In the EU, belantamab mafodotin was granted a Conditional Marketing Authorisation on 25 August 2020 for the treatment of MM in adult patients who have received at least four prior therapies and whose disease is refractory to at least one PI, one immunomodulatory agent, and an anti-CD38 mAB, and who have demonstrated disease progression on the last therapy. Because of the risk of ocular toxicity, the European Medicines Agency (EMA) required additional monitoring and additional risk minimisation measures in the

form of educational materials for prescribers and patients as detailed in the Risk Management Plan (RMP) (Summary RMP, 2021). The goal of the EU RMP is to mitigate the risk of ocular toxicity of belantamab mafodotin by educating prescribers and patients. The EU Summary of Product Characteristics (SmPC) states ophthalmic examinations should be performed at baseline, before initiation of each of the subsequent 3 treatment cycles and during treatment as clinically indicated (BLENREP SmPC, 2021).

6.2. Rationale

To better understand the real-world management of RRMM patients exposed to belantamab mafodotin and the occurrence of ocular toxicity in routine clinical practice, this study aims to evaluate the real-world use, safety and effectiveness of belantamab mafodotin in 150 RRMM patients in Europe.

7. RESEARCH QUESTION AND OBJECTIVE(S)

The primary purpose of this multinational, multisite, non-interventional study is to understand the real-world use of belantamab mafodotin by characterizing RRMM patients treated with belantamab mafodotin in routine clinical practice in Europe. In addition, this study will provide further evidence on belantamab mafodotin's risk-benefit profile by collecting safety and effectiveness data. This information will be used to inform current and future clinical practice. No formal hypotheses are being tested in this study.

7.1. Primary Objective

The **primary objective** of this study is to characterize RRMM patients treated with belantamab mafodotin per routine clinical care in terms of demographics, disease status, clinical characteristics and treatment history (overall and by line of treatment).

7.2. Secondary Objectives

The **key secondary objective** of this study is to characterize patients who experience ocular adverse events (AEs) that have been associated with belantamab mafodotin treatment (ocular Adverse Events of Special Interest [AESIs]) (overall and by line of treatment) in terms of:

- Belantamab mafodotin treatment received (i.e., dose and duration)
- Ophthalmic disease history
- Ocular AESI type, duration and severity
- The frequency and timing of ophthalmic monitoring visits relative to belantamab mafodotin administration (for each cycle; overall and by line of treatment, occurrence of ocular AESIs as well as treatment dose and frequency).

Other secondary objectives are the following (overall and by line of treatment):

- Assess the incidence of ocular AESIs and their impact on treatment discontinuation, interruption/delay, or dose modifications (additionally evaluated by comorbidity, ocular AESI type and severity as well as treatment dose and frequency)
- Evaluate persistence and adherence with belantamab mafodotin
- Describe reasons for treatment discontinuation
- Describe the duration and reasons of treatment interruptions/delays, or dose modifications
- Evaluate effectiveness in terms of disease response to treatment, DoR, duration of treatment (DoT), real-world progression-free survival (rwPFS) and OS.

8. RESEARCH METHODS

8.1. Study Design

This multinational, multisite, non-interventional study will collect real-world data on the use, safety and effectiveness of belantamab mafodotin. Data will be analysed from approximately 150 RRMM patients from sites in selected countries across Europe.

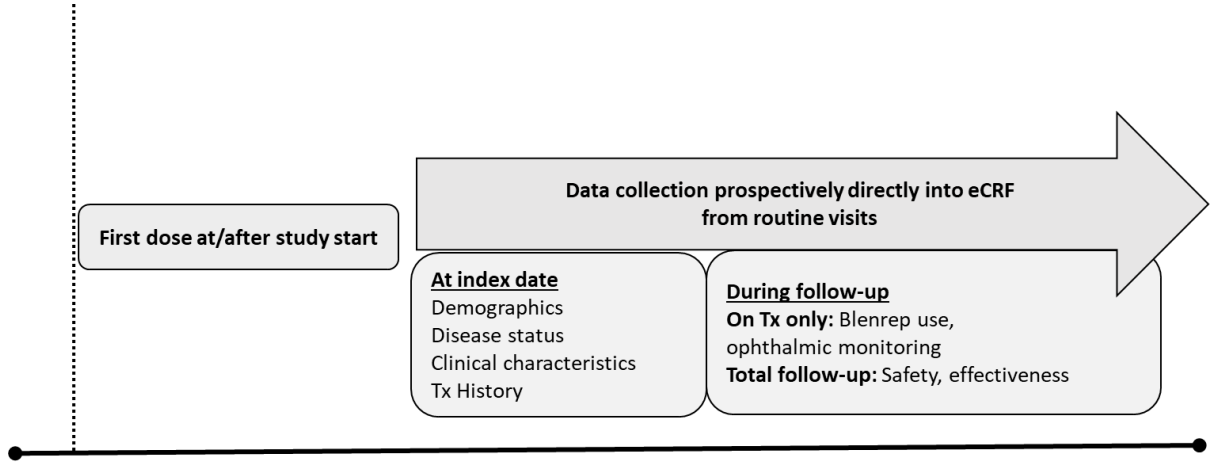
Eligible RRMM patients from EU sites who are due to receive belantamab mafodotin will be consecutively invited for study enrolment by haematologists and/or oncologists affiliated with investigator sites participating in this study. In the event the enrolment rate after study start is too low to meet the expected 150 RRMM patients within the planned enrolment timeframe, eligible RRMM patients from sites who received their first belantamab mafodotin dose before study enrolment will be invited for study participation.As the study is non-interventional, the decision to treat patients with belantamab mafodotin will be made prior to and independent from the decision to enrol patients into the study, and baseline and follow-up assessments will be in accordance with local standard medical care. Investigators must refer to the SmPC (for European patients) for information on contraindications, warnings and precautions as well as use in specific populations.

Written informed consent will be obtained from all patients before enrolment into the study. Written informed consent may be obtained from family members of deceased patients, if allowed according to the regulatory and legal country-specific requirements of the participating site.

After obtaining informed consent, data will be collected retrospectively from medical records and prospectively, where applicable, from the time of the first dose of belantamab mafodotin to the end of follow-up at 15 months, study discontinuation for any reason, informed consent withdrawal or death, whichever comes first. The Investigator will follow ocular AESIs until resolved or until the last study visit of the patient.

Figure 1 shows the patient and data flow in this study. For patients who will receive a first dose of belantamab mafodotin at or after study enrolment, baseline and outcome data will be entered into the electronic case report form (eCRF).

Figure 1 Patient and data flow



Abbreviations: eCRF=electronic case report form; Tx=treatment.

As shown in Figure 1, eligible RRMM patients from sites who received their first belantamab mafodotin dose before study enrolment will only be invited for study participation if this is deemed necessary based on the enrolment rate in the EU.

Belantamab mafodotin use and ophthalmic monitoring data will be collected while patients are on treatment. Safety and effectiveness data will be collected regardless of whether patients are on treatment or have discontinued treatment during follow-up.

8.2. Study Population and Setting

It is planned to include approximately 150 evaluable RRMM patients from sites in selected countries across Europewho are due to receive belantamab mafodotin as part of routine clinical care after study enrolment.

Once the treatment decision has been made, independent from the decision to enrol patients into the study, eligible RRMM patients EU sites due to receive belantamab mafodotin as part of routine clinical care will be consecutively invited for prospective enrolment by health care providers affiliated with investigator sites participating in this study. Prospective data will be collected during a 15-month follow-up period from visits scheduled as part of routine clinical care. In the event the enrolment rate after study start is too low to meet the expected 150 RRMM patients within the planned enrolment timeframe, eligible RRMM patients from sites who received their first belantamab mafodotin dose before study enrolment will be invited for study participation.Available retrospective baseline and outcomes data from the time of the first belantamab mafodotin dose will be extracted from medical records. Data will be collected prospectively from study enrolment for the length of follow-up time (i.e., 15 months minus the time from the first belantamab mafodotin dose until study enrolment), if applicable. All efforts will be made to ensure that the data of retrospectively enrolled patients are of good quality and provide sufficient information.

The estimated study enrolment period is approximately 12 months for inclusion of approximately 150 eligible RRMM patients, though this may be altered based on the actual use of belantamab mafodotin during the feasibility assessment component of site initiation. It is planned to follow patients for 15 months. Belantamab mafodotin is required to be approved for use before the start of local study enrolment.

The total study duration is estimated to be a maximum of two years and three months per site based on an estimated study enrolment period of 12 months and a follow-up period of 15 months.

8.2.1. Inclusion Criteria

A patient who meets **all** of the following criteria is eligible for inclusion:

- Written informed consent
- Male or female, ≥18 years of age at the start of belantamab mafodotin treatment
- Confirmed diagnosis of RRMM
- Received (if deemed required for EU based on enrolment rate) or due to receive belantamab mafodotin treatment per routine clinical care by an oncologist or haematologist consistent with the approved labelling

8.2.2. Exclusion Criteria

A patient who meets **any** of the following criteria is not eligible for inclusion:

- Concurrent enrolment in an interventional clinical trial involving either an investigational medicinal product (including belantamab mafodotin) or medical device
- Concurrent enrolment in a belantamab mafodotin early access program (EAP), Named Patient Program (NPP) or temporary authorization for use (ATU) program

8.2.3. EU Setting Considerations

8.3. Variables

8.3.1. Definitions

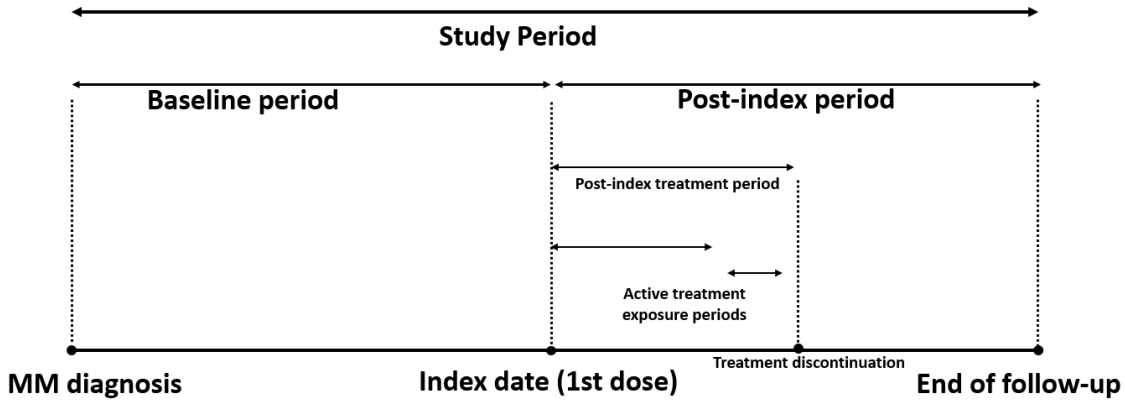
The following definitions apply to the different timings of data collection (see Figure 2):

- ***Index date*** is defined as the time of the first (non-missing) dose of belantamab mafodotin.
- ***The baseline period*** for data collection is defined as the time from the initial MM diagnosis until the index date (the first dose of belantamab mafodotin).
- ***The post-index period*** spans from the index date until the end of follow-up at 15 months, study discontinuation for any reason, informed consent withdrawal or death; whichever comes first.
- ***The post-index treatment period*** is defined as the duration of the belantamab mafodotin line of treatment (DoT). This spans from the index date until the confirmed decision date of permanent discontinuation of belantamab mafodotin treatment, the

confirmed date of a new line of treatment or the date of the end of follow-up at 15 months, study discontinuation for any reason, informed consent withdrawal or death; whichever comes first.

- ***The study period*** spans from the time from the initial MM diagnosis until the end of follow-up at 15 months, study discontinuation for any reason, informed consent withdrawal or death; whichever comes first.
- ***Active treatment exposure periods*** are defined as the time that belantamab mafodotin is considered to have a treatment effect during the post-index treatment period. This period includes all doses occurring within 70 days of the previous dose (belantamab mafodotin's half-life) from the date of the first belantamab mafodotin dose of that sequence to the date of the last dose +70 days or the date of the end of the post-index treatment period; whichever comes first.

Figure 2 Timings of Data Collection



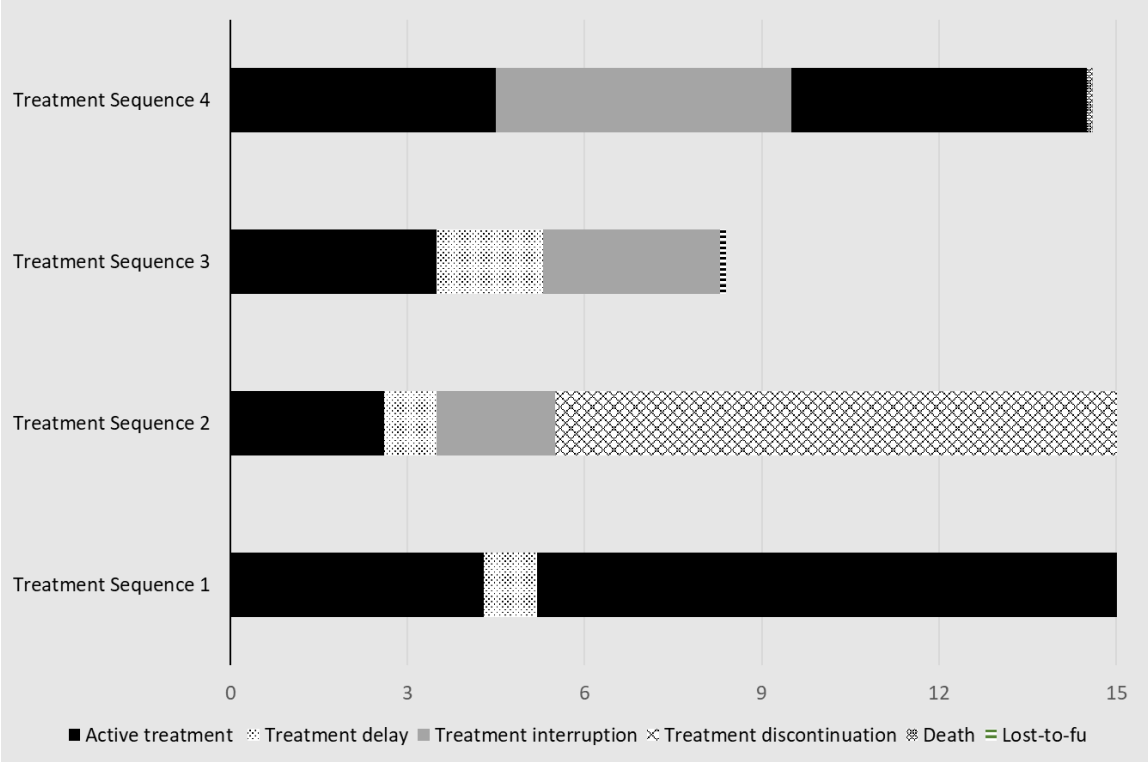
Abbreviations: MM=multiple myeloma.

The following definitions apply to collection of treatment data:

- ***Line of treatment*** is defined as one or more completed cycles of a single agent, a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens (Rajkumar, 2015).
- ***A treatment cycle*** is defined as the belantamab mafodotin label-approved dosing interval, which is 21 days (with a real-world scheduling grace period of +7 days).
- ***Treatment discontinuation*** is defined as a recorded clinician decision (with an associated decision date) to permanently discontinue belantamab mafodotin treatment.
- ***Treatment interruption*** is defined as withholding ≥1 belantamab mafodotin dose for any reason without a confirmed clinician decision to permanently discontinue treatment or initiate a new line of treatment. The time interval between doses will be >2 treatment cycles (+ 7-day grace periods).
- ***Treatment delay*** is defined as a delay (intentionally or unintentionally) in receiving belantamab mafodotin without skipping a dose. The time interval between doses will be >1 treatment cycle (+ a 7-day grace period) and <2 treatment cycles.

Figure 3 shows examples of treatment sequences that patients might undergo during the 15-month follow-up period.

Figure 3 Examples of treatment sequences during the post-index period



The following definitions apply to derived outcomes for statistical analyses:

- ORR is defined as the proportion of patients with a best response (sCR, CR, VGPR or partial response [PR]) during the study period evaluated by a responsible physician based on International Myeloma Working Group [IMWG] criteria if feasible or to local standard practice
- OS is defined as the time in months from the start of belantamab mafodotin treatment to the date of death due to any cause
- rwPFS is defined as the time in months from the start of belantamab mafodotin treatment to the date of the first documented disease progression or death, whichever occurs first
- DoR is defined as the time from the first documented evidence of PR or better until the earliest date of progressive disease (PD) or death among patients who achieved a response

8.3.2. Baseline Characteristics

For the primary objective of characterizing RRMM patients treated with belantamab mafodotin per routine clinical care, data at the time of the first belantamab mafodotin dose (i.e., the index date) or from the initial MM diagnosis until the index date (i.e., the

baseline period) will be collected retrospectively or at study enrolment, where applicable. Data to be collected are shown in Table 2.

Table 2 Demographics, disease and treatment history

Item	Variable	Definition	Timing
Demographics	Date of birth	Year of birth	Index date
	Sex	Categorical variable: • Male • Female	Index date
	Height	Continuous variable	Index date
	Weight	Continuous variable	Index date
	ECOG Performance Status	Categorical variable: • 0 • 1 • 2 • 3 • 4	Index date
MM History	Date initial diagnosis	Date of first MM diagnosis	Baseline period
	Extramedullary disease	Categorical variable	Baseline period
	ISS stage	Categorical variable: stage at initial MM diagnosis • I • II • III	Baseline period
	MM subtype	Categorical variable: subtype at initial diagnosis • IgG • IgA • IgM • IgD • Biclonal (G,A) • Light chain MM • Other	Baseline period
	Cytogenetic risk	Categorical variable: • High [e.g., t(4;14), t(14;16), del17p] • Standard	Baseline period
	Progression status	Categorical variable: disease progression (per IMWG criteria or to local standard practice) on last line of therapy: • Yes • No	Baseline period
	Refractory status	Categorical variable: • Triple refractory • Quad refractory • Penta refractory	Index date

Item	Variable	Definition	Timing
MM Treatment History	Prior MM therapies	Categorical variable: therapy type* by line per EHA-ESMO (Dimopoulos, 2021) and NCCN guidelines (Kumar, 2020)	Baseline period
	Dates of prior MM therapies	Date of first and last dose of each prior therapy	Baseline period
Medical History	Pre-existing comorbidities	Categorical variable: type of comorbidity** per category such as: • Renal diseases • Pulmonary diseases • Cardiac diseases • Diabetes • Eye diseases including history of dry eye/eye injuries affecting the BCVA • Other	Baseline period
Ophthalmic Health	BCVA	Continuous variable per type of measurement	Baseline period
	Slit lamp exam	Categorical variable: most recent corneal examination finding: • Keratopathy • Microcyst-like epithelial changes • Other corneal findings/ conditions	Baseline period
Laboratory measurements	Lactate dehydrogenase, creatinine	Continuous variables: based on most recent assessments: • Lactate dehydrogenase • Serum creatinine • Creatinine clearance using the Cockcroft-Gault formula	Baseline period

Abbreviations: BCVA=Best Corrected Visual Acuity, ECOG=Eastern Cooperative Oncology Group; EHA=European Hematology Association; ESMO= European Society for Medical Oncology; Ig=Immunoglobulin; IMWG=International Myeloma Working Group; ISS=International Staging System; NCCN=National Comprehensive Cancer Network.
*The World Health Organization (WHO) Drug Dictionary for medications will be used for coding drugs.
**The Medical Dictionary for Regulatory Activities (MedDRA) will be used for coding concomitant diseases.

8.3.3. Belantamab Mafodotin Treatment

Belantamab mafodotin treatment data to be collected during follow-up from standard of care visits are shown in Table 3. Data will be collected from the time of the first belantamab mafodotin dose until permanent discontinuation of belantamab mafodotin treatment, the end of follow-up at 15 months, study discontinuation for any reason, informed consent withdrawal or death; whichever comes first.

Table 3 Belantamab mafodotin treatment

Variable	Definition	Timing
Date(s) of Administration	Date of each administration	Index date and post-index treatment period
Dose	Continuous variable: prescribed and administered doses	Index date and post-index treatment period
Treatment status change	Categorical variable: prospectively captured or derived retrospectively • Dose modification • Treatment interruption / delay • Discontinued	Post-index treatment period
Primary reason dose modification	Categorical variable: • Any AE • Other	Post-index treatment period
Primary reason treatment interruption/delay	Categorical variable: • Any AE • Patient decision unrelated to AEs • Other	Post-index treatment period
Primary reason treatment discontinuation	Categorical variable: • Disease progression • Any AE • Patient decision unrelated to AEs • End of treatment • Death (unrelated to therapy) • Other	Post-index treatment period
Concomitant Medications	Categorical variable: type of concomitant medication* Continuous variable: dose at index date for each concomitant medication	Index date and post-index treatment period

Abbreviations: AE=adverse event.

8.3.4. Ophthalmic Monitoring

As part of the key secondary objectives, ophthalmic monitoring information (Table 4) will be collected during follow-up from standard of care visits from the time of the first belantamab mafodotin dose until permanent discontinuation of belantamab mafodotin treatment, the end of follow-up at 15 months, study discontinuation for any reason, informed consent withdrawal or death; whichever comes first.

Table 4 Ophthalmic Monitoring

Variable	Definition	Timing
Date(s) ophthalmic examination(s)	Date of each examination	Index date and post-index treatment period
Type(s) of ophthalmic examination(s)	Categorical variable: • BCVA score (Snellen test or equivalent test) • Slit lamp examination • Other	Index date and post-index treatment period

Result of Examination	Categorical variable, result for each eye:
	• BCVA score (continuous variable)
	• Corneal examination findings:
	  • No change
	  • Mild superficial keratopathy
	  • Moderate superficial keratopathy
	  • Severe superficial keratopathy
	  • Corneal epithelial defect /ulcer
	KVA scale grade for worst eye (see ANNEX 2):
	  • Normal
	  • Grade 1
	  • Grade 2
	  • Grade 3
	  • Grade 4
		Index date and post-index treatment period

Use of contact lenses while on treatment*	Categorical variable: • Yes – specify use • No	Index date and post-index treatment period
Use of preservative-free lubricant eye drops while on treatment	Categorical variable: • Yes – specify use • No	Index date and post-index treatment period
Use of bandage contact lenses while on treatment	Categorical variable: • Yes – specify use • No	Index date and post-index treatment period
Use of cooling eye masks	Categorical variable: • Yes – specify use • No	Index date and post-index treatment period

Abbreviations: BCVA=best Corrected Visual Acuity; KVA=Keratopathy and Visual Acuity.
*Patients should avoid using contact lenses until the end of treatment unless directed by an ophthalmologist.

8.3.5. Safety

All ocular AESIs that occur during and/or after administration of belantamab mafodotin will be recorded regardless of a causal relationship to belantamab mafodotin. Data shown in Table 5 will be collected for any ocular AESI (serious or non-serious) until the end of follow-up at 15 months, study discontinuation for any reason, informed consent withdrawal or death; whichever comes first.

Table 5 Ocular Adverse Events of Special Interest

Variable	**Definition**	**Timing**
Date(s) ocular AESI(s)	Date of onset of each ocular AESIs	Index date and post-index period
Ocular AESI type	Categorical variable: type of ocular AESI* categorized by: • Keratopathy** • Blurred vision events# • Dry eye events## • Photophobia • Eye irritation • Ulcerative keratitis • Infective keratitis • Corneal erosion/defect • Other	Index date and post-index period
Ocular AESI severity at onset	Categorical variable: NCI CTCAE Version 5.0 grading: • Grade 1 • Grade 2 • Grade 3 • Grade 4 • Grade 5 KVA scale grade (see ANNEX 2): • Normal • Grade 1 • Grade 2 • Grade 3 • Grade 4	Index date and post-index period
Ocular AESI severity increase after onset	Categorical variable: • Yes – specify highest grade • No	Index date and post-index period
Ocular AESI seriousness at onset	Categorical variable: • Fatal • Life-threatening • Persistent or significant disability/incapacity • Inpatient (or prolongation of existing) hospitalization • Medically important event • None of the above	Index date and post-index period
Ocular AESI seriousness increase after onset	Categorical variable: • Yes – specify most serious event • No	Index date and post-index period
Ocular AESI impact on daily living	Categorical variable (e.g., need for caregiver support, eye irritation/pain, driving impairment, reading impairment)	Index date and post-index period

Action taken	Categorical variable:
	• Concomitant medication@ and other mitigation strategies (e.g., bandage contact lenses)
	• Belantamab mafodotin treatment change
	  • Dose decrease
	  • Treatment interruption/delay
		Index date and post-index period

	• Treatment discontinuation • Change in ophthalmic monitoring • Withdrawn from study • No action taken	
Documented relationship to belantamab mafodotin	Categorical variable: • Yes • No • Unknown	Index date and post-index period
Ocular AESI outcome	Categorical variable: • Fatal • Not recovered/not resolved • Recovered/resolved • Resolved with sequelae • Recovering/resolving • Unknown	Index date and post-index period Please refer to Section 10
Ocular AESI stop date, if applicable	Date of ocular AESI resolution	Post-index period

Abbreviations: AESI=adverse event of special interest; KVA=Keratopathy and Visual Acuity; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.
*MedDRA will be used for coding AEs. **Based on eye examination, characterised as corneal epithelium changes with or without symptoms. #Includes diplopia, vision blurred, visual acuity reduced and visual impairment. ##Includes dry eye, ocular discomfort, and eye pruritus @The WHO Drug Dictionary for medications will be used for coding drugs.

8.3.6. Effectiveness

Table 6 shows the effectiveness data to be collected during the study period from the time of the first belantamab mafodotin dose until the end of follow-up at 15 months, study discontinuation for any reason, informed consent withdrawal or death; whichever comes first.

Table 6 Effectiveness

Variable	**Definition**	**Timing**
Date of death	Date of death	Post-index period
Tumour response	Assessment dates and categorical variable per IMWG response criteria (IMWG,.2021 Criteria) if feasible or to local standard practice: • sCR • CR • VGPR • PR • No change/stable disease • PD	Post-index period

Abbreviations: CR=complete response IMWG=International Myeloma Working Group; PD=Progressive disease; PR=partial response; sCR=stringent complete response; VGPR; very good partial response.

8.3.7. Timings of Assessment

Data will be collected from patients' visits per routine clinical care either prospectively, directly into the eCRF or retrospectively from data already available in medical records into the eCRF (Table 7).

Table 7 Data Collection Plan

Variables	Baseline period	Standard of Care Visits*
Informed Consent	X	
Patient Eligibility	X	
Subject Characteristics	X	
Medical/Treatment History	X	
Concomitant Medications	X	X
Belantamab Mafodotin Treatment	X	X
Ophthalmic Monitoring and Results**	X	X
Ocular AESIs#	X	X
Effectiveness Evaluations		X

Abbreviations: AESI=adverse event of special interest.
*Data will be collected only if reported as part of standard of care visits, which are assumed to take place about every three weeks during treatment in accordance with local treatment guidelines until the end of follow-up. ** In the EU, eye examinations are required before the first three treatment cycles. Additional eye examinations are required promptly as clinically indicated (e.g., on worsening of ocular symptoms (BLENREP SmPC, 2021). #Other AEs and serious adverse events (SAEs) will not be actively solicited and based on spontaneous reporting.

8.4. Data Sources

Data will be collected by Investigators or their designees (i.e., haematologists, oncologists and ophthalmologists) for all patients enrolled into this study from sites in elected countries across Europe. Countries and sites in Europe will be included based on the expected belantamab mafodotin market uptake and site availability.

Baseline and outcome data will be extracted retrospectively from medical records or entered prospectively directly into the eCRF, where applicable.

8.5. Study Size

Approximately 150 evaluable RRMM patients are planned for the study. The sample size is not based on statistical power consideration but on a conservative estimate for each country of interest based on country-specific MM incidence and prevalence rates, the percentage of patients expected to be eligible for belantamab mafodotin treatment, the expected belantamab mafodotin market uptake, site availability and the treatment landscape in terms of ongoing clinical trials.

The sample size 150 RRMM patients from EU sites is considered sufficient to meet the primary objective of describing RRMM patients treated with belantamab mafodotin per

routine clinical care in terms of demographics, disease status, clinical characteristics and treatment history.

To meet the planned number of 150 evaluable RRMM patients, the enrolment period may be extended if needed based on the actual uptake of belantamab mafodotin and site participation. Eligible RRMM patients from sites who received their first belantamab mafodotin dose before study enrolment will be invited for study participation if this is deemed necessary based on the enrolment rate in the EU. The number of patients who received their first belantamab mafodotin dose before study enrolment is expected to be low as belantamab mafodotin was either only recently launched or is in the process of being launched.

8.6. Data Management

All information outlined in Section 8.3 will be recorded prospectively directly into an eCRF or retrospectively from medical records, if applicable, into the study database.

Data collection will be completed in a suitable electronic data capture (EDC) platform (Veeva EDC). All data collected will be stored at secure servers ensuring compliance with local or national regulations. Database lock is anticipated on the date the study is closed, i.e., when all documents and data have been collected, and reviewed and necessary data changes have been made after the last visit for the last subject. Additional details regarding data collection and validation procedures will be detailed in a data management plan.

The investigator is responsible for ensuring data is entered in a timely manner and verifying that data are accurate and correct. When the study is completed, the investigators must retain essential documents, e.g., source data that support information entered in the eCRF, for as long as needed to comply with regulatory guidelines and Sponsor requirements. The investigator must permit study-related monitoring, audits, institutional review board (IRB) review, and regulatory agency inspections and provide direct access to source data documents. The investigator will notify the Sponsor prior to moving or destroying any of the study documents. 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.

8.7. Data Analysis

A detailed statistical analysis plan (SAP) will be prepared before the start of data collection. The SAP will detail the most appropriate statistical methodology and analyses to be performed in accordance with the study design and objectives. The SAP will provide further information to that discussed below (e.g., on handling of missing data). All analyses will be performed using SAS Version 9.4 or later.

Details of interim analyses will be described in the SAP.

8.7.1. Analysis Populations

8.7.1.1. Enrolled Population (EP)

The EP will consist of all patients for whom written informed consent has been obtained. This population will be used for disposition summaries.

8.7.1.2. Safety Population (SP)

The SP will include all patients in the EP who received at least one dose of belantamab mafodotin. The SP will be used for descriptive, safety and effectiveness analyses.

8.7.2. Statistical Methods

8.7.2.1. Descriptive Analysis

Continuous variables will be described (distribution) by their mean, standard deviation, median, Q1, Q3, extreme values (minimum and maximum) and the number of non-missing and missing data. Categorical variables will be described using frequency counts and percentages.

8.7.2.2. Analysis of Primary Objective

The primary objective for the study is to characterize RRMM patients treated with belantamab mafodotin. The following data on demographics, disease status, clinical characteristics and treatment history collected before or at the time of the first dose will be summarized for the SP (overall and by line of treatment):

- Age (years)
- Sex
- Body mass index (BMI) (kg/m2; derived from weight and height)
- ECOG performance status at index date
- Time from initial MM diagnosis to index date (months)
- Details of initial MM diagnosis (ISS stage, subtype, cytogenetic risk)
- Number of previous regimens by drug (combination) and class
- Refractory status (triple refractory, quad refractory, penta refractory)
- Progression status on last line of therapy
- Comorbidities during the baseline period
- Ocular health (Snellen visual acuity, slit lamp examination results) before/at index date
- Concomitant medications to belantamab mafodotin
- Laboratory measurements (i.e. lactate dehydrogenase, serum creatinine, creatinine clearance)

8.7.2.3. Analysis of Key Secondary Objectives

For the key secondary objectives, the following will be described for the SP (overall and by line of treatment) during active treatment exposure periods:

- Average cycle dose (sum of all doses divided by total number of administrations per patient)
- Frequency and timing of ophthalmic monitoring relative to belantamab mafodotin administration for each cycle (type(s), number of examinations; overall and according to monitoring before and after the occurrence of ocular AESIs as well as treatment dose and frequency)
- Ocular AESIs in RRMM patients exposed to belantamab mafodotin occurring during the study period:
    - Number, proportions, co-occurrence and time to (specific) ocular AESIs; overall and by System Organ Class (SOC) and Preferred Term (PT) terms (MedDRA classification) and according to severity, grade, seriousness, action taken, duration, impact on daily living and relationship to treatment as well as treatment dose and frequency
    - Number, proportion, severity, grade, seriousness and duration of ocular AESIs by ophthalmic monitoring frequency, type(s) and timing relative to administration
    - Severity, grade, seriousness and duration of ocular AESIs by their treatment impact (e.g., dose changes, duration of interruptions/delays, discontinuation), use of artificial tears and dry eye comorbidity

8.7.2.4. Analysis of Other Secondary Objectives

In addition, the following will be described for the SP (overall and by line of treatment):

- Exposure-adjusted incidence rate with 95% CI, overall and by SOC and PT names
    - Defined as the number of patients with at least one (specific) AE during follow-up divided by the sum of person-months at risk in the study.
    - Person-months at risk is defined as the duration of follow-up for patients without AEs plus the duration of follow-up until the date of the first (specific) AE for patients with an AE.
- Exposure-adjusted event rate with 95% CI, overall and by SOC and PT names
    - Defined as the number of (specific) AESIs during follow-up divided by the sum of person-months at risk in the study.
    - Person-months at risk is defined as the duration of follow-up.
- For patients with dose reductions, interruptions/delays or discontinuation of belantamab mafodotin treatment **due to an ocular AESI** during the study period, the following will be summarized (overall and by comorbidity, ocular AESI type and ocular AESI severity as well as treatment dose and frequency):
    - Number and proportions of patients
    - Primary reasons for dose reductions, interruptions/delays or discontinuation of treatment due to any AE
    - Belantamab mafodotin treatment patterns after occurrence of an ocular AESI (i.e., order of treatment changes and timing)

    - Median, 95% CIs and 25th and 75th percentiles using the Kaplan-Meier (KM) method for time to dose reductions, interruptions/delays or discontinuation
    - Duration of dose reductions and interruptions/delays or discontinuations
- Belantamab mafodotin treatment adherence, i.e., the total duration of treatment in days divided by the total follow-up time in days.
- Belantamab mafodotin treatment persistence, i.e., the proportion of patients still on treatment at specified time points, including 3-, 6-, 12- and 15-months of follow-up
- Treatment response (e.g., sCR, CR, VGPR or PR):
    - Best treatment response during follow-up
    - Treatment response at specified time points, including 12- and 15-months of follow-up
    - Proportion of patients with a maintained response (PR or better) at specific time points, including 12- and 15-months of follow-up
    - ORR with 95% CIs calculated based on the exact binomial distribution (Clopper-Pearson method)
- Median, 95% CIs and 25th and 75th percentiles using the KM method for:
    - OS (overall and based on response / non-response to treatment)
    - rwPFS (overall and based on response / non-response to treatment)
    - DoR
    - DoT
- OS rates with 95% CIs at specified time points, including 12- and 15-months of follow-up

8.7.2.5. Subgroup analyses

In addition, the following key subgroup analyses are planned (as described above):

- Line of treatment
- Presence or absence of ocular AESIs
- Treatment dose and frequency
- Ophthalmic disease history
- Presence or absence of (specific) comorbidities
- Response / non-response to treatment

Additional subgroup analyses will be described in the SAP including rules for the minimum number of patients required per category and rules for merging categories including:

- ECOG performance status
- Age groups at the index date
- MM subtype
- Renal impairment
- Retrospective vs prospective data
- Dose interruptions vs continuous treatment
- Presence of extramedullary disease

8.8. Quality Control and Quality Assurance

To ensure compliance with all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. See Section 8.8.5 for more details regarding the audit process.

8.8.1. Data Quality Assurance

Syneos Health and GSK are responsible for following standard operating procedures (SOPs) to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, and description of available data. All sites will be trained by the Site Management Associate (SMA) on the protocol, study logistics, and the EDC system. Investigators will be reminded of the processes and importance of reporting all ocular AESIs and other information.

Veeva EDC, used to manage data collection during this study, is a software tool designed to ensure quality assurance and facilitate data capture during clinical studies. The investigator is responsible for ensuring prospective data is entered in a timely manner and verifying that data are accurate and correct by physically or electronically signing the eCRF.

On-line logic checks will be built into the EDC system as much as possible, so that missing or illogical data are not submitted. In the event that inconsistent data persist, queries may be issued electronically to the clinical study center and answered electronically by that study center's personnel.

This study will be conducted according to GSK SOP52213 (Conducting Quality Control Review of Study Results generated using Existing Data in Value, Evidence and Outcomes [VEO] and US VEO). This procedure requires documented evidence that the study protocol has been correctly interpreted and executed.

An independent QC analyst will document their review of the work of the Project Analyst. Analysts will reach and document agreement that the study results are complete, internally consistent, and accurately reflect the source data and intended purpose of this protocol.

8.8.2. Access to Source Data/Documents

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and IRB to have direct access to all documents pertaining to the study.

8.8.3. Archiving Study Documents

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. All study materials will be returned to the Sponsor after the study has been completed.

Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations. According to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment.

8.8.4. Study Monitoring

Subject data will be monitored remotely. Monitoring visits may be scheduled throughout the study, if needed. Monitoring visits will be scheduled in advance, to ensure that the investigator has sufficient time to meet with the SMA and discuss all relevant findings. Subject data will be reviewed and/or audited, and all deficiencies corrected on site, if possible. A complete audit trail of all monitoring visits and data changes will be maintained. A virtual close-out visit will be scheduled when all documents and data have been collected, reviewed and necessary data changes have been made after the last visit for the last subject. If the study is terminated, a virtual study close-out visit may be scheduled with the site if needed to retrieve all remaining study records. As long as COVID-19 restrictions apply, on-site study initiation and monitoring visits will not be scheduled until restrictions are alleviated.

The SMA will review the study conduct to determine compliance with the study protocol and good clinical practice (GCP) guidelines. The SMA will review and/or audit the electronic forms and source documents to ensure the accuracy and completeness of the data captured for the study. The SMA will review the subject informed consent forms (ICFs) to ensure that no forms were signed prior to the date of IRB approval of the study. The system for record-keeping will be reviewed.

8.8.5. Audits and Inspections

Responsible IRB/ Independent ethics committee (IEC)/Competent Authorities and/or the Sponsor’s clinical quality assurance group, or its designee, may request access to all source documents, case report forms, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

8.9. Limitations of the Research Methods

8.9.1. Selection Bias

All eligible RRMM patients from sites who are due to receive belantamab mafodotin will be consecutively invited for study enrolment to reduce selection bias. In addition, key data, e.g., patient characteristics, ophthalmic monitoring, safety and effectiveness, will be compared with results from clinical trials and global, prospective, real-world MM studies published in the literature.

Reasons for patient non-participation, withdrawal or loss-to-follow-up will be recorded in the eCRF, if available, to address any remaining selection bias,. There will also be a risk associated with including patients who are due to receive belantamab mafodotin after study enrolment as these patients might not contribute to the primary analyses if they do not receive treatment. If a patient will not initiate treatment with belantamab mafodotin after being enrolled in the study, baseline data will still be collected, if feasible, to understand reasons for not being treated and differences between those who did and did not receive treatment after study enrolment.

8.9.2. Information Bias

Relying on investigators to fill out the assessment forms might induce the presence of missing data, which can result in bias. Entry of prospectively collected data into eCRFs will minimise missing or incorrect data by having automated queries. Clear instructions and engagement with the study staff with appropriate training will minimise the amount of missing data.

Some data, including multiple myeloma history and treatment history will be collected retrospectively. Retrospectively collected data may be of lesser quality than prospectively collected data, with more missing data and fewer details. It is therefore important to determine the impact of this in sensitivity analyses and include rules about how missing data will be handled in the SAP. Also, if retrospectively collected data is regarded of poor quality or insufficient during the first interim analysis, these patients will be regarded non-evaluable.

8.9.3. Site Selection Bias

After the feasibility assessment for sites to be included in this study, site selection bias will be reduced by taking a representative sample of sites when feasible given the number of sites per country and the requirement for EU sites to have haematology/oncology and ophthalmology departments co-located within the same organisation.

8.9.4. Effect Modifiers

Effect modification occurs when the effects of a treatment vary by presence/level of another factor (effect modifier). Subgroup analyses or analyses restricted to a selection of the study population will be conducted when deemed applicable and feasible (see Section 8.7.2.5).

8.9.5. Patients Lost to Follow-up or without Follow-up Data

Because the follow-up duration will be 15 months, the proportion of discontinued patients might be significant given the severity of disease of the enrolled patient population. As standard of care visits are assumed to take place approximately every three weeks during belantamab mafodotin treatment this is expected to reduce loss to follow-up. Reasons for loss-to-follow-up will be recorded in the eCRF if available. Patients lost to follow-up will be compared with regard to baseline characteristics to patients with complete follow-up. Also, baseline characteristics will be compared between patients with and without follow-up data.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical Approval and Subject Consent

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (version 2008) and applicable legal and regulatory requirements and related guidances, especially Directive 2001/83/EC, Regulation (EC) No 726/2004 (REG) and Commission Implementing Regulation (EU) No 520/2012 (IR) as detailed in Good Pharmaco Vigilance Practices (GVP) Modules V, VI and VIII.

It is the responsibility of GSK and the Investigators to have prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., ICFs), if applicable, from the IRB/IEC/Competent Authorities. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study such as amendments to the protocol, the Informed Consent Form (ICF), or other study documentation.

Informed consent will be obtained from all patients before enrolment into the study. Each investigator will ensure that each patient who needs to provide informed consent is given full and adequate oral and written information in the local language about the nature and purpose of the study. The patient will be given the opportunity to ask questions and allowed time to consider the information provided. All parties will ensure protection of participant personal data and will not include names on any sponsor forms, reports, publications, or in any other disclosures, except where required by the local laws and regulations. For eligible patients who received belantamab mafodotin and deceased before study enrolment, informed consent will be obtained from relatives if allowed according to the regulatory and legal country-specific requirements of the participating site.

The signed and dated informed consent (when applicable) must be obtained before any data is entered into the eCRF or available data is transferred to the analysis database. The investigator must store the original, signed ICF. A copy of the signed ICF must be given to the patient. If the patient decides not to participate, the reason will be collected in the eCRF.

9.2. Participant Withdrawal

Participation in this study is voluntary and patients may withdraw from the study at any time without prejudice. If the patient withdraws or is withdrawn, the reason will be collected in the eCRF. The ICF will explain that in case of withdrawal, all study data collected before withdrawal will be kept in the study database.

The Sponsor reserves the right, at any time, to discontinue enrolment of additional patients into the study, at any site; or to discontinue the study, for medical or administrative reasons.

9.3. Subject Confidentiality

The ICF will incorporate wording that complies with relevant data protection and privacy legislation in the participating country. Pursuant to this wording, patients will authorise the collection, use and disclosure of their personal data by the investigator and by those persons who need that information for the purposes of the study. The Sponsor and the Investigators will follow the EU General Data Protection Regulation that replaces the

Data Protection Directive 95/46/EC and that was designed to harmonize data privacy laws across Europe, to protect and empower all EU citizens' data privacy, and to reshape the way organizations across the region approach data privacy.

The ICF will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with the local law for data protection. The ICF will also explain that for quality check or data verification purposes, a monitor of Syneos Health will require direct access to the signed ICF or source documents that are part of the hospital or practice records relevant to the study.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1. Key Definitions

This study adopts the following ICH definitions:

AE: Any untoward medical occurrence in a patient, or clinical investigation subject, administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with the use of a Medicinal Product including those used in combination with a medical device. For a marketed Medicinal Product, this can also include failure to produce expected benefits (i.e., lack of efficacy, with or without an AE), and AEs associated with circumstances of Overdose whether accidental or intentional, Medication Errors, Abuse or effects of drug withdrawal, or Misuse or those related to a deficiency occurring with a medical device or combination product.

Adverse (Drug) Reaction (ADR): A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. An adverse reaction, in contrast to an AE, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

SAE: any untoward medical occurrence that at any dose 1) results in death, 2) is life threatening, 3) requires inpatient hospitalization or prolongs existing hospitalization, 4) results in persistent or significant disability/incapacity or 5) is a congenital anomaly or birth defect. Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (Annex IV, ICH-E2D Guideline).

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse (Annex IV, ICH-E2D Guideline).

Solicited Events: those AEs related to the GSK product under evaluation and identified for collection as per study objectives.

Spontaneous Events:

- Those AEs observed related to the GSK product under evaluation but exempted from collection, as justified in the protocol, are reported as spontaneous events.
- Those AEs observed related to any other GSK product (not under evaluation) are reported as spontaneous events.

- If any ADRs are observed related to drug product(s) not related to the Sponsor (GSK), the Investigator should report the ADRs to the appropriate marketing authorization application of the product(s) or Health Authority per local regulations.

The Investigator must provide a causality assessment regarding the relationship of any AE to the medicinal product.

Relationship: the relationship of belantamab mafodotin to an AE will be determined by the investigator. Investigators should use their knowledge of the patient, the circumstances surrounding the event, the temporal sequence between the event and the use of belantamab mafodotin, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to belantamab mafodotin. The investigator will use the following definitions to assess the relationship of the AE to the use of the product:

Not Related: There is evidence against a reasonable causal relationship between the use of belantamab mafodotin and the occurrence of the event, either due to lack of temporal relationship, or lack of biological plausibility, or to the existence of more plausible alternative explanations for the occurrence of the event of concern such as underlying or concurrent illness.

Related: There is evidence in favour of a reasonable causal relationship between the use of belantamab mafodotin and the occurrence of the event due to plausible temporal relationship (the event occurred within a reasonable time after drug administration) and also biological plausibility, despite the potential existence of alternative explanations for the occurrence of the event of concern such as the event could not be reasonably explained by known characteristics including concomitant therapies and/or the AE abated after discontinuing the study drug.

10.2. Collection of Adverse Events/Reactions

This study will evaluate ocular AESIs in patients exposed to belantamab mafodotin. For belantamab mafodotin-exposed patients, all ocular AESIs, including serious ocular AESIs will be collected. These will be summarised in interim and final study reports. Pre-defined ocular AESIs are keratopathy (i.e., corneal epithelium changes with or without symptoms), blurred vision events (including diplopia, vision blurred, visual acuity reduced and visual impairment), dry eye events (including dry eye, ocular discomfort, and eye pruritus), photophobia, eye irritation, corneal ulcers (ulcerative keratitis, infective keratitis, corneal erosion/defect).

Severity and seriousness need to be independently assessed by the investigator for each ocular AESI recorded on the eCRF. Severity of ocular AESIs will be classified using the using NCI CTCAE Version 5.0 (see Table 8; of note a Semi-colon indicates ‘or’ within the description of the grade) and the KVA scale (see ANNEX 2).

Table 8 Severity Rating Adverse Events

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

As they are not related to study objectives, 'non-ocular' AEs related to belantamab mafodotin, other GSK products, or non-GSK products, are not systematically collected, but will follow the process for spontaneous reporting (see reporting Section 10.3).

10.3. Reporting of Adverse Events/Reactions

Ocular AESIs systematically collected according to study objectives and considered causally related to the GSK product being evaluated (ADRs), as well as all ocular SAEs of special interest should be reported to the Safety department. These will be classified as solicited individual case safety reports (ICSRs).

'Non-ocular' adverse reactions related to the GSK product under evaluation or related to any other GSK product, are not systematically collected/solicited under the study objectives and instead will be classified as spontaneous reports.

Healthcare professionals (and any study vendor) will be informed of the possibility to report these spontaneous 'non-ocular' adverse reactions to the marketing authorisation holder of the suspected medicinal product (studied or not) OR to the concerned competent authority via the national spontaneous reporting system. It is the responsibility of the Sponsor of the product in question rather than the Investigator to report these spontaneous 'non-ocular' ADRs to the Regulatory Authorities according to applicable regulations.

Reporting timelines are provided in the study-specific Safety Management Plan (SMP).

Exemption of specific adverse events from collection:

Ocular AESIs are the most frequently reported AEs associated with belantamab mafodotin and keratopathy (an identified risk) and have the most impact on the benefit: risk of treatment with belantamab mafodotin. Therefore, a secondary objective of this study will focus on collection of ocular AESIs as solicited events, and their duration and severity.

As they are not related to the study objectives, 'non-ocular' AEs will not be solicited during this protocol and will instead be reported to GSK outside the study protocol as spontaneous events.

10.4. Safety Collection and Reporting Study Documentation

A SMP will be developed for the study and will provide detailed information on the study specific pharmacovigilance processes and procedures to ensure a comprehensive approach to safety event collection, reconciliation, follow-up and reporting.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

GSK and/or a designated party will prepare safety and other summary reports, as required by the appropriate regulatory authority. In addition, these data may be summarised periodically for presentation at professional conferences and sessions, as appropriate.

GSK is responsible for presentations and/or publications. For studies that are fully or partially conducted by investigators who are not employees of the GSK group of companies, GSK and the investigator should agree in advance a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. GSK should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

In order to allow national competent authorities to review in advance the results and interpretations to be published, the Marketing Authorisation Holder will communicate to the Agency the final manuscript of the article within two weeks after first acceptance for publication.

12. REFERENCES

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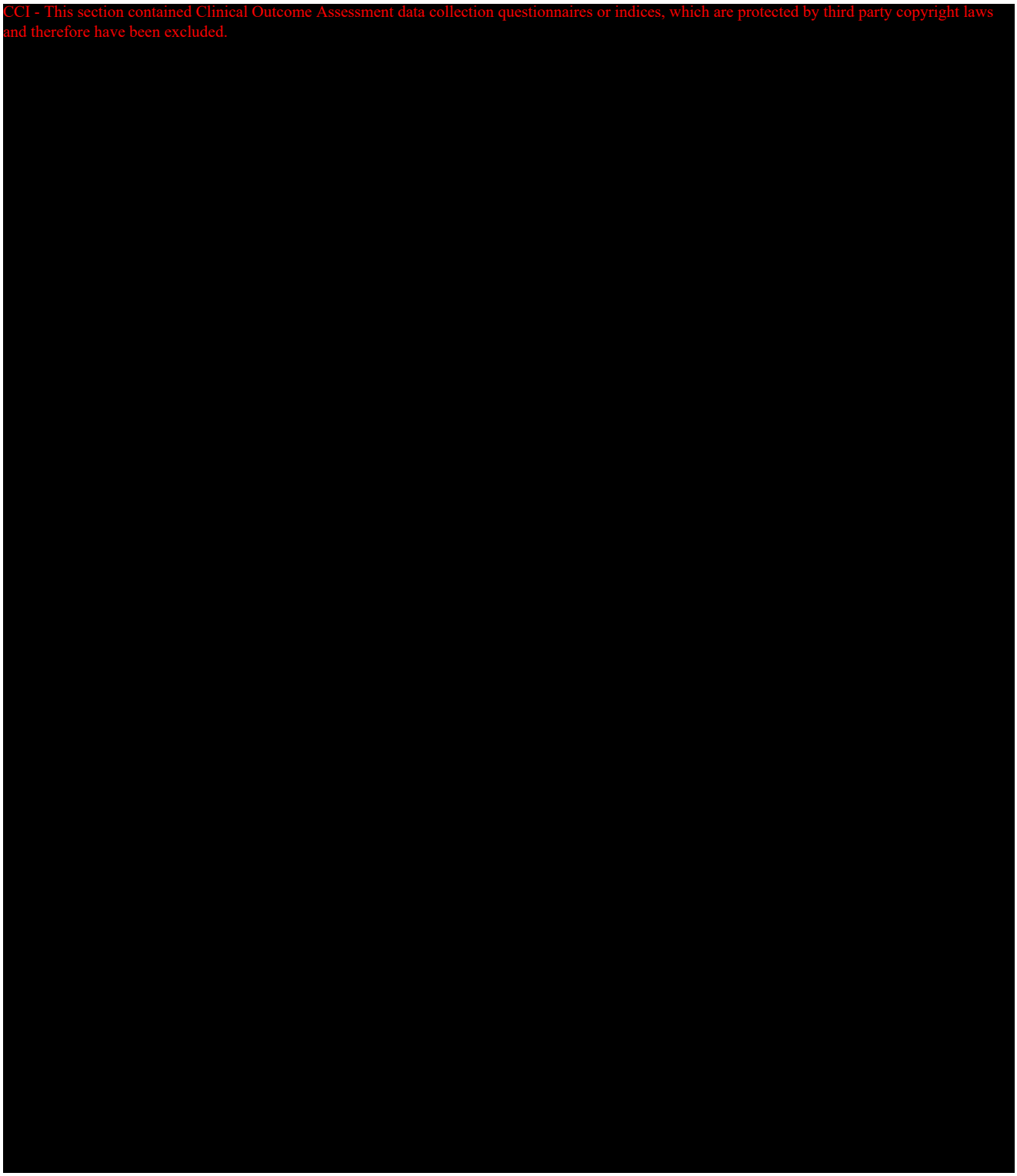
13. ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Contact details of all Investigators participating in the study and the Study Advisory Committee will be kept in stand-alone documents.

14. ANNEX 2. DOSE MODIFICATION PER KVA SCALE

Recommended belantamab mafodotin dose modifications based on eye examination findings per the KVA scale per the USPI and the EU SmPC combined (Lonial, 2021b).

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



15. ANNEX 3. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

15.1. ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

BLENREP Effectiveness and Safety in Multiple Myeloma (BEaMM) – Real-World Evidence on Patients Taking Belantamab Mafodotin in Europe.

EU PAS Register number: Not registered yet.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	5

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS Register	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Interim analyses will be described in the SAP

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

This is a descriptive study (not hypothesis-driven)

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.1/8.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	8.1/8.2/ 8.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	8.2
4.2.2 Age and sex	☒	☐	☐	8.2.1
4.2.3 Country of origin	☒	☐	☐	8.2
4.2.4 Disease/indication	☒	☐	☐	8.2.1
4.2.5 Duration of follow-up	☒	☐	☐	8.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2/8.4

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	8.3.3
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	7/8.7
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3/8.7
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	8.3
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

For 6.3, references for validated assessment instruments/scales etc. are provided

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	8.9
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.9

Comments:

No ways to measure confounding are described (e.g. multivariate analyses) as no comparative analyses are planned

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.9

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.1/8.2/ 8.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.1/8.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	8.1/8.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.3
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.3
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.3
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.3
	9.3.3 Covariates and other characteristics?	☒	☐	☐	8.3
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7
10.2	Is study size and/or statistical precision estimated?	☐	☒	☐	
10.3	Are descriptive analyses included?	☒	☐	☐	8.7
10.4	Are stratified analyses included?	☒	☐	☐	8.7
10.5	Does the plan describe methods for analytic control of confounding?	☐	☐	☒	

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7	Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	8.7

Comments:

The sample size is not based on statistical power consideration but on a conservative estimate for each country of interest based on country-specific MM incidence and prevalence rates, the percentage of patients expected to be eligible for belantamab mafodotin treatment, the expected belantamab mafodotin market uptake, site availability and the treatment landscape in terms of ongoing clinical trials.

Rules about how missing data will be handled and additional subgroup analyses will be set in the SAP as indicated in 8.7.

Section 11: Data management and quality control		**Yes**	**No**	**N/A**	**Section Number**
11.1	Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.6
11.2	Are methods of quality assurance described?	☒	☐	☐	8.8
11.3	Is there a system in place for independent review of study results?	☒	☐	☐	11

Comments:

Section 12: Limitations		**Yes**	**No**	**N/A**	**Section Number**
12.1	Does the protocol discuss the impact on the study results of:				
	12.1.1 Selection bias?	☒	☐	☐	8.9
	12.1.2 Information bias?	☒	☐	☐	8.9
	12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2	Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.5

Comments:

Section 13: Ethical/data protection issues		**Yes**	**No**	**N/A**	**Section Number**
13.1	Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9
13.2	Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3	Have data protection requirements been described?	☒	☐	☐	9

Comments:

Section 14: Amendments and deviations		**Yes**	**No**	**N/A**	**Section Number**
14.1	Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results		**Yes**	**No**	**N/A**	**Section Number**
15.1	Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2	Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Name of the main author of the protocol: PPD

Date: 01/October/2021

Signature: PPD

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Reason for signing: Approved	PPD

Reason for signing: Approved	PPD

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