TITLE PAGE

Protocol Title: A Phase 1, Randomized, Dose and Schedule Evaluation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of Belantamab Mafodotin Administered in Combination with Standard of Care in Participants with Newly Diagnosed Multiple Myeloma

Protocol Number: 209664 /Amendment 04

Compound Number: GSK2857916

Study Phase: Phase 1

Brief Title: DREAMM-9: Phase 1 Study of Belantamab Mafodotin Plus SoC in Newly Diagnosed Multiple Myeloma

Acronym: DREAMM-9

Sponsor Name and Legal Registered Address:

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

Medical Monitor Name and Contact Information will be provided separately OR can be found in the Study Reference Manual

Regulatory Agency Identifying Number(s): IND: 119333; EU CT: 2023-507060-39-00

Approval Date: 18 Oct 2024

©2024 GSK group of companies or its licensor. Trademarks are property of their respective owners.

SPONSOR SIGNATORY

Protocol Title: A Phase 1, Randomized, Dose and Schedule Evaluation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of Belantamab Mafodotin Administered in Combination with Standard of Care in Participants with Newly Diagnosed Multiple Myeloma

Protocol Number: 209664 / Amendment 04

Compound Number: GSK2857916

Brandon Kremer, MD, PhD Executive Medical Director, Oncology R&D; Clinical Development Lead, Belantamab Mafodotin	**Date**

The signed page is a separate document.

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment 04 Investigator Agreement

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with Good Clinical Practice (GCP) and all applicable regulatory requirements.
- That I will comply with the terms of the clinical study site agreement.
- To ensure that all persons assisting me with the study are adequately informed about the GlaxoSmithKline SA (GSK) study intervention and other study-related duties and functions as described in the protocol.

To cooperate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.

Study identifier	209664
Abbreviated title	DREAMM-9
EU CT number	2023-507060-39-00
Approval date	18 Oct 2024
Title	A Phase 1, Randomized, Dose and Schedule Evaluation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of Belantamab Mafodotin Administered in Combination with Standard of Care in Participants with Newly Diagnosed Multiple Myeloma
Investigator name	
Signature	
Date of signature (DD Month YYYY)	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Protocol Amendment 04	18 Oct 2024	TMF-19347105
Protocol Amendment 03 GBR-1	15-Mar-2022	TMF-14521011
Protocol Amendment 03	12-Jan-2022	TMF-14223056
Protocol Amendment 02	28-Jul-2021	TMF-13825366
Protocol Amendment KOR01	31-May-2021	TMF-13779216
Protocol Amendment 01	03-Aug-2020	2019N395761_01
Protocol Amendment DEU01	21-Jan-2020	2019N395761_00/DEU01
Protocol Amendment GBR01	31-Oct-2019	2019N395761_00/GBR01
Protocol	28-Aug-2019	2019N395761_00

Amendment 04: 18 Oct 2024

Where this Protocol Amendment applies:

Protocol Amendment 04 applies to all countries and all sites.

Overall rationale for the current Amendment:

- The protocol has been amended to allow patients who at the time of the final analysis are still benefiting to continue to have access to belantamab mafodotin through Post Analysis Continuation of Treatment (PACT) or via another continued treatment access provision outside of this protocol.
- Clarification of the timing of completion of the patient questionnaires in relation to the laboratory assessments.
- Clarification of the confirmation of progressive disease (PD) based on laboratory parameters to be performed from a second sample on the same day, or preferably within 14 days.
- Replacement of the term 'anti-cancer therapy' with 'anti-myeloma therapy' throughout the document.
- Addition of rationale for the decision to not replace non-dose-limiting toxicity (DLT)-evaluable participants enrolled into Cohort 8c or into the expansion cohorts of Cohort 6 and Cohort 7.
- Addition of ±1 month window for collection of follow-up minimal residual disease (MRD) samples.
- Updated risk language.
- Updated with mandatory wording and tables from the newly effective GSK protocol template.
- Updated guidance for delays in belantamab mafodotin dosing.
- Administrative updates to add clarification, correct or remove discrepancies.

All changes are listed in table below.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE

Section # and title	Description of Change	Brief Rationale
1.1 Synopsis 1.3 SoA 4.1 Overall Design 4.4 End of Study Definition 6.7 Continued Access to Study Intervention after the End of the Study 8.3.1 Time Period and Frequency for Collecting AE and SAE Information 8.3.4. Regulatory reporting requirements for SAEs	Added language regarding PACT Phase or another continued treatment access program.	To allow flexibility for eligible patients to receive study treatment after final analysis via PACT Phase or another continued treatment access program.
1.3 SoA 8.1.1. Minimal Residual Disease	Added ±1 month window for collection of follow-up MRD samples.	To allow flexibility for the collection of MRD samples.
8.1.1. Minimal Residual Disease	Removal of a specific named assay and replacement with a general description regarding type of assay and testing.	Commercially confidential information.
1.3 SoA 8.2.10. Visual Function Safety Assessment 8.2.11. PRO-CTCAE	Clarification of when the patient questionnaire can be performed at start of every visit.	Clarification to allow blood samples to be taken prior to the completion of the patient questionnaires.
2.3.1. Risk Assessment	Language in Table 5 (Summary of Risk Assessment for the Combination of Belantamab Mafodotin plus VRd and VRd alone) updated with recent safety information.	To provide the most up to date information in alignment with the current IB.
4.1. Overall Study Design 6.5.2. Prohibited Concomitant Therapies 7.1. Discontinuation of Study Treatment 8.2.9. Ophthalmic Examinations	Replacement of the term 'anti-cancer therapy' with 'anti-myeloma' therapy.	To align with the belantamab mafodotin program preferred terminology

Section # and title	Description of Change	Brief Rationale
4.1.1.1. Criteria for Belantamab Mafodotin Dose-Limiting Toxicity	Added rationale for not replacing non-DLT-evaluable participants enrolled into Cohort 8c or into the expansion cohorts of Cohort 6 and Cohort 7.	The doses on Cohort 6 and Cohort 7 have been well characterized and the dose in Cohort 8c is a reduced and stretched dose, so the need to have a specific number of DLT-evaluable patients was no longer mandated.
4.1.1. Dose Evaluation 4.1.1.2. Cohort Expansion	Added language regarding number of patients to be enrolled in expansion.	To allow flexibility in the patient recruitment.
6.1. Study Interventions administered	Included the table of Study Interventions administered.	To be in line with new protocol template.
6.1.1. Belantamab Mafodotin	Corrections made to dose and schedule in cohorts.	To correct error in previous document version.
6.6.1 Belantamab Mafodotin Dose Reduction Schedule	Additional language included for belantamab mafodotin dose delays.	To provide additional clarification on restarting treatment after a delay in belantamab dosing.
6.6.2.3. Dose Modification Guidance for Lenalidomide, Bortezomib, Dexamethasone	In Table 13 of Dose Modification Guidelines for Adverse Events Associated with Belantamab Mafodotin updated with dose modification for creatinine and ACR.	To incorporate the latest safety information for belantamab mafodotin
Minor editorial and document formatting revisions	To improve overall clarity and typographical corrections.	Minor editorial and document formatting revisions
	Unused abbreviations and references removed.	No longer required in document

TABLE OF CONTENTS

PAGE

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE 5

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 16

1. PROTOCOL SUMMARY 22
   - 1.1. Synopsis 22
   - 1.2. Schema 25
   - 1.3. Schedule of activities 27

2. INTRODUCTION 38
   - 2.1. Background 38
   - 2.2. Study rationale 38
     - 2.2.1. Newly diagnosed multiple myeloma 38
     - 2.2.2. Nonclinical evidence 39
     - 2.2.3. Human experience with belantamab mafodotin 40
       - 2.2.3.1. Clinical studies 40
     - 2.2.4. Pharmacokinetics and pharmacodynamics in humans 43
     - 2.2.5. Summary 44
   - 2.3. Benefit/risk assessment 44
     - 2.3.1. Risk assessment 44
     - 2.3.2. Benefit assessment 54
     - 2.3.3. Overall benefit/risk conclusion 54

3. OBJECTIVES AND ENDPOINTS 55

4. STUDY DESIGN 56
   - 4.1. Overall study design 56
     - 4.1.1. Dose evaluation 58
       - 4.1.1.1. Criteria for Belantamab Mafodotin Dose-Limiting Toxicity 59
       - 4.1.1.2. Cohort Expansion 61
   - 4.2. Scientific rationale for study design 61
   - 4.3. Justification for dose 62
     - 4.3.1. Justification for starting dose 62
     - 4.3.2. Justification for lower doses 63
     - 4.3.3. Alternate schedule for belantamab mafodotin 63
     - 4.3.4. Justification for dose and schedule for VRd 63
   - 4.4. End of study definition/study completion 64

5. STUDY POPULATION 64
   - 5.1. Inclusion criteria 64
   - 5.2. Exclusion criteria 67
   - 5.3. Lifestyle considerations 70
   - 5.4. Screen failures 70

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY 70
   - 6.1. Study Interventions administered 71
     - 6.1.1. Belantamab mafodotin 72
       - 6.1.1.1. Belantamab mafodotin pre/post-medication 73

6.1.1.2. Corneal supportive care guidelines for belantamab mafodotin 74
6.1.2. VRd administration (induction & maintenance) 75
6.1.2.1. Bortezomib (SC) administration 75
6.1.2.2. Lenalidomide 76
6.1.2.3. Dexamethasone 77
6.1.3. Dosing schedule 77
6.1.3.1. Induction treatment (Q3W) – belantamab mafodotin + VRd; up to Cycle 8 77
6.1.3.2. Maintenance treatment (Q4W) – belantamab mafodotin +Rd; Cycle 9 onward 78
6.2. Preparation/handling/storage/accountability 79
6.3. Measures to minimize bias: randomization and blinding 80
6.4. Study intervention compliance 81
6.5. Concomitant therapy 81
6.5.1. Permitted concomitant therapies 81
6.5.2. Prohibited concomitant therapies 82
6.6. Dose modification or delay 82
6.6.1. Belantamab mafodotin dose reduction schedule 83
6.6.2. Dose modification guidelines for adverse events 85
6.6.2.1. Dose modification for overlapping hematological toxicities 85
6.6.2.2. Dose Modification Guidelines for Belantamab Mafodotin 86
6.6.2.3. Dose Modification Guidance for Lenalidomide, Bortezomib, Dexamethasone 86
6.6.2.4. Dose Modification Guidance for Dexamethasone 93
6.6.3. Management of Hepatitis B positive participants 93
6.7. Continued access to study intervention after the end of the study 94
6.7.1. Continued access to study intervention after data cut-off prior to EoS 94
6.8. Treatment of overdose 95
6.8.1. Belantamab mafodotin overdose 95
6.8.2. Lenalidomide overdose 95
6.8.3. Bortezomib overdose 95
6.8.4. Dexamethasone overdose 96

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 96
7.1. Discontinuation of study intervention 96
7.1.1. Liver chemistry stopping criteria 98
7.1.1.1. Study Treatment Restart or Rechallenge after liver stopping criteria met 99
7.1.2. Pregnancy 100
7.1.3. Corneal event stopping criteria 100
7.1.4. Infusion-related reactions stopping criteria 100
7.1.5. Allergic reactions and anaphylactic reactions stopping criteria 100
7.2. Participant discontinuation/withdrawal from the study 100
7.3. Lost to follow-up 101

8. STUDY ASSESSMENTS AND PROCEDURES 102
8.1. Efficacy assessments 103
8.1.1. Minimal residual disease 103
8.1.2. Response evaluation 103
8.2. Safety assessments 104
8.2.1. Physical examinations 104
8.2.2. Vital signs 105
8.2.3. ECOG performance status 105
8.2.4. IMWG frailty score 105
8.2.5. New York Heart Association functional scale 105
8.2.6. Electrocardiograms 106
8.2.7. Echocardiogram 106
8.2.8. Clinical safety laboratory assessments 106
8.2.9. Ophthalmic examinations 107
8.2.9.1. Ocular Examinations and Procedures 108
8.2.10. Visual function safety assessment 108
8.2.11. PRO-CTCAE 109
8.2.12. Suicidal ideation and behavior risk monitoring 109
8.3. AEs, SAEs and other safety reporting 109
8.3.1. Time period and frequency for collecting AEs, SAEs and other safety information 110
8.3.2. Method of detecting AEs and SAEs 111
8.3.3. Follow-up of AEs and SAEs 112
8.3.4. Regulatory reporting requirements for SAEs 112
8.3.5. Pregnancy 113
8.3.6. Cardiovascular and death Events 113
8.3.7. Adverse events of special interest 113
8.4. Pharmacokinetics 114
8.4.1. Blood sample collection for pharmacokinetics 114
8.4.2. Belantamab mafodotin pharmacokinetic sample analysis 115
8.4.3. Bortezomib, lenalidomide and dexamethasone PK sample collection and analysis 116
8.5. Genetics 116
8.6. Biomarkers 116
8.6.1. Tumor-related biomarkers 117
8.6.1.1. BCMA expression on multiple myeloma cells 117
8.6.2. sBCMA in blood serum 117
8.7. Immunogenicity assessments 118
8.8. Health-related quality of life 118

9. STATISTICAL CONSIDERATIONS 119
9.1. Statistical hypotheses 119
9.2. Sample size determination 120
9.2.1. Statistical operating characteristics 120
9.3. Analysis sets 121
9.4. Statistical analyses 122
9.4.1. Efficacy analyses 122
9.4.2. Safety analyses 123
9.4.2.1. Dose-limiting toxicities (DLTs) 123
9.4.2.2. AEs 123
9.4.2.3. Clinical laboratory evaluations 124
9.4.2.4. Other safety measures 124

9.4.3. Belantamab mafodotin pharmacokinetic analyses 124
9.4.4. Pharmacokinetic/pharmacodynamic analyses 125
9.4.5. Health-related quality of life data analyses 125
9.4.6. Immunogenicity 125
9.4.7. Biomarker analyses 125
9.5. Interim analyses 126
9.5.1. Safety stopping rules 126

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 127
10.1. Appendix 1: Regulatory, ethical, and study oversight considerations 127
10.1.1. Regulatory and ethical considerations 127
10.1.2. Financial disclosure 127
10.1.3. Informed consent process 128
10.1.4. Data protection 128
10.1.5. Publication policy 128
10.1.6. Dissemination of clinical study data 129
10.1.7. Data quality assurance 129
10.1.8. Source documents 130
10.1.9. Study and site closure 131
10.2. Appendix 2: Clinical laboratory tests 131
10.3. Appendix 3: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting 133
10.3.1. Definition of AE 133
10.3.2. Definition of SAE 134
10.3.3. Definition of cardiovascular events 136
10.3.4. Definition of TEAE 136
10.3.5. Recording and follow-up of AE and SAE 136
10.3.5.1. Assessment of intensity 137
10.3.5.2. Assessment of causality 137
10.3.5.3. Assessment of outcomes 138
10.3.5.4. Updating of SAE, AESI, and pregnancy information after removal of write access to the participant's eCRF 139
10.3.6. Reporting of SAE to GSK 140
10.4. Appendix 4: Contraceptive guidance and collection of pregnancy information 142
10.4.1. Definitions 142
10.4.2. Contraception guidance: 143
10.4.3. Collection of pregnancy information 144
10.5. Appendix 5: Genetics 145
10.6. Appendix 6: Liver safety: required actions and follow-up assessments and study treatment rechallenge guidelines 146
10.6.1. Phase *1/2* liver chemistry stopping criteria 146
10.6.2. Rechallenge following liver stopping events that are possibly related to study treatment 148
10.6.3. Restart following transient resolving liver stopping events NOT related to study treatment 149
10.7. Appendix 7: IMWG frailty score 151
10.8. Appendix 8: New York Heart Association classification 151
10.9. Appendix 9: Country specific requirements 152

10.10. Appendix 10: Eastern Cooperative Oncology Group (ECOG) functional status 155
10.11. Appendix 11: Modified Diet in Renal Disease (MDRD) formula 155
10.12. Appendix 12: Eye care specialist's qualifications and requirements 155
10.13. Appendix 13: Home healthcare and telemedicine approaches 156
10.14. Appendix 14: Operating characteristics of safety stopping rule 159
10.15. Appendix 15: Data management and monitoring 159
10.16 Appendix 16: Trademarks 160
10.17 Appendix 17: Protocol amendment history 161

11. REFERENCES 178

LIST OF TABLES

PAGE

Table 1 Schedule of activities - Belantamab Mafodotin + VRd 27

Table 2 Hepatitis B SoA – Additional Procedures 35

Table 3 Hepatitis C SoA – Additional Procedures 36

Table 4 Bone marrow sample collection 37

Table 5 Summary of risk assessment for the combination of belantamab mafodotin plus VRd and VRd alone 45

Table 6 Dose-limiting toxicity criteria (3, 21-Day Cycles) for belantamab mafodotin 60

Table 7 Adequate organ system function based on safety assessments 65

Table 8 Study interventions administered 71

Table 9 Belantamab mafodotin study treatment information 72

Table 10 Prophylactic measures for ocular events associated with belantamab mafodotin 74

Table 11 Recommendations for dose reduction of belantamab mafodotin 84

Table 12 Dose modification guidelines for overlapping hematological toxicities 85

Table 13 Dose modification guidelines for adverse events associated with belantamab mafodotin 87

Table 14 Keratopathy and Visual Acuity scale for treatment-related corneal toxicities 89

Table 15 Dosage modifications for belantamab mafodotin based on the Keratopathy and Visual Acuity scale: 90

Table 16 Dose modification guidelines for hematologic and other toxicities attributed to bortezomib[a] 91

Table 17 Dose modification guidelines for hematologic and other toxicities attributed to lenalidomide[a] 92

Table 18 Dose modification guidelines for hepatitis B reactivation 93

Table 19 Timeframes for submitting SAE, pregnancy and other events reports to GSK 112

Table 20 PK and sBCMA samples for participants on Day 1 dose regimens 115

CCI [redacted] 121

Table 22 Populations for analyses 121

Table 23 Statistical analysis methods 122

Table 24 Safety stopping rules 126

Table 25 Protocol-required safety laboratory assessments 132

LIST OF FIGURES

PAGE

Figure 1 Study design schema 26

Figure 2 Summary of dosing schedules: belantamab mafodotin & VRd 79

Figure 3 Hierarchy of dose modification for overlapping hematological toxicities 85

Figure 4 Liver chemistry stopping and increased monitoring algorithm 99

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACR	Albumin/creatinine ratio
ADA	Anti-drug antibodies
ADC	Antibody-drug conjugate
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
AxMP	Auxiliary medicinal product
BCMA	B-cell maturation antigen
BIB	GSK Bioanalysis Immunogenicity and Biomarkers group
BM	Bone marrow
BMI	Body mass index
BSA	Body surface area
CBC	Complete blood count
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
Cmax	Maximum concentration
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CR	Complete Response
CRF	Case Report Form
CRR	Complete Response Rate
CRT	Calreticulin
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
CYP	Cytochrome P
Cys-mcMMAF	Microtubule inhibitor monomethyl auristatin-F with a cysteine linker
DCO	Data cut-off
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of Response
DREAMM	Driving Excellence in Approaches to Multiple Myeloma
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency

Abbreviation	Definition
EMD	Extramedullary disease
EOI	End of Infusion
EORTC	European Organization for Research and Treatment of Cancer
EoS	End of study
EOT	End of Treatment
EQ-5D-3L	Eurpoqual 5 Dimension 3 Level
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FISH	Fluorescence-in-situ hybridization
FLC	Free light chain
FSH	Follicle-stimulating hormone
FTIH	First-Time-in-Human
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GSK	GlaxoSmithKline
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HMGB1	High mobility group box 1
HRQL	Health-related quality of life
HRT	Hormonal replacement therapy
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
ImiD	Immunomodulatory drugs
IMP	Investigational medicinal product
IMWG	International Myeloma Working Group
INR	International normalized ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRT	Interactive Response Technology
ISS	International Staging System
ITT	Intention-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
KVA	Keratopathy and Visual Acuity
LDH	Lactate dehydrogenase
LPFD	Last Patient First Dose
LSLV	Last subject last visit
LTFU	Lost to follow-up
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume

Abbreviation	Definition
MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MM	Multiple myeloma
MMAF	Monomethyl auristatin-F
MoA	Mechanism of action
MP	Monitoring Plan
mPFS	Median progression-free survival
MR	Minimal Response
MRD	Minimal Residual Disease
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NDMM	Newly diagnosed multiple myeloma
NGS	Next-generation sequencing
NOS	Not otherwise specified
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall Survival
OU	Oculus Uterque (Both Eyes)
OSDI	Ocular Surface Disease Index
PACT	Post Analysis Continued Treatment
PCR	Polymerase chain reaction
PD	Progressive disease
PE	Pulmonary embolism
PET	Positron emission tomography
PFS	Progression-free Survival
PFS2	Progression-free Survival on Subsequent Line of Therapy
P-gp	P-glycoprotein
PI	Proteasome inhibitors
PK	Pharmacokinetic(s)
PO	Per os (oral)
POEMS	Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma proliferative disorder, skin changes
PR	Partial Response
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient-reported outcome
PRO CTCAE	Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events
Q3W	Three-weekly
Q4W	Four-weekly
Q6W	Six-weekly
Q8W	Eight-weekly
Q9W	Nine-weekly
Q12W	Twelve-weekly
QD	Once daily
QID	Four times daily
QLQ	Quality of life questionnaire
QoL	Quality of life
QT	Q and T waves in ECG
QTc	Corrected QT
QTcF	Fridericia's formula

Abbreviation	Definition
QTL	Quality Tolerance Limit
RAP	Reporting and Analysis Plan
RBC	Red blood cell
Rd	*Revlimid* (lenalidomide), dexamethasone
RDI	Relative dose intensity
RMST	Restricted mean survival time
RNA	Ribonucleic acid
RP3D	Recommended Phase 3 dose
RP2D	Recommended Phase 2 dose
RPLS	Reversible posterior leukoencephalopathy syndrome
RRMM	Relapsed/Refractory multiple myeloma
SAE	Serious adverse event
sBCMA	Soluble B-cell maturation antigen
SC	Subcutaneous
sCR	stringent Complete Response
SCT	Stem cell transplant
SD	Standard deviation of the mean
SMM	Smoldering Multiple Myeloma
SoA	Schedule of activities
SoC	Standard of care
SOI	Start of Infusion
SPD	Sum of the products of the maximal perpendicular diameters of measured lesions
SPEP	Serum protein electrophoresis
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
t1/2	Serum half-life
TE	Transplant eligible
TI	Transplant ineligible
TLS	Tumor lysis syndrome
TMF	Trial Master File
tmax	Time to maximum plasma concentration
TNF	Tumor necrosis factor
TTBR	Time to Best Response
TTP	Time to Progression
TTR	Time to Response
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
VGPR	Very Good Partial Response
VRd	*Velcade* (bortezomib), *Revlimid* (lenalidomide), dexamethasone
VZIG	Varicella zoster immune globulin
WBC	White blood cell
WOCBP	Woman of childbearing potential

Term	Definition
AxMP	Medicinal products used in the context of a clinical trial but not as IMPs, such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess endpoints in a clinical trial. AxMPs should not include concomitant medications, i.e., medications unrelated to the clinical trial and not relevant for the design of the clinical trial. Authorized AxMP = Medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any member state concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product. Note: Safety reporting with regard to authorized AxMPs shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC. Unauthorized AxMP = Medicinal product not authorized in accordance with Regulation (EC) No 726/2004 Safety reporting for unauthorized AxMPs will follow the same processes and procedures as SUSAR safety reporting.
Background treatment	Type of medicinal product administered to each of the clinical trial participants, regardless of randomization group, to treat the indication that is the object of the study. Background treatment is generally considered to be the current standard of care for the particular indication. In these trials, the IMP is given in addition to the background treatment and safety/efficacy are assessed. The protocol may require that the IMP plus the background treatment is compared with an active comparator or with placebo plus background treatment.
Blinding:	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of an SAE.
Challenge agent	A product given to trial participants to produce a physiological response that is necessary before the pharmacological action of the IMP can be assessed.
Co-administered product	A product given to clinical trial participants as required by the protocol as part of their standard care for a condition that is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.
Comparator	Any product used as a reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
IMP	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

Term	Definition
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the Principal Investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual(s) or party(ies) to perform those study-related duties and functions.
LSLV	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, or AEs (that is, the last participant's last visit or LSLV).
Medicinal products used to assess endpoints	A product given to the participant in a clinical trial as a tool to assess a relevant clinical trial endpoint; it is not being tested or used as a reference in the clinical trial.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine[s]/product[s]/control). Synonym: subject.
Participant identifier	A unique identification number assigned to each participant who consents to participate in the study.
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Remote visit	A visit conducted in a place other than the study site.
Rescue medication	Medicine(s) identified in the protocol as those that may be administered to the participants when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the participant, or to manage an emergency situation.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Standard of care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries.
Study intervention	Term used throughout the clinical study to cover all types of investigational and non-investigational products, including medical devices and vaccines, intended to be administered to the study participants during the study conduct. Procedures conducted to manage participants or to collect data are excluded from the usage of this term.
Study monitor	An individual assigned by the sponsor and responsible for ensuring proper conduct of clinical studies at 1 or more investigational sites.
Subcohort	A group of participants for whom specific study procedures are planned as compared with other participants or a group of participants who share a common characteristic (e.g., ages, vaccination schedule) at the time of enrollment.
SUSAR	In a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., IB for an unapproved IMP). All ADRs that are both serious and unexpected are subject to expedited reporting.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1 Randomized, Dose and Schedule Evaluation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of Belantamab Mafodotin Administered in Combination with Standard of Care in Participants with Newly Diagnosed Multiple Myeloma.

Brief Title: DREAMM-9: Phase 1 Study of Belantamab Mafodotin Plus SoC in Newly Diagnosed Multiple Myeloma.

Rationale: The treatment of newly diagnosed multiple myeloma (NDMM) has changed dramatically over the past 20 years, from near uniform application of chemotherapy to a patient performance status- and risk-based approach. The standard of care (SoC) for fit multiple myeloma patients is to receive high-dose chemotherapy, with autologous stem cell transplant, after completion of induction therapy. However, some patients, especially the elderly, are ineligible for transplant due to frailty and/or comorbidities. For such patients, treatment with highly active doublet or triplet combination regimens such as lenalidomide (*Revlimid*)/dexamethasone (Rd), daratumumab plus Rd, or bortezomib (*Velcade*), Lenalidomide (*Revlimid*), and dexamethasone (VRd) are considered.

B-cell maturation antigen (BCMA) is a target present on mature B cells and on tumor cells in patients with multiple myeloma (MM). Belantamab mafodotin (GSK Compound ID: GSK2857916) is an antibody-drug conjugate (ADC) consisting of an afucosylated humanized anti-BCMA monoclonal antibody (mAb, belantamab) that is conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF) via a protease resistant maleimidocaproyl (mc) linker. Single-agent belantamab mafodotin has demonstrated a strong single-agent activity with a well-defined manageable safety profile in heavily pre-treated participants with RRMM (Q3W schedule via IV administration).

The choice of therapy in NDMM patients depends largely on an individual's suitability for autologous stem cell transplant (ASCT). ASCT is usually only suitable for fitter patients, and typically younger than 65-75 years old; therefore, transplant ineligible (TI) patients constitute a large proportion of NDMM patients. Clinical prognosis for these patients is worse in terms of progression-free survival (PFS), overall survival (OS), or achieved minimal residual disease (MRD) negativity rates compared to patients who can undergo ASCT. Thus, there is an unmet clinical need to improve prognosis through the addition of effective novel therapies to SoC first line NDMM backbone agents.

Triplet therapy with VRd is an accepted clinical SoC regimen in TI NDMM. This is based on the findings of the SWOG S0777 Phase 3 clinical trial which evaluated VRd against lenalidomide and dexamethasone (Rd) doublet treatment. The addition of bortezomib to Rd during the first 8 cycles of treatment on a Q3W dosing schedule (i.e., induction treatment) was intended to achieve rapid disease responses followed by 4-weekly (Q4W) doublet Rd treatment until disease progression (i.e., maintenance treatment) which was intended to maintain response post-induction. In SWOG S0777, VRd was shown to be highly active compared to continuous treatment with the Rd doublet alone (overall response rate [ORR]: VRd: 82%; Rd: 72%). This resulted in an increase in mPFS of 29 months in the Rd arm to 41 months in the VRd arm, and the result of this study lead to EMA approval of this regimen for patients with NDMM who are not eligible for transplant.

Belantamab mafodotin has undergone nonclinical testing in combination with SoC agents including bortezomib, dexamethasone, and lenalidomide in xenograft models bearing multiple myeloma OPM2 and MOLP8 cells. Lenalidomide and bortezomib were demonstrated to have independent effects on the pharmacodynamic activity of belantamab mafodotin in vivo: Combining belantamab mafodotin and bortezomib led to significant tumor growth inhibition and increased survival compared to belantamab mafodotin and bortezomib single agents in the OPM2 model, but not in the MOLP8 model. Combining belantamab mafodotin and lenalidomide led to significant increased survival compared to belantamab mafodotin and lenalidomide single-agent in both the OPM2 and MOLP8 MM xenograft models, and significant tumor growth inhibition compared to single agents in the OPM2, but not in the MOLP8 model.

Overall, given the demonstrated clinical activity of single-agent belantamab mafodotin in RRMM patients and the potential for lenalidomide and bortezomib to combine with the multi-model mechanisms of action of belantamab mafodotin, the quadruplet regimen of belantamab mafodotin plus VRd could potentially provide additional therapeutic benefit for patients with TI NDMM.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Determine safety and tolerability of belantamab mafodotin in combination with VRd to establish a recommended dose for participants with Transplant ineligible (TI) Newly diagnosed multiple myeloma (NDMM).	• Number (%) of participants with dose-limiting toxicities (DLTs). • Number (%) of participants with adverse events (AEs).
Secondary	
Effect of combining belantamab mafodotin with VRd in relation to lenalidomide & bortezomib relative dose intensity (RDI).	• Lenalidomide RDI after 4 cycles of treatment with belantamab mafodotin in combination with VRd. • Bortezomib RDI after 4 cycles of treatment with belantamab mafodotin in combination with VRd. • Cumulative administered dose of belantamab mafodotin after 4 cycles of treatment in combination with VRd.
To evaluate the pharmacokinetics (PK) profile of belantamab mafodotin, when administered in combination with VRd.	• Belantamab mafodotin, and cys-mcMMAF pharmacokinetic (PK) parameters, as data permit.
To assess anti-drug antibodies (ADAs) against belantamab mafodotin.	• Incidence and titers of ADAs against belantamab mafodotin.
Assess the efficacy of belantamab mafodotin in combination with VRd in TI NDMM.	• Overall Response Rate (ORR), defined as the percentage of participants with a confirmed partial response (PR) or better (i.e., PR, [Very Good Partial Response, VGPR], Complete Response [CR], stringent Complete Response [sCR]). • Complete Response Rate (CRR), defined as the percentage of participants with a confirmed CR or better (i.e., CR, sCR). • Rate of VGPR or better, defined as the percentage of participants with a confirmed VGPR or better (i.e., VGPR, CR, sCR).

Overall Design:

Study 209664 is a randomized, Phase 1, dose and schedule evaluation study investigating the safety, pharmacokinetics, pharmacodynamics and clinical activity of belantamab mafodotin in combination with SoC in adult participants with NDMM. Currently, VRd is the SoC backbone that will be evaluated in protocol 209664, and all participants must be transplant ineligible. Other regimens and/or populations may be explored at a later date after regulatory approval of a substantial protocol amendment. The study will evaluate different doses/dose schedules of belantamab mafodotin in combination with VRd in up to 8 cohorts and will determine the Recommended Phase 3 dose (RP3D) for future studies in the newly diagnosed setting.

Number of Participants:

Up to 8 different dose cohorts may be evaluated, and up to 160 participants may be enrolled, in order to determine the RP3D for future studies in the newly diagnosed setting.

Intervention Groups and Duration:

- **Induction treatment**: Different doses/dose schedules of belantamab mafodotin plus VRd – 8 cycles (21-day cycles).
- **Maintenance treatment**: Different doses/dose schedules of belantamab mafodotin plus Rd – Cycle 9 onwards (28-day cycles).

Participants will receive study treatment until disease progression, or unacceptable toxicity.

Data Monitoring Committee: No

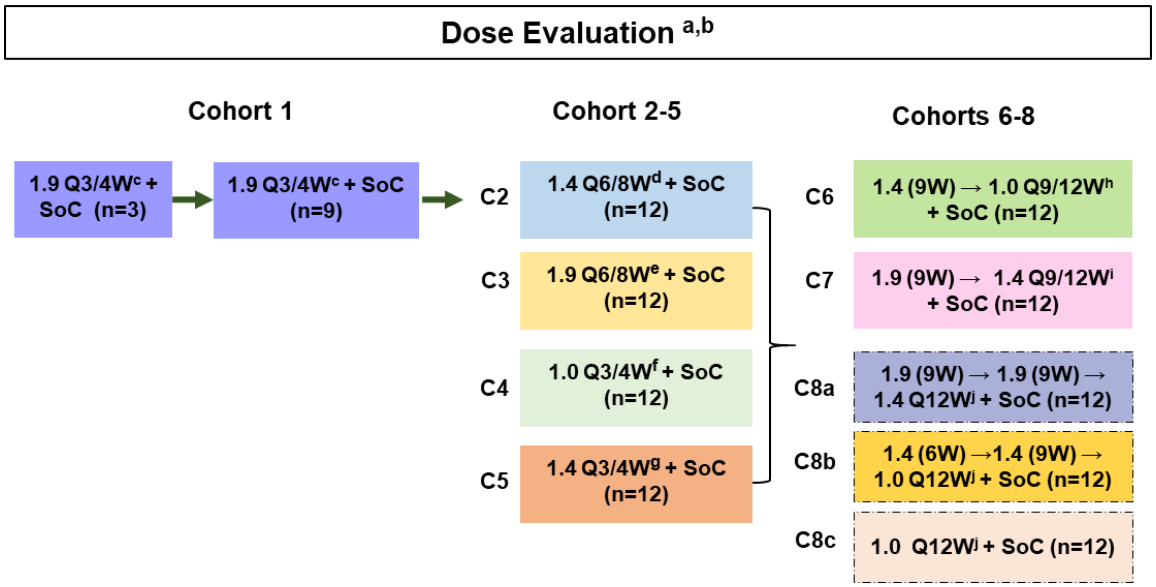
PACT Phase: Following the DCO date for the final analysis, study 209664 (DREAMM-9) participants may move into the PACT Phase where the study remains open only to provide continued access to study intervention for participants who are continuing to derive clinical benefit in the opinion of the investigator and cannot access the treatment outside of the clinical study protocol at the time of final DCO date. At that time, the collection of new data for participants who no longer receive study intervention will stop entirely. The clinical study database will be closed to new data following the final DCO date. Participants still benefiting from study intervention at the time of the PACT phase may continue to receive study intervention and only SAEs, AEs leading to study intervention discontinuation, overdose, prespecified ocular data and pregnancy cases will be reported directly to GSK. Alternative continued treatment access outside of this study may be implemented, as it becomes available. For instance, participants may access the treatment outside of the clinical study protocol at the DCO (data cut-off) date for the final analysis by a rollover/extension study, expanded access route inclusive of group program or single patient compassionate use or if the product is commercially available and accessible.

1.2. Schema

The study schema is displayed in Figure 1.

Participants will receive the combination of bortezomib, lenalidomide and dexamethasone on a 3-week cycle until Cycle 8, followed by the combination of lenalidomide and dexamethasone on a 4-week cycle thereafter. The dose and schedule of VRd will not vary, except as required for individual participants based on toxicity and/or tolerability. Belantamab mafodotin will be administered in combination with VRd every Q3W, Q6W, Q9W or Q12W to Cycle 8, and then in combination with Rd every Q4W, Q8W, or Q12W thereafter.

Figure 1 Study design schema



SoC = Standard of care; VRd = *Velcade* (bortezomib), *Revlimid* (lenalidomide), dexamethasone.

a. Based upon emerging data, not all dose cohorts may be explored.
b. Cohort expansion (the enrolment of approximately 8 additional participants) may be considered for a cohort(s) after the interim analysis.
c. Cohort 1: 1.9 Q3/4W = 1.9mg/kg on Day 1 of each cycle.
d. Cohort 2: 1.4 Q6/8W = 1.4mg/kg on Day 1 of every other cycle.
e. Cohort 3: 1.9 Q6/8W = 1.9mg/kg on Day 1 of every other cycle.
f. Cohort 4: 1.0 Q3/4W = 1.0mg/kg on Day 1 of each cycle.
g. Cohort 5: 1.4 Q3/4W = 1.4 mg/kg on Day 1 of each cycle.
h. Cohort 6: 1.4 mg/kg on Day 1 of Cycle 1, then 1.0 mg/kg on Day 1 of every third cycle from Cycle 4.
i. Cohort 7: 1.9 mg/kg on Day 1 of Cycle 1, then 1.4 mg/kg on Day 1 of every third cycle from Cycle 4.
j. Cohort 8: Based on emerging data, either a) 1.9 mg/kg on Day 1 of Cycle 1 and Cycle 4, then 1.4 mg/kg on Day 1 of every third cycle from Cycle 7; OR b) 1.4 mg/kg on Day 1 of Cycle 1 and Cycle 3, then 1.0 mg/kg on Day 1 of every third cycle from Cycle 6; OR c) 1.0 mg/kg on Day 1 of Cycle 1 and Cycle 5, then 1.0 mg/kg on Day 1 of every third cycle from Cycle 9.

1.3. Schedule of activities

Table 1 Schedule of activities - Belantamab Mafodotin + VRd

- **Screening** assessments do not need to be repeated on C1D1 if conducted within 72 hours of C1D1 dosing, unless otherwise specified.
- **Study treatment** should be initiated within 72 hours after treatment allocation.
- Assessments scheduled on days of dosing should be done prior to drug administration unless otherwise specified. All assessments should be carried out even if a participant is not dosed **except for the following**: vital signs, weight, and PK where applicable.
- **Treatment Visits:** Participants are scheduled to receive treatment cycles Q3W for Cycles 1-8, and Q4W for Cycle 9 onward. Precise timing of treatment cycles may vary due to treatment delays, but participants must still visit for efficacy assessments regularly regardless of when they receive treatment.
- **Fixed Visits:** The schedule for disease assessments is Q3W for 6-months (Weeks 1-24), Q4W for a further 18-months (Weeks 25-104), and Q8W thereafter (Week 105+). These are referred to as 'fixed visits' or 'weeks visits' and should be scheduled from C1D1.
- **PFS Follow-up**: Participants who discontinue study treatment for a reason other than PD, will continue to have disease evaluations performed at the timepoints indicated below until confirmed PD, death, start of a new anti-*myeloma* treatment, withdrawal of consent, lost to follow-up or end of the study whichever occurs first.
- **End of Treatment (EOT) Visit:** to occur within 30 days from the last dose of study treatment, or prior to the new anti-MM treatment (whichever occurs first).
- Participants will have a **70-day Safety Follow-up** Visit that may be a clinic visit or a phone call to collect AEs, SAEs and Concomitant Medication 70 days after their last dose of study treatment. An exception is participants who have ocular symptoms at EOT who will be followed up for ocular examinations and OSDI questionnaire as described in Section 8.2.9.
- An end of treatment is not carried out if the participant continues to receive study intervention(s) by post-trial access route outside of this study protocol.
- **PACT Phase**: Following the final DCO date, the study may move into the PACT phase (see Section 6.7.1for details). Participants who continue to receive study intervention during the PACT phase will be monitored and will receive follow-up care in accordance with standard local clinical practice. Assessments will revert to the standard of care at a participant's particular study site and only SAEs, AEs leading to discontinuation of study intervention, overdose, prespecified ocular data and pregnancy cases will be reported directly to the sponsor via paper forms (Section 8.3).
- For a participant discontinuing treatment in the PACT Phase, no end of treatment visit is required.
- For details on Home Healthcare and Telemedicine approaches, please refer to Section 10.13.

Procedure	Screening	Treatment Period								End of Treatment Visit	Follow-up	
Cycle / Visit		C1	C2-8	C1-8	C1-8	C1-8	C1 only	C9 +	Fixed Visits Q3W (Mth 1-6) Q4W (Mth 6-Yr2) Q8W (>Yr2)		PFS Q3W (Mth1-6) Q4W (Mth 6-Yr2) Q8W (>Yr2)	Safety F-Up: 70 days post last dose
Day		D1		D4	D8	D11	D15	D1				
Window	-21	±3 days for all dosing schedules (Q3W, Q4W, Q6W, Q8W, Q9W, Q12W)							±3 days/ ±7 days		±3 days/ ±7 days	+14 days
Informed Consent[1]	X											
Baseline Demographics	X											
Medical History, Disease History and Characteristics	X											
Body Weight	X	X	X					X		X		
Height	X											
Safety												
ECOG Performance Status	X	X	X					X		X	X	
Physical Examination[2]	X	X	X					X		X	X	
Ocular Examination[3]	X		X[3]					X[3]		X	X[3]	X[3]
Vital Signs (BP, Heart rate, Body temp)[4]	X	X	X					X		X		
12-Lead ECG[5]	X	As clinically indicated										
Echocardiogram – LVEF	X	As clinically indicated										
Laboratory Assessments[6]												
Hematology[7]	X	X	X	X	X	X	X	X		X	X	
Clinical Chemistry[8]	X	X	X					X		X	X	
HbA1c	As clinically indicated, to be performed within 72 hours prior to C1D1											
eGFR[9]	X	X	X					X		X		
Urine dipstick for protein OR Spot Urine for Albumin/Creatinine ratio[10]	X	X	X					X				
HBsAg, HBcAb, Hepatitis C Ab, Hepatitis C RNA[11]	X											
Pregnancy Test for WOCBP[12]	X	X	X					X		X		

Procedure	Screening	Treatment Period								End of Treatment Visit	Follow-up	
Cycle / Visit		C1	C2-8	C1-8	C1-8	C1-8	C1 only	C9 +	Fixed Visits Q3W (Mth 1-6) Q4W (Mth 6-Yr2) Q8W (>Yr2)		PFS Q3W (Mth1-6) Q4W (Mth 6-Yr2) Q8W (>Yr2)	Safety F-Up: 70 days post last dose
Day		D1		D4	D8	D11	D15	D1				
Window	-21	±3 days for all dosing schedules (Q3W, Q4W, Q6W, Q8W, Q9W, Q12W)							±3 days/ ±7 days		±3 days/ ±7 days	+14 days
Disease Evaluations: Baseline disease assessments completed within 21 days (30 days for imaging) of C1D1 do not need to be repeated on C1D1. For participants who are discontinuing IP due to PD, the confirmation based on laboratory parameters must be performed from a different blood collection preferably within 14 days of the original date of the disease progression, preferably before institution of any new anti-myeloma therapy. Visit windows are ±3 days for Q3W and Q4W Disease Assessments, and ±7 days for Q8W Disease Assessments.												
β2 Microglobulin	X								X	X	X	
SPEP (Serum Protein Electrophoresis)	X								X	X	X	
UPEP (Urine Protein Electrophoresis) (on 24-hour collected urine)	X								X	X	X	
Serum M-Protein Calculation	X								X	X	X	
Serum Kappa Lambda FLC, FLC Ratio	X								X	X	X	
Serum Immunofixation	X		Should be performed at time of first achieving SPEP or Urine M-protein approximately zero g/dl (suspected CR) and repeated Q3W (Weeks 1-24), Q4W (Weeks 25-104) and Q8W (Week 105+) until suspected PD after CR or sCR.									
Urine Immunofixation	X											
Calcium Corrected for Albumin (serum)	X								X	X	X	
IgG, IgM, IgA	X								X	X	X	
IgD/IgE[13]	X								X	X	X	
Imaging for Extramedullary Disease[14]	Only for participants with Extramedullary Disease. At screening then Q12W for 1 yr then as clinically indicated.											
Skeletal Survey[15]	X	As clinically indicated										
Response Assessment by IMWG[16]									X	X	X	

Procedure	Screening	Treatment Period							End of Treatment Visit	Follow-up	
Cycle / Visit		C1	C2-8	C1-8	C1-8	C1-8	C1 only	C9 +	Fixed Visits Q3W (Mth 1-6) Q4W (Mth 6-Yr2) Q8W (>Yr2)		PFS Q3W (Mth1-6) Q4W (Mth 6-Yr2) Q8W (>Yr2)	Safety F-Up: 70 days post last dose
Day		D1		D4	D8	D11	D15	D1				
Window	-21	±3 days for all dosing schedules (Q3W, Q4W, Q6W, Q8W, Q9W, Q12W)							±3 days/ ±7 days		±3 days/ ±7 days	+14 days
Bone Marrow (BM) Assessments												
BM Biopsy or Aspirate for BCMA Expression and Biomarker Research	Please refer to Table 4 for detailed schedule of BM collection at all timepoints, including Screening.											
BM Aspirate for FISH Testing												
BM Biopsy and/or Aspirate for Disease Assessments												
BM Aspirate for MRD Testing												
BM Biopsy to Confirm sCR by IHC												
Optional BM Sample at PD for BCMA Expression												
Treatments Administered												
Belantamab mafodotin[17]		X	X		(X)			X				
Bortezomib[18]		X	X	X	X	X						
Lenalidomide		Days 1-14 of a 21-Day cycle (Cycles 1-8). Days 1-21 of a 28-day cycle for Cycle 9+. Dose modifications will follow guidance in Section 6.6.										
Pregnancy Prevention Counselling[19]	X	X	X					X		X	X	X
Dexamethasone		Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-Day cycle (Cycles 1-8). Days 1, 8, 15, 22 of a 28-day cycle (Cycle 9+). Dose modifications will follow guidance in Section 6.6.										
Supportive Medication		Supportive medication to be provided for each agent as per institutional guidelines, see Section 6.5.										
Dispense/Return Medication Diary[19]		X	X					X		X		

Procedure	Screening	Treatment Period								End of Treatment Visit	Follow-up	
Cycle / Visit		C1	C2-8	C1-8	C1-8	C1-8	C1 only	C9 +	Fixed Visits Q3W (Mth 1-6) Q4W (Mth 6-Yr2) Q8W (>Yr2)		PFS Q3W (Mth1-6) Q4W (Mth 6-Yr2) Q8W (>Yr2)	Safety F-Up: 70 days post last dose
Day		D1		D4	D8	D11	D15	D1				
Window	-21	±3 days for all dosing schedules (Q3W, Q4W, Q6W, Q8W, Q9W, Q12W)							±3 days/ ±7 days		±3 days/ ±7 days	+14 days
Ocular Supportive Care for Belantamab Mafodotin												
Preservative-free Artificial Tears		4 to 8 times daily in each eye. Daily beginning on Cycle 1 Day 1 until EOT. In the event of ocular symptoms (i.e., dry eyes), the use of artificial tears may be increased up to every 2 hours as needed.										
Cooling Eye Masks		At the start of each belantamab mafodotin infusion, apply for approximately 1hr or as long as tolerated to both eyes. Participants may continue to apply for up to 4 hours in the clinic.										
Health Outcomes - PROs will be completed at the start of every visit either before or after sample collection for laboratory assessment and prior to any other procedures or provision of results.												
PRO-CTCAE, EORTC-QLQ-C30, PGIS, PGIC[21]		X							X	X		
OSDI[22]		X							X[22]	X	X[22]	
Biomarkers and Genetics												
Pharmacokinetics[23]		PK sampling schedule can be found in Section 8.4.1.										
Soluble BCMA[23]		sBCMA samples should be collected at all PK timepoints (Section 8.4.1) and at all MRD assessments.										
ADA[23]		ADA samples will be collected prior to the Day 1 belantamab mafodotin infusion at Dose 1, 2, 3, 4, 6, 9 and 12 at the same time as the pre-infusion belantamab mafodotin PK samples are taken. For treatment beyond 12 doses, ADA will be collected every sixth dose of belantamab mafodotin (Dose 18, Dose 24, Dose 30 and so on) prior to the D1 belantamab mafodotin infusion. A further sample will be collected at EOT.										

Procedure		**Treatment Period**								**Follow-up**	
Cycle / Visit		**C1**	**C2-8**	**C1-8**	**C1-8**	**C1-8**	**C1 only**	**C9 +**	**Fixed Visits Q3W (Mth 1-6) Q4W (Mth 6-Yr2) Q8W (>Yr2)**	**PFS Q3W (Mth1-6) Q4W (Mth 6-Yr2) Q8W (>Yr2)**	**Safety F-Up: 70 days post last dose**
Day	**Screening**	**D1**		**D4**	**D8**	**D11**	**D15**	**D1**			
Window	**-21**	**±3 days for all dosing schedules (Q3W, Q4W, Q6W, Q8W, Q9W, Q12W)**							**±3 days/ ±7 days**	**±3 days/ ±7 days**	**+14 days**
Optional Genetic Sample		Informed consent for optional genetic research must be obtained before collecting a sample. The sample will be collected at the first opportunity after a participant has met all eligibility requirements preferably on C1D1. May be taken at another visit if not taken at C1D1.									
Ongoing Participant Review											
AEs/SAEs		AEs and SAEs will be collected throughout the study and until at least 70 days after the last dose of study treatment. SAEs related to study participation will be collected from time of consent.									
Concomitant Medications [24]	Concomitant medications will be collected, as reported by the participant or through participant medical record review.										
Others											
Safety Follow-up Phone call											X

End of Treatment Visit

ADA = Anti-drug antibody; BM= Bone marrow; BCMA= B-cell maturation antigen; BP = Blood pressure; C1D1 = Cycle 1 Day 1; CR = Complete response; ECG = Electrocardiogram; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; eGFR = Estimated glomerular filtration rate; EM = Extramedullary; EMD = Extramedullary disease; EOI = End of Infusion; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module; FISH = Fluorescence-in-situ hybridization; EOT = End of Treatment; FLC = Free light chain; FSH = Follicle-stimulating hormone; F-Up = Follow-up; Ig = Immunoglobulin; IgD = Immunoglobulin D; IgE = Immunoglobulin E;IHC = Immunohistochemistry; IMWG = International Myeloma Working Group; IP = Investigational product; IV = Intravenous; IRR = Infusion-related reaction; LVEF = Left ventricular ejection fraction; MRD = Minimal residual disease; Mth = Month; OSDI = Ocular Surface Disease Index; NGS = Next-generation sequencing; PD = Progressive disease; PFS = Progression-free Survival; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = Pharmacokinetics; PO = Per os (oral); PRO-CTCAE = Patient-Reported Outcomes Version of the Common Term Criteria for Adverse Events; Q3W = Three-weekly; Q4W = Q4 weekly; Q6W = Six-weekly; Q9W = Nine-weekly; Q12W = Twelve-weekly; RNA = Ribonucleic acid; SAE = Serious adverse event; sCR = stringent Complete Response; SOI = Start of Infusion; SPD = Sum of the Products of the maximal perpendicular Diameters; SPEP = Serum protein electrophoresis; UPEP = Urine protein electrophoresis; WOCBP = Women of childbearing potential; Yr = Year.

1. Must be signed before any study specific assessments are performed. Assessments performed as SoC assessment prior to signing consent need not be repeated if done within the appropriate screening window. Informed consent may be obtained 28 days prior to C1D1 for participants who are women of childbearing potential who need to take required contraception measures.
2. Physical exam must be within 72 hours prior to the first dose of study drugs to be administered in that cycle.
3. C1D1 ocular examination does not need to be performed if C1D1 is within 21 days of screening exam. Participants will be assessed by a qualified eye care specialist (Section 10.12) at screening/baseline. On-treatment ocular examinations will be performed Q3W for the first 8 Cycles and Q4W for Cycle 9 onward, up to the fifth dose of belantamab mafodotin (fourth dose of belantamab mafodotin for participants in cohorts 8c), assessment window of up to 5 days prior to dosing, but all effort should be made to schedule as close to belantamab mafodotin dosing as possible. If there are no significant (Grade 2 and above) ocular examination findings, patient's symptoms, or vision changes at the fifth dose of belantamab mafodotin (fourth dose of belantamab mafodotin for participants in cohorts 8c), reduce ocular exams to prior to scheduled dosing or as clinically indicated by the qualified eye care specialist. Participants with treatment-related ocular examination findings, ocular symptoms, or vision changes AEs present at the EOT will continue to be followed at least every 3 months for up to 12 months, or until resolution (to Grade 1 or baseline) by a qualified eye care specialist, whichever comes first. Participants in PFS follow-up or OS follow-up will only have ocular examinations if they had ocular signs or symptoms at EOT. See Section 8.2.9 and for full details of ocular exam procedures.
4. Belantamab mafodotin dosing day, Cycle 1, vital signs must be assessed within 30 minutes prior to SOI, 15 mins after SOI (±5 min), within 15 min after End of Infusion (EOI), and at 1 hour (±10 min) after EOI. No additional vital signs are required for bortezomib unless clinically indicated.
   Belantamab mafodotin dosing days, Cycles 2+: vital signs must be assessed at pre-dose (within 30 minutes prior to SOI) and within 15 min after EOI, and as clinically indicated. On days where vital sign time points align with blood sampling time points, vital signs should be assessed prior to blood samples being drawn. No additional vital signs are required for bortezomib unless clinically indicated.
   On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated. Vital signs should be measured after resting for at least 5 mins. On days where have multiple procedures, please see Section 8 for details.
5. Single ECG unless QTcF is prolonged in which case triplet ECG is required. To be performed after resting for at least 5 mins. Where triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.
6. All laboratory tests with values considered clinically significantly abnormal during participation in the study until at least 70 days after the last dose of study treatment should be repeated until the values return to normal or baseline.
7. See Section 10.2 for comprehensive list of tests.
   During Induction Treatment (Cycles 1-8), hematology to be performed on bortezomib dosing days prior to dosing, or weekly if bortezomib is discontinued. At Day 1, hematology taken up to 72 hours prior to dosing may be used. At Day 4, 8, and 11, hematology taken up to 1 day prior to dosing may be used. An additional hematology sample should be taken at C1D15. Hematology may be repeated as clinically necessary. Please repeat if platelet count decreases to <50K.
   During Rd Maintenance (Cycle 9+) hematology to be performed at the start of every cycle (or within 72 hours prior to D1 of the cycle).
   On belantamab mafodotin dosing days (i.e., D1, or D1 & D8), hematology testing must be performed prior to belantamab mafodotin administration or up to 72 hours prior to administration.
   Results must be received and evaluated prior to dosing with any drug. Hematology may be repeated as clinically necessary.
8. See Section 10.2 for comprehensive list of tests
   Clinical chemistry to be performed within 72 hours prior to dosing at the start of every cycle. Creatinine Clearance to be performed on Day 1 of each VRd cycle.
   Results must be received and evaluated prior to dosing of any agents. Clinical Chemistry may be repeated as clinically necessary.
9. As calculated by Modified Diet in Renal Disease (MDRD) formula (Section 10.11).

10. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥1+ (at screening visit), or ≥2+ (during study treatment), or with positive protein if urine dipstick protein quantification is not available. Albumin/creatinine will be performed at a local lab. If local testing is not available, then central testing will be performed (first void). If testing to be performed at a central lab, may be conducted 7 days prior to dosing.
11. Hepatitis B virus DNA testing will be done to determine a participant's eligibility if HBcAb and/or HBsAg is positive. Hepatitis C virus RNA testing will be done to determine a participant's eligibility if Hepatitis C Ab is positive. This will be performed at a local lab, or if not available then at a central lab. Results must be received prior to dosing. For additional procedures during Screening and upon enrolment for participants who have a history of Hepatitis B and/or Hepatitis C, please refer to Table 2 and Table 3, respectively.
12. Perform only on women of childbearing potential (WOCBP), see Section 10.4 or definition. For questionable cases, follicle-stimulating hormone (FSH) and estradiol (as needed in women of non-childbearing potential) should be performed at local lab to determine childbearing potential. Two highly sensitive serum pregnancy tests must be performed during screening, one within 10-14 days prior to C1D1 and one within 24 hours prior to starting lenalidomide at C1D1. Subsequent pregnancy tests on dosing days may be either serum or urine. After the first dose, pregnancy tests will be done weekly during the first month, then every cycle thereafter (or every 2 weeks in females with irregular menstrual Cycles). Each pregnancy test must be performed within 24 hours prior to any study treatment. Final pregnancy test (serum or urine) must be performed at the EOT Visit. Follow-up pregnancy assessment by telephone (for WOCBP only) should be performed monthly until 4 months after the last dose of belantamab mafodotin.
13. Only in participants with IgD/IgE myeloma.
14. Imaging is only required for participants with known EMD, all EMD lesions should be measured per IMWG criteria, and the sum of product of perpendicular diameters should be monitored for response/progression. Screening assessments may be performed up to 30 days prior to C1D1. Subsequent imaging should be performed at Week 13, 25, 37, 49 (±7 days) and then if clinically indicated by either CT, MRI, or PET/CT per local guidance. Needs to be performed by the same method throughout the study as was done at baseline. Selected target lesion needs to be measured and followed over time. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For participants with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD of measured lesions.
    Participants undergoing PET/CT should have all blood samples taken before the PET/CT is performed.
    For participants with PD due to extramedullary disease, confirmatory scans are not required. The laboratory parameters do not need to be repeated if the extramedullary disease is the only site of progression. If the last radiographic assessment occurred ≥8 weeks prior to the participant's withdrawal from study treatment, and PD has NOT been documented, a new assessment for extramedullary disease should be obtained at EOT. If participant continues in PFS follow-up, perform scans for extramedullary disease as clinically indicated. Digital copies of all scans must be maintained at investigator site as source document.
15. Survey results within 30 days prior to C1D1 date are acceptable. Imaging of bones for lytic lesions should be performed by a method aligned with institutional guidance (e.g., X-ray, CT or MRI). At later Cycles, repeat as clinically indicated, or if worsening clinical symptoms suggest PD. Needs to be performed by the same method throughout the study as was done at baseline. May be the same imaging as used for extramedullary disease. Sites shall maintain an archive of all study-related images/scans as source documentation.
16. Response to treatment will be assessed, based on laboratory tests and imaging (if applicable), using the IMWG criteria [2016]. Response will be assessed by the Investigator based on the IMWG criteria [2016].
17. Belantamab mafodotin will be administered as an IV infusion (see Pharmacy Manual for details) followed by a 1 to 2 hours observation period on Day 1 of every cycle for Q3/4W dosing, Day 1 of every other cycle for Q6/8W dosing, Day 1 of every third cycle for Q9/12W dosing, or Day 1 of every 12W in cohort 8c. For all cohorts, a window of ±3 days is acceptable for administration of study treatment after C1D1. Dose modifications will follow guidance in Section 6.6.
18. If a bortezomib dose was delayed, subsequent doses should be adjusted to account for delay as all bortezomib doses must be at least 72 hours apart. Doses that need to be withheld are skipped and will not be made up later in the cycle. Individual doses within a cycle have a ±1-day window if beyond 72 hours after last dose. Dose administration will follow guidance in Section 6.1.2.1.

19. Counseling about pregnancy precautions and the potential risks of fetal exposure from study drugs must be conducted at a minimum of every 28 days, recommended to be at D1 of each cycle.
20. Participant diary will be used to keep a record of self-administered oral lenalidomide and dexamethasone.
21. PRO-CTCAE, EORTC-QLQ-C30, and PGIS should be collected at C1D1 then Q3W for the first 6 months (Weeks 1-24), Q4W thereafter (Months 6 – Year 2), and Q8W (>Year 2) until EOT, and at the EOT Visit. PGIC will follow the same schedule but will not be collected on C1D1.
22. OSDI should be collected at C1D1, then Q3W through Month 6 (Weeks 1-24) and Q4W thereafter until EOT. In addition, all participants will complete the OSDI at the EOT Visit. Participants with no treatment-related ocular AEs at the EOT ocular assessment will have no further OSDI collection. Participants with treatment-related ocular AEs present at the EOT will have OSDI collected Q12W until ocular signs resolve (to Grade 1 or baseline) OR for up to 1 year, whichever is soonest.
23. PK, sBCMA and ADA sample collection is relative to dose of belantamab mafodotin which is independent of cycle number to account for a) the Q6W, Q8W, Q9W or Q12W cohorts, and b) the possibility that belantamab mafodotin may be held whilst other agents continue.
24. All concomitant medications will be collected from screening until the 70-day safety follow-up after EOT Visit.

Table 2 Hepatitis B SoA – Additional Procedures

Note: The procedures listed in this table apply ONLY to participants in screening and who have been enrolled and who have positive serology for Hepatitis B; all procedures must be done as needed in addition to the required procedures for all participants detailed in Table 1

HBV Study Assessments	During Screening / Prior to starting treatment	During Treatment	EOT	Notes
HBV related Liver Imaging[3]	X[1]	X[1]	X[1]	1. Liver imaging (specific test per SoC at local institution) in HbsAg+ participants to rule-out/identify cirrhosis, focal hepatic lesions, and/or biliary abnormalities at baseline. Repeat imaging at one year after starting treatment if still on treatment and twice yearly thereafter as long as participant remains on study treatment or as clinically indicated. 2. HBV-DNA testing prior to the start of belantamab mafodotin and subsequently every 3 months, or if liver function test elevations requiring increased monitoring or stopping criteria occur, or for any clinical suspicion of Hepatitis reactivation. 3. For HbsAg+ participants, appropriate antiviral treatment per local guidance (e.g., tenofovir or entecavir) is started before starting study treatment, continues through to completion of treatment and should not be stopped unless advised by local hepatology or virology services.
HBV-DNA testing	X[2]	X[2]	X[2]	
Prevention of HBV reactivation	X[3]	X[3]	X[3]	

HbsAg = Hepatitis B surface antigen; HBV = Hepatitis B virus.

Table 3 Hepatitis C SoA – Additional Procedures

HCV Study Assessments	During Screening / Prior to starting treatment	During Treatment	Notes
HCV-RNA testing	X[1]	X[1]	1. HCV-RNA testing prior to the start of belantamab mafodotin and subsequently every 3 months, or if liver function test elevations requiring increased monitoring or stopping criteria occurs, or for any clinical suspicion of Hepatitis reactivation. 2. Antiviral treatment should be given to participants with HCV before enrolment using an 8 (to 12) week antiviral treatment course with curative intent per local guidance. HCV-RNA should be negative at 4 weeks washout period post anti-HCV therapy prior to enrolment. 3. Notify the GSK Medical Monitor within 24 hours of learning of the HCV-RNA positivity during the study treatment.
Treatment of active HCV	X[2]	X[3]	

HCV = Hepatitis C virus; RNA = Ribonucleic acid.

Table 4 Bone marrow sample collection

Time point	BM aspirate and/or biopsy for disease assessment[1,2]	BM aspirate FISH testing (if not tested)[2,4]	BM aspirate for MRD testing[3,5]	BM biopsy or aspirate for BCMA expression and biomarker research[3,7]	Optional BM biopsy or aspirate at PD for BCMA expression and biomarker research[3,8]
Screening period	X[1]	X	X	X	
First VGPR			X		
Suspected CR/sCR	X[6]		X		
Suspected PD (only if PD is not otherwise evident)	X				
PD					X

BCMA = B-cell maturation antigen; BM = Bone marrow; CR = Complete response; FISH = Fluorescence-in-situ hybridization; IMWG = International Myeloma Working Group; MRD = Minimal residual disease; PD = Progressive disease; sCR = Stringent complete response; VGPR = Very good partial response.

1. For Disease assessment: BM aspirate and/or biopsy per institutional practice. If the screening BM cellularity content does not meet the IMWG criteria for confirmation of MM, the results of the participant's BM taken at the time of their original diagnosis of MM can be used, so long as it is no more than 6 weeks before dosing on C1D1. The result should be recorded in the CRF on the first Local Lab Collection screen.
2. These assessments will be performed at a local laboratory.
3. These assessments will be performed at a central laboratory.
4. FISH testing to be performed locally at least for: t(4;14), t(14;16), amp(1q), del(1p) and del(17p13). If participant is known to have tested positive for t(4;14) or t(14;16) on previous tests, FISH for those translocations does not need to be repeated and results from previous tests are acceptable regardless of when those tests were performed. For amp(1q), del(1p) and del(17p13), FISH results from samples taken within 60 days prior to first dose are acceptable. If testing cannot be performed at a local lab, the samples can be sent to the central lab. **FISH results are not required prior to randomization**.
5. MRD sample to be collected as soon as possible when first achieving response of VGPR or better, and repeated every 6 months (±1 month window) for 2 years, and then yearly after until PD. In case of deepening of response from VGPR to CR, MRD sample should be collected at the time of CR assessment and then repeated every 6 months (±1 month window) for 2 years, and then yearly after until PD.
6. For participants achieving a CR, a bone marrow core **biopsy is required** to confirm sCR by IHC for absence of clonal cells. Only one bone marrow procedure required for confirming CR and sCR assessment. If IHC testing cannot be performed at a local lab, the samples can be sent to the central lab.
7. BM core biopsy or aspirate samples to be collected at Screening for BCMA expression and biomarker research. When medically feasible and consistent with institutional practice, BM biopsy is the preferred sample for these exploratory analyses. If BM biopsy is not obtainable, then an aspirate should be collected for BCMA expression and biomarker research. Any remaining biopsy and/or aspirate sample may be used for biomarker research (which may include, but not be limited to, immune cell characterization and/or profiling and/or DNA/RNA analyses).
8. An optional bone marrow sample may be collected at PD for BCMA expression and biomarker research. Informed consent for the optional bone marrow sample must be obtained before collecting a sample. When medically feasible and consistent with institutional practice, BM core biopsy is the preferred sample to be collected for BCMA expression and biomarker research at PD. If BM biopsy is not obtainable, a bone marrow aspirate may be collected. Any remaining biopsy and/or aspirate sample may be used for biomarker research (which may include, but not be limited to, immune cell characterization and/or profiling and/or DNA/RNA analyses).

2. INTRODUCTION

2.1. Background

BCMA is a target present on mature B cells and on tumor cells in patients with multiple myeloma [Tai, 2006; Tai, 2015]. Belantamab mafodotin (GSK2857916) is an ADC consisting of an afucosylated humanized anti-BCMA monoclonal antibody (mAb, belantamab) that is conjugated to the microtubule inhibitor monomethyl auristatin-F (MMAF) via a protease resistant maleimidocaproyl (mc) linker. Upon binding to the cell surface, belantamab mafodotin is rapidly internalized and active cytotoxic drug (cys-mcMMAF) is released inside the cell. Additionally, the antibody is afucosylated, which increases binding to FcγRIIIa receptors and enhances recruitment and activation of immune effector cells, which can kill tumor cells by antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). The mechanisms of action of belantamab mafodotin are designed to enable anti-tumor activity of cells by ADCC activity as well as ADC activity (dividing cells). Moreover, ADC induced cell death by belantamab mafodotin has been shown to be immunogenic as measured by cell surface externalization of calreticulin (CRT) and secretion of high mobility group box 1 (HMGB1) and adenosine triphosphate (ATP). Immunogenic cell death induced by belantamab mafodotin results in activation of dendritic cells in vitro and is believed to contribute to T cell-mediated anti-tumor responses and durable anti-MM plasma cell immunity. Preclinical studies have also shown that the efficacy of the multi-model mechanisms of action of belantamab mafodotin can be enhanced by individual co-administration with lenalidomide or bortezomib making this a rational combination to evaluate in the clinic.

2.2. Study rationale

2.2.1. Newly diagnosed multiple myeloma

The treatment of NDMM has changed dramatically over the past 20 years, from near uniform application of chemotherapy to a patient performance status and risk-based approach. The SoC for fit multiple myeloma patients is to receive high-dose chemotherapy with ASCT, after completion of induction therapy. However, some patients, in particular the elderly, are ineligible for transplant due to frailty or comorbidities. For these patients, treatment with highly active doublet or triplet combination regimens such as lenalidomide/dexamethasone (Rd) [Benbouker, 2014], daratumumab plus Rd [Facon, 2019], or VRd [Durie, 2017] are considered.

The choice of therapy in NDMM patients depends largely on an individual's suitability for ASCT. ASCT is usually only a suitable option for fitter patients, and typically for patients younger than 65-75 years old. TI patients constitute the largest proportion of NDMM patients [Cook, 2019], but clinical prognosis for these patients is worse in terms of PFS and OS compared to patients who are transplant eligible (TE). This means that TI NDMM patients do not typically achieve MRD negativity rates and PFS which is comparable to their TE counterparts who undergo ASCT. Therefore, there is an unmet clinical need to improve prognosis through the addition of novel therapies, which are highly effective as single agents in the RRMM setting, to SoC first line NDMM backbone agents.

Triplet therapy with VRd is an accepted clinical SoC regimen in TI NDMM [Kumar, 2018; Moreau, 2017]. This is based on the findings of the SWOG S0777 Phase 3 clinical trial [Durie, 2017] which evaluated VRd against Rd doublet treatment. The addition of bortezomib to Rd during the first 8 Cycles of treatment on a Q3W dosing schedule (i.e., induction treatment) was intended to achieve rapid disease responses followed by Q4W doublet Rd treatment until disease progression (i.e., maintenance treatment) which was intended to maintain response post-induction. In SWOG S0777, VRd was shown to be highly active compared to continuous Q4W treatment with the Rd doublet alone (ORR, defined as ≥PR: VRd 81.5% vs. Rd 71.5%) [Durie, 2017]. This resulted in an increase in mPFS from 29 months in the Rd arm to 41 months in the VRd arm [Durie, 2018]. Importantly, time-to-next-treatment with VRd in the real-world setting has been shown to be similar to the PFS results of the SWOG S0777 Phase 3 clinical trial [Chari, 2017].

2.2.2. Nonclinical evidence

Belantamab mafodotin has undergone nonclinical testing in combination with SoC agents including bortezomib, dexamethasone, lenalidomide in xenograft models bearing multiple myeloma OPM2 and MOLP8 cells. Lenalidomide and bortezomib were demonstrated to have independent effects on the pharmacodynamic activity of belantamab mafodotin *in vivo*: combining belantamab mafodotin and bortezomib led to significant tumor growth inhibition and increased survival compared to belantamab mafodotin and bortezomib single agents in the OPM2 model, but not in the MOLP8 model. Combining belantamab mafodotin and lenalidomide led to significant increased survival compared to belantamab mafodotin and lenalidomide single agents in both the OPM2 and MOLP8 MM xenograft models, and significant tumor growth inhibition compared to single agents in the OPM2, but not in the MOLP8 model. As such belantamab mafodotin in combination with the SoC agents will potentially lead to significant tumor growth inhibition and increased survival compared to belantamab mafodotin and bortezomib or lenalidomide as single-agent.

2.2.3. Human experience with belantamab mafodotin

2.2.3.1. Clinical studies

Single-agent belantamab mafodotin has demonstrated to have a strong single-agent activity with a well-defined manageable safety profile in heavily pre-treated participants with RRMM (Q3W schedule via IV administration). Safety data for single-agent belantamab mafodotin were pooled (data as of 20 September 2019) for study 205678 (DREAMM-2; NCT03525678) and supportive first-time-in-human (FTIH) study BMA117159 (DREAMM-1; NCT02064387), by treatment cohorts of 2.5 mg/kg and 3.4 mg/kg.

FTIH study BMA117159/DREAMM-1

In the FTIH DREAMM-1 study, which consisted of a dose escalation Phase (Part 1, n=38) and a dose expansion Phase (Part 2, n=35), as of the primary analysis cut-off date of 31 August 2018, a total of 73 participants with RRMM received at least 1 dose of belantamab mafodotin (see IB) [Trudel, 2019].

As of the efficacy cut-off date of 31 August 2018, a total of 35 participants were treated at the 3.4 mg/kg dose in Part 2 of the DREAMM-1 study. Participants were heavily pre-treated: 57% of participants had 5 or more prior lines of therapy. The ORR was 60% (95% CI: 42.1, 76.1): comprised of PR, 6%; VGPR, 40%; CR, 9%; and stringent CR (sCR), 6%. The median duration of response (DoR) was 14.3 months (95% CI: 10.6, NR). The median PFS (mPFS) in this population was 12.0 months (95% CI: 3.1, not estimable [NE]). For participants refractory to both ImiDs and Pis (n=32/35), the confirmed ORR was 56% (95% CI: 37.7, 73.6) and mPFS was 7.9 months (95% CI: 2.3, NE) [Trudel, 2019].

Phase *2* study 205678/DREAMM-2

The ongoing Phase 2 study 205678/DREAMM-2 is evaluating these 2 IV single-agent doses (2.5 and 3.4 mg/kg) administered Q3W until disease progression in participants who have failed at least 3 prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and who are refractory to an ImiD and a proteasome inhibitor. A total of 194 participants received frozen drug product in the main cohort and 24 participants received 3.4 mg/kg lyophilized drug product. The study met its primary endpoint for ORR in both the 2.5 mg/kg and 3.4 mg/kg treatments, and the benefit of belantamab mafodotin was supported by the secondary endpoints. Primary analysis data from this study indicated no new safety signals, and the profile of adverse events (AEs) was similar to the experience in the DREAMM-1 study for both arms. Both dose levels, 2.5 and 3.4 mg/kg, were shown to have a positive benefit/risk profile [Li, 2017; Lonial, 2020].

As of the cut-off date of 31 January 2020, the ORR in the 2.5 mg/kg treatment was 31% (97.5% CI 21.7,43.6)] and in the 3.4 mg/kg treatment 35% (97.5% CI 24.8,47.0)]. The median DoR was 11.0 months (95% CI: 4.2, NR) at 2.5 mg/kg and 6.2 months (95% CI: 4.8, NR) at 3.4 mg/kg. The mPFS in this population was 2.8 months (95% CI: 1.6, 3.6) and 3.9 months (95% CI: 2.0, 5.8), respectively, and the median overall survival (mOS) was 13.7 months (95% CI: 9.9, NR) at 2.5 mg/kg and 13.8 months (95% CI: 10.0, NR) at 3.4 mg/kg. Positive clinical activity was also demonstrated at the 3.4 mg/kg lyophilized dose (ORR 52% [97.5% CI 28.9,74.5]).

Safety

Single-agent belantamab mafodotin was demonstrated to have a manageable safety profile in heavily pre-treated participants with RRMM. Safety data for single-agent belantamab mafodotin were pooled (data as of 20 September 2019) for 205678/DREAMM-2 study and supportive FTIH study DREAMM-1 by treatment cohorts of 2.5 mg/kg and 3.4 mg/kg.

The most common AEs in both treatment cohorts were keratopathy (corneal epithelium changes observed on ophthalmic examination), thrombocytopenia and anemia. The incidence of AEs, including Grade 3 and Grade 4 AEs was comparable between belantamab mafodotin 2.5 mg/kg and 3.4 mg/kg cohorts. Adverse events leading to dose delays, and reductions were less frequent in 2.5 mg/kg cohort, 51% and 32% compared with the 3.4 mg/kg cohort, 67% and 52%, respectively. AEs leading to permanent treatment discontinuation occurred in 10% and 11% of participants in the 2.5 and 3.4 mg/kg cohorts, respectively. More participants in the 3.4 mg/kg cohort experienced SAEs (50%) and fatal SAEs (6%) compared with the 2.5 mg/kg cohort (41% and 3%, respectively).

Single-agent belantamab mafodotin 2.5 mg/kg was selected as the recommended dose based on comparable efficacy with a more favorable safety profile (i.e., lower incidence of thrombocytopenia and neutropenia and less frequent dose delays or reductions) compared with the 3.4 mg/kg dose.

Adverse Events of Special Interest

Adverse events of special interest (AESIs) for belantamab mafodotin are corneal events, thrombocytopenia and infusion-related reactions, and are described below.

Corneal Events

Corneal events, reported in most cases as keratopathy, blurred vision and dry eye events are the most frequently reported AEs with belantamab mafodotin.

In 205678/DREAMM-2 (data as of 31 January 2020), events in the eye disorders SoC occurred in 78% of participants treated with belantamab mafodotin 2.5 mg/kg. The most common ocular AEs were keratopathy (71%, changes in corneal epithelium identified on eye exam, with or without symptoms), blurred vision (22%), and dry eye (13%). Decreased vision defined as Snellen score worse than 20/50 in the better seeing eye was reported in 18% of participants receiving belantamab mafodotin 2.5mg/kg. Severe vision loss defined as 20/200 or worse in the better seeing eye was reported in 1% of participants receiving belantamab mafodotin 2.5 mg/kg.

The median time to onset of Grade 2 or above corneal findings (best corrected visual acuity or corneal examination) was 36 days (range: 19 to 143 days) in participants receiving belantamab mafodotin 2.5 mg/kg. The median time to resolution of these corneal findings was 91 days (range: 21 to 201 days).

Participants with history of dry eye were more prone to develop corneal examination findings. Therefore, active management of dry eye symptoms prior to and during treatment is recommended (i.e., administration of preservative-free artificial tears).

The ocular sub-study of 205678/DREAMM-2 provided no evidence that corticosteroid eye drops are beneficial in preventing or mitigating corneal events.

Thrombocytopenia

In 205678/DREAMM-2 (data as of 31 January 2020), thrombocytopenic events (thrombocytopenia and platelet count decreased) occurred in 38% participants treated with belantamab mafodotin 2.5 mg/kg; severity ranging between Grade 1 and 4. The incidence of Grade 3 bleeding events was low (2%), with no Grade 4 or Grade 5 events reported in participants treated with belantamab mafodotin 2.5 mg/kg.

Most participants had a decrease from baseline in their platelet counts during the study. In general, participants who initiated treatment with lower platelet numbers tended to continue to have thrombocytopenia while on treatment with belantamab mafodotin.

Infusion-related reactions

Infusion-related reactions (IRRs) are expected for biologic agents. In 205678/DREAMM-2 (data as of 31 January 2020), IRRs occurred in 21% of participants in the belantamab mafodotin 2.5 mg/kg, which were Grade 1 – 3 in severity. Most IRRs occurred with the first infusion and few participants experienced IRRs with subsequent infusions.

Although not protocol-mandated, pre-medications for IRR prophylaxis (including paracetamol, antihistamines, and steroids) were administered to 26%–27% of participants. One participant (2.5 mg/kg cohort) discontinued treatment due to IRRs (Grade 3 IRRs at first and second infusion).

2.2.4. Pharmacokinetics and pharmacodynamics in humans

The pharmacokinetics and pharmacodynamics of belantamab mafodotin (ADC, including complex with soluble BCMA [sBCMA]) and total monoclonal antibody (total mAb; including complex), and cys-mcMMAF were investigated in 291 participants with RRMM following IV administration at doses from 0.03 to 4.6 mg/kg Q3W in Study BMA117159 (n=73) and at doses of 2.5 or 3.4 mg/kg Q3W in Study 205678 (n=218).

Maximum concentrations (Cmax) of belantamab mafodotin and total monoclonal antibody were observed at or shortly after the End of Infusion (EOI), while cys-mcMMAF Cmax values were generally observed on Day 2. On a molar basis, plasma concentrations of cys-mcMMAF were <1% of belantamab mafodotin concentrations. There was limited accumulation (less than 2-fold) of belantamab mafodotin or cys-mcMMAF during subsequent cycles.

Belantamab mafodotin pharmacokinetics were well described by a linear, 2-compartment population model, with a time-varying decrease in clearance in a population pharmacokinetic analysis. At Cycle 1, belantamab mafodotin had a systemic clearance of 0.92 L/day, steady-state volume of distribution of 10.8 L, and an elimination half-life of 12 days in participants with RRMM in Study 205678. Over time, clearance was reduced by 28%, with an elimination half-life of 14 days. The time to 50% change in clearance was approximately 50 days.

No clinically significant differences in the pharmacokinetics of belantamab mafodotin or cys-mcMMAF were observed based on age (34 to 89 years), sex, race (African American/Black and White), body weight (42 to 130 kg), mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] $\geq$ 30 ml/min/1.73m^2) or mild hepatic impairment (NCI-ODWG classification). Higher serum levels of β_2-microglobulin, immunoglobulin G (IgG), and soluble BCMA (sBCMA) and lower levels of albumin are associated with more advanced multiple myeloma or a higher multiple myeloma disease burden. Higher baseline IgG and sBCMA levels, and lower baseline albumin levels were associated with higher belantamab mafodotin clearance leading to lower average and trough concentrations (Ctau) of belantamab mafodotin. Higher baseline IgG and sBCMA levels were associated with higher cys-mcMMAF central volume of distribution leading to lower cys-mcMMAF Cmax.

In nonclinical studies, cys-mcMMAF had limited metabolic clearance. In vitro data suggested that belantamab mafodotin and cys-mcMMAF are unlikely to perpetrate a drug-drug interaction or to be a victim of a drug-drug interaction with inhibitors or inducers of cytochromes (CYP) P450. Cys-mcMMAF was an in vitro substrate of organic anion transporting polypeptides (OATP)1B1 and OATP1B3, multidrug resistance associated proteins (MRP)1, MRP2, and MRP3, a borderline substrate of bile salt export pump (BSEP), and a possible substrate of P-glycoprotein (P-gp). Following the administration of belantamab mafodotin to participants with RRMM, only intact cys-mcMMAF was detected in pooled human urine, with no evidence of other MMAF-related urinary metabolites.

Free sBCMA levels were measured in Study BMA117159 and Study 205678/DREAMM-2. All participants exhibited reductions in free sBCMA concentration at End of Infusion compared to baseline at Cycle 1, with a return to near-baseline level by 7 days after dosing, reflecting binding of belantamab mafodotin to sBCMA. Maximum decreases ranged from 2% to 97%, which were qualitatively dose dependent, with larger reductions in free sBCMA at higher doses.

Exposure-response analyses performed for Study 205678 and/or Study BMA117159 found that ocular safety endpoints were most strongly associated with belantamab mafodotin exposure, while efficacy endpoints had a weaker association with belantamab mafodotin exposure. Both safety and efficacy endpoints were associated with patient characteristics. Belantamab mafodotin Ctau was associated with probability of corneal events and keratopathy and cys-mcMMAF, Cmax was associated with probability of thrombocytopenia. Probability of occurrence of dry eye, blurred vision, neutropenia and infusion-related reaction were not associated with an exposure measure. In addition, the results of the analysis of concentration against corrected QT interval (QTc) demonstrated that belantamab mafodotin or cys-mcMMAF did not have a significant effect on cardiac repolarization.

Additional information related to belantamab clinical PK, PD, and exposure-response relationships can be found in the IB.

2.2.5. Summary

Given the demonstrated clinical activity of single-agent belantamab mafodotin in RRMM patients [Trudel, 2018; Trudel, 2019; Lonial, 2020], the established efficacy of the VRd backbone in NDMM [Durie, 2017], and the potential for belantamab mafodotin to combine with lenalidomide, bortezomib, and dexamethasone in a synergistic fashion (e.g., via the multi-model mechanisms of action of belantamab mafodotin), the quadruplet belantamab mafodotin plus VRd regimen could potentially lead to improved response rates and provide deeper responses relative to published data on VRd alone [Durie, 2017].

2.3. Benefit/risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of belantamab mafodotin may be found in the IB. More detailed information for bortezomib, lenalidomide, and dexamethasone may be found in the respective representative package inserts.

2.3.1. Risk assessment

A quadruplet investigational regimen comprising belantamab mafodotin in combination with VRd in TI NDMM population, may present with potential overlapping toxicities. The emerging safety profile of belantamab mafodotin from preclinical and ongoing clinical studies, and approved labeling for lenalidomide and bortezomib have informed the development of a comprehensive safety monitoring plan. The potential for overlapping toxicities is considered manageable, with the proposed mitigation activities described below in Table 5.

Table 5 Summary of risk assessment for the combination of belantamab mafodotin plus VRd and VRd alone

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential Overlapping Toxicities of Belantamab Mafodotin/Lenalidomide/Bortezomib/Dexamethasone Combination Treatment		
Thrombocytopenia	**Belantamab mafodotin**: Belantamab mafodotin may cause transient thrombocytopenia in some participants which, for most cases, recovered between doses. In study 205678, which included participants treated with belantamab mafodotin 2.5 mg/kg, thrombocytopenia was noted in 38% of participants and ranged between Grade 1 to Grade 4 in severity. Bortezomib is associated with thrombocytopenia that follows a cyclical pattern with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of the subsequent cycle. Lenalidomide can cause significant thrombocytopenia.	Routine monitoring of hematologic panels as outlined in the SoA. Supportive therapy per local medical practice (e.g., platelet transfusion). Recommendations for dose reduction and modification are outlined in Section 6.6 and treatment discontinuation guidelines are outlined in Section 7.
Pneumonitis	**Belantamab mafodotin:** Nonclinical safety experiments have demonstrated the presence of progressive microscopic changes in the lungs (prominent alveolar macrophages associated with eosinophilic material; mixed perivascular/neutrophilic inflammation) in rats at all doses tested. Cases of pneumonitis, including fatal events, have been observed with belantamab mafodotin although a causal association has not been established. **Bortezomib:** Acute Respiratory Distress Syndrome and acute diffuse infiltrative pulmonary disease of unknown etiology, such as pneumonitis, interstitial pneumonia, and lung infiltration have been reported rarely in patients receiving bortezomib. Some of these events have been fatal. There have been reports of pulmonary hypertension associated with	Monitoring for clinical signs and symptoms related to pulmonary toxicity.If a participant experiences new or worsening pulmonary symptoms, (e.g., cough, dyspnea) without obvious etiology, further diagnostic tests and management should be performed and further treatment with belantamab mafodotin delayed (refer to Section 6.6.2.2). An overall benefit/risk assessment should be considered for the participant prior to continuing belantamab mafodotin treatment. In the event of new or worsening cardiopulmonary symptoms, consider interrupting bortezomib until a prompt and comprehensive diagnostic evaluation is conducted.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	bortezomib administration in the absence of left heart failure or significant pulmonary disease.	
Increased Infections due to immunosuppression or neutropenia	**Belantamab mafodotin:** In nonclinical studies, belantamab mafodotin has been associated with decreases in immunoglobulins (IgM, IgG) in monkeys at all doses. An increase in immunoglobulins was seen in rats (rats are not an antigen-specific species for belantamab mafodotin). Immunosuppression is frequently associated with an increased risk of infection. Serious and nonserious infections have been reported in belantamab mafodotin studies, including respiratory infections, pneumonia and sepsis. Neutropenic events, including febrile neutropenia have been observed with treatment with belantamab mafodotin. In a study of belantamab mafodotin in combination with lenalidomide/ dexamethasone, 2 fatal cases of severe infections associated with neutropenia have been observed. Lenalidomide has been associated with severe neutropenia. **Bortezomib:** Cases of herpes zoster infection have been reported in patients receiving bortezomib. Neutropenia that follows a cyclical pattern with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of the subsequent cycle has also been observed. **Dexamethasone:** Patients who are on corticosteroids are more susceptible to infections or exacerbation of latent infections than healthy individuals. Chickenpox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids.	Participants with active infections are excluded. Monitoring for infections and immediate treatment according to standard practice. Supportive therapy per local medical practice (e.g., growth factors). Prophylactic antibiotics per local institutional guidance, in participants with Grade 3-4 neutropenia (ANC $<1.0 \times 10^9$/L). Immediate hospitalization of participants with febrile neutropenia. Participants on bortezomib will receive antiviral prophylaxis (e.g., acyclovir or other antiviral agent) according to institutional guidelines. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immune globulin may be indicated. Dose modification guidelines for neutropenia are provided in Section 6.6.
Keratopathy (changes to the corneal epithelium,	Belantamab mafodotin: Changes in the corneal epithelium on ocular examination have been frequently observed with belantamab mafodotin such as superficial punctate keratopathy, microcyst-like changes, subepithelial haze, corneal erosions and corneal ulcers. This was most	Active monitoring of the corneal epithelium and visual acuity as outlined in the SoA (Section 1.3). In the event of new-onset eye-related symptoms

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
potentially resulting in vision changes)	commonly associated with dry eyes, photophobia, blurred vision and changes in visual acuity. Corneal ulcers or erosions are distinguished by the presence or absence of stromal involvement, respectively. The precise incidence has yet to be defined. The corneal defects (with or without stromal involvement) appeared as early as the second or third cycle but in most cases after 5 or more cycles of treatment. Participants with a history of dry eye were more prone to develop changes in the corneal epithelium. Based on available follow-up data, vision returned to, or near, baseline in most cases and no permanent loss of vision reported. Dexamethasone: Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.	(such as pain, significant loss of visual acuity), participants are to urgently seek medical attention. Evaluation and management by an eye care professional. Dose modification guidelines are outlined in Section 6.6.
Risks Related to Belantamab mafodotin not listed under potential overlapping toxicities		
Infusion-related reactions (IRR)	IRRs were reported in patients treated with belantamab mafodotin. Most IRRs observed to date were mostly Grade 1 to 2 and manageable with medical treatment.	Close monitoring for signs of IRR. Consider premedication for IRR in participants at risk. If an IRR occurs, follow guidance in Section 6.6.2.2 and Section 7.1.4.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Nephrotoxicity	Nonclinical safety experiments have demonstrated primary glomerular injury and tubular degeneration/regeneration (in rat and monkey). These morphologic changes were accompanied by large molecular weight proteinuria (albuminuria) and enzymuria. Single cell necrosis of the kidney and bladder urothelium was also noted in the chronic study. The renal changes were dose dependent and reversible. Severe tubular degeneration/regeneration and marked glomerulonephritis as a result of immune complex disease associated with ADA led to the early euthanasia of 1 monkey following 5 weekly doses of 10 mg/kg. Increased albumin/creatinine ratio (albuminuria) not indicative of disease progression has been reported in clinical trials and named patient programs with belantamab mafodotin.	Kidney function monitoring including albumin/creatinine ratio (ACR). Education of participants on the need to maintain adequate urinary output. Dose modification guidelines for increased serum creatinine and urinary albumin/creatinine ratio are outlined in Section 6.6.2.2.
Risks Related to Bortezomib not listed under potential overlapping toxicities with belantamab mafodotin		
Allergic Reactions	Bortezomib is contraindicated for patients with hypersensitivity to bortezomib, boron, or mannitol, including anaphylactic reactions.	Participants with known hypersensitivity reactions to bortezomib, boron, or mannitol are not allowed on study. Bortezomib will be discontinued if such reactions are confirmed.
Peripheral Neuropathy	Bortezomib treatment causes a peripheral neuropathy that is predominantly sensory; however, cases of severe sensory and motor peripheral neuropathy have been reported.	Participants with ≥Grade 2 or higher peripheral neuropathy at Screening are excluded from enrolment. Monitor for symptoms of neuropathy. Dose should be adjusted accordingly. Bortezomib will be administered subcutaneously to reduce the risk of peripheral neuropathy.
Hypotension	The incidence of hypotension (postural, orthostatic, and hypotension not otherwise specified [NOS]) was 8%.	Participants with a history of syncope, or receiving medications associated with hypotension, or dehydrated will be closely monitored. Adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics will follow the institutional guidelines.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Posterior Reversible Encephalopathy Syndrome (PRES)	PRES; formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in patients receiving bortezomib.	Discontinue bortezomib if PRES develops. The safety of reinitiating bortezomib therapy in patients previously experiencing PRES is not known.
Gastrointestinal Toxicity	Treatment with bortezomib can cause nausea, diarrhea, constipation, and vomiting sometimes requiring use of antiemetic and antidiarrheal medications; ileus can occur.	Maintain adequate hydration; fluid and electrolyte replacement should be administered to prevent dehydration. Interrupt bortezomib for severe symptoms.
Hepatotoxicity	Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include Hepatitis, increases in liver enzymes, and hyperbilirubinemia.	Only participants with well-preserved liver function per the inclusion/exclusion criteria will be enrolled. Liver function tests will be monitored per SoA. Liver stopping criteria are found in Section 7.1.1. and Section 10.6.
Tumor Lysis Syndrome (TLS)	TLS has been reported with bortezomib therapy.	Participants at risk for TLS (i.e., high tumor burden) should be monitored and appropriate precautions instituted per local practice.
Thrombotic Microangiopathy	Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients receiving bortezomib.	Monitor for clinical signs and symptoms potentially related to thrombotic microangiopathy. If suspected, stop bortezomib and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting bortezomib.
Cardiotoxicity	Acute development or exacerbation of congestive heart failure and new-onset of decreased left ventricular ejection fraction have occurred during bortezomib therapy, including reports in patients with no risk factors for decreased left ventricular ejection fraction (LVEF).	Participants with significant cardiac risk factors will be excluded from study participation. Monitoring of cardiac parameters as clinically indicated. Treatment as medically indicated.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Seizures	Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.	Participants with a history of seizures or epilepsy will be closely monitored. In the event of new-onset or worsening seizures, consider interrupting bortezomib until a prompt and comprehensive diagnostic evaluation is conducted.
Progressive multifocal leukoencephalopathy (PML)	Very rare cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with bortezomib. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their first dose of bortezomib.	Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of central nervous system problems. If a diagnosis of PML is suspected, patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue bortezomib if PML is diagnosed.
Embryo-fetal toxicity	Bortezomib can cause fetal harm when administered to a pregnant woman. Bortezomib administered to rabbits during organogenesis at a dose approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area caused post-implantation loss and decreased number of live fetuses.	Pregnancy testing outlined in the SoA (Section 1.3). Contraception requirements in Section 5.1, Section 10.4, and Section 10.4.2
Risks Related to Lenalidomide not listed under overlapping toxicities with belantamab mafodotin		
Venous and Arterial Thromboembolism	Increased risk of venous thromboembolic events, such as deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thromboembolic events such as myocardial infarction (MI) and stroke has been reported in participants with MM receiving lenalidomide with dexamethasone.	Antithrombotic prophylaxis will be implemented in participants at risk, according to investigator judgement. Use of drugs that may increase thromboembolic risk (e.g., erythropoietic agents, estrogens, etc) should be avoided, if possible
Second Primary Malignancies (SPM)	Higher incidences of SPM were observed in controlled studies with participants with MM receiving lenalidomide.	Monitor for the occurrence of new malignancies.
Severe Cutaneous Reactions	Severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported.	Consider dose interruption or discontinuation for Grade 2-3 skin rash. Permanently discontinue lenalidomide for Grade 4 rash, exfoliative or bullous rash, or for other severe cutaneous reactions such as SJS, TEN or DRESS.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hypersensitivity	Hypersensitivity, angioedema, anaphylaxis and anaphylactic reactions have been reported.	Discontinue lenalidomide for angioedema and anaphylaxis.
TLS including fatalities	Fatal instances of TLS have been reported during treatment with lenalidomide.	Participants at risk for TLS (i.e., high tumor burden) should be monitored and appropriate precautions instituted per local practice.
Altered Thyroid Function	Both hypothyroidism and hyperthyroidism have been reported with lenalidomide treatment.	Monitor thyroid function, and implement treatment as clinically indicated.
Dose Adjustment for Renal Impairment	The starting dose of lenalidomide should be adjusted for participants with renal impairment.	The starting dose of lenalidomide will be adjusted for participants with eGFR 30-60 ml/min/1.73 m^2 (10 mg/dL). If renal impairment develops during the clinical trial, dose adjustment based on the creatinine clearance will be implemented and for participants on dialysis (Refer to SRM for lenalidomide prescribing information for guidance on Dosage and Administration).
Hepatotoxicity	Hepatic failure, including fatal cases, have occurred in patients treated with lenalidomide in combination with dexamethasone.	Only participants with well-preserved liver function per the inclusion/exclusion criteria will be enrolled. Participants with chronic Hepatitis B and C will be excluded. Liver function tests will be monitored per SoA. In case of liver abnormalities, refer to Section 7.1.1 and Section 10.6 for further details. Liver stopping criteria are found in Section 7.1.1.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Embryo-fetal toxicity	Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Lenalidomide is available only through a pregnancy prevention/controlled distribution program.	Pregnancy testing outlined in the SoA (Section 1.3). Contraception requirements in Section 5.1, Section 10.4, and Section 10.4.2 Participants receiving lenalidomide provided by GSK must follow the manufacturing guidelines of any treatment-specific Pregnancy Prevention Program. Participants receiving lenalidomide from local supply e.g., United States (US), will follow their local pregnancy prevention/controlled distribution program (see Pharmacy Manual for details).
Risks Related to Dexamethasone not listed under overlapping toxicities with belantamab mafodotin		
Vaccinations	Administration of live or live-attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.	Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted. Immunizations with live vaccines are not allowed in the study.
Allergic or Hypersensitivity Reactions	Contraindicated in patients who are hypersensitive to any components of this product. Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy.	Enrolment of participants with known hypersensitivity reactions to components of the strength is prohibited.
Endocrine	Hypothalamic-pituitary adrenal axis suppression with the potential for corticosteroid insufficiency after withdrawal of treatment.	Avoid rapid withdrawal of corticosteroids if used at high doses for prolonged period of time.
Gastrointestinal (GI)	Use with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation, or GI bleeding.	Hematologic parameters will be monitored as outlined in the SoA. New cases of anemia should be fully investigated, including the possibility of GI bleeding.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Musculoskeletal	Decreased bone formation and increased bone resorption. Acute myopathy has been observed with high doses of corticosteroids, most often occurring in patients with neuromuscular disorders, or in patients receiving neuromuscular blocking drugs	Ongoing monitoring of adverse events (AEs).
Neuropsychiatric	Psychic derangements may appear when corticosteroids from mild symptoms to severe depression, and frank psychotic manifestations. Also, existing emotional ranging from mild symptoms to severe depression, to frank psychotic manifestations. Existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.	Ongoing monitoring of AEs.
Potential for cardiotoxicity	Average and large doses of corticosteroids can cause elevation of blood pressure, sodium and water retention, and increased excretion of potassium.	Participants with significant cardiovascular risk factors will be excluded from study participation.
Risks from Study Procedures		
Bone Marrow Aspiration/biopsy	Pain, infection, bleeding may occur after the procedure.	Participants will be treated according to local institutional practice.
Incidental Findings During Image Acquisition	During the acquisition of imaging data (e.g., MRI, CT, PET), non-MM disease or clinically relevant abnormalities could be found by the radiographer or echocardiographer performing the exams.	Copies of all medical images that include non-disease, clinically relevant abnormalities will be shared with the site for storage.

For data sources, refer to belantamab mafodotin Investigator's Brochure (IB) and local prescribing information for lenalidomide, bortezomib and dexamethasone.

2.3.2. Benefit assessment

In the FTIH Study (BMA117159/DREAMM-1), single-agent belantamab mafodotin demonstrated high ORR together with rapid time to first response and durability of response in participants with RRMM. The ORR was 60% (95% CI: 42.1, 76.1) with a median time to first response (i.e., PR) of 1.2 months (95% CI: 0.7-1.4 months) and 54% participants (n = 19/35) achieving deep responses of VGPR or better (sCR) 6%, CR 9%, VGPR 40%, and PR 6%. The median DoR was 14.3 months (95% CI: 10.6, NR). The median PFS in this population was 12.0 months (95% CI: 3.1, NR) [Trudel, 2019].

In the ongoing Phase 2 study 205678/DREAMM 2 (NCT03525678), the 2 single-agent doses (2.5 mg/kg and 3.4 mg/kg) are being studied via a 2-arm, randomized design in participants who have failed at least 3 prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and who are refractory to an ImiD and a proteasome inhibitor (PI). Overall, there were no new safety signals identified in the 205678 study, and the profile of adverse events was similar to the experience in DREAMM-1 for both arms. Data show both dose levels of belantamab mafodotin (2.5 and 3.4 mg/kg) to have a positive benefit/risk profile [Lonial, 2020].

Overall, given the strong clinical activity data of belantamab mafodotin monotherapy in RRMM patients and signals of preclinical synergy of belantamab mafodotin with lenalidomide and bortezomib, it is reasonable to hypothesize that a belantamab mafodotin-containing quadruplet combination with a VRd backbone could potentially improve therapeutic outcomes for NDMM population compared to current SoC.

2.3.3. Overall benefit/risk conclusion

Belantamab mafodotin is a highly active agent in RRMM [Trudel, 2019; Lonial, 2020]. On this basis, its combination with VRd – a highly active triplet combination in NDMM – has the potential to provide increased clinical benefit for patients than can be currently attained with VRd alone in TI NDMM. Considering the measures taken to minimize risk to participants in this study, in particular, stringent monitoring and safety stopping criteria, which includes corneal toxicity, the potential risks associated with belantamab mafodotin in combination with VRd are justified by the anticipated benefits that may be afforded to participants with TI NDMM.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Determine safety and tolerability of belantamab mafodotin in combination with VRd to establish a recommended dose for participants with TI NDMM.	• Number (%) of participants with dose-limiting toxicities (DLTs). • Number (%) of participants with adverse events (AEs).
Secondary	
Effect of combining belantamab mafodotin with VRd in relation to lenalidomide & bortezomib relative dose intensity (RDI).	• Lenalidomide RDI after 4 Cycles of treatment with belantamab mafodotin in combination with VRd. • Bortezomib RDI after 4 Cycles of treatment with belantamab mafodotin in combination with VRd. • Cumulative administered dose of belantamab mafodotin after 4 Cycles of treatment in combination with VRd.
To evaluate the pharmacokinetics profile of belantamab mafodotin, when administered in combination with VRd.	• Belantamab mafodotin, and cys-mcMMAF PK parameters, as data permit.
To assess anti-drug antibodies (ADAs) against belantamab mafodotin.	• Incidence and titers of ADAs against belantamab mafodotin.
Assess the efficacy of belantamab mafodotin in combination with VRd in participants with NDMM.	• Overall Response Rate (ORR), defined as the percentage of participants with a confirmed Partial Response (PR) or better (i.e., PR, Very Good PR [VGPR], Complete Response [CR], stringent Complete Response [sCR]). • Complete Response Rate (CRR), defined as the percentage of participants with a confirmed CR or better (i.e., CR, sCR). • Rate of VGPR or better, defined as the percentage of participants with a confirmed VGPR or better (i.e. VGPR, CR, sCR).
Exploratory	
Assess MRD in participants who achieve ≥VGPR or better.	• Number (%) of participants achieving MRD negativity.
Further assess the efficacy of belantamab mafodotin in combination with VRd in participants with TI NDMM.	• DoR, defined as the time from first documented evidence of PR or better until PD or death due to PD among participants who achieve confirmed PR or better. • TTP, defined as the time from the date of randomization until the earliest date of documented PD or death due to PD. • Time to Best Response (TTBR), defined as the interval of time between the date of randomization and the earliest date of achieving best response among participants with a confirmed PR or better. • TTR, defined as the time between the date of randomization and the first documented evidence of response (PR or better) among participants who achieve confirmed PR or better.
To evaluate the pharmacokinetics of total mAb when belantamab mafodotin is administered in combination with VRd.	• Total mAb PK parameters, as data permit.

Objectives	Endpoints
To explore the exposure-response relationship between belantamab mafodotin exposure and clinical endpoints or combination drug(s) relative dose intensity (RDI) in participants treated with belantamab mafodotin in combination with VRd.	• Belantamab mafodotin exposure (e.g., concentration, Cmax, or area under the concentration-time curve [AUC]) vs. efficacy and/or safety endpoints (e.g., ORR, CRR, ocular events) and/or combination drug(s) RDI, as data permit.
To explore the relationship and dynamics between certain biologic characteristics and clinical response in participants treated with belantamab mafodotin in combination with VRd.	• Analysis of protein, DNA, and/or RNA in tumor, at baseline and PD, and peripheral blood at baseline and on treatment to evaluate the relationship of biomarkers, including but not limited to BCMA expression and serum sBCMA concentration, with response to belantamab mafodotin.
To investigate the relationship between host genetic variation and the drugs under study.	• Effect of host genetic variation on response to drugs under study including but not limited to belantamab mafodotin.
To evaluate the safety and tolerability of belantamab mafodotin based on self-reported symptomatic adverse effects when administered in combination with VRd.	• Changes from baseline in symptoms and related impacts as measured by PRO-CTCAE.
To evaluate self-reported ocular symptomatic adverse effects of belantamab mafodotin in combination with VRd.	• Changes from baseline in symptoms and related impacts as measured by OSDI.
To further evaluate and compare changes in health-related quality of life (HRQOL).	• Change from baseline in HRQOL as measured by EORTC-QLQ-C30 and Patient Global Impression of Severity (PGIS). • Change over time in HRQOL as measured by Patient Global Impression of Change (PGIC).

4. STUDY DESIGN

4.1. Overall study design

See Figure 1 for the study design schema.

Study 209664 (DREAMM-9) is a randomized, Phase 1, multicenter study evaluating the safety, pharmacokinetics, pharmacodynamics and clinical activity of different doses/dosing schedules of belantamab mafodotin in combination with VRd in up to 8 cohorts and will determine the RP3D for future studies in the newly diagnosed setting. Participants will undergo visits and assessments in accordance with the SoA (Section 1.3).

The dosing of VRd will be as described previously [Durie, 2017]. Briefly, participants will receive the combination of bortezomib, lenalidomide and dexamethasone on a 3-week cycle until Cycle 8, followed by the combination of lenalidomide and dexamethasone on a 4-week cycle thereafter. The dose and schedule of VRd will not vary, except as required for individual participants based on toxicity and/or tolerability. Belantamab mafodotin will be administered in combination with VRd every Q3W, Q6W, or Q9W to Cycle 8, and then in combination with Rd every Q4W, Q8W, or Q12W thereafter.

The belantamab mafodotin dose cohorts are as follows:

- **Cohort 1**: 1.9 mg/kg Q3/4W dose of belantamab mafodotin on Day 1 of every cycle.
- **Cohort 2**: 1.4 mg/kg Q6/8W dose of belantamab mafodotin on Day 1 of every other cycle.
- **Cohort 3**: 1.9 mg/kg Q6/8W dose of belantamab mafodotin on Day 1 of every other cycle.
- **Cohort 4**: 1.0 mg/kg Q3/4W dose of belantamab mafodotin on Day 1 of every cycle.
- **Cohort 5**: 1.4 mg/kg Q3/4W dose of belantamab mafodotin on Day 1 of every cycle.

Based upon emerging data from Cohorts 2-5, the following cohorts may be explored:

- **Cohort 6**: 1.4 mg/kg dose of belantamab mafodotin on Day 1 of Cycle 1, then 1.0 mg/kg on Day 1 of every third cycle from Cycle 4.
- **Cohort 7**: 1.9 mg/kg dose of belantamab mafodotin of Cycle 1, then 1.4 mg/kg on Day 1 of every third cycle from Cycle 4.

Based upon emerging data from Cohort 6 and Cohort 7, the following cohort may be explored:

- **Cohort 8**: Either a) 1.9 mg/kg dose of belantamab mafodotin on Day 1 of Cycle 1 and Cycle 4, then 1.4 mg/kg on Day 1 of every third cycle from Cycle 7; OR b) 1.4 mg/kg dose of belantamab mafodotin on Day 1 of Cycle 1 and Cycle 3, then 1.0 mg/kg on Day 1 of every third cycle from Cycle 6; OR c) 1.0 mg/kg dose of belantamab mafodotin on Day 1 of Cycle 1 and Cycle 5, then 1.0 mg/kg on day 1 of every third cycle from Cycle 9.

Participants will complete a Screening Period, a Treatment Period, and a Follow-up period.

During the 21-day Screening Period, participants will be evaluated for study eligibility per protocol as defined in the Inclusion/Exclusion criteria (Section 5.1 and Section 5.2).

Following screening, participants in cohort 1 will be enroled until the cohort is full. Following screening, participants in cohorts 2-5 will be randomized in a 1:1:1:1 ratio to one of the 4 cohorts. Participants recruited in cohorts 6- 7 will be assigned in a 1:1 ratio, and cohort 8 will be enroled into a dose cohort open at the time of recruitment. Further details on participant enrolment and cohort evaluation can be found in the study Dose Evaluation Plan. During the Treatment Period, safety and disease assessments will be performed regularly according to the SoA (Section 1.3). Participants will receive their allocated treatment until PD, unacceptable toxicity, or other reason such as death, withdrawal of consent, lost to follow-up (LTFU), whichever comes first. All participants will complete an EOT Visit at the point of study treatment discontinuation, followed by a Safety Follow-up Visit 70 days after the last dose of study treatment.

Participants who discontinue study treatment for reasons other than PD, death, or withdrawal of consent from the study, will continue for PFS Follow-up. Disease evaluations will continue according to the SoA until confirmed PD (documented), death, start of a new anti-myeloma treatment, withdrawal of consent, or LTFU, whichever occurs first.

A participant is considered to have completed the study if the participant has completed all scheduled visits listed in the SoA (Section 1.3). This will be different for each participant depending on tolerability of study drug, disease response, and ocular symptoms.

PACT Phase: Following the DCO date for the final analysis, study 209664 (DREAMM-9) participants may move into the PACT phase where the study remains open only to provide continued access to study intervention for participants who are continuing to derive clinical benefit in the opinion of the investigator and cannot access the treatment outside of the clinical study protocol at the time of final DCO date. At that time, the collection of new data for participants who no longer receive study intervention will stop entirely. The clinical study database will be closed to new data following the final DCO date. Participants still benefiting from study intervention at the time of the PACT phase may continue to receive study intervention and only SAEs, AEs leading to study intervention discontinuation, overdose, prespecified ocular data and pregnancy cases will be reported directly to GSK. Alternative continued treatment access outside of this study may be implemented, as it becomes available. For instance, participants may access the treatment outside of the clinical study protocol at the DCO (data cut-off) date for the final analysis by a rollover/extension study, expanded access route inclusive of group program or single patient compassionate use or if the product is commercially available and accessible.

4.1.1. Dose evaluation

The purpose of dose evaluation is to safely investigate the doses/dose schedules of belantamab mafodotin in combination with fixed doses of VRd. Dose evaluation of belantamab mafodotin will be based on evaluation of (dose-limiting toxicity) DLTs in the first 3, 21-day**,** cycles of treatment (defined as the DLT period), and an overall evaluation of the doses/dose schedules at the time of the primary analysis (see Table 6 for DLT criteria).

To minimize the overall number of SAEs potentially caused by overlapping toxicity (e.g., thrombocytopenia and neutropenia) and other toxicities when belantamab mafodotin is combined with VRd, in the initial 1.9 mg/kg Q3/4W cohort, the first 3 participants will be dosed with an interval of at least 8 days between participants. The complete blood count (CBC) performed at Cycle 1 Day 4 and Day 8 will inform on any hematological toxicities. This CBC result in the first and second participants will contribute to the decision whether the second and third participants, respectively, should be administered their first cycle of belantamab mafodotin plus VRd cycle.

After evaluation of the available safety data for cohort 1 (1.9 mg/kg Q3/4W), cohorts 2-5 (all doses of which are lower in relative dose intensity (RDI) than 1.9 mg/kg Q3/4W) will be opened in parallel and enrolled in a randomized fashion. Safety data from all enrolled participants will be reviewed regularly while the study is ongoing, both by cohort and by monitoring for overall trends across all cohorts. The study team may, upon review of the in-stream safety data, halt enrolment into a dose cohort(s) as deemed appropriate at any time during the study.

Safe dose cohort(s) are defined as that (those) dose cohort(s) which meet the DLT criteria at the interim and primary analyses and the RP3D will be based on the one with the highest probability of having a DLT rate within the target toxicity interval and other safety/PK/efficacy data. Please see Section 9.2.1 for further details. The DLT assessment period will be the first ***3*** cycles of treatment for individual participants. The decision for cohort expansion or closure of the dose cohort will take into account all available data, including but not limited to the safety parameters, clinical activity and PK data of all cohorts assessed.

Based upon emerging data in randomized cohorts 2-5, as well as emerging data from other clinical studies in the belantamab mafodotin clinical development program, cohort expansion (enrolment of 6 additional participants) may be applied to the selected safe dose cohort(s) after the last participant completes the end of Cycle 4. In addition, cohorts 6, 7 and 8 may be opened for enrolment. If cohorts 6-8 are open, then cohort expansion (enrolment of approximately 8 additional participants) may be applied to the selected safe dose cohort(s) after the last participant completes the end of Cycle 8 or if participants who experienced treatment cycle delays due to any reasons prior to the end of Cycle 8, they shall have completed at least 2 disease assessments and ocular examinations after the last dose of belantamab mafodotin.

Dose-related decisions will be made by the GSK study team with input from the investigator(s). GSK personnel will include, but are not limited to, the Medical Monitor, Study Delivery Lead, Clinical Scientist, Clinical pharmacology modeling and simulation (CPMS) representative, Study statistician, and Pharma Safety. The decision and rationale will be documented in written format and distributed to the investigator(s), GSK Medical Monitor, CPMS representative, and statistician. The GSK Medical Monitor has ultimate responsibility for the decisions made during the review meetings, and the decision and rationale for these meetings will be documented in writing with copies maintained at each study site and in the Trial Master File (TMF). Further details on cohort evaluation and dose-related decision making can be found in the study Dose Evaluation Plan.

4.1.1.1. Criteria for Belantamab Mafodotin Dose-Limiting Toxicity

Any participant who has received at least 1 full dose of belantamab mafodotin (dependent on dose schedule. Please see Figure 1 for more information on the dosing schedules) in Cycles 1-3, and ≥75% of the planned administration of VRd combination dose in Cycle 1 will be evaluated for DLTs using National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.

For all cohorts, DLTs are assessed during the DLT observation period, which is defined as the first 3**,** 21-day**,** cycles of treatment after administration of belantamab mafodotin begins. Participants that are not DLT-evaluable will be replaced as defined in Section 9.3.

A participant who develops a DLT will be allowed to continue on the study if the toxicity did not meet predefined stopping criteria (Section 7.1), recovered to at least Grade 1, and if the Investigator and GSK Medical Monitor agree that for a given participant the potential benefits may outweigh the risks.

An event will be considered a DLT if it is unequivocally attributed to belantamab mafodotin as outlined in Table 6 and occurs within the DLT observation period, i.e., the first 3**,** 21-day**,** treatment cycles for each participant.

Cohort 8c will evaluate a lower belantamab mafodotin dose and a stretched schedule. Should a participant in Cohort 8c be non-DLT-evaluable (as defined in Section 4.1), further participants will not be enrolled to replace them. In addition, any non-DLT-evaluable participants enrolled in the expansion of Cohort 6 and Cohort 7 will not be replaced if there are no DLTs that lead to discontinuation.

Table 6 Dose-limiting toxicity criteria (3, 21-Day Cycles) for belantamab mafodotin

Criteria for Identification of Belantamab Mafodotin Dose-Limiting Toxicities (DLTs)	
Toxicity Type and Grade[1]	**DLT Definition and Grade**
Hematologic	• Grade 3, 4 and 5 febrile neutropenia of any duration. • Grade 4 neutropenia >7 days. • Grade 3 or greater thrombocytopenia accompanied by clinically significant bleeding.
Non-hematologic including corneal toxicity	• Any Grade 3 or Grade 4 non-hematologic toxicity not due to underlying disease or other extraneous causes or which does not resolve with appropriate supportive treatment within 48 hours, or Grade 5 non-hematologic toxicity. – Any Grade 3 or Grade 4 non-hematologic laboratory value if: a) The laboratory abnormality persists for >72 hours despite supportive treatment. b) The abnormality leads to hospitalization. – Grade 5 non-hematological laboratory value. • Grade 3 or greater corneal toxicity (See Table 14).
Other organ-specific toxicities	• Liver toxicity meeting prespecified GSK liver stopping criteria.

1. Toxicities graded according to NCI-CTCAE Version 5.0 criteria with the exception of keratopathy and visual acuity changes that should be graded according to the Keratopathy and Visual Acuity (KVA) scale for the purposes of DLT identification.

4.1.1.2. Cohort Expansion

A total of 12 patients per cohort will be recruited into each respective cohort. Additionally, the Sponsor may decide to add approximately 8 additional patients to better characterize the safety, pharmacokinetics, pharmacodynamics, and clinical activity of the cohort(s) most likely to be deemed the RP3D for future studies in the newly diagnosed setting.

4.2. Scientific rationale for study design

Based on clinical data from the DREAMM-1 and 205678/DREAMM-2 studies, which demonstrated high ORR, together with rapid time to first response and durability of response for single-agent belantamab mafodotin in participants with RRMM, as well as preclinical in vivo data which showed that both lenalidomide and bortezomib separately synergizes the anti-myeloma activity of belantamab mafodotin (see IB), the combination belantamab mafodotin plus VRd has been selected for investigation in the TI NDMM population.

VRd is an accepted clinical SoC for the treatment of transplant ineligible NDMM patients based on the findings of the SWOG S0777 Phase 3 trial which showed that VRd treatment had superior efficacy compared to doublet Rd [Kumar, 2018; Moreau, 2017; Durie, 2017]. Based on the SWOG S0777 study, the EMA approved this treatment regimen for treatment of adult patients with previously untreated MM who are not eligible for transplant.

The overall duration of treatment in this first line 209664 study is consistent with SoC VRd dosing as described in the SWOG S0777 trial consisting of 8 Cycles of triplet induction therapy followed by Rd doublet maintenance treatment (starting at Cycle 9) until disease progression, development of unacceptable toxicities, death, withdrawal of consent or LTFU, whichever comes first.

The treatment schedule for belantamab mafodotin in the 209664 study is based upon the SWOG S0777 study, which has defined the therapeutic paradigm for NDMM. This study proposes to add on to this paradigm. To date, all studies of belantamab mafodotin have treated patients until progression, and these studies have not demonstrated a minimum efficacious duration of therapy. Analysis of the 13-month data from 205678/DREAMM-2 demonstrates ongoing responses (32% ORR [97.5% CI 21.7, 43.6%] with 58% of responders achieving VGPR or better, including 2 sCRs and 5 CRs) and continued clinical benefit from long-term therapy with belantamab mafodotin (median DoR in the 2.5 mg/kg Q3W was 11.0 months). These 13-month data do not demonstrate any evidence of cumulative toxicity that would preclude ability to administer the drug longer-term. Therefore, GSK proposes to add continuous dosing of belantamab mafodotin to the existing VRd regimen (8 cycles of VRd, followed by Rd maintenance) in order to maximize the therapeutic potential of the ADC. CCI [redacted]

4.3. Justification for dose

4.3.1. Justification for starting dose

Belantamab mafodotin was studied as monotherapy in the FTIH study (BMA117159) in a heavily pre-treated RRMM patient population over the dose range of 0.03 mg/kg to 4.6 mg/kg Q3W with a dose expansion portion performed with 3.4 mg/kg Q3W. Based on the data from this study, GSK initiated a Phase 2 study (205678) evaluating belantamab mafodotin monotherapy at doses of 2.5 mg/kg and 3.4 mg/kg Q3W administered until disease progression in participants who have failed at least 3 prior lines of anti-myeloma therapy, including an anti-CD38 antibody, and who are refractory to an ImiD and a PI (n=218). Belantamab mafodotin monotherapy has generally been well tolerated, with manageable toxicities [Lonial, 2020].

Additional studies have also been initiated or are planned to investigate belantamab mafodotin with novel combinations in 4L+ RRMM patients, as well as in combination with accepted backbone doublets (i.e., lenalidomide / dexamethasone and bortezomib / dexamethasone in Study 207497 or pomalidomide / dexamethasone in Study 209418) in 2L+ RRMM patients. For ImiD- or bortezomib-containing combinations, belantamab mafodotin is being evaluated with Q3W and Q4W dosing schedules, with planned doses ranging from 1.9 mg/kg dose administered on Day 1, to 2.5 and 3.4 mg/kg administered on either Day 1 or Day 1 and Day 8 (i.e., 1.25 mg/kg on Day 1 and Day 8 and 1.7 mg/kg on Day 1 and Day 8 respectively).

A starting dose of 1.9 mg/kg Q3/4W of belantamab mafodotin is considered an appropriate starting dose for the combination therapy with VRd based on the following:

- The 1.9 mg/kg Q3/4W dose is one dose level lower than the current dose of 2.5 mg/kg being evaluated, along with the 3.4 mg/kg dose, as monotherapy in the ongoing Phase 2 trial (Study 205678) in patients with RRMM.
- Following administration of 1.9 mg/kg Q3W in the FTIH monotherapy study (BMA117159), target engagement was greater than 90% at the end of the first infusion based on decrease in plasma free sBCMA from baseline.
- Based on the Bayesian logistic regression modeling of efficacy data in the FTIH monotherapy study (BMA117159 – 31 August 2018 cut-off), the 1.9 mg/kg Q3W dose has a low posterior probability of observing a response (predicted response rate for 1.9 mg/kg is 27.9% with a 95% credible interval of 11.8% and 45.0%).
- Based on in vitro and xenograft data with each component of the combination, it is anticipated that the combination will have additive or synergistic effects (see IB).
- Based on in vitro information, DDI are not anticipated between VRd and cys-mcMMAF or belantamab mafodotin (see IB).
- As there is a potential for overlapping hematological toxicities (see Section 2.3), 1.9 mg/kg Q3/4W is considered an appropriate starting dose to investigate belantamab mafodotin in combination with VRd in the TI NDMM participant population.

The cycle length for belantamab mafodotin will mirror the SoC cycle length (i.e., Q3W for the first 8 Cycles and Q4W for Cycle 9 onward).

4.3.2. Justification for lower doses

Based on the emerging clinical data with the starting dose, lower doses will be evaluated. The lowest dose would be 1.0 mg/kg administered on Day 1; in the FTIH study, BMA117159, responses were observed at doses as low as 0.96 mg/kg Q3W (1 out 3 participants) for single-agent belantamab mafodotin in RRMM patients. In the setting of combination therapy with anticipated additive or synergistic effects, doses as low as 1.0 mg/kg may provide additional benefit on the top of the SoC regimen.

4.3.3. Alternate schedule for belantamab mafodotin

Q6/8W Schedule:

Based on the population pharmacokinetics performed on the DREAMM-1 and 2 studies, belantamab mafodotin clearance decreases over time with an elimination half-life of 14 days after repeated administration. This leads to a moderate accumulation over time. It has been noted that safety events related to corneal toxicity occurred more frequently after repeated administration than after the first dose and tended to still occur after repeated administration at a reduced dose. These findings may be related to the long half-life and the decrease in clearance over time, both leading to drug accumulation.

To reduce increased exposure over time and potentially improve the benefit/risk, an extended interval of every 6 to 8 weeks will be evaluated; 6 to 8 weeks represents 3 to 4 half-lives and is anticipated to lead to minimal accumulation.

Q9/12W Schedule:

Based on emerging data from this study as well as other studies, lower dose exposure was associated with delayed onset of the first occurrence of corneal toxicity and a lower rate of Grade 3 or higher treatment-related ocular adverse events. To further improve the tolerability of belantamab mafodotin in combination with SoC, schedules with lower doses and less frequent dosing such as Q9/12W and Q12W will be evaluated in the study.

4.3.4. Justification for dose and schedule for VRd

VRd is an accepted SoC for the treatment of first line transplant ineligible NDMM patients based on the findings of the SWOG077 Phase 3 trial [Durie, 2017]. This study will use doses and schedule of bortezomib, lenalidomide and dexamethasone in line with those from the SWOG007 trial. Individual constituents of VRd are described in Section 6.

4.4. End of study definition/study completion

A participant is considered to have completed the study if the participant has completed all scheduled visits, is followed until death or the end of study. This will be different for each participant depending on tolerability of study drug, disease response, and ocular examination findings.

The EoS is defined as the date of the last participant last visit (LSLV) related to primary and secondary endpoints. If EoS is not equal to LSLV, it must be achieved no later than 8 months after LSLV.

A final DCO representing the end of data collection, prior to EoS, is defined as the DCO date for the final analysis. Following the final DCO date, the study may move into the PACT Phase and the clinical study database will be closed to new data. Participants who have not transitioned to continue treatment access to outside of the study at the time at final DCO who are receiving study intervention(s) may continue, as described in Section 6.7.1, to receive study intervention(s) if they are deriving clinical benefit as assessed by the investigator. Although the clinical study database will be closed to new data, the study remains open until all participants discontinue study intervention and complete the 70-day safety follow-up and the EoS definition is reached.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Up to 8 different dose cohorts may be evaluated, and up to 160 participants may be enrolled, in order to determine the RP3D for future studies in the newly diagnosed setting.

Participants who are withdrawn or subsequently found to be ineligible from the study may be replaced with new participants if deemed non-evaluable.

5.1. Inclusion criteria

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

Age

1. Participant must be over 18 years of age inclusive, at the time of signing the informed consent.
   Note: In Republic of Korea, participants must be over 19 years of age inclusive, at the time of signing informed consent.

Type of participant and disease characteristics

2. Diagnosis of multiple myeloma with a requirement for treatment as documented per International Myeloma Working Group (IMWG) criteria [Rajkumar, 2014]. Must have at least ONE aspect of measurable disease, defined as one of the following:
   a. Urine M-protein excretion ≥200 mg/24 hours (≥0.2g/24 hours), or
   b. Serum M-protein concentration ≥0.5 g/dL (≥5.0 g/L), or
   c. Serum free light chain (FLC) assay: involved FLC level ≥10 mg/dL (≥100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65).
3. Not a candidate for high-dose chemotherapy with ASCT due to presence of significant comorbid condition(s), such as cardiac, pulmonary or other major organ dysfunction that are likely to have a negative impact on tolerability of high-dose chemotherapy with stem cell transplantation, as judged by the investigator. The reason(s) for transplant ineligibility will be collected in the case report forms (CRFs).
4. ECOG performance status of 0-2.
5. Adequate organ system functions as defined by the laboratory assessments listed in Table 7.

Table 7 Adequate organ system function based on safety assessments

Organ System and Laboratory Tests	Laboratory Values
Hematologic[a]	
Absolute neutrophil count (ANC)	≥1.5 × 10^9/L
Hemoglobin	≥8.0 g/dL
Platelets	≥75 x 10^9/L
Hepatic	
Total bilirubin	<1.5 x upper limit of normal (ULN); (Isolated bilirubin >1.5 x ULN is acceptable if bilirubin is fractionated, and direct bilirubin is <35%)
Alanine aminotransferase (ALT)	≤2.5 x ULN
Renal	
Estimated glomerular filtration rate[b]	≥30 mL/min/1.73 m^2
Urine Dipstick for protein OR Albumin/creatinine ratio (from spot urine)	Negative/trace (if ≥1+ only eligible if confirmed ≤500 mg/g (56 mg/mmol) by albumin/creatinine ratio (spot urine from first void) ≤500 mg/g (56 mg/mmol)
Cardiac	
Left ventricular ejection fraction (LVEF) by ECHO	LVEF of ≥35% For participants with low LVEF (per institutional standards), consider referring to cardiology per local standards of care.

NOTE: Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the Investigator may re-test the participant and the subsequent within range screening result may be used to confirm eligibility.

a. Without growth support, transfusion, or platelet stimulating agents within 14 days of the assessment.
b. As calculated by Modified Diet in Renal Disease (MDRD) formula (Section 10.11).

6. Sex and Contraception/Barrier Requirements

Female Participants:
Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is NOT a woman of childbearing potential (WOCBP) as defined in Section 10.4.

OR

- Due to lenalidomide being a thalidomide analogue with risk for embryo-fetal toxicity and prescribed under a pregnancy prevention/controlled distribution program, and bortezomib having the potential to cause fetal harm, WOCBP participants will be eligible if they commit to either:
  - abstain continuously from heterosexual sexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

  - to use birth control as follows:

    Two methods of reliable birth control (one method that is highly effective and one additional effective (barrier) method), beginning 4 weeks prior to initiating treatment with lenalidomide, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of lenalidomide treatment.

    Thereafter, WOCBP participants must use one method of reliable birth control that is highly effective for *a total of* 4 months following discontinuation of belantamab mafodotin, or *a total of* 7 months following discontinuation of bortezomib, whichever is longer.
  - WOCBP must also agree not to donate eggs (ova, oocytes) for the purpose of reproduction during treatment, during dose interruptions and for 28-days following the last dose of lenalidomide, 4 months following discontinuation of belantamab mafodotin treatment or 7-months following the last dose of bortezomib, whichever is longer.
  - Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing the start of lenalidomide therapy. The participant should not receive lenalidomide until the investigator has verified that the results of these pregnancy tests are negative. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Additional requirements for pregnancy testing during and after study intervention are located in Section 10.4 and in the Section 1.3.

Male Participants:

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Male participants are eligible to participate if they agree to the following from the time of first dose of study treatment until 28-days after the last dose of lenalidomide, 4-months after the last dose of bortezomib, or 6 months after the last dose of belantamab mafodotin, whichever is longer, to allow for clearance of any altered sperm:

- Refrain from donating sperm.

PLUS, either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below:
  Agree to use a male condom, even if they have undergone a successful vasectomy, and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Section 10.4 when having sexual intercourse with a WOCBP who is not currently pregnant. Male participants should also use a condom when having sexual intercourse with pregnant females.

7. Informed Consent

Capable of giving signed informed consent as described in Section 10.1 (Section 10.1.3), which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Note: In France a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

5.2. Exclusion criteria

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

Type of participant and disease characteristics

1. Smoldering multiple myeloma (SMM).
2. Prior systemic therapy for multiple myeloma, or SMM.

   NOTE: An emergency course of steroids (defined as no greater than 40 mg of dexamethasone, or equivalent per day for a maximum of 4 days (that is, a total of 160 mg) is permitted.

NOTE: Focal palliative radiation is permitted prior to enrolment, provided that it occurred at least 2 weeks prior to the first dose of study drug, that the patient has recovered from radiation-related toxicities, and that the patient did not require corticosteroids for radiation-induced adverse events.

3. Participant is eligible for high-dose chemotherapy with ASCT, as determined by a frailty score of 0 as assessed by the IMWG frailty index.

Medical conditions

4. Peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the NCI-CTCAE Version 5.
5. Major surgery within 4 weeks prior to the first dose of study drug.
6. Presence of active renal condition (infection, requirement for dialysis or any other significant condition that could affect participant's safety). Participants with isolated proteinuria resulting from MM are eligible, provided they fulfill criteria given in Table 7.
7. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions (including lab abnormalities) that could interfere with participant's safety, obtaining informed consent or compliance to the study procedures.
8. Evidence of active mucosal or internal bleeding uncontrolled by local therapy and not explained by reversible coagulopathy.
9. Current active liver or biliary disease (except for Gilbert's syndrome or asymptomatic gallstones, or otherwise stable chronic liver disease as per the Investigator's assessment).
10. Participants with previous or concurrent malignancies other than multiple myeloma are excluded. Exceptions are surgically treated cervical carcinoma in situ, or any other malignancy that has been considered medically stable for at least 2 years. The participant must not be receiving active therapy, other than hormonal therapy for this disease.

Note: Participants with curatively treated non-melanoma skin cancer are allowed without a 2-year restriction.

11. Evidence of cardiovascular (CV) risk including any of the following:
    a. Evidence of current clinically significant untreated arrhythmias, including clinically significant ECG abnormalities including second degree (Mobitz Type II) or third degree atrioventricular (AV) block.
    b. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within 3 months of Screening.
    c. Class III or IV heart failure as defined by the New York Heart Association functional classification system (Section 10.8).
    d. Uncontrolled hypertension.

12. Active infection requiring treatment.
13. Known HIV infection.
14. Presence of Hepatitis B surface antigen (HbsAg), or Hepatitis B core antibody (HbcAb), at screening or within 3 months prior to first dose of study treatment, unless the following criteria can be met.

Serology result	Screening	During Study Treatment
HbcAb+, HbsAg-	HBV-DNA undetectable.	Monitoring per protocol (Table 18). Initiating antiviral treatment if HBV-DNA becomes detectable.
HbsAg+ at screening or within 3 months prior to first dose	HBV-DNA undetectable Highly effective antiviral treatment started at least 4 weeks prior to first dose of study treatment. Baseline imaging per protocol Participants with cirrhosis are excluded.	Antiviral treatment maintained throughout study treatment. Monitoring and management per protocol (Table 18).

Note: presence of Hepatitis B surface antibody (HbsAb) indicating previous vaccination will not exclude a participant.

15. Positive Hepatitis C antibody test result or positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment unless the participant can meet the following criteria:
    a. RNA test negative.
    b. Successful antiviral treatment (usually 8 weeks duration) is required, followed by a negative HCV-RNA test after a washout period of at least 4 weeks upon completion of antiviral treatment.
16. Current corneal epithelial disease except for mild punctate keratopathy. See Table 14.

Note: Participants with mild punctate keratopathy are allowed.

17. Intolerance or contraindications to antiviral prophylaxis.
18. Unable to tolerate antithrombotic prophylaxis.
19. AL amyloidosis (light chain amyloidosis), active POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma proliferative disorder, skin changes) or active plasma cell leukemia at the time of screening.
20. Exhibiting clinical signs of or has a known history of meningeal or central nervous system involvement by multiple myeloma.
21. Known immediate or delayed hypersensitivity reaction or idiosyncratic reaction to drugs chemically related to belantamab mafodotin, or any of the components of the study treatment.

Prior/concomitant therapy

22. Use of an investigational drug within 14 days or ***5*** half-lives (whichever is longer) preceding the first dose of study drug.
23. Plasmapheresis within 7 days prior to the first dose of study drug.

5.3. Lifestyle considerations

The following lifestyle restrictions apply while participants are in the study:

- Contact lenses are prohibited while on the study treatment (from first dosing to the EoS treatment). Contact lens use may be restarted after the eye care specialist confirms there are no other contraindications.
- Use of bandage contact lenses is permitted during study treatment as directed by the treating eye care specialist.
- Participants must not donate blood when receiving lenalidomide, during dose interruptions, and for 28 days following discontinuation of lenalidomide, as transfused blood might be given to a pregnant female whose fetus must not be exposed to lenalidomide.

5.4. Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals identified as Screen Failures may be rescreened if the failure was based on elements of eligibility that may change, e.g., laboratory test results. Rescreened participants should be assigned a different participant number from the one assigned for the initial screening. Rescreening of a participant more than once requires discussion with the Medical Monitor.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

The definition of study intervention is provided in the DEFINITIONS OF TERMS**.**

6.1. Study Interventions administered

Table 8 Study interventions administered

Intervention name	GSK2857916 (belantamab mafodotin)	Bortezomib	Lenalidomide	Dexamethasone
Intervention description	Powder for solution for infusion	Powder for solution for injection	Capsules for oral administration	Tablets for oral administration
Type	Drug	Drug	Drug	Drug
Dose formulation	Powder for solution for infusion	Powder for solution for injection	Capsules	Tablets
Unit dose strength(s)	100 mg lyophilized powder	3.5 mg lyophilized powder	25 mg, 10 mg and 5 mg	2 mg and 8 mg
Dosage level(s)	0.75 mg/kg 1.0 mg/kg 1.4 mg/kg 1.9 mg/kg	1.3 mg/m^2	25 mg PO, QD (if eGFR >60 mL/min/1.73 m^2) 10 mg PO, QD (if eGFR 30-60 mL/min/1.73 m^2).	Cycle 1 – 8: Dose: 20 mg PO Cycle 9 onward: Dose: 40 mg PO*
Route of administration	IV infusion	SC bolus**	Oral	Oral
Use	IMP	IMP	IMP	IMP
Non-IMP	NA	NA	NA	NA
Authorized AxMP/Unauthorized AxMP	NA	Authorized AxMP	Authorized AxMP	Authorized AxMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor or locally by the study site	Provided centrally by the sponsor or locally by the study site	Provided centrally by the sponsor or locally by the study site
Packaging and labeling	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.	Study intervention will be provided in blisters. Each blister will be labeled as required per country requirement.	Study intervention will be provided in bottles and blisters. Each bottle and blister will be labeled as required per country requirement.
Current/former name(s) or alias(es)	NA	*Velcade*	*Revlimid*	NA

AE = Adverse event; AxMP = Auxiliary medicinal product; eGFR = Estimated glomerular filtration rate; IMP = Investigational medicinal product; IV = Intravenous; NA = Not applicable; PO = Per os (oral); QD = Once daily; SC = Subcutaneous.

*For participants who are older than 75 years, underweight (BMI <18.5), have poorly controlled diabetes mellitus, or prior intolerance/AEs to steroid therapy, the dexamethasone dose may be administered at a dose of 10 mg (Cycles 1-8) and 20 mg (Cycle 9+) on the days indicated in the protocol.

**IV as a 3 to 5 second bolus infusion (only if SC not tolerated).

6.1.1. Belantamab mafodotin

Specifications for belantamab mafodotin treatment in this study are given in Table 9.

Table 9 Belantamab mafodotin study treatment information

Product name	Belantamab mafodotin
Dosage form	Powder for solution for infusion.
Unit dose strength/Dose level	100 mg/0.75 mg/kg. 100 mg/1.0 mg/kg. 100 mg/1.4 mg/kg. 100 mg/1.9 mg/kg.
Route/Administration/Duration	Intravenous infusion/30 minutes to 1 hour.
Dosing instructions	Reconstitute belantamab mafodotin for injection, 100 mg with 2.0 mL of sterile water for injection, dilute with saline before use. Dilute belantamab mafodotin in normal 0.9% saline to the appropriate concentration for the dose. Doses of belantamab mafodotin are to be administrated as an IV infusion via an infusion pump. See Investigator's Brochure for compatible administration materials (see IB)).

Refer to the Pharmacy Manual for more details on preparation and handling, and administration instructions.

For all cohorts dosing on Day 1, belantamab mafodotin will be administered as the first agent in the clinic (prior to VRd or Rd) as a full single dose on Day 1 for 30-60 minute infusion, followed by a 1 to 2 hour rest period. In the induction period, planned bortezomib dose should be administered approximately 1 hour after belantamab mafodotin infusion is complete. In the maintenance period, recommend observing 1-2 hours after belantamab mafodotin infusion is complete, assuming the participant is clinically stable.

For cohorts with dosing on Day 1 of every cycle (Q3/4W), if a planned dose of belantamab mafodotin was held/missed for any reason, the next dose can be administered at Day 1 of the next planned 21-day or 28-day cycle, as long as the interval between 2 consecutive doses is at least 21 (±3) days or 28 (±3) days, respectively.

For cohorts with dosing on Day 1 of every other cycle (Q6/8W), if a planned dose of belantamab mafodotin was held/missed for any reason, the next dose can be administered at Day 1 of the next planned 21-day or 28-day cycle, as long as the interval between 2 consecutive doses is at least 42 (±3) days or 56 (±3) days, respectively.

For cohorts with dosing on Day 1 of every third cycle (Q9/12W), if a planned dose of belantamab mafodotin was held/missed for any reason, the next dose can be administered at Day 1 of the next planned 21-day or 28-day cycle, as long as the interval between 2 consecutive doses is at least 63 (±3) days or 84 (±3) days, respectively.

Cohort 1: 1.9 mg/kg Q3/4W dose of belantamab mafodotin on Day 1 of every cycle.

Cohort 2: 1.4 mg/kg Q6/8W dose of belantamab mafodotin on Day 1 of every other cycle.

Cohort 3: 1.9 mg/kg Q6/8W dose of belantamab mafodotin on Day 1 of every other cycle.

Cohort 4: 1.0 mg/kg Q3/4W dose of belantamab mafodotin on Day 1 of every cycle.

Cohort 5: 1.4 mg/kg Q3/4W dose of belantamab mafodotin on Day 1 of every cycle.

Cohort 6: 1.4 mg/kg dose of belantamab mafodotin on Day 1 of Cycle 1, then 1.0 mg/kg on Day 1 of every third cycle from Cycle 4.

Cohort 7: 1.9 mg/kg dose of belantamab mafodotin on Day 1 of Cycle 1, then 1.4 mg/kg on Day 1 of every third cycle from Cycle 4.

Cohort 8: Based on emerging data, administration of either a) 1.9 mg/kg dose of belantamab mafodotin on Day 1 of Cycle 1 and Cycle 4, then 1.4 mg/kg on Day 1 of every third cycle from Cycle 7; OR b) 1.4 mg/kg dose of belantamab mafodotin on Day 1 of Cycle 1 and Cycle 3, then 1.0 mg/kg on Day 1 of every third cycle from Cycle 6; OR c) 1.0 mg/kg dose of belantamab mafodotin on Day 1 of Cycle 1 and Cycle 5, then 1.0 mg/kg on Day 1 of every third cycle from Cycle 9.

The belantamab mafodotin dose for both induction and maintenance treatment in combination with VRd is based on actual body weight calculated at baseline (Cycle 1 Day 1). However, if the change in body weight is greater than 10%, the dose should be recalculated based on the actual body weight at the time of dosing.

6.1.1.1. Belantamab mafodotin pre/post-medication

Premedication is not required prior to infusion unless deemed medically appropriate by the Investigator. Premedication should be considered in any participant who experienced an IRRs at first or any subsequent infusion with belantamab mafodotin.

Corneal events, which commonly manifest as superficial microcystic keratopathy, have been observed with ADCs, including those conjugated to MMAF.

In order to minimize corneal events, the corneal supportive care guidance below should be followed including both pre and post infusion care.

6.1.1.2. Corneal supportive care guidelines for belantamab mafodotin

Prophylactic interventions for corneal toxicity associated with belantamab mafodotin is provided in Table 10.

Table 10 Prophylactic measures for ocular events associated with belantamab mafodotin

Prophylactic Measure[a]	Dose and Administration	Timing
Preservative-free artificial tears	Administer in each eye at least 4 to 8 times daily	Administer daily beginning on Cycle 1 Day 1 until EOT.
Cooling eye mask (for use in the clinic)	May apply cooling eye mask to both eyes for approximately 1 hour, or as much as tolerated by the participant	During belantamab mafodotin infusion administration in the first hour for up to 4 hours, as tolerated

a. Dose modifications and treatment for ocular toxicities are discussed in Section 6.6.2.2.

While not yet clinically demonstrated, it is theoretically possible that the application of a cooling eye mask during belantamab mafodotin administration, and in the first few hours after infusion may decrease ocular side effects.

Corticosteroid eye drops are not required as prophylaxis but can be used therapeutically if clinically indicated per discretion of an eye care specialist. Allow at least 5-10 minutes between administration of artificial tears and steroid eye drops (if administered together). If steroid eye drops are deemed medically necessary and prescribed, intraocular pressure must be monitored if used for >7 days.

For all participants in the study, contact lenses are prohibited while on the study treatment (from first dosing to the EoS treatment). Contact lens use may be restarted after the eye care specialist confirms there are no other contraindications.

A qualified eye care specialist (Section 10.12) consult is required for all participants who develop signs or symptoms of corneal events or require steroid eye drops for more than 7 days.

Treatment-related ocular AEs other than corneal exam findings and visual acuity are to be reported based on NCI-CTCAE v5.0 criteria for eye disorders. Only CTCAE v5.0 term AEs are to be reported on AE pages. Corneal exam findings are to be recorded on ocular corneal exam pages in eCRF (not on AE pages). Treatment-related corneal exam findings and visual acuity will be graded according to the guidelines of the Keratopathy and Visual Acuity (KVA) Scale (Table 14).

See Table 15 for dose modification guidelines for belantamab mafodotin treatment-related corneal events based on KVA scale.

Participants who have treatment-related corneal abnormalities per KVA scale present at the EOT will continue to be followed by qualified eye care specialist at least every 3 months for up to 12 months or until resolution (to Grade 1 or baseline), whichever comes first.

6.1.2. VRd administration (induction & maintenance)

6.1.2.1. Bortezomib (SC) administration

Bortezomib for injection is supplied as individually-cartoned 10 mL vials containing 3.5 mg of bortezomib as a white to off-white cake or powder (NDC 63020-049-01 – 3.5 mg single-use vial). Retain in original package to protect from light. Details of pharmaceutical presentation can be found in the representative information for bortezomib. The starting dose for bortezomib is 1.3 mg/m^2. Dose reductions and interruptions are permitted per bortezomib labels. Guidance from the most recent applicable prescribing information, together with EMA-ESMO clinical practice guidelines [Dimopoulos, 2021], should be followed. Decisions regarding dose reduction or modification will be made by the Investigator in consultation with the GSK Medical Monitor, based on the clinical evaluation of the participant.

On days when belantamab mafodotin is administered, subcutaneous bortezomib should be administered approximately 1 hour after the belantamab mafodotin infusion is complete, assuming the participant is clinically stable. In participants who experience an IRR during or after belantamab mafodotin administration, the administration of bortezomib will be delayed until the IRR has resolved and the participant is considered clinically stable.

Dose modifications may be required for safety. Refer to Section 6.6.2.3 for more information.

- At least 72 hours should elapse between consecutive doses of bortezomib.
- If a bortezomib dose is delayed, subsequent doses should be adjusted to account for delay as all bortezomib doses must be at least 72 hours apart. Doses that need to be withheld are skipped and will not be made up later in the cycle.
- Individual doses within a cycle have a ±1-day window if beyond 72 hours after last dose.
- Sites for each SC injection should be rotated. New injections should be given at least 2.5 cm (1 inch) from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.

If local injection site reactions occur following administration of bortezomib SC, a less concentrated solution (1 mg/mL instead of 2.5 mg/mL) may be administered SC.

Alternatively, substitution to the IV route of administration could be considered for participants who are intolerant to subcutaneous injections or have developed significant edema at potential SC injection sites.

Refer to the Pharmacy Manual for further details on preparation, handling, and administration contained in package inserts.

Dose Calculation

Bortezomib dosing is based on the participant's body surface area (BSA), which is calculated in accordance with local practice, for example using a nomogram [West, 2000]. The reconstituted concentration of bortezomib for subcutaneous administration (2.5 mg/mL) is greater than the reconstituted concentration of bortezomib for intravenous administration (1 mg/mL). Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered.

After determining the participant's BSA in m^2, use the following equations to calculate the total volume (mL) of reconstituted bortezomib to be administered:

For subcutaneous administration (2.5 mg/mL concentration):

[bortezomib dose (mg/m^2) × participant BSA (m^2)] ÷ [2.5 mg⁄mL] = Total bortezomib volume (mL) to be administered

For intravenous administration (1 mg/mL concentration):

[bortezomib dose (mg/m^2) × participant BSA (m^2)] ÷ [1 mg⁄mL] = Total bortezomib volume (mL) to be administered

6.1.2.2. Lenalidomide

Lenalidomide Pharmaceutical Presentation

Lenalidomide is available in 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg capsules for oral administration. Different capsule strengths may be used in different countries to allow for the required dose modifications. Details of pharmaceutical presentation can be found in the representative information for lenalidomide.

Lenalidomide Administration

Lenalidomide is administered at a fixed dose level of 25 or 10 mg orally, depending upon renal function. Participants with eGFR >60 mL/min/1.73 m^2 will receive 25 mg. Participants with eGFR 30- 60 mL/min/1.73 m^2 will be administered 10 mg.

Dose modifications may be required for safety. Refer to Section 6.6.2.3 for more information.

Participants receiving lenalidomide provided by GSK must follow the manufacturing guidelines of any treatment-specific Pregnancy Prevention Program, refer to the Pharmacy Manual for additional details. Participants receiving lenalidomide from local supply e.g., US, will follow their local controlled distribution program.

6.1.2.3. Dexamethasone

Dexamethasone Pharmaceutical Presentation

Dexamethasone is available as tablets for oral administration. Details of the pharmaceutical presentation can be found in the representative information for dexamethasone.

Dexamethasone Administration

Dexamethasone is administered orally at a fixed dose level of 20 mg in Cycles 1-8 and 40 mg in Cycle 9 onward. Dexamethasone should be taken at the same time of the day and may be taken at home.

For participants who are older than 75 years, underweight (BMI <18.5), have poorly controlled diabetes mellitus, or prior intolerance/AE to steroid therapy, the dexamethasone dose may be administered at a dose of 10 mg (Cycles 1-8) and 20 mg (Cycle 9+) on the days indicated above.

Refer to the Pharmacy Manual for further details on preparation, handling, and administration contained in package inserts.

6.1.3. Dosing schedule

A total of 8 Cycles of belantamab mafodotin + VRd induction treatment followed by belantamab mafodotin + doublet Rd maintenance treatment is based on the individual constituent dosing schedules in the SWOG777 Phase 3 trial [Durie, 2017] (Figure 2).

6.1.3.1. Induction treatment (Q3W) – belantamab mafodotin + VRd; up to Cycle 8

Belantamab mafodotin: Belantamab mafodotin will be administered intravenously (IV) on Day 1, either every 21-day cycle, every other 21-day cycle, every third 21-day cycle, or every fourth 21-day cycle (cohort 8c) for the first 8 (induction) Cycles in combination with VRd.

Bortezomib: Bortezomib will be administered at a dose of 1.3 mg/m^2 subcutaneously (SC) on Days 1, 4, 8, and 11 of every 21-day cycle for the 8 induction Cycles.

Lenalidomide: Lenalidomide will be administered at a dose of 25 mg, orally, on Days 1-14 of a 21-day cycle for the 8 induction Cycles.

In participants with eGFR 30-60 mL/min/1.73 m^2 lenalidomide will be administered at 10 mg daily on Days 1-14 of each 21-day cycle. In participants whose renal function improves during the study to eGFR >60 mL/min/1.73 m^2 (confirmed over 2 measurements 2 weeks apart) the dose of lenalidomide can be increased accordingly based on the Investigator judgement.

Dexamethasone:

Dexamethasone will be administered at 20 mg, orally, on Days 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day cycle for the ***8*** induction Cycles. Dexamethasone should be taken at the same time of the day and may be taken at home.

For participants who are older than 75 years, underweight (body mass index (BMI) <18.5), have poorly controlled diabetes mellitus, or prior intolerance/AE to steroid therapy, the dexamethasone dose may be administered at a dose of 10 mg on the days indicated above.

6.1.3.2. Maintenance treatment (Q4W) – belantamab mafodotin +Rd; Cycle 9 onward

After the first 8 induction Cycles, belantamab mafodotin in combination with Rd will be administered as maintenance treatment until disease progression, unacceptable toxicity, death, withdrawal of consent or LTFU, whichever comes first.

Belantamab mafodotin: Belantamab mafodotin will be administered intravenously (IV) on Day 1, either every 28-day cycle, every other 28-day cycle or every third 28-day cycle in combination with Rd.

Lenalidomide: Lenalidomide will be administered at a dose of 25 mg orally on Days 1-21 of each 28-day cycle until PD or unacceptable toxicity.

In participants with eGFR 30-60 mL/min/1.73 m^2 lenalidomide will be administered at 10 mg daily on Days 1-21 of each 28-day cycle. In participants whose renal function improves during the study to eGFR >60 mL/min/1.73 m^2 (confirmed over 2 measurements 2 weeks apart) the dose of lenalidomide can be increased accordingly based on the Investigator judgement.

Dexamethasone:

Dexamethasone will be administered at 40 mg, orally, on Days 1, 8, 15 and 22 of a 28-day cycle from Cycle 9 onward, until PD or unacceptable toxicity.

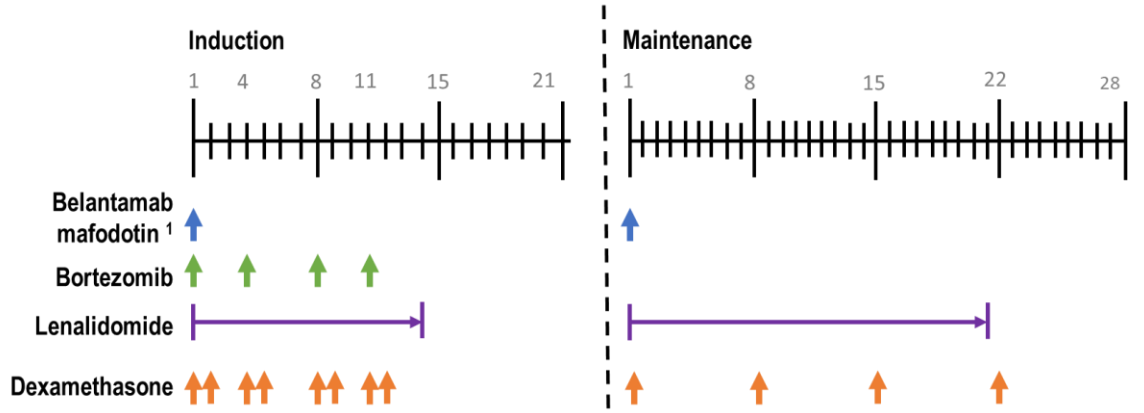
Dexamethasone should be taken at the same time of the day and may be taken at home.

For participants who are older than 75 years, underweight (BMI <18.5), have poorly controlled diabetes mellitus, or prior intolerance/AE to steroid therapy, the dexamethasone dose may be administered at a dose of 20 mg on the days indicated above.

Bortezomib will not be administered as part of maintenance treatment.

The doses of all treatments may be reduced to address toxicity according to protocol guidelines. Further details can be found in Section 6.6.

Figure 2 Summary of dosing schedules: belantamab mafodotin & VRd



1. Belantamab mafodotin will be given at Day 1. Belantamab mafodotin will be given every other cycle for the Q6/8W schedule, every third cycle for the Q9/12W schedule, and every fourth 21-day cycle in cohort 8c schedule.

6.2. Preparation/handling/storage/accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment.

All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff. Returned study treatment should not be re-dispensed to the participants.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the Investigator, where this is required by local laws, or is available upon request from GSK.

In the case of unintentional occupational exposure notify the monitor, Medical Monitor, or GSK study contact.

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

6.3. Measures to minimize bias: randomization and blinding

This is an open-label study; therefore, no blinding of treatment identity is needed for any of the dose cohorts and sponsor will have access to the participant-level data throughout the study. However, there will be no intention to summarize and interpret data from the ongoing study at any time point except predefined analyses.

The Sponsor will supply a range of unique numbers to each site and participants eligible for enrolment will be assigned a unique number by the site.

The unique number will not be reassigned to another participant if a participant assigned that number is subsequently found to be a Screen Failure. The unique participant number will remain for the duration of the study.

Participants in Cohorts 2-5 will be assigned to study treatment in accordance with the randomization schedule.

Randomization will be done centrally using a randomization schedule generated by the GSK Clinical Statistics Department. Participants in Cohorts 2-5 will be assigned in a 1:1:1:1 ratio to:

- Cohort 2: 1.4 mg/kg belantamab mafodotin Q6/8W.
- Cohort 3: 1.9 mg/kg belantamab mafodotin Q6/8W.
- Cohort 4: 1.0 mg/kg belantamab mafodotin Q3/4W.
- Cohort 5: 1.4 mg/kg belantamab mafodotin Q3/4W.

Also, participants in Cohorts 6-7 will be assigned in a 1:1 ratio to:

- Cohort 6: 1.4 mg/kg belantamab mafodotin 9W→ 1.0 mg/kg belantamab mafodotin 9W→ 1.0 mg/kg belantamab mafodotin Q12W.
- Cohort 7: 1.9 mg/kg belantamab mafodotin 9W→ 1.4 mg/kg belantamab mafodotin 9W → 1.4 mg/kg belantamab mafodotin Q12W.

Participants will not be randomized in Cohort 1 and Cohort 8.

Once a randomization number has been assigned it must not be reassigned even in cases of errors.

Upon completion of all the required screening assessments, eligible participants will be registered via an Interactive Response Technology (IRT), by the Investigator or authorized site staff.

Study Specific User Guide for IRT system will be provided to the study site in the SRM.

6.4. Study intervention compliance

When participants have parenteral study, treatments administered at the site, they will receive study treatment in the clinic under supervision of the Investigator or designee. The date and time of each dose administered in the clinic will be recorded in the participant's CRF and source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

When participants self-administer oral study treatment(s) at home, such dosing will be recorded in the Participant's Study Diary. The entries in the Diary will be assessed through querying the participant during the site visits and documented in the source documents and CRF. A record of the number of doses dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

6.5. Concomitant therapy

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements and/or ocular supportive care, other than those mandated by the protocol) that the participant is receiving from the time of enrolment until the EOT Visit must be recorded along with:

- reason for use.
- dates of administration including start and end dates.
- dosage information including dose and frequency of administration.

Anti-myeloma treatments received by the participant up to the Safety Follow-up Visit must be recorded.

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

6.5.1. Permitted concomitant therapies

Participants should receive full supportive care during the study, including transfusions of blood products, growth factors, and treatment with antibiotics, anti-emetics, antidiarrheals, and analgesics, as appropriate.

- While the participants are receiving treatment with lenalidomide in either arm of the study, thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the participant's underlying risks, in accordance with local prescribing information.
- Antiviral prophylaxis is recommended in accordance with local prescribing information in participants being treated with bortezomib.

- Concomitant therapy with bisphosphonates is allowed and recommended.
- Concomitant prophylactic treatment for tumor lysis syndrome (according to local standards) in participants with high tumor load should be considered.
- Participants may receive local irradiation for pain or stability control. Appropriate imaging should be performed to establish presence of new lesions, which would constitute disease progression. Please contact the GSK Medical Monitor to discuss options for local radiotherapy.
- In the event that IV dexamethasone is indicated, this may take the place of the oral dose of dexamethasone on that day, if appropriate.

6.5.2. Prohibited concomitant therapies

Chronic treatment with oral steroids other than treatment specified in the SoA is prohibited while the participant is on study with the exception of low dose prednisone (≤10 mg/day) as substitution in participants with adrenal insufficiency. A short course (7 days) of steroids is allowed for the management of AEs. Steroids may be used to treat IRRs. Inhaled and topical ophthalmic steroids are not prohibited. Ophthalmic steroids are allowed for treatment of ocular symptoms.

Any other anti-myeloma therapy not specified in this protocol, and any investigational agents other than belantamab mafodotin are prohibited until confirmed disease progression as per IMWG criteria.

Elimination pathways for belantamab mafodotin and cys-mcMMAF have not been characterized in humans. Cys-mcMMAF was not an inhibitor, an inducer, or a good substrate of cytochrome P450 enzymes in vitro. In addition, cys-mcMMAF was shown to be a substrate of P-glycoprotein (P-gp), OATP1B1, and OATP1B3 transporters in vitro. Caution should be exercised when belantamab mafodotin is combined with strong inhibitors of P-gp, and strong inhibitors of OATP1B1 and OATP1B3 should be avoided unless considered medically necessary. See Study Reference Manual (SRM) for further information.

Administration of live or live-attenuated vaccines are contraindicated 30 days prior to the first dose of study treatment and while on the study. Use of live or live-attenuated vaccines is further contraindicated for at least 70 days following the last dose of belantamab mafodotin. Killed or inactivated vaccines may be administered, however, the response to such vaccines cannot be predicted.

Prohibited concomitant medication for bortezomib and lenalidomide are as per the representative information for each product.

6.6. Dose modification or delay

Dose modifications for individual participants may be required for safety reasons. Dose interruptions and reductions are permitted throughout the study.

Dosing delays are also permitted for medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, participant vacation, and/or holidays) but not simply for participant's choice to delay treatment.

For dose delays or interruptions lasting >21 days, the Medical Monitor should be contacted to discuss restarting treatment.

The reason for any dose delay must be documented in the participant's eCRF and clinic record. Where safety findings cannot be ascribed solely to one study treatment, follow the guidance provided in Table 11.

6.6.1. Belantamab mafodotin dose reduction schedule

The dose allowed for belantamab mafodotin may be reduced on up to 4 separate occasions from the originally assigned dose. Depending on the schedule of dosing, the lowest dose of belantamab mafodotin allowed on study is 0.75 mg/kg Q12W. When participant in confirmed CR/sCR, belantamab mafodotin may be reduced to 0.75 mg/kg Q12W depending on the schedule of dosing. See Table 11.

If a dose is delayed, the participant should wait for the next scheduled VRd/Rd cycle to resume belantamab mafodotin treatment. In individual cases where, in the judgement of the investigator, waiting a full cycle to resume treatment after delay (skipping dose) related to toxicity which has resolved would be detrimental to the participant's health, the Principal Investigator should contact the Medical Monitor to discuss an earlier restart.

During the induction Phase (i.e., B-VRd) of the study, if a participant must permanently discontinue belantamab mafodotin treatment, they may continue to receive VRd treatment for the remainder of the induction Phase. Prior to starting maintenance Rd, participants should have their EOT Visit as per the SoA followed by a PFS Follow-up or 70-day Safety Follow-up (if applicable).

During the maintenance Phase (i.e., B-Rd) of the study, if a participant must permanently discontinue belantamab mafodotin treatment, participants should have their EOT Visit as per the SoA followed by a PFS Follow-up or 70-day Safety Follow-up (if applicable).

Participants who have treatment-related ocular AEs at the EOT should be followed to resolution, as described in the SoA and Section 8.2.9 before discontinuing from the study.

If a participant enrolled prior to the implementation of Amendment 1 is unable to receive Rd or an acceptable alternative as an available SoC, they may continue receiving Rd treatment and remain on study, following the visit schedule as per the SoA.

A consideration can be given on a case-by-case basis and after discussion with the Sponsor Medical Monitor to resume treatment of belantamab mafodotin at the last dose level provided the AE leading to dose interruption has fully resolved.

In case a dose reduction is necessary, the study intervention will be administered as follows:

Table 11 Recommendations for dose reduction of belantamab mafodotin

	Q3/Q4W Dosing			Q6/8W Dosing		Q9/12W Dosing		
Assigned Dose	1.0 mg/kg	1.4 mg/kg	1.9 mg/kg	1.4 mg/kg	1.9 mg/kg	1.0 mg/kg Q12W	1.4 mg/kg	1.9 mg/kg
Dose upon first reduction from assigned dose	1.0 mg/kg Q6/8W	1.0 mg/kg	1.4 mg/kg	1.0 mg/kg	1.0 mg/kg	0.75 mg/kg Q12W	1.0 mg/kg Q12W	1.4 mg/kg
Dose second reduction from assigned dose	1.0 mg/kg Q12W	1.0 mg/kg Q6/8W	1.0 mg/kg	1.0 mg/kg Q12W	1.0 mg/kg Q12W	No dose reduction allowed	0.75 mg/kg Q12W	1.0 mg/kg Q12W
Dose upon third reduction from assigned dose	0.75 mg/kg Q12W	1.0 mg/kg Q12W	1.0 mg/kg Q12W	0.75 mg/kg Q12W	0.75 mg/kg Q12W	No dose reduction allowed	No dose reduction allowed	0.75 mg/kg Q12W
Dose upon forth reduction from assigned dose	No dose reduction allowed	0.75 mg/kg Q12W	0.75 mg/kg Q12W	No dose reduction allowed	No dose reduction allowed	No dose reduction allowed	No dose reduction allowed	No dose reduction allowed
At complete response (CR)/ stringent complete response (sCR)‡	Could reduce to 0.75 mg/kg Q12W							

No full dose below 0.75 mg/kg Q12W allowed for participants.
‡ Apply to participants who achieved confirmed CR/sCR.

6.6.2. Dose modification guidelines for adverse events

6.6.2.1. Dose modification for overlapping hematological toxicities

There may be situations where the Investigator will not be able to attribute hematological toxicity to a single-agent. In this event, the hierarchy shown in Figure 3 is provided as a suggestion to guide modification of the combination agents for overlapping hematological toxicities. Full guidance is given in Table 12.

Where the relatedness of the hematological toxicity is clear e.g., due to timing of dosing, the Investigator may apply judgement to reduce any of the agents as appropriate.

Figure 3 Hierarchy of dose modification for overlapping hematological toxicities

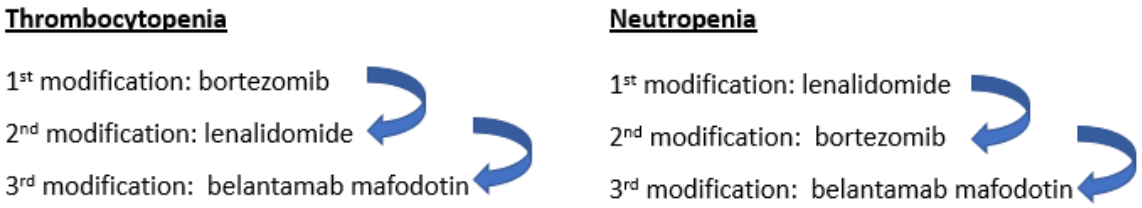


Table 12 Dose modification guidelines for overlapping hematological toxicities

Hematological toxicity	Recommended Actions
Thrombocytopenia	
Interrupt all treatments until platelet count returns to 50x10^9/L. • Conduct weekly hematology assessments. • Consider additional supportive treatment (e.g., transfusion), as clinically indicated and per local practice.	
Platelets count decrease to <50 x 10^9/L at the start of new cycle or <30x10^9/L at any point during cycle	Following recovery, resume bortezomib at the next lower dose[a]. Resume lenalidomide and belantamab mafodotin at the most recent dose.
Further drop in platelets to <50 x 10^9/L at the start of new cycle or <30x10^9/L at any point during cycle	Following recovery, resume lenalidomide at the next lower dose[a]. Do not dose below 5 mg daily. Resume bortezomib and belantamab mafodotin at the most recent dose.
Subsequent drop in platelets to <50 x 10^9/L at the start of new cycle or <30x10^9/L at any point during cycle	Following recovery, resume bortezomib and lenalidomide at the most recent dose. Follow guidance for belantamab mafodotin: <u>Day 1 Dosing:</u> • No bleeding: continue treatment at the next lower dose[b]. Consider reverting to previous dose once thrombocytopenia recovered to Grade 2, or less. • With bleeding: withhold dose. Treatment at the next lower dose may continue after thrombocytopenia has recovered to Grade 2 or less.

Hematological toxicity	Recommended Actions
For additional occurrences, alternate dose modification of bortezomib, lenalidomide and belantamab mafodotin, as described above	
Neutropenia	
Interrupt all treatments until absolute neutrophil count (ANC) returns to 1x10^9/L. • Conduct weekly hematology assessments. • Consider prophylactic antimicrobials per physician discretion and institutional guidelines. • Consider additional supportive treatment, per local practice (*e.g.*, growth factors). • Immediate hospitalization for febrile neutropenia is required.	
ANC fall to <1.0 x 10^9/L	• Following recovery, resume lenalidomide at the next lower dose[a]; do not dose below 5 mg daily. • Resume bortezomib and belantamab mafodotin at the most recent dose.
Further drop in ANC to <1.0 x 10^9/L	• Following recovery, resume bortezomib at the next lower dose[a]. • Resume lenalidomide and belantamab mafodotin at the most recent dose.
Subsequent drop in ANC to <1.0 x 10^9/L	Following recovery, resume bortezomib and lenalidomide at the most recent dose. Follow guidance for belantamab mafodotin: <u>Day 1 Dosing:</u> • If noted on Day 1 of any cycle, withhold belantamab mafodotin. Repeat hematology (CBC) as clinically indicated. • Resume belantamab mafodotin at pre-held dose once neutropenia recovers to Grade ≤ 2 (ANC ≥ 1.0x10^9/L) on Day 1 of the subsequent cycle.
For additional occurrences, alternate dose modification of bortezomib, lenalidomide and belantamab mafodotin, as described above	

a. Next lower dose according to prescribing information
b. Belantamab mafodotin dose reduction strategy, see Section 6.6.1.

6.6.2.2. Dose Modification Guidelines for Belantamab Mafodotin

See Table 13 for dose modification guidelines for AEs associated with belantamab mafodotin.

See Table 14 and Table 15 for dose modification guidelines for corneal toxicity related to belantamab mafodotin. Determination of the recommended dose modification of belantamab mafodotin should be based on the most severe corneal toxicity per the KVA scale.

6.6.2.3. Dose Modification Guidance for Lenalidomide, Bortezomib, Dexamethasone

See Table 16 and Table 17 for bortezomib and lenalidomide dose modification guidelines, respectively.

Table 13 Dose modification guidelines for adverse events associated with belantamab mafodotin

Toxicity	Grade/Symptoms	Recommendations
Serum creatinine Graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE criteria)	Grade 2 >1.5–3.0xbaseline >1.5–3.0xULN	• Repeat within 48 hours if elevation cannot be explained by concomitant sepsis, tumor lysis syndrome (TLS), other severe condition with fever or dehydration. • If confirmed: withhold belantamab mafodotin, initiate treatment and monitoring as clinically indicated, and follow for resolution. • Discuss any further dosing with Medical Monitor.
	Grade 3 >3.0xbaseline >3.0–6.0xULN Or Grade 4 >6.0xULN	• Provide appropriate medical treatment. • If drug related, permanently discontinue treatment with belantamab mafodotin. • If due to another cause (e.g., sepsis, dehydration), withhold treatment with belantamab mafodotin. Upon recovery to Grade 1, restart treatment at the same dose level.

Spot urine (albumin/creatinine ratios)	>2000 mg/g (224 mg/mmol)	• Re-test (at least 7 days apart).
		• If not confirmed, continue belantamab mafodotin at pre-held dose.
		• If confirmed on re-test and no clear evidence of disease progression
		  ○ Interrupt treatment with belantamab mafodotin.
		  ○ Repeat testing within 4 weeks.
		  ○ If spot urine ≤2000 mg/g (224 mg/mmol) may restart belantamab mafodotin with 1 dose level reduction[b].
		  ○ If spot urine remains >2000 mg/g (224 mg/mmol) after 4 weeks, consider permanently discontinuing belantamab mafodotin, provide treatment as clinically indicated, and follow for resolution.

Urine Dipstick	2+	• May continue belantamab mafodotin dosing. • Confirm by quantitative assessment using albumin/creatinine (spot urine from first void). • If albumin/creatinine ≥2000 mg/g, at the next cycle follow guidance above for Spot Urine.
	3+	• Interrupt treatment and follow-up for recovery. Implement quantification of albumin/creatinine ratio.
Thrombocytopenia	See Table 12 for Dose Modification for Overlapping Hematological Toxicities	
Febrile neutropenia Graded according to NCI-CTCAE criteria	Defined as: single temperature of 38.3°C, or sustained 38°C for	• Withhold belantamab mafodotin and immediate hospitalization is recommended with appropriate management, per local institutional guidance.

Toxicity	Grade/Symptoms	Recommendations
	>1 hour and absolute neutrophil count (ANC) <1.0×10⁹/L	• Consider additional supportive treatment per local practice (e.g., growth factors). Upon recovery, consider a dose reduction[b] of belantamab mafodotin, if neutropenia was drug related. • See also Table 12 for guidelines for overlapping toxicity.
Neutrophil Count Decreased (Neutropenia)	See Table 12 for Dose Modification for Overlapping Hematological Toxicities	
Infusion Reaction Graded according to NCI-CTCAE criteria	Note: If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/h to 50 mL/h). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated at the next scheduled dose.	
	Grade 2	• Stop infusion, provide medical treatment, and continue at slower infusion rate after resolution to Grade 0-1.
	Grade 3	• Further treatment with belantamab mafodotin needs to be discussed with Medical Monitor. Continuation only allowed after recovery to ≤Grade 1 and with premedication, and extension of infusion time to 2-4 h. Any future infusion needs to be premedicated.
	Grade 4	• Permanently discontinue.
Pneumonitis Graded according to NCI-CTCAE criteria	Grade 2	• Withhold treatment with belantamab mafodotin. • Upon recovery, restart treatment with 1 dose level reduction. • If participant is already at the lowest dose level, then rechallenge with the same dose must be discussed with the Medical Monitor.
	Grade 3-4	• Permanently discontinue treatment with belantamab mafodotin.

a. Medical Monitor may consult GSK's renal panel about plans to continue therapy.
b. Belantamab mafodotin dose reduction strategy; see Table 11.

Table 14 Keratopathy and Visual Acuity scale for treatment-related corneal toxicities

Grade per KVA scale		Grade 1	Grade 2	Grade 3	Grade 4
Corneal Toxicities	**Corneal examination finding(s)**	Mild superficial keratopathy[a]	Moderate superficial keratopathy[b]	Severe superficial keratopathy[c]	Corneal epithelial defect[d]
	Change in best corrected visual acuity (BCVA)	Decline from baseline of 1 line on Snellen Visual Acuity	Decline from baseline of 2 or 3 lines (and Snellen Visual Acuity not worse than 20/200)	Decline from baseline by more than 3 lines (and Snellen Visual Acuity not worse than 20/200)	Snellen Visual Acuity worse than 20/200

a. Mild superficial keratopathy = mild superficial punctate keratopathy (documented worsening from baseline), with or without symptoms.
b. Moderate superficial keratopathy = any/or a combination of moderate superficial punctate keratopathy, patchy microcyst-like deposits, subepithelial haze (peripheral), or a new peripheral stromal opacity.
c. Severe superficial keratopathy = any/or a combination of severe superficial punctate keratopathy, diffuse microcyst-like deposits involving the central cornea, subepithelial haze (central), or a new central stromal opacity.
d. Corneal epithelial defect such as corneal ulcers. Corneal ulcer by definition means an epithelial defect with underlying stromal infiltration.

Table 15 Dosage modifications for belantamab mafodotin based on the Keratopathy and Visual Acuity scale:

Grade per (Keratopathy and Visual Acuity) KVA scale	Grade 1	Grade 2	Grade 3	Grade 4
Recommended **Dosage Modifications**[1]	Continue treatment at current dose.	Withhold belantamab mafodotin until improvement in both corneal examination findings and changes in best corrected visual acuity (BCVA) to Grade 1 or better and resume at reduced dose[2].	Withhold belantamab mafodotin until improvement in both corneal examination findings and changes in BCVA to Grade 1 or better and resume at reduced dose.[2]	Consider permanent discontinuation of belantamab mafodotin. If based on benefit-risk assessment, treatment of belantamab mafodotin is being considered, withhold treatment until improvement in **both** corneal examination findings and change in BCVA to Grade 1 or better and resume at reduced dose[2].

1. Dose modification should be based on the most severe grade. If eyes differ in severity, dose modification guideline should be applied based on the more severe eye. Changes in visual acuity due to treatment-related corneal findings.

- For participants who have BCVA worse than 20/20 in either eye at baseline, dose modification for that eye will be determined by the worsening of vision from baseline only (not by absolute BCVA at the visits).
- If a participant has a baseline BCVA of 20/200 or worse in one eye, then belantamab mafodotin-related changes in vision in the other eye will drive the change in BCVA grading.
- If a participant has baseline BCVA of 20/200 or worse in both the eyes, then the decision to delay or reduce belantamab mafodotin dose will be based on Principal Investigator's assessment of benefit vs. risk-based on corneal exam findings following a discussion with the qualified eye care specialist.

2. If already on the lowest allowed dose level, the participant should resume treatment at that dose.

Table 16 Dose modification guidelines for hematologic and other toxicities attributed to bortezomib[a]

Toxicity	Grade[a]/Symptoms	Recommendations[a]
Thrombocytopenia	See Table 12 for Dose Modification for Overlapping Hematological Toxicities	
Neutropenia Absolute Neutrophil Counts (ANC)	See Table 12 for Dose Modification for Overlapping Hematological Toxicities	
Other hematological toxicity Graded according to NCI-CTCAE criteria	Grade ≥4	• Withhold bortezomib therapy until symptoms of toxicity have resolved. • Bortezomib may be reinitiated with 1 dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). • Further dose adjustment from 0.7 mg/m^2 twice weekly to 0.7 mg/m^2 weekly would be permitted based on investigator judgement).
Non-hematological toxicities (excluding peripheral neuropathy)[b]	Grade ≥3	• Withhold bortezomib therapy until symptoms of toxicity have resolved. Then, bortezomib may be reinitiated with 1 dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). • For bortezomib-related neuropathic pain and/or peripheral neuropathy, hold or modify bortezomib as outlined in local/regional prescribing information (further detail given below).
Peripheral Neuropathy	Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	• No action.
	Grade 1 with pain, or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living [ADL[b]])	• Reduce bortezomib to 1 mg/m^2. Or • Change bortezomib treatment schedule to 1.3 mg/m^2 once per week.
	Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL[b])	• Withhold bortezomib therapy until toxicity resolves. When toxicity resolves, reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 once per week.
	Grade 4 (life-threatening consequences; urgent intervention indicated)	• Discontinue bortezomib.

a. Dose modifications for bortezomib will follow guidelines in local/regional prescribing information.
b. Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc. Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Data Source: *Velcade* (bortezomib) prescribing information.

Table 17 Dose modification guidelines for hematologic and other toxicities attributed to lenalidomide[a]

Toxicity	Grade/Symptoms	Recommendations
Thrombocytopenia	See Table 12 for Dose Modification for Overlapping Hematological Toxicities.	
Neutropenia Absolute Neutrophil Counts (ANC)	See Table 12 for Dose Modification for Overlapping Hematological Toxicities.	
For other toxicities judged to be related to lenalidomide	Grade 3 to 4	• Hold lenalidomide treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to ≤Grade 2.

a. Investigators should use their clinical judgement for lenalidomide dose reductions, following local/regional prescribing information. Available doses of lenalidomide capsules are 25 mg, 20 mg, 15 mg, 10 mg, 5 mg. Participants should not be dosed below 5mg.

Data Source: *Revlimid* (lenalidomide) prescribing information.

6.6.2.4. Dose Modification Guidance for Dexamethasone

Dexamethasone should be taken at the same time of the day and may be taken at home. For participants who are older than 75 years, underweight (BMI <18.5), have poorly controlled diabetes mellitus, or prior intolerance/AE to steroid therapy, the dexamethasone dose may be administered at a dose of 10 mg (Cycles 1-8) or 20 mg (Cycles 9+) on the days indicated above.

Dose modifications for dexamethasone other than those above should be made in line with local prescribing information, including reduction below 10 mg if necessary, and including if bortezomib is reduced to weekly dosing [O'Donnell, 2018].

6.6.3. Management of Hepatitis B positive participants

Management by local hepatology or infectious disease services is required. If no subspecialist support is available, consultation with GSK Medical Monitor is required prior to enrolment into the study for participants with positive titers to Hepatitis B.

- Participants should be monitored according to SoA (Section 1.3).
- Participants who experience clinically significant elevations in liver chemistry should follow liver event monitoring and stopping criteria (Section 7.1.1 and Section 10.6), and careful evaluation should be immediately initiated for evaluation of etiology including hepatitis B virus (HBV)-DNA testing.
- Participants who develop detectable HBV-DNA levels during study treatment should be reviewed by local specialist(s) **immediately (within 1 week)**, initiate appropriate therapy and monitoring.
- Study treatment should be withheld, and GSK Medical Monitor should be contacted for any participant who develops detectable HBV-DNA levels.

Table 18 Dose modification guidelines for hepatitis B reactivation

Toxicity	Grade/description of toxicity	Recommendations
Hepatitis B reactivation	Detectable HBV-DNA	• Immediate consult with local specialist to initiate/modify treatment. • Hold study treatment. • Contact GSK Medical Monitor promptly, agreement with Medical Monitor must be obtained prior to further dosing of study treatment. • Follow liver monitoring/stopping guidelines per protocol for elevated liver function tests.

6.7. Continued access to study intervention after the end of the study

There is no planned study intervention following the EoS.

The investigator is responsible for ensuring that consideration has been given to the post-trial care of the participants' medical condition.

If a rollover/extension study, expanded access route inclusive of group program or single patient compassionate use, or if the product is commercially available for the concerned indication at the time of the final DCO, participants continuing to derive benefit from intervention(s) may transition at the final DCO to continue treatment. This would depend on what access route(s) are available in a given country.

During the PACT phase, alternative continued treatment access route(s) outside of this study may be implemented, as it becomes available.

6.7.1. Continued access to study intervention after data cut-off prior to EoS

Following the DCO date for the final analysis, study 209664 (DREAMM-9) may move into the PACT phase. Participants receiving study intervention(s) at the time of the final analysis DCO date, may continue to receive study intervention(s), if in the opinion of their treating physician, they are benefiting from continued treatment, and they do not meet any protocol-defined treatment discontinuation criteria (Section 7.1). Study intervention will continue until transition to an alternative method of continued treatment access outside of the study, or until manufacturing of the product ceases, or until a study intervention discontinuation criterion (Section 7.1), as assessed by the investigator, has been met whichever occurs first. Other alternative continued treatment access outside of this study may be implemented, as it becomes available.

Participants who continue study intervention(s) in the PACT phase will be cared for in accordance with local standard clinical practice. Additional guidance on treatment with the study intervention and participant management is provided in the SRM.

Participants will continue to be monitored for all SAEs, AEs leading to study intervention discontinuation, overdose, prespecified ocular data and pregnancy while receiving study intervention(s) and these events must continue to be reported to GSK in accordance with Section 8.3.1). Information relating to participant care will be recorded on participant medical records, but will not be reported for the purposes of this study.

For dispensing of study intervention and maintaining study intervention accountability in the PACT phase please refer to the pharmacy manual. All other assessments will revert to standard of care at their site.

6.8. Treatment of overdose

6.8.1. Belantamab mafodotin overdose

There is no specific information on overdose of belantamab mafodotin. GSK does not recommend specific treatment for an overdose of belantamab mafodotin.

In the event of an overdose (defined as administration of more than the protocol-specified dose) of belantamab mafodotin, the Investigator should:

- Contact the GSK Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, if possible, whether study intervention should be interrupted or delayed.
- Closely monitor the participant for AEs, SAEs, and laboratory abnormalities until these have resolved and belantamab mafodotin concentrations are predicted to be within the anticipated range in absence of the overdose.
- Obtain an additional PK and serum sBCMA sample as soon as the overdose situation is recognized and contact the GSK Medical Monitor for further guidance with regards to additional sample collection (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the GSK Medical Monitor based on the clinical evaluation of the participant.

6.8.2. Lenalidomide overdose

There is no specific experience in the management of lenalidomide overdose in participants with MM. In dose-ranging studies in healthy participants, some were exposed to up to 200 mg (administered 100 mg BID [twice daily]) and in single dose studies, some participants were exposed to up to 400 mg. Pruritis, urticaria, rash, and elevated liver transaminases were the primary reported AEs. In clinical trials, the dose-limiting toxicities were neutropenia and thrombocytopenia.

The participants' dosing diary should accurately reflect what dose has been taken.

6.8.3. Bortezomib overdose

There is no known specific antidote for bortezomib over-dosage. In humans, fatal outcomes following the administration of more than twice the recommended therapeutic dose have been reported, which were associated with the acute onset of symptomatic hypotension and thrombocytopenia. In the event of an overdose, the participant's vital signs should be monitored, and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or inotropic agents) and body temperature as per the bortezomib label.

6.8.4. Dexamethasone overdose

An overdose or prolonged use of dexamethasone may exaggerate glucocorticoid adverse effects. Treatment should be symptomatic and supportive with the dosage of dexamethasone being reduced or slowly withdrawn where possible.

The participants' dosing diary should accurately reflect what dose has been taken.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

See the SoA for data to be collected at the time of discontinuation of study treatment i.e., the EOT Visit, 70-day Safety Follow-Up and Ocular Follow-up.

Study treatment must be permanently discontinued in the case of:

- Confirmed disease progression, as defined by IMWG criteria [Kumar, 2016].
- Unacceptable toxicity to the combination.
  Note: See below for advice on unacceptable toxicity for individual agents.
- Meeting any of the protocol-defined safety stopping criteria.

In addition, study treatment may be permanently discontinued for any of the following reasons:

- Deviation(s) from the protocol.
- Request of the participant or proxy (withdrawal of consent by participant or proxy).
- Investigator's discretion.
- Participant is LTFU.
- The study is closed or terminated.

If the participant voluntarily discontinues from treatment due to toxicity, the AEs will be recorded as the primary reason for permanent discontinuation on the electronic case report form (eCRF).

Once a participant has permanently discontinued from a study treatment, the participant will not be allowed to restart study treatment.

All participants who permanently discontinue study treatment will have safety assessments at the time of discontinuation and during EOT follow-up as specified in Section 1.3.

Participants who permanently discontinue study treatment for reasons other than disease progression will remain in the study and will be followed for PFS Follow-up visits according to the SoA until:

- New anti-myeloma therapy is initiated, or
- Disease progression according to IMWG criteria, or
- Death, or
- Withdrawal of consent, or
- LTFU.

Discontinuation of Individual Components of Combination Regimens

At the discretion of the investigator, participants who must permanently discontinue any of the individual SoC agents may continue belantamab mafodotin plus the remaining SoC agent(s) until PD, unacceptable toxicity, or death occurs or EoS.

During the induction Phase (i.e. B-VRd) of the study, if a participant must permanently discontinue belantamab mafodotin treatment, they may continue to receive VRd treatment for the remainder of the induction Phase. Prior to starting maintenance Rd, participants should have their EOT Visit as per the SoA followed by a PFS Follow-up or 70-day Safety Follow-up (if applicable).

During the maintenance Phase (i.e., B-Rd) of the study, if a participant must permanently discontinue belantamab mafodotin treatment, participants should have their EOT Visit as per the SoA followed by a PFS Follow-up or 70-day Safety Follow-up (if applicable).

Participants who have treatment-related ocular AEs at the EOT should be followed to resolution, as described in the SoA and Section 8.2.9 before discontinuing from the study.

If a participant enroled prior to the implementation of Amendment 1 is unable to receive Rd or an acceptable alternative as an available SoC, they may continue receiving Rd treatment and remain on study, following the visit schedule as per the SoA.

Participants are not permitted to move into other cohorts in the study and will continue in their current dose cohort.

The primary reason for discontinuation of any of the individual components of the combination regimen study treatment must be documented independently in the medical record and on the eCRF based on the list below:

Reasons
Completed follow-up
Death
LTFU
Physician decision, specify
Protocol deviation, specify
Site terminated by sponsor, specify
Study terminated by sponsor
Participant reached protocol-defined stopping criteria
Withdrawal by participant

AE = adverse event; LTFU = Lost to follow-up.

7.1.1. Liver chemistry stopping criteria

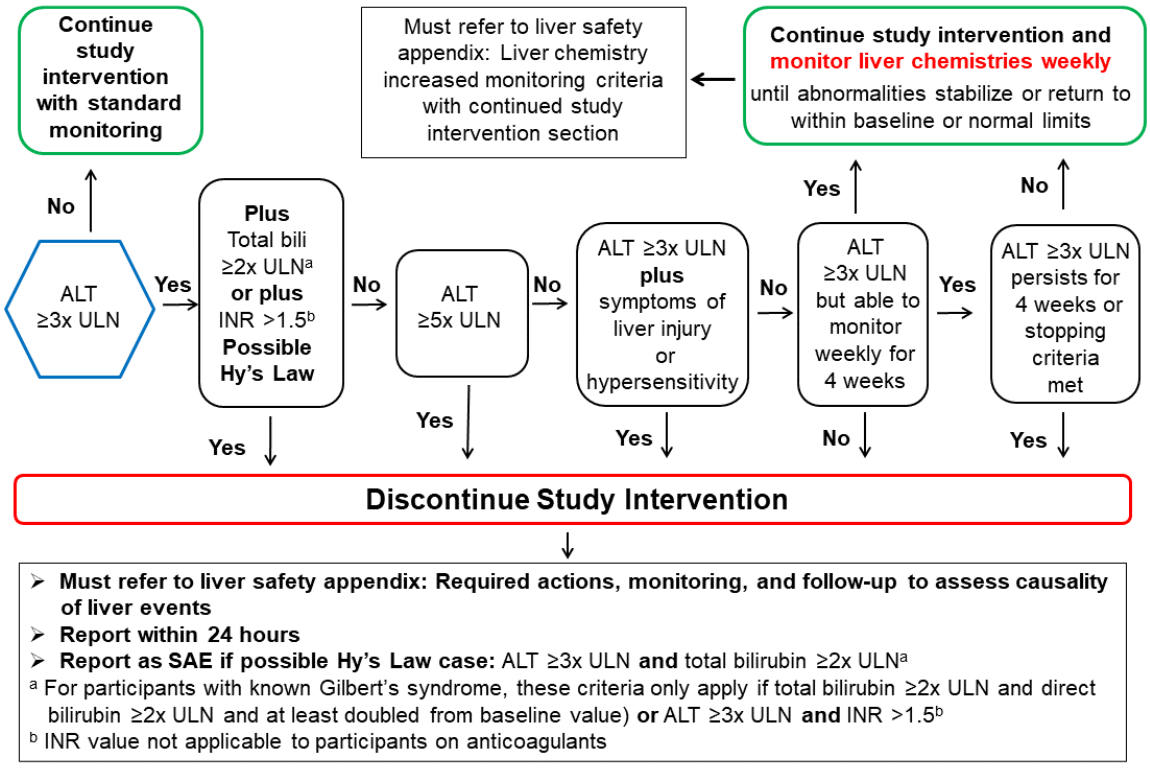
Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study treatment for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in Figure 4, or
- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the Investigator believes study treatment discontinuation is in the best interest of the participant.

Participants with ALT ≥3xULN but <5xULN may continue treatment but must have increased monitoring as outlined in Figure 4.

Figure 4 Liver chemistry stopping and increased monitoring algorithm



ALT = Alanine aminotransferase; INR = International normalized ratio; SAE = Serious adverse event; Total bili = total bilirubin; ULN = upper limit of normal.

Refer to Section 10.6 for required Liver Safety Actions, monitoring, and follow-up to assess the causality of liver events.

Participants who do not meet protocol-specified liver event stopping criteria but met protocol-defined increased monitoring criteria may continue study intervention with increased (weekly) liver chemistry monitoring. Refer to Section 10.6.2 for required liver event increased monitoring criteria with continued study intervention.

7.1.1.1. Study Treatment Restart or Rechallenge after liver stopping criteria met

If participant meets liver chemistry stopping criteria do not restart/rechallenge participant with study treatment unless:

- GSK Medical Governance approval is granted,
- Ethics and/or Institutional Review Boards (IRB) approval is obtained, if required, and,
- Separate consent for treatment restart/rechallenge is signed by the participant.

Refer to Section 10.6 for details.

If GSK Medical Governance approval to restart/rechallenge participant with study treatment **is not granted**, then participant must permanently discontinue study treatment and may continue in the study for protocol-specified follow-up assessments.

7.1.2. Pregnancy

Participants should immediately stop study treatment if they become pregnant and follow the pregnancy reporting requirements in Section 10.4.

7.1.3. Corneal event stopping criteria

All belantamab mafodotin dose modifications and stopping criteria for corneal events are to be based on the KVA scale for belantamab mafodotin corneal events (Table 14).

Participants who develop Grade 4 corneal events according to the KVA scale must be discussed in detail between the treating eye care specialist, and the GSK Medical Monitor, in order to determine whether the participant can be allowed to continue treatment with belantamab mafodotin, or permanently discontinue treatment (Table 15). The decision will be documented in study files, together with individual assessment of risk-benefit.

7.1.4. Infusion-related reactions stopping criteria

For belantamab mafodotin, premedication is not required prior to infusion unless deemed medically appropriate by the Investigator following evaluation of IRRs. Premedication should be considered in any participant who experienced an IRR at first or any subsequent infusion with belantamab mafodotin. For infusion reactions of any grade/severity, immediately interrupt the belantamab mafodotin infusion and manage symptoms. Once reaction symptoms resolve, resume the infusion at a reduced rate. Premedication may be required with subsequent infusions (Section 6.1.1.1).

A participant that experiences a Grade 4 IRR associated with belantamab mafodotin should be permanently withdrawn from study treatment but will be followed up for assessments in accordance with the SoA.

7.1.5. Allergic reactions and anaphylactic reactions stopping criteria

All participants will be monitored carefully for evidence of allergic response to treatment. A participant that exhibits signs or symptoms of severe hypersensitivity or anaphylaxis will receive appropriate medical treatment and will permanently discontinue study treatment.

7.2. Participant discontinuation/withdrawal from the study

A participant may withdraw from the study at any time at the participant's request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

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

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

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.5.3).

7.3. Lost to follow-up

A participant will be considered LTFU if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

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

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

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Key assessments to be performed are listed below, with more detailed information provided for some specific assessments in the Appendices or the SRM.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Whenever vital signs, 12-lead ECGs, and procedures (e.g., blood draws, BM aspiration/biopsy, imaging) are scheduled for the same nominal time, the assessments will ideally occur in the following order: 12-lead ECG, vital signs, blood draws, procedures. This is to allow the timing of the blood draw to occur at the exact nominal time. Detailed procedures for obtaining each assessment are provided in the SRM.
- Visit windows:
  - Baseline disease assessments must be completed within 21 days prior to dosing start unless otherwise specified.
  - Screening assessments performed within the permitted time need not be repeated on C1D1 unless otherwise specified.
  - Safety labs completed within 72 hours of first dose do not need to be repeated on C1D1 unless clinically indicated. Lab assessments that do not meet eligibility criteria on C1D1 may be repeated as long as they can be done in time to allow randomization within the 21-day Screening Period.
  - Pregnancy testing must be completed twice during screening: the first within 10 to 14 days of Cycle 1 Day 1, and the second within 24 hours prior to starting lenalidomide at Cycle 1 Day 1 using a highly sensitive serum pregnancy test. During treatment pregnancy test must be performed within 24 hours prior to any study treatment at Day 1 of each cycle.
  - ECHO must be completed within 30 days prior to first dose.
  - Imaging, which is only performed on participants with extramedullary disease (EMD), must be completed within 30 days prior to Cycle 1 Day 1.

  - On-study Q3W, Q4W, Q6W, Q8W, Q9W and Q12W treatment or ‘cycles’ visits have a ±3-day window.
  - On-study Q3W, Q4W disease assessment or ‘weeks’ visits have a ±3-day window. Q8W disease assessment visits have a ±7-day window.
  - The 70-day Safety Follow-up Visit has a +14-day window.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy assessments

8.1.1. Minimal residual disease

MRD will be assessed on participant bone marrow (BM) aspirate samples using a next-generation sequencing (NGS)-based assay at a central testing laboratory. MRD sample is to be collected at screening and as soon as possible when first achieving response of VGPR or better, and repeated every 6 months (±1 month window) for 2 years, and then yearly after until PD. In case of deepening of response from VGPR to CR, MRD sample should be collected at the time of CR assessment and then repeated every 6 months (±1 month window) for 2 years, and then yearly after until PD.

MRD by NGS will not be used for modification of participant treatment.

8.1.2. Response evaluation

Response will be assessed according to the IMWG criteria [Kumar, 2016] by the Investigator. Response assessments will be performed Q3W for 6-months, Q4W a further 18-months, then Q8W thereafter. These are fixed time point visits regardless of any delays or modification to **treatment Cycles**.

Standard disease assessments for NDMM will include the following assessments:

- Urine protein electrophoresis (UPEP), urine immunofixation, 24-hour collection for urine M-protein.
- Serum protein electrophoresis (SPEP), serum M-protein, serum immunofixation.
- Calcium corrected for albumin.
- IgG, IgM, IgA.
- Immunoglobulin D (IgD), Immunoglobulin E (IgE) (only in participants with IgD or IgE myeloma).
- Serum kappa, lambda FLC ratio.
- BM (aspirate preferred) at Screening and to confirm CR/sCR. Additional testing required where:
  - VGPR or better is achieved: Aspirate to assess MRD status.

  - CR is achieved: Aspirate to assess MRD status, and biopsy to confirm CR and for immunohistochemistry (IHC) to confirm sCR.
- Imaging of EMD (in participants with EMD).
- Physical examination (as indicated for palpable/superficial lesions).
- Skeletal surveys at Screening and as clinically indicated.
- Optional tissue sample at diagnosis of PD.

Baseline serum/urine disease assessment will be completed during the Screening Period (within 21 days prior to the first dose of study treatment) and baseline imaging within 30 days prior to the first dose of study treatment. On-study serum and urine-based assessments (M-protein, FLC, immunofixation) will be performed Q3W for 6-months, Q4W for a further 18-months, and Q8W thereafter. Details for the preparation and shipment of samples for central laboratory assessments will be provided in the Laboratory Manual.

In participants with extramedullary myeloma, the disease assessments must include imaging (e.g., CT, MRI, or PET-CT scans: the same method should be used throughout the study) and physical examination (as indicated for palpable/superficial lesions).

For participants who are followed by imaging for EMD the imaging should be performed as described in the SoA (Section 1.3).

All assessments on study must be performed on a calendar schedule and must not be affected by dose interruptions/delays.

For participants who are discontinuing IP due to PD, the confirmation of laboratory parameters must be performed from a different blood collection preferably within 14 days of the original date of suspected disease progression, preferably before initiation of any new anti-myeloma therapy. For participants with PD due to EMD, confirmatory scans are not required. The laboratory parameters do not need to be repeated if the EMD is the only site of progression.

8.2. Safety assessments

Planned time points for all safety assessments are provided in the SoA. Key assessments are summarized below.

8.2.1. Physical examinations

Physical examinations will be performed during Screening, pre-dose on Day 1, and pre-dose on Day 1, of each Cycle, and upon discontinuation from Study Treatment (EOT Visit and PFS FU Visit). A physical examination will include, at a minimum, assessments of the head, eyes, ears, nose, throat, skin, thyroid, lungs, CV, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured at Screening and recorded, with weight repeated at the start of each cycle (SoA, Section 1.3).

During the physical examinations, Investigators should pay special attention to clinical signs related to previous serious illnesses and record any changes noted during study treatment, if any.

8.2.2. Vital signs

Vital sign measurements will include systolic and diastolic blood pressure, temperature, and pulse rate. Vital signs should be measured after resting for at least 5 min. Vital signs will be measured more frequently if warranted by the clinical condition of the participant. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

First infusion: vital signs must be assessed prior to each infusion of belantamab mafodotin at pre-dose, defined as within 30 min prior to Start of Infusion (SOI), 15 min after SOI (± 5mins), within 15 min after EOI, and at 1 hour after EOI (±10 min). No additional vital signs assessments are required for bortezomib unless clinically indicated.

Subsequent infusions: vital signs must be assessed prior to each infusion of belantamab mafodotin at pre-dose, defined as within 30 min prior to SOI, within 15 min after EOI, and then as clinically indicated. No additional vital signs assessments are required for bortezomib unless clinically indicated.

In general, participants must also be monitored for at least 1 hour after the completion of the infusion of belantamab mafodotin and may be discharged if considered clinically stable and all other study procedures have been completed.

On days where, vital sign time points align with PK sampling time points, vital signs should be assessed prior to PK samples being drawn.

In case of IRRs monitoring will be performed with higher frequency (as clinically indicated).

8.2.3. ECOG performance status

The participant's performance status will be assessed using the ECOG scale (Section 10.10) as specified in the Schedule of Activities (Section 1.3).

8.2.4. IMWG frailty score

Participants frailty score at screening will be assessed using the IMWG Frailty Score [Palumbo, 2015]. See Section 10.7 for further details.

8.2.5. New York Heart Association functional scale

Criteria for rating participants for heart failure status according to the New York Heart Association (NYHA) criteria are provided in Section 10.8.

8.2.6. Electrocardiograms

A 12-lead electrocardiogram (ECG) is obtained at screening/baseline and then as clinically indicated as specified in the SoA (Section 1.3). The ECG machine must automatically calculate the heart rate and measure PR, QRS, QT, and corrected QT (QTc) intervals according to Fridericia's formula (QTcF). No further ECGs are required, but if obtained as part of medical care a 12-lead ECG should be performed by qualified personnel at the site after the participant has at least a 5-minute rest.

Triplicate ECG should be performed if during treatment QTcF is >530 msec.

Where triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicate ECGs should be completed in 4 minutes or less.

8.2.7. Echocardiogram

Echocardiograms (ECHOs) must be performed at screening/baseline to assess cardiac ejection fraction for the purpose of study eligibility, and then as clinically indicated. The evaluation of the echocardiographer must include an evaluation for left ventricular ejection fraction (LVEF). For ECHOs performed on study, the results must be documented in the eCRF.

8.2.8. Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).

Prior to administration of the first dose of study treatment, results of laboratory assessments should be reviewed. Any laboratory test with a value outside the normal range may be repeated (prior to the first dose) at the discretion of the Investigator.

If additional non-protocol-specified laboratory assessments are performed at the institution's local laboratory and result in a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification) the results must be recorded. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or until at least 70 days after the last dose of study treatment should be repeated until the values return to normal, or baseline are no longer considered significantly abnormal by the investigator or Medical Monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

Asymptomatic elevations of lactate dehydrogenase (LDH) and creatine kinase (CK) and AST have been observed in Study BMA117159. Participants with significant elevations (≥3xULN) should, where possible, have a sample sent for central testing of CK and LDH isoenzyme levels.

8.2.9. Ophthalmic examinations

Study sites are required to establish a close collaboration with a qualified eye care specialist who will be responsible for assessing participants while they are on-study and managing participants who develop a corneal event in close communication with the GSK Medical Monitor.

Participants will be assessed by a qualified eye care specialist (See Section 10.12 for qualifications and requirements of the eye care specialist) at screening/baseline and then on D1 prior to belantamab mafodotin dosing for the first 5 Doses of belantamab mafodotin (assessment window of up to 5 days prior to dosing, but all effort should be made to schedule as close to belantamab mafodotin dosing as possible). Participants in a Q6/8W or Q9/12W dosing schedule will follow the same ophthalmic exam schedule at Q3/4W for the first 5 doses.

- If there are no significant (Grade 2 and above) ocular examinations findings, participant's symptoms or vision changes at the exam of the fifth dose of belantamab mafodotin, participants may have their ophthalmologic exams decreased to prior to scheduled dosing or as clinically indicated by the qualified eye care specialist.
- If a participant subsequently develops vision changes or other ocular symptoms, the participant should be promptly evaluated by a qualified eye care specialist.
- In case of persistent ophthalmic exam findings, newly developed ocular symptoms or vision changes at the Dose 5 exam, the participants will have further ophthalmologic exams, at least every cycle until resolution (to Grade 1 or baseline for both corneal exam findings and visual acuity) or more frequently as clinically indicated by the qualified eye care specialist.

Participants who have treatment-related ocular AEs or KVA (Grade 2 or higher for either corneal exam findings or visual acuity) at the EOT Visit will be followed once every 3 months (±7 days) until full resolution of ophthalmic changes (Grade 1 or baseline for both corneal exam findings and visual acuity) by a qualified eye care specialist or start a new anti-myeloma therapy, or up to 1 year (whichever comes first).

If steroid eye drops are deemed medically necessary and prescribed for >7 days, intraocular pressure must be monitored.

8.2.9.1. Ocular Examinations and Procedures

A full screening/baseline ophthalmic examination for all participants must include for both eyes (OU):

1. Best corrected visual acuity.
2. Documentation of manifest refraction and the method used to obtain best corrected visual acuity.
3. Current glasses prescription (if applicable).
4. Selected anterior segment (slit lamp) examination with focus on the cornea and lens, including fluorescein staining of the cornea.
5. Intraocular pressure measurement.
6. Dilated funduscopic exam.

The on-treatment and follow-up ophthalmic exams should be performed as described below and in the SoA (Section 1.3).

This should include:

1. Best corrected visual acuity.
2. Documentation of manifest refraction and the method used to obtain best corrected visual acuity.
3. Anterior segment (slit lamp) examination with focus on the cornea and lens, including fluorescein staining of the cornea.
4. Intraocular pressure measurement.
5. Dilated funduscopic exam (if clinically indicated).

The EOT, and **last follow-up** ophthalmic exam, if required, should match the **screening/baseline** exam.

Additional examinations should be performed at the discretion of the treating eye care specialist.

8.2.10. Visual function safety assessment

The impact of potential ocular toxicity on function and HRQOL will be assessed with the use of the visual function questionnaire the Ocular Surface Disease Index (OSDI).

PROs will be done at the start of every visit either before or after laboratory sample collection, and prior to any other procedures or provision of results. All participants will complete the self-administered version of the questionnaire, unless their vision or other factors prevent them from being able to complete the questionnaire on their own. Participants who are not able to complete the questionnaire on their own and require assistance should have the PROs administered to them in an interview format. The questionnaires should be read to the participants verbatim, and participant responses

should be recorded directly without any interpretation. For any additional assessments conducted via telephone (either during participation in the Treatment Period or during Follow-up), an interview format should be used where a site staff member administers the questionnaires over the telephone.

The OSDI is a 12-item questionnaire designed to assess both the frequency of dry eye symptoms and their impact on vision-related functioning [Dimopoulos, 2021; Dougherty, 2011; Schiffman, 2000]. The OSDI has demonstrated good reliability, validity, sensitivity, and specificity, and can be used as a complement to other clinical and participative measures of dry eye disease by providing a quantifiable assessment of dry eye symptom frequency and the impact of these symptoms on vision-related functioning. The OSDI will be completed by the participants at the times shown in the Schedule of Activities (Section 1.3).

The OSDI will be administered to participants in different regions based on the availability of translated versions.

8.2.11. PRO-CTCAE

PROs, including the PRO-CTCAE, will be done at the start of every visit either before or after laboratory sample collection, and prior to any other procedures or provision of results. The PRO-CTCAE includes an item library of 124 items representing 78 symptomatic toxicities drawn from the CTCAE. PRO-CTCAE provides a systematic yet flexible tool for descriptive reporting of symptomatic treatment side effects in cancer clinical trials. In the present study, a subset of items selected from the PRO-CTCAE Version 1.0 Item Library will be administered [Cella, 1993; Cocks, 2007; Kluetz, 2016]. The PRO-CTCAE will be completed by the participants at the times shown in the Schedule of Activities (Section 1.3).

The PRO-CTCAE will be administered to participants in different regions based on the availability of translated versions. All participants will complete the self-administered version of these assessments unless they are unable to do so due to vision impairment, site restrictions or the Principal Investigator or site feels it is in the best interest of the participant not to come to the site. Participants who cannot complete the self-administered version should use an interviewer-administered format.

8.2.12. Suicidal ideation and behavior risk monitoring

Not applicable.

8.3. AEs, SAEs and other safety reporting

The definitions of an AE or SAE can be found in Section 10.3.

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (Section 6).

8.3.1. Time period and frequency for collecting AEs, SAEs and other safety information

All SAEs will be collected from the start of treatment until at least 70 days following discontinuation of study treatment at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study up to and including any follow-up.

All AEs will be collected from the start of treatment until at least 70 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice at the time points specified in the SoA.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF and not in the AE section.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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

For participants in the PACT phase of the study, GSK will continue to collect safety information. Investigators must report directly to GSK all SAEs, AEs leading to study intervention discontinuation, overdose, prespecified ocular data and pregnancy cases via paper forms.

SAEs, overdose, prespecified ocular data and pregnancy cases will be reported during the PACT study intervention period and for up to 70 days after the participant's last dose.

Any pregnancies that occur within 28 days following the last dose of lenalidomide, 4 months following the last dose of belantamab mafodotin, or 7-months from the last dose of bortezomib will be reported, in accordance with section 8.3.5.

For all the PACT phase participants transitioned to continue treatment outside of the study, the day of their last dose of study intervention is the end date for safety collection and reporting for the PACT Phase.

Additionally, any SAEs that are ongoing at the time of the final DCO must be followed up to resolution unless the event is considered by the investigator unlikely to resolve, or the participant is lost to follow-up. Updates to these events will also occur via paper forms directly to GSK. GSK retains the right to request additional information for any participant with ongoing AEs/SAEs and ocular examination findings, at EoS, if judged necessary.

Ocular Follow-up:

For participants continuing on belantamab mafodotin-containing study treatment as part of PACT Phase:

- Ocular exam schedule during PACT Phase:
  - Participants without ocular (including corneal) examinations findings, symptoms or vision changes when entering the PACT Phase will be required to have an ocular assessment prior to each dose of belantamab mafodotin, or as clinically indicated, until the end of treatment.
  - For participants who enter PACT Phase with ocular (including corneal) examinations findings, symptoms or vision changes (or develop these during PACT Phase), whilst holding drug the ocular assessments will occur as clinically indicated until resolution (KVA Grade 1 or baseline). After resolution, ocular examinations will be performed prior to each dose of belantamab mafodotin, or as clinically indicated, until the end of treatment.
- Ocular exam schedule after end of PACT Phase:
  - It is advised that participants with treatment-related ocular (including corneal) examination findings, symptoms or vision changes at the end of the PACT Phase continue to have ocular assessments as SoC until resolution.

For participants who stopped belantamab mafodotin prior to PACT Phase but have ongoing treatment-related ocular (including corneal) examination findings, symptoms or vision changes at the time of final study DCO/start of PACT Phase, it is advised that their ocular assessments continue as SoC until resolution.

Note: Participants who continue to receive belantamab mafodotin via another drug supply program (e.g., an expanded access route, rollover/compassionate use) should follow ocular examination guidance provided by the source/program from which they are receiving belantamab mafodotin.

8.3.2. Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AESIs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is LTFU (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.3.4. Regulatory reporting requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

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

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

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

Table 19 Timeframes for submitting SAE, pregnancy and other events reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic/paper AEs report	24 hours*	electronic/paper AEs report
Pregnancies	24 hours*	electronic/paper pregnancy report	24 hours*	electronic/paper pregnancy report
Applicable to PACT phase only AE leading to discontinuation	24 hours	paper AEs Report	24 hours	paper AEs Report

AE = Adverse event; PACT = Post Analysis Continued Treatment; SAE = Serious Adverse Event.
*Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
‡For each SAE, the investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality.

8.3.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and for 4 months following last dose of belantamab mafodotin. If belantamab mafodotin is discontinued and other agents continue, details of all pregnancies in female participants will be collected for 28 days after the last dose of lenalidomide, or 7-months following the last dose of bortezomib, whichever is longer. Details may be collected by telephone.
- Details of all pregnancies for female partners of male participants will be collected after the start of study treatment and 6 months following last dose of belantamab mafodotin. If belantamab mafodotin is discontinued and other agents continue, details of all pregnancies in female partners of male participants will be collected for 28 days after the last dose of lenalidomide, or 4-months following the last dose of bortezomib, whichever is longer. Details may be collected by telephone.
- If a pregnancy is reported, the Investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4 as well as those outlined in Participant the Lenalidomide Global Pregnancy Prevention Plan or other country specific program.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

8.3.6. Cardiovascular and death Events

For any CV events detailed in Section 10.8 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the CRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-cardiovascular death.

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

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

8.3.7. Adverse events of special interest

AESI for belantamab mafodotin are corneal events, thrombocytopenia, and IRRs. Severity of all AESIs will be graded using the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE, v5.0). Severity of corneal events will be graded using the KVA scale for corneal events provided in Table 14. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in Section 6.6.

8.4. Pharmacokinetics

8.4.1. Blood sample collection for pharmacokinetics

Blood samples for pharmacokinetic analysis of belantamab mafodotin (ADC) and cys-mc MMAF will be collected for all participants at the time points outlined in Table 20. Alterations may be made to the sampling schedule based on the results from analyses of emerging data. Such alterations, if made, will not require a protocol amendment and will be documented in the laboratory manual.

Each pharmacokinetic sample should be collected as close as possible to the planned time relative to the administration of the drug being measured on pharmacokinetic sampling days. The actual date and time of each blood sample collection will be recorded. Details on pharmacokinetic blood sample collection including blood volumes, processing, storage, and shipping procedures are provided in the SRM.

All PK, sBCMA, and ADA samples once collected (regardless of dosing) can be analyzed if the sample date and time have been recorded.

PK and accompanying sBCMA sample collection may be terminated when sufficient data have been collected.

Table 20 PK and sBCMA samples for participants on Day 1 dose regimens

sBCMA sample should be taken at every PK timepoint. In addition, sBCMA sample should be taken at all MRD assessments and at EOT.

Dose/Day	Timing[1]	Notes
Dose1 D1	Pre-dose	To be collected within 30 min prior to SOI on Day 1.
	EOI	To be collected within 15 min after EOI on Day 1.
	SOI+2 hours	To be collected at 2 hours (± 15 min) after SOI on Day 1.
Dose1 D2	SOI+24 hours	To be collected at 24 hours (± 2 h) after SOI of Dose 1.
Dose1 D4	Prior to Bor dosing	To be collected 72 hours (± 24 h) after SOI of Dose 1 prior to bortezomib administration.
Dose1 D8-Dose1 D15	N/A	One PK sample to be taken at any time between Dose 1 D8 and Dose 1 D15. If this coincided with a bortezomib administration day PK sample should be taken prior to bortezomib administration.
Dose 1 D22	N/A	One PK sample to be taken on Dose 1 D22 (±3 days) for participants on Q6/8W or Q9/12W schedule.
Dose2 D1* Dose3 D1* Dose4 D1 Dose6 D1	Pre-Dose	To be collected within 30 min prior to SOI of Dose 2 D1, Dose 3 D1, Dose 6 D1. *If Dose 2 D1 is delayed, one PK sample must be taken at Dose 1 D22 for Q3/4W schedule, on Dose 1 Day 43 for Q6/8W schedule, and at Dose 1 Day 64 for Q9/12W schedule. *If Dose 3 D1 is delayed, one PK sample must be taken at Dose 2 D22 for Q3/4W schedule, on Dose 2 Day 43 for Q6/8W schedule, and at Dose 2 Day 64 for Q9/12W schedule.
	EOI	To be collected within 30 min after EOI on Dose2 D1, Dose3 D1, Dose6 D1.
Dose9 D1 Dose12 D1	Pre-dose	To be collected within 30 min prior to SOI on Dose9 D1, Dose12 D1.
Dose12+ D1	Pre-dose	Treatment beyond belantamab mafodotin Dose12, pre-infusion samples (within 30 min prior to SOI) will be collected on Day 1 only every sixth dose of belantamab mafodotin (Dose 18, 24, 30 and so on until the last sample at EoT).

Bor = Bortezomib; D = Day; EOI = End of Infusion; EOT = End of Treatment; PK = Pharmacokinetic(s); Q = Every; sBCMA = soluble BCMA; SOI = Start of Infusion; W = Week.

1. This PK sample is tied to the dose of belantamab mafodotin. This may not correspond to the cycle of treatment e.g., in the event that belantamab mafodotin is held whilst VRd continues.

* If Dose 2 or Dose 3 is delayed within 4 days of original schedule, Pre-Dose PK sample do not need to be collected if a PK sample has been taken respectively on Dose 1 or Dose 2 D22 (Q3/4W) / D43 (Q6/8W) / D64 (Q9/12W).

8.4.2. Belantamab mafodotin pharmacokinetic sample analysis

Plasma analysis will be performed under the control of GSK. Concentrations of belantamab mafodotin, total antibody, and cys-mcMMAF will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site.

Once the plasma has been analyzed for belantamab mafodotin, total antibody, and cys-mcMMAF, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate GSK BIB protocol.

8.4.3. Bortezomib, lenalidomide and dexamethasone PK sample collection and analysis

No PK sampling or analysis is required for bortezomib or lenalidomide or dexamethasone in this study.

8.5. Genetics

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study. The sample will be collected at the first opportunity after a participant has met all eligibility requirements preferably on C1D1. May be taken at another visit if not taken at C1D1.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Information regarding genetic research is included in Section 10.5. In approving the clinical protocol, the IEC/IRB and, where required, the applicable regulatory agency, are also approving the genetic research described in Section 10.5 unless otherwise indicated. Where required by regulatory authorities, approval of the genetic assessments can occur after approval is obtained for the rest of the study. In that case, written approval will indicate that approval of the genetic assessments is being deferred and the study, except for genetic assessments, can be initiated. If genetic assessments are not approved, they will not be conducted.

8.6. Biomarkers

Biomarker research is part of this study and will involve peripheral blood (serum and plasma) and BM. Samples will be collected at the time points indicated in the SoA (Section 1.3). The sample collection strategy may be adjusted on the basis of emerging data from this study or other studies involving belantamab mafodotin in order to ensure optimal evaluation of any potential biomarkers. The relationship of protein, DNA and/or RNA biomarkers in blood and/or BM samples to response to belantamab mafodotin and AEs may be evaluated. Unless otherwise stated, these investigations may be performed irrespective of whether a response to belantamab mafodotin is observed.

Additionally, blood (serum and/or plasma) and/or BM samples collected for biomarker research during this study may be used to identify and measure novel biomarkers associated with responses to belantamab mafodotin and/or pathogenesis of multiple myeloma. Novel biomarkers may be identified and measured by DNA, RNA, and/or protein analysis, and may involve use of sequencing of DNA and/or RNA. If relevant, this approach may be extended to include the identification of biomarkers associated with AEs.

Biomarkers assessed in this study may include, but not be limited to:

8.6.1. Tumor-related biomarkers

BM samples will be collected during this study at the time points indicated in the SoA (Section 1.3) to evaluate the relationship of protein, DNA and/or RNA biomarkers in the BM to response to belantamab mafodotin. Biomarkers assessed in BM samples may include, but not be limited to, BCMA expression on multiple myeloma cells and molecular characteristics of BM cells.

An optional BM sample at PD (BM biopsy or aspirate), may be collected from participants who have signed a separate consent for this sample. Participation in this part of the study is optional and all enrolled participants will be given the opportunity to contribute samples. Participation may be declined without effect on medical care during the clinical study.

8.6.1.1. BCMA expression on multiple myeloma cells

BM samples collected during this study may be used to evaluate the relationship of BCMA expression on multiple myeloma cells in the BM to response to belantamab mafodotin. BCMA expression in multiple myeloma cells may be measured by analysis of protein and/or RNA.

Molecular characteristics of bone marrow cells

BM samples collected during this study may be used to interrogate the relationship of genetic alterations, transcriptional profile, and/or protein expression in BM cells, including multiple myeloma cells and cells in the BM microenvironment, with response to belantamab mafodotin. These studies may include genomic and/or RNA transcriptomic analysis, and may involve use of sequencing of DNA, RNA, and/or alternative equivalent technologies.

8.6.2. sBCMA in blood serum

The BCMA receptor undergoes gamma-secretase mediated cleavage, leading to release of the BCMA extracellular domain as soluble BCMA (sBCMA) into circulation [Laurent, 2015]. Blood samples for measurement of serum sBCMA will be collected during this study at the points indicated in the SoA (Section 1.3). In an exploratory setting, we propose examinations of the relationship of sBCMA levels and changes of sBCMA levels with response to belantamab mafodotin, including but not limited to MRD and TTP.

8.7. Immunogenicity assessments

Serum samples for the analysis of anti-belantamab mafodotin antibodies will be collected from all participants according to the SoA (Section 1.3). Additionally, serum samples should be collected at the EOT Visit. These samples will be tested by the sponsor or sponsor's designee.

The samples will be tested for anti-belantamab mafodotin antibodies using a tiered-testing scheme consisting of validated screening, confirmation, and titration assays. Briefly, all samples will be tested in the screening assay. Samples that screen positive are considered potentially positive and will be tested for specificity in a confirmation assay. Finally, titer values will be obtained for confirmed positive samples using a titration assay. The sample results (e.g., positive or negative) and titer values (positive samples only) will be reported. Samples that test positive for anti-belantamab mafodotin antibodies may be further characterized in a validated neutralizing antibody assay to determine the neutralizing activity of the antibodies.

The detection and characterization of antibodies to belantamab mafodotin will be performed using validated assays. The anti-belantamab mafodotin antibody assay was designed to detect antibodies to belantamab mafodotin, the unconjugated monoclonal antibody, and the linker-payload portion of belantamab mafodotin. Additionally, plasma samples will be collected at the same time points (see Section 1.3) as the immunogenicity samples and analyzed to determine the belantamab mafodotin plasma concentration. The belantamab mafodotin plasma concentration results will enable interpretation of the anti-belantamab mafodotin antibody data. Anti-belantamab mafodotin antibody samples will be disposed 3 months after final approved results are provided to the Clinical Study Team or its designee or upon documented study termination.

8.8. Health-related quality of life

The following health-related Quality of life (QoL) instruments will be employed in this study to assess disease severity, disease symptoms, AEs associated with the study treatment, and general quality of life in study participants with NDMM. The PROs will be administered to participants in different regions based on the availability of translated versions.

All participants will complete the self-administered version of these assessments unless they are unable to do so due to vision impairment, site restrictions or the Principal Investigator or site feels it is in the best interest of the participant not to come to the site. Participants who cannot complete the self-administered version should use an interviewer-administered format. The interview may be administered by the site staff (or delegate) or a Contract Research Organization over the telephone. If the Interviewer-Administered format is used, the questionnaires should be read to the participants verbatim, and participant responses should be recorded directly without any interpretation.

- **EORTC-QLQ-C30** is a 30-item questionnaire containing both single- and multi-item measures [Aaronson, 1993]. These include 5 functional scales (Physical, Role, Cognitive, Emotional, and Social Functioning), 3 symptom scales (Fatigue, Pain, and Nausea/Vomiting), a Global Health Status/QoL scale, and 6 single items (Constipation, Diarrhea, Insomnia, Dyspnea, Appetite Loss, and Financial Difficulties). Scores for each scale and single-item measure are averaged and transformed linearly to a score ranging from 0–100. A high score for functional scales and for Global Health Status/QoL represent better functioning ability or health-related quality of life (HRQOL), whereas a high score for symptom scales and single items represents significant symptomatology [Proskorovsky, 2014].
- **PGIS** (Patient Global Impression of Severity) and PGIC (Patient Global Impression of Change): The PGIS assesses global impression of symptoms severity at baseline and subsequent time points. The second question, the PGIC serves to rate the global change in symptoms compared to study start. In addition to evaluating symptom severity and change, these questions serve as anchors to establish thresholds of clinically meaningful change for the questionnaires in the study [Guy, 1976].

9. STATISTICAL CONSIDERATIONS

This section briefly describes the planned analyses to be performed for study 209664. Analyses will be fully described in the Statistical Analysis Plan (SAP).

This study is a dose and schedule evaluation study to select the RP3D for future studies in the newly diagnosed setting. An interim analysis (IA) will be performed after the last participant reaches the end of Cycle 4 in cohorts 2-5 to determine cohort expansion of the selected cohort(s) and a possible evaluation of Cohort 6, Cohort 7, and Cohort 8. If cohorts 6-8 are open, then after the last participant completes the end of Cycle 8 (this includes participants in Cohort 6 to Cohort 8 who experienced treatment delays prior to completing the end of Cycle 8 if they have completed at least 2 disease assessments and ocular exams after the last dose of belantamab mafodotin), additional interim analyses may also be conducted to aid in decision making regarding dose identification, cohort expansion or closure, and safety monitoring, if necessary, after at least 6 participants are enrolled in each dose cohort. Details of treatment cycle can be found in the SRM. The primary analysis will take place close to when the last participant reaches the end of Cycle 8 in all dose cohorts after cohort expansion. The final analysis will be based on a data cut-off taken approximately 1 year after Last Patient First Dose (LPFD). If deemed appropriate, the primary and final analyses may be combined and performed at the planned time of the final analysis.

9.1. Statistical hypotheses

No formal statistical hypothesis is tested. Analysis of the data obtained will only utilize descriptive methods.

Safety data will be reviewed in an ongoing fashion. The number of participants in cohorts 2-5 and, if applicable, cohort 6, 7, and 8 who permanently discontinue study treatment due to AEs related to belantamab mafodotin within the first 3, 21-day, cycles of treatment will be continuously monitored. If there is evidence that the proportion of participants permanently discontinuing belantamab mafodotin in a dose cohort is higher than 12% (at 1-sided alpha of 0.01), then the combination treatment at that dose level will be considered to have unacceptable toxicity and the cohort will be closed.

9.2. Sample size determination

The total number of participants to be enrolled will depend on the number of participants needed to characterize individual dose cohorts. The sample size is not driven by statistical considerations. However, based on assumptions that up to 8 different dose cohorts may be evaluated, it is anticipated that up to 160 participants will be enrolled.

For dose evaluation, the total sample size will depend on the number needed to adequately characterize the DLT profile and determine the safe dose.

9.2.1. Statistical operating characteristics

The sample size and associated operating characteristics were evaluated.

Dose evaluation will be based on DLT and a dose cohort will be deemed safe at the primary analysis if:



CCI

[redacted]

9.3. Analysis sets

For purposes of analysis, the populations are defined as in Table 22.

Table 22 Populations for analyses

Population	Description
All-Screened	The All-Screened Population will consist of all participants who sign the ICF to participate in the clinical trial. Participants in this population will be used for screen failure summary.
Enrolled	All participants who entered the study (who were randomized or received study intervention or underwent a post screening study procedure).
DLT-Evaluable Population	The DLT-evaluable Population is defined as participants who have received treatment containing all agents (1 full dose of belantamab mafodotin, dependent on dose schedule, and ≥75% of planned VRd in Cycle 1) and followed up for the first 3, 21-day, treatment cycles or withdrawn within first 3, 21-day, cycles due to an AE meeting the definition of a DLT.
ITT	ITT Population will be the primary population for the analysis of efficacy data and defined in the following: • Cohort 1 and Cohort 8 will consist of non-randomized participants who take at least 1 dose of any study treatment. • Cohorts 2-7 will consist of randomized participants whether or not randomized treatment was administered. This population will be based on the treatment to which the participant was randomized. Any participant who receives a treatment randomization number will be considered to have been randomized.

Population	Description
Safety	All participants who received at least 1 dose of study treatment(s). Participants will be analyzed according to the treatment they actually received.
Pharmacokinetic	Participants in Safety analysis set from whom at least one PK sample has been obtained and analyzed. This population will be the primary population for PK analyses.
Efficacy	All participants with documented multiple myeloma and measurable disease who have not received any prior therapies and are transplant ineligible, who have received at least 1 dose of study treatment(s). Participants will be analyzed according to the treatment they were planned for.

AE = Adverse event; DLT = Dose-limiting toxicity; ICF = Informed Consent Form; ITT = Intention-to-treat; PK = Pharmacokinetic(s); VRd = Bortezomib (Velcade), Lenalidomide (Revlimid), and dexamethasone.

9.4. Statistical analyses

Statistical analyses (interim(s) and final) will be performed by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

9.4.1. Efficacy analyses

Analysis of secondary efficacy endpoints will be based on the response assessed by the investigator.

Primary analysis for all efficacy endpoints will be based on the intention-to-treat Population.

Table 23 Statistical analysis methods

Endpoint	Statistical Analysis Methods
Secondary	**Overall Response Rate (ORR)**, defined as the percentage of participants with a confirmed PR or better (i.e., PR, VGPR, CR, and sCR). **Complete Response Rate (CRR)**, defined as the percentage of participants with a confirmed complete response (CR) or better (i.e., CR, sCR). **Rate of VGPR or better**, defined as the percentage of participants with a VGPR or better (i.e. VGPR, CR, sCR). The number and percentage of participants with the best confirmed response in the following response categories will be summarized by treatment arm: sCR, CR, VGPR, PR, overall response (sCR+CR+VGPR+PR), CR (sCR+CR), minimal response (MR), stable disease (SD), progressive disease (PD), and not evaluable. The corresponding exact 95% CI for ORR will also be provided. CCI [redacted]

Endpoint	Statistical Analysis Methods
Exploratory	**Duration of Response (DoR)** is defined as the time from first documented evidence of PR or better until the earliest date of disease progression (PD), or death due to PD among participants who achieve a response (i.e., confirmed PR or better). **Time to Response (TTR)** is defined as the time between the date of randomization and the first documented evidence of response (PR or better), among participants who achieve a response (i.e., confirmed PR or better). **Time to Best Response (TTBR)**, defined as the interval of time between the date of randomization and the earliest date of achieving best response among participants with a confirmed PR or better. **Time to disease progression (TTP),** defined as the time from first dose until the earliest date of PD per IMWG, or death due to PD. Determination of dates of TTP event and dates for censoring will be described in the SAP. **MRD** negativity rate is defined as the proportion of participants who are MRD negative as assessed by next generation sequencing (NGS). For analysis purposes, participants in the ITT Population without MRD assessment will be considered as having non-negative MRD. The corresponding 95% exact CI will be provided.

9.4.2. Safety analyses

All safety analyses will be performed on the Safety Analysis Set. All available data, including adverse events, changes in laboratory values and other safety parameters will be evaluated by dose levels. Complete details of safety analyses will be provided in the SAP.

9.4.2.1. Dose-limiting toxicities (DLTs)

Dose evaluation of belantamab mafodotin will be based on evaluation of DLTs in the first ***3,*** 21-day**,** cycles of treatment.

The dose decisions of a RP3D for future studies will be based on the totality of data including DLTs, adverse events that are not DLTs, other safety and tolerability data, combination drug RDI, pharmacokinetics, and preliminary efficacy measures.

Incidence of DLTs will be summarized and listed based on the DLT-evaluable analysis set.

9.4.2.2. AEs

All adverse events whether serious or nonserious, will be reported from the start of treatment until at least 70 days after the last dose of study treatment, until the participant withdraws consent for study participation, or until the participant starts subsequent anti-***myeloma*** therapy, whichever occurs first. For AE reporting, the verbatim term used in the CRF by Investigators to identify adverse events will be coded using the latest version of MedDRA coding dictionary.

AEs will be summarized by frequency and proportion of total participants, by system organ class and preferred term. Separate summaries will be given for all AEs, common (>5%) AEs, treatment-related AEs, SAEs, and AEs leading to discontinuation of study treatment. AEs, if listed in the NCI-CTCAE (v5.0) will be summarized by the maximum grade.

The incidence of deaths and the primary cause of death will be summarized.

Characteristics (e.g., number of occurrences, action taken, grade, etc.) of the following AEs of special interest will also be summarized separately:

Ocular events, thrombocytopenia, and IRRs.

Additional AEs of special interest may be identified during the study and will also be summarized separately.

9.4.2.3. Clinical laboratory evaluations

The evaluation of clinical laboratory tests will focus on selected laboratory analytes from the hematology and blood chemistry panel.

Descriptive statistics (mean, standard deviation, median, range) will be used to summarize laboratory values and changes from baseline in observed value at each scheduled visit or worst-case post baseline, as appropriate.

The worst-case- toxicity grade in hematology and chemistry result during the treatment will be summarized.

9.4.2.4. Other safety measures

Data for vital signs, ECGs, ECHOs, and ophthalmic examination findings will be summarized. For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages. Further details will be provided in the SAP.

9.4.3. Belantamab mafodotin pharmacokinetic analyses

Concentration-time data: Linear and semi-logarithmic individual concentration-time profiles and mean and median profiles by each cohort (when appropriate) will be plotted for belantamab mafodotin, total mAb, and cys-mcMMAF. Concentrations of belantamab mafodotin, total mAb, and cys-mcMMAF will be listed for each participant and summarized (when appropriate) by planned time point and cohort.

Derived pharmacokinetic parameters: Pharmacokinetic analyses will be the responsibility of Clinical Pharmacokinetics/Modeling and Simulation, GSK.

PK analysis using non-compartment and/or population PK method will be used.

Standard NCA, if performed, will be conducted using the WinNonlin software. Calculations will be based on the actual sampling times recorded during the study. Calculated PK parameters may include Cmax, tmax and area under the concentration-time curve (AUC) among others, as data permit.

Plasma belantamab mafodotin concentration-time data may be combined with data from other studies and analyzed using a population pharmacokinetic approach. The initial analysis will use the then-current population pharmacokinetic model to generate post-hoc belantamab mafodotin PK parameter estimates. Based on the individual post-hoc parameter values, dosing information, and sample collection times, belantamab mafodotin plasma concentrations at the time of sample collection will be predicted for each participant. Model evaluation will consist of comparison of model-predicted and observed concentrations. Summary exposure measures (e.g., Cmax, AUC) may also be computed. Results of this analysis may be provided in a separate report.

Pharmacokinetic parameters will be listed and summarized descriptively (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV%, and 95% CI of log-transformed parameters) by cycle and cohort.

9.4.4. Pharmacokinetic/pharmacodynamic analyses

If deemed appropriate and if data permits, exposure-response relationships between belantamab mafodotin exposure (e.g., dose, dose intensity, concentration, Cmax, or AUC) and clinical activity and/or toxicity (e.g., response, corneal event) or combination drugs(s) RDI may be explored using modeling approach. If data permit, the effects of covariates may be explored. If data permits, these analyses may include data from other studies. Results of this analysis may be provided in a separate report.

9.4.5. Health-related quality of life data analyses

Descriptive statistics will be used to summarize scores derived from different questionnaires and change from baseline at each scheduled visit. Additional details will be provided in the SAP.

9.4.6. Immunogenicity

For each participant, the results and titers of anti-belantamab mafodotin antibodies will be listed for each assessment time point, along with the time-matched total mAb plasma concentration. The frequency and percentage of participants with positive and negative results will be summarized for each assessment time and overall, for each participant. The details will be provided in the SAP.

9.4.7. Biomarker analyses

Biomarker exploratory analyses will be described in the SAP.

9.5. Interim analyses

After the last participant from cohorts 2-5 completes 4 cycles of study treatment(s), an IA will be performed for cohorts 2-5 to support the cohort expansion (approximately an additional 8 participants) of the selected cohort(s). In addition, based on emerging data from other clinical studies in the belantamab mafodotin clinical development program, the decision on whether to evaluate Cohort 6, Cohort 7, or Cohort 8 can take place. If cohorts 6-8 are open, after the last participant completes the end of Cycle 8 and/or participants who experienced treatment delays prior to the end of Cycle 8 have completed at least 2 disease assessments and ocular exams after the last dose of belantamab mafodotin, after at least 6 participants have completed the above-mentioned treatment in each dose cohort, additional interim analyses may also be conducted to aid in decision making regarding dose identification, cohort expansion or closure, and safety monitoring. Details of treatment cycle can be found in the SRM. Data considered to support dose decision will include but not limited to safety, available PK profile, and observed signs of clinical activity in addition to the DLT evaluation.

9.5.1. Safety stopping rules

Continuous monitoring will be conducted starting from when 5 participants are dosed at each dose level. The observed number of participants who permanently discontinue study treatment due to AEs related to belantamab mafodotin within the first 3 cycles will be compared against the safety stopping rule in Table 24. Enrolment may stop for the specific cohort if the safety stopping rule is met based on totality of safety data. For example, if out of 5 participants, 4 participants permanently discontinued study treatment within the first 3 cycles due to AE related to belantamab mafodotin, enrolment for the specific cohort(s) may stop after review of all safety data; otherwise, enrolment will continue. Operating characteristics for the stopping rule are provided in Section 10.14.

Table 24 Safety stopping rules

Number of dosed participants	Stop if number of participants discontinuing study treatment within the first 3 cycles due to AE related to belantamab mafodotin is larger or equal to this this number	Observed rate
5-8	4	0.50-0.80
9-12	5	0.42-0.56
13-16	6	0.38-0.46
17-20	7	0.35-0.41

AE = Adverse event.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1. Regulatory and ethical considerations

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

10.1.2. Financial disclosure

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

10.1.3. Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enroled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4. Data protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.

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

10.1.6. Dissemination of clinical study data

- Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the Clinical Study Report (CSR). The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.

10.1.7. Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in eCRF Completion Guidelines.
- Quality tolerance limits (QTLs) will be predefined in the Data Quality Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Study Specific Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 25 years from the issue of the final CSR/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

  Additional information regarding remote data management and monitoring are provided in Section 10.15.

10.1.8. Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the SRM or Monitoring Plan (MP).

10.1.9. Study and site closure

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

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

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

For study termination:

- Discontinuation of further study treatment development.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any Contract Research Organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate participant therapy and/or follow-up.

10.2. Appendix 2: Clinical laboratory tests

- The tests detailed in Table 25 will be performed by either the local laboratory or the central laboratory as indicated.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy Testing: Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria and the SoA for pregnancy testing schedule.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator, or required by local regulation, to establish the absence of pregnancy at any time during the participant’s participation in the study.

Table 25 Protocol-required safety laboratory assessments

Hematology[1]			
Platelet count	RBC Indices: MCV MCH MCHC	Automated WBC Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Red blood cell (RBC) count			
White blood cell (WBC) count (absolute)			
Reticulocyte count			
Hemoglobin			
Hematocrit			
Clinical Chemistry[1]			
Creatinine	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin
Glucose	Chloride	Alanine aminotransferase (ALT)	Uric acid
Sodium	Total bicarbonate	Gamma-glutamyl transferase (GGT)	Albumin
Magnesium	Calcium	Alkaline phosphatase (ALP)	Total protein
Estimated glomerular filtration rate (eGFR)	Phosphorus	Creatine kinase (CK)[7]	Lactate dehydrogenase (LDH)[7]
Urinalysis[1]			
Optional Urine dipstick for protein[8]			
Other Laboratory Tests			
Spot urine (from first void) for albumin/creatinine ratio[1, 3]; Coagulation screen ± International normalized ratio (INR) if on coumarin (warfarin)[1]; HbA1c[1]; Pregnancy Test (urine or blood)[1]; Follicle-stimulating hormone (FSH)[1] and estradiol[1] (as needed in women of non-childbearing potential only); Hepatitis B surface antigen (HBsAg)[1]; Hepatitis B core antibody (HBcAb)[1], Hepatitis C Antibody, Hepatitis C RNA test[1,3] (optional), eGFR[1]. Note: Hepatitis C RNA testing will be done to determine participant's eligibility if Hepatitis C antibody positive. HBV-DNA testing will be done to determine participant's eligibility if HBcAb positive or HBsAg positive.			
PK and ADA[2]			
Belantamab mafodotin pharmacokinetics (PK) Anti-drug antibodies (ADAs) to belantamab mafodotin			
Disease Evaluation Laboratory Tests			
Urine protein electrophoresis (UPEP)[2]	Serum immunofixation[2]	Ca corrected for albumin (serum)[2]	Serum M-protein calculation[2]
Serum protein electrophoresis (SPEP)[2]	Urine immunofixation[2]	IgG, IgM, IgA, IgD/IgE[2,4]	
Serum kappa/lambda free light chain (FLC) ratio[2]	24-hour urine collection for M protein[2]	Beta-2 microglobulin[2]	
Bone Marrow (BM) Aspiration / Biopsy			
BM (aspirate and biopsy) for disease assessment[1], BM for FISH analysis[1, 3, 5]; BM aspirate and biopsy for BCMA expression and biomarker research[2]; BM biopsy to confirm sCR (by IHC) [1, 3]; BM aspirate for Minimal Residual Disease testing[2]			
Biomarker Measurements[2]			
sBCMA (serum); Plasma cfDNA			
Optional Testing[2]			
Pharmacogenomics sample[6]; Optional tissue sample[6] (BM aspirate, biopsy, or fresh tissue/block for extramedullary tumor) for BCMA expression and biomarker research[2] may be collected at PD.			

1. To be performed at local laboratory.
2. To be performed at central laboratory.
3. If not available locally it can be performed centrally.
4. Only for participants with IgD/E myeloma.

5. FISH testing to be performed locally at least for: t(4;14), t(14;16), amp(1q), del(1p) and del(17p13). If participant is known to have tested positive for t(4;14) or t(14;16) on previous tests, FISH for those translocations does not need to be repeated and results from previous tests are acceptable regardless of when those tests were performed. Other FISH results from samples taken within 60 days prior to first dose are acceptable. If testing cannot be performed at a local lab, the samples can be sent to the central lab. FISH results are not required prior to randomization or dosing.
6. Informed consent for optional sub-studies (e.g., genetic research) must be obtained before collecting a sample.
7. Participants with significant lab elevations (≥3xULN) should, where possible, have a sample sent for central testing of CK and LDH isoenzyme levels.
8. Urine dipstick for protein may be used to assess for presence of urine protein. Albumin/creatinine ratio needs to be done in any participant with urine dipstick result of ≥1+ (at screening visit), or ≥2+ (during study treatment), or with positive protein if urine dipstick protein quantification is not available.

10.3. Appendix 3: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. Definition of AE

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

Events meeting the AE definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • **Significant failure of an expected pharmacologic or biological action.** • **Events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen).**

- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT meeting the AE definition

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

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose, *meets one or more of the criteria listed:*

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgement should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Possible Hy's Law case: ALT ≥ 3x ULN AND total bilirubin ≥ 2x ULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2x ULN, and direct bilirubin ≥2x ULN and at least doubled from baseline value) or INR >1.5 must be reported as SAE.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

Refer to Section 10.6 for liver chemistry follow-up procedures.

10.3.3. Definition of cardiovascular events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

10.3.4. Definition of TEAE

TEAE definition
• **A TEAE is an event that emerges during treatment, having been absent pre-treatment or worsens relative to the pre-treatment state.**

10.3.5. Recording and follow-up of AE and SAE

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

10.3.5.1. Assessment of intensity

Investigators should assess the severity of AEs according to the NCI-CTCAE v5.0 [US Department of Health and Human Services, 2017]. In general, NCI-CTCAE severity grades are as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; easily tolerated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADLs (instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, or managing money).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and being not bedridden).
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

A distinction should be made between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria presented in Section 10.3.2. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but may not be considered an SAE.

10.3.5.2. Assessment of causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgement to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.

- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.5.3. Assessment of outcomes

The investigator will assess the outcome of all serious and nonserious unsolicited AEs recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

Follow-up of AEs, SAEs, AESIs, pregnancies or any other events of interest
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals. • New or updated information will be recorded in the originally completed CRF. • The Investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information. After the initial AE/SAE/AESI/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AESIs (as defined in the Section 8.3.7), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is LTFU. Other nonserious AEs must be followed until the event is resolved, stabilized, otherwise explained or until the participant is LTFU.

Follow-up during the study.

- AEs/AESIs such as corneal events, thrombocytopenia, and IRR documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until at least 70 days after the last dose of study treatment, until the participant withdraws consent for study participation, or until the participant starts subsequent anti-myeloma therapy, whichever occurs first.
- If a participant dies during their participation in the study or during a recognized Follow-up period, GSK will be provided with any available postmortem findings, including histopathology.

Follow-up of pregnancies

- Pregnant participants/Pregnant partners of male participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the paper pregnancy follow-up report/electronic pregnancy report and the AE Report if applicable. Generally, the Follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.
- Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.
- Furthermore, the investigator must report any SAE occurring as a result of a post-study pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.3.6.

10.3.5.4. Updating of SAE, AESI, and pregnancy information after removal of write access to the participant's eCRF

When additional SAE, AESI, or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the study contact for reporting SAEs (refer to Section 10.3.6).

Collection of AE and SAE in the follow-up period and beyond (up to 70-day safety follow-up visit)

- Any AE or SAE that occurs between the time of study drug discontinuation and Safety Follow-up Visit should be captured. This 70-day time period covers the period of 5 half-lives for belantamab mafodotin. These events should be captured even if new chemotherapy has been started – the SAE's causality assessment to belantamab mafodotin is required. Inclusion of new chemotherapy agents and causality assessment to them would also be helpful but is not mandatory.

- AEs and SAEs should be followed until resolution or considered 'stable' even if the subject has completed the study participation, or subject is LTFU to the extent possible.
- Investigators should use their clinical judgement in conjunction with subject circumstances as to whether they will assess patients for AEs/SAEs in some interval periods between study discontinuation and Safety Follow-up Visit (as this is not mandatory), or if they will collect the information at the Safety visit only.
- For AEs/SAEs that are anticipated to be long-standing (such a new malignancy, or chronic disease), it is reasonable to assume that these will be not resolved for a time period beyond the reasonable scope of follow-up and therefore can be documented as not resolved.
- It is not the intent of GSK to place undue burden on clinical trial subjects or Investigators/staff to obtain follow-up data after study completion – most would be expected to have resolved or become stable within a period of months and if not, could be reported as unresolved, with focus on those of medical significance and/or potentially related to belantamab mafodotin.
- Participants with treatment-related ocular AEs ongoing after the 70-day Safety Follow-up will have OSDI collected Q12W until ocular signs resolve (to Grade 1 or baseline) OR for up to 1 year, whichever is soonest.

10.3.6. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The Investigator or medically-qualified sub-Investigator must review and verify the relationship of each SAE to IP/study participation (causality) and documented in source.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).

- If the site during the course of the study or post-study becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK product that is not part of the study design, they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous individual case safety reports.
- Contacts for SAE reporting can be found in the SRM.

SAE reporting to GSK via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the SAE coordinator. Details provided in the SRM.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SRM.

10.4. Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

Women in the following categories are not considered WOCBP (for the purposes of this study)

1. Premenarchal
2. Premenopausal female with 1 of the following:

   - Documented hysterectomy.
   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female

   - A postmenopausal state is defined as no menses for at least 24 consecutive months without an alternative medical cause.
   - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 24 months of amenorrhea, confirmation with more than one FSH measurement is required. In questionable cases a blood sample with simultaneous FSH >40 mIU/mL and estradiol <40 pg/mL (<147 pmol/L) is confirmatory.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception guidance:

Because of the increased risk of venous thromboembolism in participants with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a participant is currently using combined oral contraception the participant should switch to another one of the highly effective methods listed below. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b, c] That Have Low User Dependency Failure rate of <1% per year when used consistently and correctly.
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c,d]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c,d]
• Bilateral tubal occlusion
• Vasectomized partner Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential (WOCBP) and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
Highly effective methods[b, c] that are user dependent failure rate of <1% per year when used consistently and correctly.
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
• Sexual abstinence Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c. **Male condoms must be used in addition to hormonal contraception**. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
d. Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in participants with neutropenia.

Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction).

10.4.3. Collection of pregnancy information

Male participants with partners who become pregnant

Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while participating in this study. This applies only to male participants who receive study treatment.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.

Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study and for 28 days following the last dose of lenalidomide, 4 months following the last dose of belantamab mafodotin, or 7-months from the last dose of bortezomib, whichever is longest.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to GSK as described in Section 10.3. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating must discontinue study treatment immediately.

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study treatment, susceptibility, severity and progression of disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to belantamab mafodotin or multiple myeloma and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to belantamab mafodotin, or study treatments of this drug class, and multiple myeloma. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analyzed for relationships between genetic variants in the host and response to belantamab mafodotin (including the drugs under study). A detailed description of any planned analyses will be documented in a RAP prior to initiation of analyses. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and CSR, or in a separate genetics RAP and report, as appropriate.
- DNA Samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to belantamab mafodotin or study treatments of this class. The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on belantamab mafodotin (or study treatments of this class) or multiple myeloma continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

10.6. Appendix 6: Liver safety: required actions and follow-up assessments and study treatment rechallenge guidelines

Phase 1/2 liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

10.6.1. Phase *1/2* liver chemistry stopping criteria

<table>
<tr><th colspan="2">Liver chemistry stopping criteria – Liver stopping event</th></tr>
<tr><td>ALT - absolute</td><td>ALT ≥ 5xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥ 3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥ 3xULN and total bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥ 3xULN and INR>1.5</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required actions, monitoring and follow-up assessments</th></tr>
<tr><th>Actions</th><th>Follow-up assessments</th></tr>
<tr><td>• Immediately discontinue study intervention.
• Report the event to GSK within 24 hours.
• Complete the liver event form and complete SAE data collection tool if the event also meets the criteria for an SAE[2].
• Perform liver event follow-up assessments as described in the follow-up assessment column.
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING:).

For the purpose of these guidelines “baseline” refers to laboratory assessments performed closest and prior to first dose of study intervention.

MONITORING:

If ALT≥3xULN AND total bilirubin ≥ 2xULN or INR >1.5:

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within 24 hours.</td><td>• Viral Hepatitis serology[4].
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend.
• Blood sample for pharmacokinetic (PK) analysis of belantamab mafodotin and a blood sample for sBCMA, obtained within 70 days (or sooner) after last dose[5].
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH), gamma-glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin.
• Fractionate bilirubin if total bilirubin≥2xULN.
• Obtain complete blood count (CBC) with differential to assess eosinophilia.
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form.
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter medications
• Record alcohol use on the liver event alcohol intake form</td></tr>
</table>

Liver chemistry stopping criteria – Liver stopping event	
• Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline. • A specialist or hepatology consultation is recommended. **For All other criteria (bilirubin <2xULN and INR ≤1.5):** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within **24-72 hours** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline **RESTART/RECHALLENGE** • **Restart/rechallenge is allowed per protocol but do not resume study intervention unless GSK approval is granted;** If restart/rechallenge is **not granted,** permanently discontinue study intervention and continue participant in the study for any protocol-specified follow-up assessments. Refer to Restart/Rechallenge guidelines in Section 7.1.1.1.	**If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5** obtain the following in addition to the assessments listed above: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins) • Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week. (e.g., where the participant has been resident in the clinical unit throughout) [James, 2009]. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease; complete Liver Imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance: ○ In participants when serology raises the possibility of autoimmune Hepatitis (AIH) ○ In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention ○ In participants with acute or chronic atypical presentation: • If liver biopsy conducted complete liver biopsy form.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥ 3xULN **and** total bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** total bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; the INR threshold value stated will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B core antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody. In those with underlying chronic Hepatitis B at study entry (identified by positive Hepatitis B surface antigen) quantitative Hepatitis B DNA and Hepatitis delta antibody. If Hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of Hepatitis D RNA virus (where needed) [Le Gal, 2005].
5. Record the date/time of the PK/sBCMA blood sample draw and the date/time of the last dose of study intervention prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK/sBCMA sample cannot be collected in the time period indicated above, do not obtain a PK/sBCMA sample. Instructions for sample handling and shipping are in the SRM.

Phase 1-2 Liver chemistry increased monitoring criteria with continued therapy

Liver chemistry increased monitoring criteria and actions with continued study intervention liver monitoring event	
Criteria	**Actions**
ALT ≥3xULN **but** <5xULN **and** total bilirubin <2xULN or INR ≤1.5, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks**.**	• Notify the GSK ***M***edical ***M***onitor **within 24 *hours*** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline. • If at any time participant meets the liver chemistry stopping criteria, proceed as described above. • If, after 4 weeks of monitoring, ALT <3 x ULN and bilirubin <2 x ULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

ALT = Alanine aminotransferase; ULN = Upper limit of normal.

10.6.2. Rechallenge following liver stopping events that are possibly related to study treatment

Following drug-induced liver injury (DILI), **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies** [Andrade, 2009**]**. Clinical outcomes vary by drug, with nearly 50% fatality with halothane re-administered within 1 month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- Hypersensitivity with initial liver injury (e.g., fever, rash, eosinophilia).
- Jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total).
- Ongoing severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5.
- SAEs or fatality has earlier been observed with drug rechallenges [Papay, 2009; Hunt, 2010].
- Evidence of drug related preclinical liability (e.g., reactive metabolites; mitochondrial impairment) [Hunt, 2010]).

Rechallenge refers to resuming study treatment following study treatment induced liver injury (DILI). Because of the risks associated with rechallenge after DILI, this should only be considered for a participant for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit-risk assessment of rechallenge is considered to be favorable.

Approval by GSK for rechallenge with study treatment can be considered where:

- The Principal Investigator requests consideration of rechallenge with study treatment for a participant who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- IRB/IEC approval for rechallenge with study treatment must be obtained.

If the rechallenge is approved by GSK in writing:

- The participant must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study file.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, participant meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- GSK Medical Monitor, and the IRB/IEC as required, must be informed of the participant's outcome following study treatment rechallenge.
- GSK to be notified of any adverse events, as per Section 8.3 and Section 10.3.

10.6.3. Restart following transient resolving liver stopping events NOT related to study treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g., biliary obstruction, pancreatic events, hypotension, acute viral Hepatitis). Furthermore, restart is not permitted following liver stopping event when the underlying cause was alcohol-related Hepatitis.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).

- Possible study treatment induced liver injury has been excluded by the Principal Investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study treatment has an identified genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate), the presence of the marker should be excluded. If study treatment-related liver injury cannot be excluded, the guidance on rechallenge described above will apply.
- There is no evidence of alcohol-related Hepatitis.
- IRB/IEC approval of study treatment restart must be obtained, as required.

If restart of study treatment is approved by GSK in writing:

- The participant must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study file.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment restart, participant meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- GSK Medical Monitor, and the IRB/IEC as required, must be informed of the participant's outcome following study treatment restart.
- GSK to be notified of any adverse events, as per Section 8.3 and Section 10.3.

10.7. Appendix 7: IMWG frailty score

	Score
Age, y	
≤75	**0**
76-80	**1**
>80	**2**
ADL	
>4	**0**
≤4	**1**
IADL	
>5	**0**
≤5	**1**
CCI	
≤1	**0**
≥2	**1**

ADL = Activities of daily living; CCI = Comorbidity index; IADL = Instrumental activities of daily living; y = Years.

Total Score	Participant status
0	**Fit**
1	**Intermediate-fitness**
≥2	**Frail**

[Palumbo, 2015]

The following link will auto-calculate the frailty score:
http://www.myelomafrailtyscorecalculator.net/

10.8. Appendix 8: New York Heart Association classification

The NYHA Functional Classification: Class I, II, III or IV Heart Failure [New York Heart Association, 1994] provides a simple way of classifying the extent of heart failure. It places participants in 1 of 4 categories based on the level of limitation experienced during physical activity:

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

10.9. Appendix 9: Country specific requirements

Inclusion/Exclusion criteria:

- In **Republic of Korea**, a participant must be over 19 years of age inclusive, at the time of signing the informed consent.
- In **France,** a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.
- In **France,** participants must have an ECOG performance status of 0-1.

FRENCH-SPECIFIC REQUIREMENTS

This appendix includes all applicable requirements of French Public Health Code/specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information to the study protocol.

1. Concerning the "SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA"

The following vulnerable subject populations will be excluded: minors, protected subjects, adult subjects not in condition to express their consent, subjects deprived of liberty, subjects receiving psychiatric cares, subjects hospitalized in a Health and Social Establishment for other purpose than the participation to the study.

A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category (French Public Health Code Law L.1121-8-1). (exception for a participant to a non-interventional study or to a participant to an interventional study if authorised by the Ethics Committee).

It is the investigator's responsibility to ensure and to document (in the source document - subject notes) that the subject:

- is either affiliated to or beneficiary of a social security category;
- has got an authorisation by the Ethics Committee.

2. Concerning the "STUDY GOVERNANCE CONSIDERATIONS"

- **In section "Regulatory and Ethical Considerations, including the Informed Consent Process" of study protocol:**
  - Concerning **the process for informing the subject** and/or his/her legally authorized representative, the following text is added:

    French Patient Informed Consent is a document which summarizes the main features of the study and allows collection of the subject and/or his/her legally authorized representative written consent. It also contains a reference to the authorisation of ANSM and the approval from the French Ethics Committee.

- Concerning **the process for obtaining** subject informed consent:
  - When a research involving human being **is carried out on a minor / on an adult in the care of a "tutelle" guardian**, consent is given by their legal representative and, if the French Ethics Committee considers that the research in question, because of the seriousness of the restraints or the specificity of the medical acts involved, entails a serious risk of affecting their private life or the integrity of their body, consent is given by the family council if it has been instated, or by the judge of "tutelle" guardians.
  - When research involving human being **is carried out on an adult in the care of a "curatelle" guardian**, consent is given by the subject assisted by his guardian. However, if the adult in the care of a "curatelle" guardian is invited to participate in research which the French Ethics Committee considers, because of the seriousness of the restraints or the specificity of the medical acts involved, to entail a serious risk of affecting their private life or the integrity of their body, the matter is submitted to the judge of guardians who decides whether the adult is capable of giving her/his consent. In the case of incapacity, the judge will decide whether or not to authorise the research involving human being.
- **Concerning the management of the Patient Informed Consent Forms**, the following text is added:

  French Patient Informed Consent Form is in duplicate (triplicate for minor subject).

  The first page of the Patient Informed Consent Form is given to the investigator. The copy is kept by the patient or legally authorized representative.

- **NOTIFICATION TO THE HOSPITAL DIRECTOR**

In accordance with Article L1123-13 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-69).

- **INFORMATION TO THE HOSPITAL PHARMACIST**

In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the IB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial.

- **Ethnic Origin**

In accordance with the data privacy regulation, the ethnic origin, as any personal data, can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

- **TESTING OF BIOLOGICAL SAMPLES**

In accordance with the French Public Health Code law – article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

3. Concerning the "DATA MANAGEMENT" the following text is added:

Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacists if applicable, involved in this clinical trial, and data regarding the subjects recruited in this clinical trial (subject number, treatment number, subjects status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GSK or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the data privacy regulation, each of these people aforesaid has a right of access, correction and opposition on their own data through GSK (Clinical Operations Department).

4. Concerning the "DATA PRIVACY"

In accordance with the applicable data privacy regulation, personal data are processed in a manner that ensures appropriate security, including protection against unauthorized or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organizational measures. The processing is whether deemed to be compliant with one of the methodology of reference **(MR-001)** or has been the subject of a request for authorization to the CNIL. The Investigator has, regarding the processing data related to her/him, a right of access, of rectification, erasure and of opposition with GSK in accordance with the legal provisions.

5. Concerning the "Investigational product accountability, reconciliation, and destruction"

In specific situations where institutional practices dictate that the site disposes of and/or destroys IP prior to allowing the "monitor' to verify and document IP accountability, the following applies:

*"During the conduct of the Study, Investigational Product (IP) will be destroyed by the Institution prior to a GSK "**monitor**" conducting final investigational product accountability. Institution agrees that such destruction will comply with Institution's investigational product accountability procedures and will provide GSK with investigational product accountability logs and supporting documentation to verify adherence to 'Bonnes Pratiques Cliniques' (decision dated on the 24th of November 2006).*

10.10. Appendix 10: Eastern Cooperative Oncology Group (ECOG) functional status

Performance Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

[Oken, 1982]

10.11. Appendix 11: Modified Diet in Renal Disease (MDRD) formula

The MDRD formula for calculating the eGFR is as follows:

$$eGFR = 175 \times (SCr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

GFR is expressed in mL/min/1.73 m^2, SCr is serum creatinine expressed in mg/dL, and age is expressed in years [Greipp, 2005].

The following link will auto-calculate the creatinine clearance: http://nephron.org/cgi-bin/MDRD_GFR/cgi

10.12. Appendix 12: Eye care specialist's qualifications and requirements

For examiners with a degree in ophthalmology or optometry, those involved in eye evaluations in the protocol will, at a minimum be able to provide comprehensive eye care to participants, which includes routine check-ups, treatment and ongoing management of visual disease.

Specifically, qualified eye care specialists must be able to:

- Perform comprehensive eye exams.
- Perform visual Acuity with manual refraction tests and analyse results.
- Perform slit lamp tests and analyse results.
- Perform intraocular pressure examination.
- Dilated fundoscopic examination.
- Diagnose and treat ocular issues and diseases such as keratopathy or glaucoma.

10.13. Appendix 13: Home healthcare and telemedicine approaches

Home healthcare (general visit)

Where applicable country and local regulations and infrastructure allow, home healthcare may be permitted. Home healthcare is defined as a remote visit(s) that is/are performed at the participant's home by qualified personnel (e.g., nurse).

Activities that may be done as part of a home healthcare visit must follow the schedule provided in the SoA (Section 1.3) and include:

- Collection of blood and urine samples including:
- Safety assessments which may include routine blood and urine sampling.
- PK and ADA specimen collection.
- Efficacy assessments to be sent to central lab.
- Biomarker, immunogenicity and genetic assessments.
- Pregnancy tests.

Note: Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until their intended use. Please refer to the SRM/lab manual for sample collection and storage requirements.

- Measurement of vital signs (BP, heart rate, body temperature) and weight.
- Physical examination.
- Administration of study drug (subcutaneous delivery only, no infusions).
- Administration of pre/post-medication.
- Identification and reporting of concomitant medications.
- Dosing diary review for medication compliance.
- Identification and reporting of AEs/SAEs.

Note: The investigator or other qualified medical professional must ensure reporting of AEs and SAEs is completed in accordance with the protocol and applicable regulations and that the appropriate medical intervention, therapeutic intervention, and/or support measures are instituted, as necessary.

The participant should be informed of any potential risks associated with home healthcare and sign a revised Informed Consent Form (ICF) if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

Home healthcare (ophthalmologic exam)

Where applicable country and local regulations and infrastructure allow, protocol-required eye exams may be done in the participant's home. Activities that may be done as part of in-home eye exams must follow the schedule provided in the SoA (Section 1.3) and include:

- Visual Acuity (VA) by near-chart VA or pinhole.
- Slit lamp exam.
- Tonometry.
- Ophthalmoscopy.

The participant should be informed of any potential risks associated with Home Healthcare Ophthalmologic exams and sign a revised ICF if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

Telemedicine

Where applicable country and local regulations and infrastructure allow, telemedicine visits may be permitted. Telemedicine visits are defined as online (virtual) visits which will use secure video conference, phone calls, a web portal and/or mobile application as a way of communicating with and monitoring the participant's progress. Telemedicine visits are conducted by an investigator or other qualified medical professional and may be done in combination with visits from Home Healthcare personnel (see above).

Activities that may be done as part of a telemedicine visit include:

- Identification and reporting of concomitant medications.
- Dosing diary review for medication compliance.
- Identification, management, and reporting of AEs and SAEs.

  Note: The investigator or other qualified medical professional must ensure reporting of AEs and SAEs is completed in accordance with the protocol and applicable regulations and that the appropriate medical intervention, therapeutic intervention, and/or support measures are instituted, as necessary. Participants utilizing telemedicine can report AEs at any time via an app, phone call or videoconference with site staff.

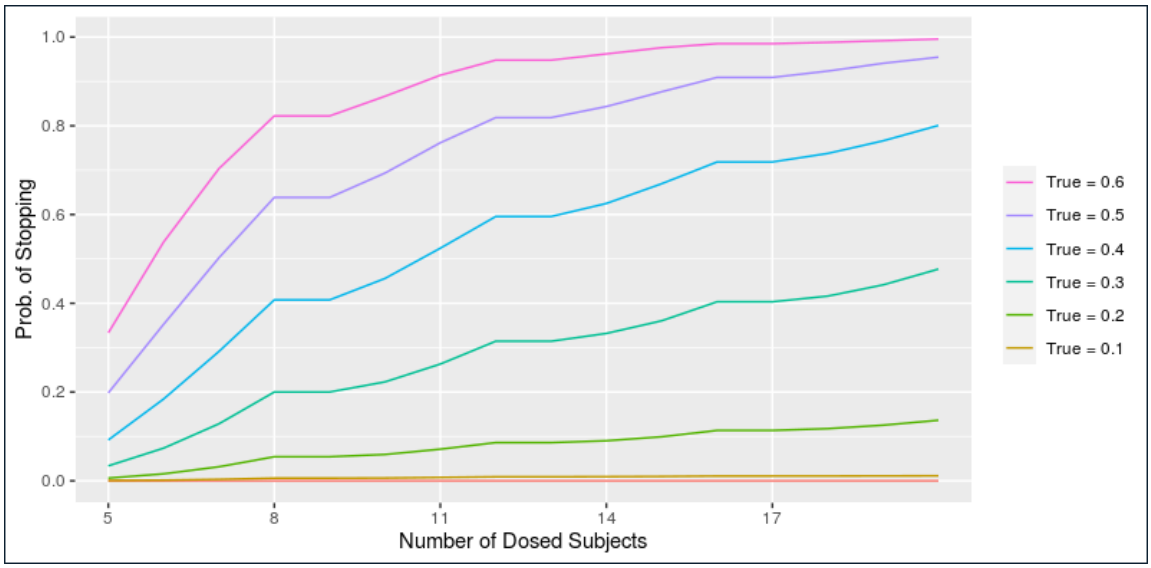
The participant should be informed of any potential risks associated with the virtual medium and sign a revised ICF if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

Remote Patient-Reported Outcomes (PRO) administration

Where applicable country and local regulations and infrastructure allow, remote PRO administration may be permitted. Remote PRO administration is defined administration of protocol PROs by a qualified third party over the telephone. Where applicable, the remote PRO Administrator will use the versions of the PROs designed for verbal administration. The remote PRO Administrator will have access to the electronic PRO portal for the study and input participant responses as the interview is being conducted.

The participant should be informed of any potential risks associated with the remote PRO administration and sign a revised ICF if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

10.14. Appendix 14: Operating characteristics of safety stopping rule



10.15. Appendix 15: Data management and monitoring

Source Data Verification/Source Document Review (SDV/SDR)

During periods in which on-site monitoring is not permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution and in accordance to with local law and regulatory guidance documents.

Remote SDV/SDR has been proposed to study sites to meet a patient and/or critical data quality need, e.g., to assess patient safety or to ensure data integrity. The study specific MP was updated in accordance with remote monitoring practices adopted for the country/study. The subject informed consent will be updated in line with local regulations to permit remote monitoring practices. In case of remote SDV/SDR, GSK will work with the site to ensure subject privacy.

eCRF/CRF final or interim sign off process:

The Principal Investigator is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study patient is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The Principal Investigator may sign/re-sign the eCRF from any computer/location by accessing the eDC platform) using his/her unique eCRF login credentials.

Essential documents sign off process:

If an investigator is unable to print and sign essential documents such as Protocol/Amendment signature page, then email approval can be accepted by replying to the relevant email that is sent by GSK. Please note that unblinding procedures remain the same as those documented in the protocol and other study-related documents.

10.16 Appendix 16: Trademarks

Trademark information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
Revlimid
Velcade
WinNonlin

10.17 Appendix 17: Protocol amendment history

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

Summary of previous amendments:

Amendment 03 (12-Jan-2022)

Where this Protocol Amendment applies:

Protocol Amendment 03 applies to all countries and all sites.

Overall Rationale for Amendment 03:

- The protocol has been amended to update belantamab mafodotin dose and schedule in cohorts 6-8, to reduce overall Grade 3 ocular toxicity rate and improve the tolerability of belantamab mafodotin in combination with SoC.
- Updated guidance for dose reduction and dose modification of belantamab mafodotin.
- Implement flexibility language in the dose evaluation and statistical analysis to support clinical decision making for RP3D.
- Updated BM sample collection guidance, removed biomarker sample collection at VGPR, suspected CR/sCR, and at suspected PD; removed extramedullary tumor biopsy sample collection.
- Updated and consolidated language biomarker exploratory endpoint and biomarker research section.
- Addition of PACT to allow eligible patients to receive study treatment after study completion.
- Additional changes were incorporated which align with program revisions and/or updates.
- Administrative updates to add clarification and/or remove discrepancies.

All changes are listed in table below.

Section # and Name	Description of Change	Brief Rationale
Throughout	Removed SPLIT doses and cohort with SPLIT dosing.	To align with the study design.
	Update of dose and schedule in cohorts 6 to 8.	To reduce overall Grade 3 ocular toxicity rate.
	Minor editorial and document formatting revisions.	To improve overall clarity and typographical corrections.
	Updated number of participants up to 160.	To reflect study design.
	Renumbering of Tables and Footnotes.	As a result of changes within the document.
1.2 Schema	Updated Figure 1.	To reflect study design.
1.3 Schedule of Activities	Updated Table 4 for the guidance of bone marrow sample collection. Removed biomarker sample collection at VGPR, suspected CR/sCR, and at suspected PD; removed optional tissue (extramedullary tumor) sample collection throughout the study (Table 4, footnote 8).	To clarify collection time point and preferred sample type.
	Updated ocular exams need to be completed Q3/4W up to the fifth dose of belantamab mafodotin (Table 1, footnote 3).	To reflect study design.
2.3.1. Risk Assessment	Change “Incidental findings during imaging data acquisition” to “Incidental findings during image acquisition”. Update mitigation strategy as ‘Copies of all medical images that include non-disease, clinically relevant abnormalities will be shared with the site for storage’.	To clarify language.
3. Objectives and Endpoints	Removed “Circulating free DNA assessment at baseline, upon response, and at End of Treatment “ as exploratory endpoint to add flexibility and consolidated biomarker endpoints.	In line with program level requirements.
4.1 Overall Study Design	Update dose and schedule in cohorts 6 to 8.	Updated to support clinical decision making in RP3D.
4.1.1 Dose Evaluation	Update dose and schedule in cohorts 6 to 8 and allow the flexibility of additional interim analyses may be performed’.	Updated to support clinical decision making in RP3D.
4.3.3. Alternate Schedule for Belantamab Mafodotin	Updated the alternate schedule for Belantamab Mafodotin information under Q9/12W.	According to current information.

Section # and Name	Description of Change	Brief Rationale
4.4. End of Study definition	Updated the EoS definition as 'last participant completes their year one visit after the first dose'. Updated the consideration of participant completing the study to 'all scheduled visits followed until death or the EoS'.	To allow continued access to belantamab mafodotin and other study drugs in feasible participants.
5.1 Inclusion Criteria	To clarify time period of using birth control in female participants, replaced 'further' to 'a total of' months following discontinuation of study drugs.	To clarify language.
6.1.1. Study Treatment –Belantamab Mafodotin	Update of unit dose strength in Table 8 and treatment information in cohorts 6-8.	To reflect study design.
6.3. Measures to Minimize Bias: Randomization and Blinding	Added the details on Randomization strategy for cohorts 6-8.	To clarify the enrolment strategy in cohorts 6-8.
6.6.1. Belantamab Mafodotin Dose Reduction Schedule	Update guidance for dose reduction depending on the schedule of dosing and status of response (Table 10).	To align with study design.
6.6.2.2. Dose Modification Guidelines for Belantamab Mafodotin	Update of dose reduction at Grade 2 corneal toxicity related events in dosage modification Table 14.	To align with program-wide requirements on belantamab mafodotin-related ocular toxicity management.
6.7. Continued Access to Study Intervention after the End of the Study	Addition an option of post analysis continued treatment (PACT) for subjects demonstrating response to therapy to continue study treatment.	To allow continued access to belantamab mafodotin and other study drugs in feasible participants.
8.1.1. Minimal Residual Disease	Added some text on MRD assessment and clarify timepoints at which MRD sample is collected.	More details added.
8.2.9 Ophthalmic Examinations	Updated ocular exams need to be completed Q3/4W up to the fifth dose of belantamab mafodotin.	To reflect study design.
8.3.1. Time Period and Frequency for Collecting AE and SAE Information	Addition of time and frequency for collecting AE/SAE during PACT period.	To reflect the addition in section 6.7.
8.6 Biomarkers	Removed specific paragraphs for RNA transcriptome research and RNA expression research of a subset of RNA species and added language inclusive of potential RNA research in sub-section of Tumor-related biomarkers "Molecular Characteristics of Bone Marrow Cells.	To clarify language and in line with program level requirements.

Section # and Name	Description of Change	Brief Rationale
9. Statistical Considerations 9.2 Sample Size Determination 9.2.1 Statistical Operating Characteristics 9.5 Interim Analyses Appendix 14	Updated sample size up to 160 participants according to the study design, allow the flexibility of additional interim analyses may be performed. Based on 160 participants: Updated operating characteristics of the study (Table 19). Updated Safety stopping Rules (Table 22). Updated Figure on operating characteristics of safety stopping rule in Appendix 14.	Updated according to study design and to support clinical decision making in RP3D.
Appendix 7 IMWG Frailty Score	Added a link to auto-calculate frailty score.	Add an instruction in the protocol.

Amendment 02 (28-Jul-2021)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

- The protocol has been amended to update exclusion criteria for Hepatitis B+ and Hepatitis C+ participants in order to align with the latest regulatory guidance for industry, to provide clarification to the administration of belantamab mafodotin.
- Replaced reference of the Celgene Pregnancy Program to manufacturing guidelines of any treatment-specific pregnancy prevention program for participants who will receive generic lenalidomide.
- Updated sections of pharmacokinetics and pharmacodynamics in humans and risk assessment to align with the changes made in current belantamab mafodotin Investigator Brochure, as appropriate.
- Allow the flexibility in bortezomib doses in elderly/frail participants.
- Change from central to local laboratory testing of immunohistochemistry assessment of BM biopsy for stringent Complete Response.
- Incorporation of the Korean country specific amendment, KOR01.
- Additional changes were incorporated which align with program revisions and/or updates.

- Administrative updates to add clarification and/or remove discrepancies.

Section # and Name	Description of Change	Brief Rationale
Throughout	Cohort 7 is the SPLIT cohort.	To clarify language.
	Clarify the ocular exam need to be completed up to the sixth dose of belantamab mafodotin.	To clarify language.
	Clarification throughout the protocol regarding all clinical chemistry values being needed for review prior to the dosing of any agent, not just lenalidomide dosing.	To clarify language.
	Clarification throughout the protocol that PRO collection will follow the fixed visit schedule (Q3W[Month1-6], Q4W [Month 6-Yr2], Q8W [>Yr2] schedule).	To clarify language.
	Replace reference of the Celgene Pregnancy Program to manufacturing guidelines of any treatment-specific pregnancy prevention program for participants who will receive generic lenalidomide.	To reflect the introduction of generic lenalidomide.
	Updated reference to belantamab mafodotin investigator brochure.	To refer to the most recent versions.
	Minor editorial and document formatting revisions.	To improve overall clarity and typographical corrections.
	Renumbering of Tables and Footnotes.	As a result of changes within the document.
1.3 Schedule of Activities	Clarify dosing schedule window for Q9W, Q12W in SoA.	To clarify language.
	Added Table 2 for additional procedures for participants with a history of Hepatitis B.	To align with the latest regulatory guidance.
	Added Table 3 for additional procedures for participants with a history of Hepatitis C.	To align with the latest regulatory guidance.
	Added flexibility of HBsAg, HBcAb, Hepatitis C Ab, Hepatitis C RNA testing during the study.	To reflect the new criteria and procedure indicated in Table 2 and Table 3.
	Added Table 4 for the guidance of bone marrow sample collection throughout the study.	To clarify language.
	Changed window for hematology lab assessment prior to bortezomib dosing from 24-hours to 1-day (footnote 7).	To clarify language.
	Clarification throughout the protocol regarding all clinical chemistry results being needed for review prior to the dosing of any agent, not just lenalidomide (footnote 8).	To clarify language.
	Replace ‘imaging for extramedullary disease will be collected and stored by a central vendor’	Central vendor for imaging is not applicable in this

Section # and Name	Description of Change	Brief Rationale
	to 'Digital copies of all scans must be maintained at Investigator site as source document' (footnote 14).	study.
	Added requirement for the storage of skeletal survey. Sites shall maintain an archive of all study-related images/scans as source documentation (footnote 15).	To clarify language.
	All concomitant medications will be collected from screening until the 70-day safety follow-up after EOT Visit (footnote 24).	To clarify language.
2.2.4 PK/PD in Humans	Update of the Pharmacokinetics and Pharmacodynamics in Humans.	Updated to reflect latest clinical pharmacology information included in the current IB.
2.3.1. Risk Assessment	Update of Risk Assessment table to reflect current information from the belantamab mafodotin program.	Updated based on emerging data from belantamab mafodotin program.
3. Objectives and Endpoints	Evaluation of pharmacokinetics of total mAb moved from secondary to exploratory endpoints.	In line with program level requirements.
4.1.1 Dose Evaluation 9. Statistical Considerations	Update of 'After the last participant completes 'the DLT period', additional interim analyses may be performed' to 'the end of Cycle 4'.	Updated to reflect the reporting and analysis plan in study design.
4.1.1.1 Criteria for Belantamab Mafodotin Dose-Limiting Toxicity	Update of DLT-evaluable dose of VRd combination in Cycle 1, and clarify the replacement for participants that are not DLT-evaluable.	To clarify language.
5.2. Exclusion Criteria	Updated exclusion criteria 14 and 15 for Hepatitis B, and Hepatitis C participants	To align with the latest regulatory guidance.
6.1.1. Study Treatment – Belantamab Mafodotin	Update of same day administration interval between belantamab mafodotin and bortezomib in the induction period; resting period after administration of belantamab mafodotin in maintenance period.	To clarify language.
6.1.1.2. Corneal Supportive Care Guidelines for Belantamab Mafodotin	Update of recording corneal exam findings on ocular corneal exam pages and treatment-related ocular AEs other than corneal exam findings on AE pages.	To clarify language.
6.1.2.1 Bortezomib Administration	Update to allow the flexibility for the initial and subsequent bortezomib doses in frail participants according to most recent prescribing information and investigator's institutional	To allow flexibility at site for more frail participants.

Section # and Name	Description of Change	Brief Rationale
6.6.2.3. Dose Modification Guidance for Bortezomib	guidance.	
6.1.2.3. Dexamethasone Administration 6.1.3.2. Maintenance Treatment	Update of dexamethasone dose may be administered at a dose of 10 mg (Cycles 1-8) and 20 mg (Cycle 9+) on the treatment days in specific participants.	To correct the error in Amendment 01.
6.5.2. Prohibited Concomitant Therapies	Addition of prohibiting use of live or live-attenuated vaccines at least 70 days following the last dose of belantamab mafodotin.	To maintain program-wide consistency.
6.6.3. Management of Hepatitis B+ participants	Added section to clarify management of Hepatitis B+ participants and dose modification guidelines for Hepatitis B reactivation (Table 17).	To align with the latest regulatory guidance.
6.6.2.2. Dose Modification Guidelines for Belantamab Mafodotin 6.6.1. Belantamab Mafodotin Dose Reduction Schedule	Update of footnote in Table 13 and Table 14 for corneal examination findings for grading per KVA scale and correlated dosage modification.	To clarify language.
7.1. Discontinuation of Study Treatment	Update of Follow-up period after EOT Visit 'followed by a PFS Follow-up or 70-day Safety Follow-up (if applicable)'.	Updated to reflect the SoA.
7.1.2. QTc Stopping Criteria 7.1.3 LVEF Stopping Criteria Appendix 13 Home Healthcare and Telemedicine Approaches	Removal of QTc and LVEF stopping criteria. Cardiac monitoring test (ECG) removed from home healthcare (General) visit.	In line with cardiac monitoring requirements across belantamab mafodotin program, based on emerging safety data.
8.1.1 Minimal Residual Disease	Clarify bone marrow sample collection schedule for MRD assessment.	To clarify language.
8.4. Pharmacokinetics and 9.4.3 Belantamab	Clarify PK and sBMCA samples collection in case of dose delay.	In line with program level requirements.

Section # and Name	Description of Change	Brief Rationale
Mafodotin Pharmacokinetic Analyses		
10.4.2. Contraception Guidance	Adding guidance of using implantable device in participants with neutropenia (footnote).	To clarify language.
Appendix 2- Clinical Laboratory Tests	Adding HBV-DNA testing to determine participant's eligibility if HBcAb positive or HBsAg positive.	To reflect new eligibility criteria.
	Change 'central laboratory' to 'local laboratory' for bone marrow biopsy by IHC to confirm sCR.	To give greater flexibility to sites.
Appendix 3 – 10.3.4. Recording and Follow-up of AE and SAE	Adding guidance of Collection of AE and SAE in the Follow-up period and beyond (up to 70-day safety follow-up visit).	To clarify language.
Appendix 3 – 10.3.5 Reporting of SAE to GSK	Removal of the requirement for Investigators to enter SAE causality in eDC within 72 hours.	In line with program level requirements.
Appendix 11 – Modified Diet in Renal Disease (MDRD) Formula	Correct the superscript in the estimated glomerular filtration rate (eGFR) formula.	Formatting error in amendment 01.
Appendix 12 – Eye Care Specialist's Qualifications and Requirements	Removal of 'Qualified eye care specialists, including optometrist, will also be able to communicate with participants on the effect of belantamab mafodotin on eye'.	In line with program level requirements.
Appendix 15 – Data Management/Monitoring	Appendix added to reflect data verification, document review and sign off process when on-site monitoring is not permitted.	To reflect data management strategy.

Amendment 01 (03-Aug-2020)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for amendment 1:

- Change to the study design and model used to evaluate additional dose levels/dose schedules of belantamab mafodotin in combination with SoC. This evaluation will determine the Recommended Phase 3 dose (RP3D) of belantamab mafodotin in combination with SoC for future studies in the newly diagnosed setting. The efficacy of belantamab mafodotin with SoC compared to SoC alone will be evaluated in a separate study.
- Based on the benefit/risk for belantamab mafodotin after review of data from the primary analyses of the 205678/DREAMM-2 study, it has been determined that the need for dose delay/reduction should be determined by ocular examination findings and changes in VA. The KVA scale will be used to evaluate ocular events.
- Additional changes have been incorporated which align with program-wide revisions and/or updates.
- Incorporation of protocol clarification memo #01 and #02 and country specific amendments GBR01 and DEU02.
- Administrative updates to add clarification and/or remove discrepancies.

Section # and Name	Description of Change	Brief Rationale
Study Title	Study title updated to reflect that this study is now a Ph 1 dose evaluation study.	To reflect the adjusted study design.
CCI	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale
Redesign of Part 1 (Dose Selection) of the study		
Synopsis, Section 3 - Objectives & Endpoints	Efficacy assessments moved from exploratory to secondary endpoints. MRD negativity added as an exploratory endpoint. HRQOL exploratory endpoints added for PRO-CTCAE, OSDI, EORTC-QLQ-C30, PGIS and PGIC.	To formalize inclusion of efficacy, and HRQOL in comparison of doses, and selection of a RP3D for future assessment.
Synopsis, Section 5 – Study Population	Update to number of participants.	To reflect adjustment in number of dose cohorts and participants to be enrolled.
Section 4 – Study Design	Update in study design to reflect new doses/dose schedules, new dose evaluation strategy, updated DLT period and DLT criteria, and rationale for study design and for cohort doses.	To reflect the redesign of the study.
Section 6 - Study Treatment	Instructions provided for new doses/dose schedules including instructions for dosing of these doses/dose schedules, adjustments to reflect the randomization strategy, new dose reduction schedule for belantamab mafodotin, and updated dose modification guidelines for belantamab mafodotin.	To reflect the new doses/dose schedules.
Amendment to Cardiac monitoring requirements		
Section 1.3 – SoA, Section 8.2.6 - Electrocardiograms	Removal of ECGs at all visits except C1D1.	In line with cardiac monitoring requirements across belantamab mafodotin program, based on emerging safety data.
Section 5.2 – Exclusion	Removal of Exclusion Criteria related to QTc Interval.	No longer required based on emerging safety data.
Section 7.1.2 - QTc Stopping	Update to QTc Stopping Criteria.	In line with cardiac monitoring requirements across belantamab mafodotin program, based on emerging safety data.

Section # and Name	Description of Change	Brief Rationale
Section 7.1.3 – LVEF Stopping, Section 8.2.7 - Echocardiogram	Removal of requirement for ECHOs to be submitted for central collect and store.	Central review of ECHOs no longer required in line with belantamab mafodotin program level cardiac requirements.
Section 1.3 – SoA, Appendix 2 -Clinical Laboratory Tests	Removal of Troponin & NT-proBNP.	No longer required in line with belantamab mafodotin program level cardiac requirements.
Amendment to ophthalmology monitoring requirements		
Section 1.3 - SoA	Removal of requirement for steroid eye drops	Emerging data demonstrated that steroid eye drops were not beneficial
Section 1.3 – SoA, Section 8.2.9 – Ophthalmic Exams	Adjustment to frequency of ophthalmology assessments.	In line with ophthalmology monitoring requirements across belantamab mafodotin program, based on emerging safety data.
Section 8.2.9 - Ophthalmic Exams, 8.2.9.1 – Ocular Procedures	Requirement for ophthalmology exams updated.	In line with ophthalmology monitoring requirements across belantamab mafodotin program, based on emerging safety data.
Section 1.3 - SoA	Expansion of ophthalmology assessments window from 72 hours to 5 days.	Increase flexibility for ophthalmology assessments.
Section 6.6.2.2 – Dose Modifications for belantamab mafodotin	GSK Grading Scale for Corneal Events updated with the Keratopathy and Visual Acuity (KVA) Scale.	Based on the benefit/risk after review of data from the primary analyses of the 205678/DREAMM-2 study, it has been determined that the need for dose delay/reduction should be determined by ocular examination findings and changes in visual acuity (VA).
Throughout the document	Update of '…ophthalmologist (or optometrist if not available)…' to 'eye care specialist'.	For simplicity and consistency of wording across study-related documents.
Amendments to contraception and pregnancy wording in line with belantamab mafodotin program-wide guidance and Celgene Global Pregnancy Prevention Program		
Section 1.3 - SoA	Pregnancy Prevention Counseling added at every dosing visit.	In accordance with requirements of Celgene Global Pregnancy Prevention Program (GPPP)

Section # and Name	Description of Change	Brief Rationale
Section 1.3 - SoA, Section 5.1 – Inclusion Criteria, Section 8.3.5 – Pregnancy & Appendix 4 – Contraceptive Guidelines	Contraception requirements adjusted to bring in line with the Celgene GPPP. Contraception requirements and pregnancy reporting instructions adjusted to make clear requirements for individual agents. Restriction of donation of eggs (ova, oocyte) for reproductive purposes added.	Central supply of lenalidomide to all countries except the US is from Celgene and the study is required to follow their GPPP. To reflect the fact that some agents may be stopped whilst others continue, and each have different contraception requirements. Restriction of donation of eggs (ova, oocyte) for reproductive purposes omitted from original protocol in error.
Section 5.3 – Lifestyle Considerations	Restriction of donation of blood adjusted to 28 days after the end of treatment with lenalidomide.	In accordance with requirements of Celgene GPPP.
Update to clinical experience of belantamab mafodotin, risk-benefit table, and pharmacokinetics		
Synopsis, Section 2.2.3 – Human Experience, Section 2.3.2 – Benefit Assessment, Section 4.3 – Justification of Dose	Update to the clinical experience with belantamab mafodotin.	Updated to reflect latest clinical and safety information included in the new IB Version 7.
Section 2.2.4 – PK/PD in Humans	Update to the pharmacokinetic and pharmacodynamic information in humans.	Updated to reflect latest clinical and safety information included in the new IB Version 7.
Section 2.3.1 – Risk Assessment	Update to Risk-Benefit table to reflect current information from the belantamab mafodotin program and updated information on bortezomib, lenalidomide and dexamethasone	Updated based on emerging data from belantamab mafodotin program and from on bortezomib, lenalidomide and dexamethasone.
Eligibility Criteria		
Section 5.2 – Exclusion Criteria	Exclusion criteria added to define “frailty” using the IMWG Frailty Score.	At the request of the US FDA, the IMWG Frailty Score has been added to the eligibility criteria.

Section # and Name	Description of Change	Brief Rationale
Section 5.1 – Inclusion Criteria	Requirement for eGFR levels at screening updated from 40 mL/min/1.73m^2 to 30 mL/min/1.73m^2.	To reflect that some patients with newly diagnosed multiple myeloma and are ineligible to for transplant (TI NDMM) may have a moderate degree of kidney disease and still be suitable for the study.
Section 1.3 – SoA, Section 5.1 – Inclusion Criteria, Section 6.6.2.3 – Dose modifications for Len, Bort, and Dex Section 10.2 – Clinical Laboratory Tests	Addition of the option to perform Spot Urine for Albumin/Creatinine ratio centrally after performing a urine dipstick first.	To give greater flexibility to sites.
Section 5.2 - Exclusion Criteria (Table 4)	Requirement for LVEF adjusted to ≥35%, regardless of symptomology.	At the request of the US FDA.
Section 5.2 – Exclusion Criteria	Exclusion criteria added to exclude participants with plasmapheresis within 7 days prior to first dose.	At the request of the US FDA.
Section 5.2 – Exclusion Criteria	Exclusion criteria added regarding hypersensitivity or idiosyncratic reaction to belantamab mafodotin or any components of the study treatment.	Omitted from original protocol in error.
Other amendments		
Throughout the document	Naming convention for doses and dose schedules updated to ensure clarity around dosing schedules.	To mitigate the risk of dosing errors.
Throughout the document	Update of wording from ‘subject’ to ‘participant’.	To be in line with new protocol template and consistency of wording across study-related documents.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 – SoA, Throughout the document	Period for collection of AEs, SAEs, Con Meds and significant laboratory abnormalities extended from 45 days to 70 days. Safety follow-up visit moved from 45 days post end of treatment to 70 days post end of treatment.	Emerging evidence from belantamab mafodotin program.
Section 1.3 - SoA	Clinical Chemistry removed from bortezomib dosing days except for Day 1.	Clinical chemistry not required on all bortezomib dosing days.
Section 4.1.1 – Dose Evaluation	Commitment added to implement alternative belantamab mafodotin doses and/or dose schedules only after regulatory approval of a substantial amendment.	Formalizing commitment within the amendment following request from a regulatory authority.
Section 6.6.1 - Belantamab Dose Reductions, Section 7.1 –Discontinuation of Study Treatment	If a patient has to discontinue belantamab mafodotine for reasons other than PD they will continue on VRd if in C1-8 but then will come off study treatment and attend for an EOT Visit and a safety follow-up visit rather than continuing indefinitely on Rd.	In recognition of the fact that Rd is a standard of care (SoC) agent that is accessible outside of the study.
Section 6.6.2.3 - Dose modifications for Len, Bort, and Dex	Additional follow-up requirements for participants who develop pneumonitis removed from dose modification guidance.	To allow flexibility for sites to investigate pneumonitis as per local SoC.
Section 6.6.2.4 - Dose modifications for Dex	Dose modification information added for ongoing dexamethasone.	Omitted from original protocol in error. Original protocol has information on dose modification of starting dose only.
Section 7.1.1 – Liver Chem Stopping Criteria, Appendix 6 – Liver Safety	Liver chemistry stopping criteria and increased monitoring criteria replaced with criteria for Phase 1 studies as opposed to Phase 3 studies	To reflect that this is now a Phase 1 study.
Section 8.1.1 – Minimal Residual Disease	Addition of details on the MRD assay to be used in this study.	At the request of the US FDA, further details of the assay used for MRD analysis has been added to the protocol.
Section 8.2.4 - IMWG Frailty Score,	Addition of the IMWG Frailty Score.	To reflect new eligibility criteria.

Section # and Name	Description of Change	Brief Rationale
Appendix 8 - IMWG Frailty Score		
Section 8.4.1 – PK Sample Collection	EOI PK sample time extended from 5 min after EOI to 15 min after EOI. PK Sampling timepoints updated to reflect new design.	To allow greater flexibility at site. To reflect new study design.
Section 8.6 - Biomarkers	Biomarkers section updated to better reflect biomarker strategy for this study.	In line with program level requirements
Section 9 – Statistical Considerations	Statistical considerations updated to reflect new study design including adjustments to the hypotheses, sample size, stats analysis methods, and addition of safety stopping rules.	To reflect new study design.
Section 1.3 – SoA, Section 8.2.9 – Ophthalmic Exams, Section 8.2.10 – Visual Function Safety Assessment, Section 8.2.11 – PRO-CTCAE, Section 8.8 – Health-Related Quality of Life	Requirement to perform PROs including the OSDI and PRO-CTCAE at the start of every visit. Addition of the potential to use an interviewer-administered method for PROs for reasons other than just visual impairment.	Omitted from original protocol in error. Mitigation strategy for COVID-19 and potential restrictions on clinic visits in the future.
Appendix 1 – Reg, Ethical, and Study Oversight	Updates made to Regulatory, Ethical, and Study Oversight Considerations to reflect current processes	In line with GSK company wide processes and procedures.
Appendix 2 – Clinical Laboratory Tests	Blood urea nitrogen (BUN) removed	No longer required
Appendix 6 – Liver Safety	sBCMA sample added alongside PK sample if participant experiences a liver event and if there is an overdose	All PK samples require an associated sBCMA sample. Missed from original protocol in error.
Appendix 6 – Liver	Liver safety requirements updated	In line with GSK company wide update

Section # and Name	Description of Change	Brief Rationale
Safety		
Clarifications and administrative amendments		
Section 6.1.2.1.1 – Dose Calculation	Flexibility added to method of calculating BSA.	Specific nomogram is not required. Calculation can be by local practice.
Section 6.8 – Treatment of Overdose	Information related to treatment of overdose moved from Section 8.4 to Study Treatment Section.	More appropriate placement of information within the protocol.
Appendix 1 – Reg, Ethical, and Study Oversight	Reference to quality tolerance limits (QTLs) added to Data Quality Assurance section. Web address for the SHARE initiative added.	In line with ICH GCP E6R2 and GSK process. Provides information on how researchers can gain access to anonymized patient-level data.
Appendix 3 – Adverse Events	Adjustment to collect 'Assessment of Grade' rather than 'Assessment of Intensity'. Update to wording in 'Definition of SAE'.	To reflect data collection strategy. To reflect liver injury and impaired liver function are classified as an SAE.
Appendix 11 – Modified Diet in Renal Disease	Criteria for International Staging System (ISS) added.	Omitted from original protocol in error.
Appendix 12 – Eye Care Specialist Qualifications	Appendix added to detail requirements for eye care specialist's qualifications and requirements.	In line with program level requirements.
Appendix 13 – Home Healthcare and Telemedicine	Appendix 13 added to introduce permitted flexible visit options.	Mitigation strategy for COVID-19 and potential restrictions on clinic visits in the future.

Section # and Name	Description of Change	Brief Rationale
Appendix 14 – Operating Characteristics of Safety Stopping Rule	Appendix 14 added to provide the operating characteristics of the safety stopping rule for DLT criteria.	Details on the operating characteristics used in the new study design
Appendix 16 – Protocol Amendment History	Appendix 16 added to provide protocol amendment history.	To reflect that there have been previous country specific amendments that have not been incorporated into this global amendment.

Type of Amendment	Title	Date / DNG Number	Summary
Country Specific	Protocol Amendment KOR01	31-May-2021 TMF-13779216	The protocol has been amended to update exclusion criteria for Hepatitis B+ and Hepatitis C+ participants in order to align with the latest regulatory guidance for industry, to provide clarification to the administration of belantamab mafodotin.
Country Specific	Protocol Amendment DEU01	21Jan20 2019N395761_00/DEU01	Confirmation that Part 2 will commence only after submission and approval of a substantial amendment to the protocol. Addition of exclusion criteria for participants with hypersensitivity to study treatment(s). Alteration of contraception text to apply to women who are currently pregnant as well as women of childbearing potential (WOCBP). Movement of text relating to replacement of participants from dose modification section to population section.
Country Specific	Protocol Amendment GBR01	31Oct19 2019N395761_00/GBR01	Confirmation that alternative doses/schedules will only be implemented after regulatory approval of a substantial amendment.

11. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. JNCI: J Natl Cancer Inst. 1993;85(5):365-76.

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8(6):709-14.

Benbouker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014;371(10):906-17.

Cella D.F., Tulsky, D.S, Gray, G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993;11:570-79.

Chari A, Ung B, Abousaid S, et al. Real-World Treatment Outcomes in Patients with Newly Diagnosed Multiple Myeloma Treated with Triplet Therapy without Stem Cell Transplant: An Enhanced Electronic Health Records Database. Blood. 2017;130:2190.

Cocks K, Cohen, D, Wisloff, F, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-MY20) in assessing the quality of life of patients with multiple myeloma. Eur J Cancer. 2007;43:1670-78.

Cook G, Royle KL, Pawlyn C, et al. A clinical prediction model for outcome and therapy delivery in transplant-ineligible patients with myeloma (UK Myeloma Research Alliance Risk Profile): a development and validation study. Lancet Haematol. 2019;6(3):e154-66.

Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32(3):309-22.

Dougherty BE, Nichols JJ, Nichols KK. Rasch analysis of the ocular surface disease index (OSDI). Invest Ophthalmol Vis Sci. 2011;52(12):8630-5.

Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomized, open-label, phase 3 trial. Lancet. 2017;389:519-27.

Durie BGM, Hoering A, Sexton R, et al. Longer Term Follow up of the Â Randomized Phase III Trial SWOG S0777: Bortezomib, Lenalidomide and Dexamethasone Vs. Lenalidomide and Dexamethasone in Patients (Pts) with Previously Untreated Multiple Myeloma without an Intent for Immediate Autologous Stem Cell Transplant (ASCT). Blood. 2018;132:1992.

Facon, et al; Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma; N Engl J Med 2019; 380:2104.

Greipp PR, Miguel JS, Durie BG, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23(15):3412-20.

Guy W. The clinician global severity and impression scales. ECDEU assessment manual for psychopharmacology. 1976:218-22.

Hunt CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatology. 2010;52(6):2216-22.

Investigator's Brochure (IB) RPS-CLIN-105644, GlaxoSmithKline, Report Date 23-May-2024.

James LP, Letzig L, Simpson PM, et al. Pharmacokinetics of acetaminophen-adduct in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos. 2009;37(8):1779-84.

Kluetz PG, Chingos,DT, Basch EM, Mitchell SA. Patient-Reported Outcomes in Cancer Clinical Trials: Measuring Symptomatic Adverse Events With the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Am Soc Clin Oncol Educ Book. 2016;35:67-73.

Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-46.

Kumar S. Callander NS, Alsina M, et al. NCCN Guideline Insights: Multiple Myeloma, Version 3.2018. J Natl Compr Canc Netw. 2018;16(1):11-20.

Laurent SA, Hoffmann FS, Kuhn PH, et al. Gamma-secretase directly sheds the survival receptor BCMA from plasma cells. Nat Commun. 2015;6:7333.

Le Gal F, Gordien E, Affolabi D, et al. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2263-369.

Li X, Wulfsohn MS, Koch GG. Considerations on testing secondary endpoints in group sequential design. Statistics in Biopharmaceutical Research. 2017;9(4):333-7.

Lonial S, Lee HC, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol. 2020;21(2): 207-21..

Moreau P, San Miguel J, Sonneveld P, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28:52-61.

NYHA (New York Heart Association). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels (9th ed.). Boston: Little, Brown & Co., 1994;253–56.

O'Donnell E, Laubach JP, Yee AJ, et al. A Phase 2 Study of Modified Lenalidomide, Bortezomib, and Dexamethasone in Transplant-Ineligible Multiple Myeloma. Br J Hematol. 2018;182(2):222-30.

Oken MM, Creeech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

Palumbo A, Bringhen S, Mateos MV, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. Blood. 2015;125(13):2068-74.

Papay JI, Clines D, Rafi R, et al. Drug-induced liver injury following positive drug rechallenge. Regul Toxicol Pharmacol. 2009;54(1):84-90.

Proskorovsky I, Lewis P, Williams CD., et al. Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. Health Qual Life Outcomes. 2014;12:35.

Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet. 2014;15:e538-48.

Schiffman RM, Christianson MD, Jacobsen G, et al. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol. 2000;118(5):615-21.

Tai YT, Anderson KC. Targeting B-cell maturation antigen in multiple myeloma. Immunotherapy. 2015;7(11):1187-1199.

Tai YT, Li XF, Breitkreutz I, et al. Role of B-cell-activating factor in adhesion and growth of human multiple myeloma cells in the bone marrow microenvironment. Cancer Res. 2006;66(13): 6675-82.

Trudel S, Lendvai N, Popat R, et al. Antibody–drug conjugate, GSK2857916, in relapsed/refractory multiple myeloma: an update on safety and efficacy from dose expansion phase I study. Blood Cancer J. 2019;9(4):37.

Trudel S, Lendvai, N., Popat, R., Voorhees, P.M., Reeves, B., Libby, E.N., Richardson, P.G., et al. Targeting B-cell maturation antigen with GSK2857916 antibody–drug conjugate in relapsed or refractory multiple myeloma (BMA117159): a dose escalation and expansion phase 1 trial. Lancet Oncol. 2018;19:1641-53.

US Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE), version 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. Published 27 November 2017. Accessed 23 September 2024.

West CD and Boyd E. Nomogram for Body Surface Area Calculation, modified from data of E. Boyd by C.D. West. Nelson textbook of pediatrics (16th ed.). Behrman, RE, Kliegman, RM and Jenson, HB. Philadelphia, W.B.Saunders; 2000.

Signature Page for 209664 TMF-19347105 v2.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 18-Oct-2024 11:32:33 GMT+0000

Signature Page for TMF-19347105 v2.0