CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2 Multi-Arm Study of Magrolimab Combinations in Patients With Relapsed/Refractory Multiple Myeloma
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	118300
EudraCT Number:	2021-001798-21
Clinical Trials.gov Identifier:	NCT04892446
Indication:	Multiple Myeloma
Protocol ID:	GS-US-558-5915
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 22 December 2020 Amendment 1: 18 March 2021 Amendment 2: 05 May 2021 Amendment 3: 12 October 2021 Amendment 4: 31 March 2022 Amendment 5: 31 May 2022 Amendment 6: 02 November 2023

This study will be conducted under United States Food and Drug Administration investigational new drug (IND) regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area, United Kingdom, and Switzerland are not included under the IND and are considered non-IND sites.

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PROTOCOL SYNOPSIS

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Dose-expansion Cohorts

Primary Objective	Primary Endpoint
• To evaluate the efficacy of magrolimab in combination with other anticancer therapies in patients with relapsed/refractory MM as determined by objective response rate (ORR)	• ORR, defined as the percentage of patients who achieve stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR)[a]
Secondary Objectives	**Secondary Endpoints**
• To evaluate the safety and tolerability of magrolimab in combination with other anticancer therapies	• The incidence of AEs and laboratory abnormalities according to the NCI CTCAE Version 5.0
• To investigate other parameters of efficacy including the duration of response	• Duration of response (DOR)[a]
• To evaluate the pharmacokinetics (PK) and immunogenicity of magrolimab in combination with other anticancer therapies in patients with relapsed/refractory MM	• Magrolimab concentration versus time • Measurements of antidrug antibody (ADA) against magrolimab

a Response assessments will be performed per the International Myeloma Working Group (IMWG) 2016 criteria.

Study Design:

Number of Patients Planned:	Approximately 153 patients will be enrolled in the study, with up to 27 in each safety run-in cohorts (up to 9 patients at each of the 3 possible dose levels; total up to 81 patients) and approximately 72 patients in the dose-expansion cohorts.
Target Population:	Patients with relapsed/refractory MM.
Duration of Treatment:	The length of Cycle 1 will be 35 days; all subsequent cycles will be 28 days. All patients will continue on study treatment until they meet study treatment discontinuation criteria.
Diagnosis and Main Eligibility Criteria:	Inclusion Criteria: All patients must meet all the following inclusion criteria to be eligible for participation in this study: 1) Patient has been previously diagnosed with MM based on the International Myeloma Working Group (IMWG) 2016 criteria and currently requires treatment.

2) Patients must have measurable disease as defined by 1 or more of the following:
   a) Serum monoclonal protein (M-protein) ≥ 0.5 g/dL (≥ 5 g/L)
   b) Urine M-protein ≥ 200 mg/24 h
   c) Serum free light chain (SFLC) assay: involved SFLC level ≥ 10 mg/dL (100 mg/L) with abnormal SFLC ratio
3) Patient has provided informed consent
4) Patient is willing and able to comply with clinic visits and procedures outlined in the study protocol.
5) Male or female ≥ 18 years of age
6) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
7) Life expectancy ≥ 3 months
8) Absolute neutrophil count ≥ 1000 cells/μL (1.0×10^9/L); granulocyte colony-stimulating factor is not permitted within 1 week of screening to meet eligibility criteria.
9) Platelet count ≥ 75,000 cells/μL (75×10^9/L); platelet transfusion is not permitted within 1 week of screening to meet eligibility criteria.
10) Hemoglobin must be ≥ 9 g/dL prior to initial dose of study treatment. NOTE: Transfusions are allowed to meet hemoglobin eligibility.
11) Criterion removed.
12) Adequate liver function as demonstrated by the following:
   a) Aspartate aminotransferase ≤ 3.0 × upper limit of normal (ULN)
   b) Alanine aminotransferase ≤ 3.0 × ULN
   c) Total bilirubin ≤ 1.5 × ULN (or ≤ 3.0 × ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or genetic equivalent).
13) International normalized ratio (INR) ≤ 1.2; patients receiving anticoagulation treatment may be allowed to participate if INR is within the therapeutic range prior to alternate assignment.
14) Patients must have adequate renal function as demonstrated by a creatinine clearance ≥ 30 mL/min calculated by the Cockcroft-Gault formula or measured by 24 hours urine collection.

15) Corrected serum calcium ≤ 2.9 mmol/L (11.5 mg/dL); measures to reduce calcium to acceptable levels, such as a short course of steroids, bisphosphonates, hydration, or calcitonin are acceptable.

16) Pretreatment blood cross-match completed.

17) Male and female patients of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception.

18) Patients must be willing to consent to mandatory pretreatment and on-treatment bone marrow biopsies (trephines).

Magrolimab in Combination with Daratumumab: In addition to fulfilling the inclusion criteria for all patients, patients who are assigned to receive magrolimab in combination with daratumumab should fulfill the following:

19) Patients must have received at least 3 previous lines of therapy for MM including an immunomodulatory drug (IMiD) such as lenalidomide and a proteasome inhibitor (PI) such as bortezomib.

20) Patients must have not had prior anti-CD38 antibody therapy for at least 6 months prior to enrollment.

21) No prior history of discontinuation of daratumumab due to toxicity

Magrolimab in Combination with Pomalidomide and Dexamethasone: In addition to fulfilling the inclusion criteria for all patients, patients who are assigned to receive magrolimab in combination with pomalidomide and dexamethasone should fulfill the following:

22) Patients must have received at least 3 previous lines of therapy for MM including an IMiD such as lenalidomide and a PI such as bortezomib.

23) Prior treatment with pomalidomide is allowed if the patient achieved at least a PR to the most recent pomalidomide therapy and will have had at least a 6-month treatment-free interval from the last dose of pomalidomide until first study treatment.

24) No prior history of discontinuation of pomalidomide due to toxicity

25) No contraindication to dexamethasone

Magrolimab in Combination with Carfilzomib and Dexamethasone: In addition to fulfilling the inclusion criteria for all patients, patients who are assigned to receive magrolimab in combination with carfilzomib and dexamethasone should fulfill the following:

26) Patient must have received at least 3 previous lines of therapy for MM including an IMiD such as lenalidomide and a PI such as bortezomib.

27) Prior treatment with a PI, including carfilzomib, is allowed if the patient achieved at least a PR to the most recent prior PI therapy, and will have had at least a 6-month PI treatment-free interval from the last dose until first study treatment.

28) No prior history of discontinuation of carfilzomib due to toxicity.

29) No contraindication to dexamethasone

Magrolimab in Combination with Bortezomib and Dexamethasone:

In addition to fulfilling the inclusion criteria for all patients, patients who are assigned to receive magrolimab in combination with bortezomib and dexamethasone should fulfill the following:

30) Patient must have received at least 1 previous line of therapy for MM.

31) Prior treatment with a PI, including bortezomib, is allowed if the patient achieved at least a PR to the most recent prior PI therapy, and will have had at least a 6-month PI treatment-free interval from the last dose until first study treatment.

32) No prior history of discontinuation of bortezomib due to toxicity.

33) No contraindication to dexamethasone.

Exclusion Criteria: Patients who meet any of the following exclusion criteria are not eligible to be enrolled in this study:

1) Patients with known amyloidosis including myeloma complicated by amyloidosis

2) Multiple myeloma of immunoglobulin M subtype

3) Patients with Waldenstrom's macroglobulinemia

4) Patients with myelodysplastic syndrome

5) Plasma cell leukemia (defined as either 20% of peripheral blood white blood cell count comprised of

plasma/CD138-positive cells) or circulating plasma cells $\geq 2 \times 10^9$/L

6) Patients with solitary bone or extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia
7) POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes)
8) Glucocorticoid therapy (prednisone > 40 mg/day or equivalent) within 14 days prior to enrollment; corticosteroid therapy for hypercalcemia is allowed
9) Chemotherapy with approved or investigational anticancer therapeutics within 28 days prior to enrollment
10) Focal radiation therapy within 7 days prior to enrollment; radiation therapy to an extended field involving a significant volume of bone marrow within 21 days prior to enrollment (ie, prior radiation must have been to less than 30% of the bone marrow)
11) Immunotherapy within 28 days prior to enrollment
12) Major surgery (excluding procedures to stabilize the vertebrae) within 28 days prior to enrollment
13) Positive serum pregnancy test (Appendix 4)
14) Breastfeeding female
15) Known hypersensitivity to any of the study drugs, the metabolites, or formulation excipient
16) Prior treatment with CD47 or signal regulatory protein alpha (SIRPα)-targeting agents
17) Current participation in another interventional trial
18) Autologous stem cell transplant (SCT) < 100 days prior to enrollment
19) Considered eligible to receive autologous or allogeneic SCT at the time of enrollment
20) Allogeneic SCT for the treatment of MM within 6 months of enrollment or active graft-versus-host disease requiring immunosuppression
21) Significant neuropathy (Grade 3 to 4, or Grade 2 with pain) within 14 days prior to enrollment
22) Known inherited or acquired bleeding disorders

	23) Known cirrhosis. 24) Clinical suspicion or documentation of central nervous system (CNS) disease. 25) Significant disease or medical conditions, as assessed by the investigator and sponsor, that would substantially increase the risk-benefit ratio of participating in the study; this includes, but is not limited to, acute myocardial infarction within the last 6 months, unstable angina, uncontrolled diabetes mellitus, significant active infections, congestive heart failure, or NYHA Class III or IV heart failure. 26) Acute active infection requiring systemic antibiotics, antiviral (except antiviral therapy directed against reactivation) or antifungal agents within 14 days prior to enrollment. 27) Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancies for which patients are not on active anticancer therapies and have had no evidence of active malignancy for at least 1 year; other exceptions may be considered with sponsor approval. Previous hormonal therapy with luteinizing hormone-releasing hormone agonists for prostate cancer and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors are not criteria for exclusion. 28) Known active or chronic hepatitis B or C infection or HIV infection in medical history. 29) Active hepatitis B virus (HBV) and/or active hepatitis C virus (HCV), and/or HIV following testing at screening: a) Patients who test positive for hepatitis B surface antigen (HBsAg). Patients who test positive for hepatitis B core antibody (anti-HBc) will require HBV DNA by quantitative polymerase chain reaction (PCR) for confirmation of active disease. b) Patients who test positive for HCV antibody. Patients who test positive for HCV antibody will require HCV RNA by quantitative PCR for confirmation of active disease. c) Patients who test positive for HIV. 30) Patients who received any live vaccine within 4 weeks prior to initiation of study treatments.
Study Procedures/ Frequency:	Screening will commence with obtaining the patient's signed informed consent and will occur up to 30 days prior to the first

	dosing of study drug. Screening procedures include medical history review; complete physical examination; vital signs; 12-lead electrocardiogram (ECG) and echocardiogram (ECHO)/multigated acquisition (MUGA) scan; ECOG Performance Status, blood collection for chemistry, for complete blood count with differential, platelets, reticulocytes, SFLC analysis, blood phenotyping or genotyping for minor antigens, serum protein electrophoresis (SPEP), serum pregnancy test, urine collection for urine analysis and 24-hour urine protein electrophoresis (UPEP), peripheral blood smear, bone marrow aspirate/biopsy, skeletal survey, computed tomography (CT) (with or without positron emission tomography [PET]) or magnetic resonance imaging (MRI) assessment for extramedullary soft tissue plasmacytoma, Functional Assessment of Cancer Therapy-Multiple Myeloma (FACT-MM) questionnaire *(not collected after Protocol Amendment 6)*, myeloma frailty score calculation (patients ≥ 65 years of age), prior/concomitant medication review, and recording of any serious adverse events (SAEs) and all AEs related to protocol-mandated procedures after signed informed consent. Eligible patients will return to the study site within 30 days after screening for completion of baseline/Day 1 assessments and enrollment into applicable treatment cohort, magrolimab + daratumumab; magrolimab + pomalidomide + dexamethasone; magrolimab + carfilzomib + dexamethasone; or magrolimab + bortezomib + dexamethasone. The length of Cycle 1 will be 35 days; all subsequent cycles will be 28 days. On-treatment assessments include clinical laboratory evaluations, PK, antidrug antibody evaluations, bone marrow aspirate/biopsy assessments, bone lesion assessments, response assessments, FACT-MM questionnaire *(not collected after Protocol Amendment 6)*, vital signs, and monitoring for AEs and concomitant medications. Patients may continue treatment unless they meet study treatment discontinuation criteria.

Test Product, Dose, and Mode of Administration:

Magrolimab Dose De-escalation and Schedule (All Safety Run-in Cohorts)

Dose Level	Magrolimab Dosing
Starting Dose 30 mg/kg	• Cycle 1: 1 mg/kg IV on Day 1, 30 mg/kg on Days 8, 15, 22, 29 • Cycle 2: 30 mg/kg IV every week on Days 1, 8, 15, 22 • Cycle 3 and onward: 30 mg/kg IV on Days 1, 15
Level −1 20 mg/kg	• Cycle 1: 1 mg/kg IV on Day 1, 20 mg/kg on Days 8, 15, 22, 29 • Cycle 2: 20 mg/kg IV every week on Days 1, 8, 15, 22 • Cycle 3 and onward: 20 mg/kg IV on Days 1, 15
Level −2 15 mg/kg	• Cycle 1: 1 mg/kg IV on Day 1, 15 mg/kg on Days 8, 15, 22, 29 • Cycle 2: 15 mg/kg IV every week on Days 1, 8, 15, 22 • Cycle 3 and onward: 15 mg/kg IV on Days 1, 15

IV = intravenous

Magrolimab Dose Level and Schedule (All Dose-Expansion Cohorts)

RP2D[a]	Dose Schedule (Cycle 1 is 35 Days; All Other Cycles are 28 Days)		
	Cycle 1	Cycle 2	Cycle 3+
30 mg/kg	1 mg/kg IV Day 1 (priming dose) and 30 mg/kg IV Days 8, 15, 22, 29	30 mg/kg IV Days 1, 8, 15, 22	30 mg/kg IV Days 1, 15
20 mg/kg	1 mg/kg IV Day 1 (priming dose) and 20 mg/kg IV Days 8, 15, 22, 29	20 mg/kg IV Days 1, 8, 15, 22	20 mg/kg IV Days 1, 15
15 mg/kg	1 mg/kg IV Day 1 (priming dose) and 15 mg/kg IV Days 8, 15, 22, 29	15 mg/kg IV Days 1, 8, 15, 22	15 mg/kg IV Days 1, 15

IV = intravenous; RP2D = recommended Phase 2 dose
a RP2D as determined in the safety run-in cohorts.

Dose Level and Schedule for Daratumumab in Combination with Magrolimab

Drug/Dose/Route	Dose Schedule (Cycle 1 is 35 Days; All Other Cycles are 28 Days)		
	Cycle 1	Cycle 2	Cycle 3+
Daratumumab 16 mg/kg IV or 1800 mg SC	Days 8, 15, 22, 29	Days 1, 8, 15, 22	Days 1 and 15 (every 2 weeks) until Cycle 6 (total of 8 doses) followed by Day 1 (every 4 weeks) for subsequent cycles

IV = intravenous; SC = subcutaneous

Dose Level and Schedule for Pomalidomide and Dexamethasone in Combination with Magrolimab

Drug/Dose/Route	Dose Schedule (Cycle 1 is 35 Days; All Other Cycles are 28 Days)		
	Cycle 1	Cycle 2	Cycle 3+
Pomalidomide 4 mg PO	Days 1 to 21 (daily)	Days 1 to 21 (daily)	Days 1 to 21 (daily)
Dexamethasone 40 mg PO[a]	Days 1, 8, 15, 22, 29	Days 1, 8, 15, 22	Days 1, 8, 15, 22

PO = orally
a Dexamethasone starting dose is 20 mg in patients more than 75 years of age.

Dose Level and Schedule for Carfilzomib and Dexamethasone in Combination with Magrolimab

Drug/Dose/Route	Dose Schedule (Cycle 1 is 35 Days; All Other Cycles are 28 Days)		
	Cycle 1	Cycle 2	Cycle 3+
Carfilzomib 20/70 mg/m^2 IV[a]	Days 8 (20 mg/m^2), 15 (70 mg/m^2), 22 (70 mg/m^2)	Days 1, 8, 15[b]	Days 1, 8 15[b]
Dexamethasone 40 mg PO or IV[c]	Days 8, 15, 22, and 29	Days 1, 8, 15, and 22	Days 1, 8, 15, and 22 until Cycle 9 and Days 1, 8, and 15 from Cycle 10 onward

IV = intravenous; PO = orally
a The recommended starting dose of carfilzomib is 20 mg/m^2 on Cycle 1, Day 8. If tolerated, escalate the dose to 70 mg/m^2 on Cycle 1, Day 15 and thereafter.
b From Cycle 2 onwards, carfilzomib will be given on Days 1, 8 and 15. Dexamethasone starting dose is 20 mg in patients more than 75 years of age.

Dose Level and Schedule for Bortezomib and Dexamethasone in Combination with Magrolimab

Drug/Dose/Route	Dose Schedule (Cycle 1 is 35 Days; All Other Cycles are 28 Days)		
	Cycle 1	Cycle 2	Cycle 3+
Bortezomib 1.3 mg/m^2 SC or IV[a]	Days 8, 15, 22, 29	Days 1, 8, 15, 22	Days 1, 8 15, 22[b]
Dexamethasone 40 mg PO[c]	Days 1, 8, 15, 22, 29	Days 1, 8, 15, 22	Days 1, 8, 15, 22[d]

IV = intravenous; PO = orally; SC = subcutaneous
a SC is preferred over IV, where feasible.
b Maximum of 8 cycles in those who have previously received bortezomib.
c Dexamethasone starting dose is 20 mg in patients more than 75 years of age.
d Days 1, 8, 15, and 22 from Cycles 3 to 9 and then Days 1, 8, and 15 from Cycle 10 onward.

Reference Therapy, Dose, and Mode of Administration:	Not applicable
Criteria for Evaluation:	
Safety:	Safety will be assessed by evaluating occurrence of DLTs in patients in the safety run-in cohorts, the incidence of AEs, clinical laboratory test findings, physical examination, 12-lead electrocardiogram, ECOG performance status, and vital signs measurements. AEs will be graded using the NCI CTCAE Version 5.0.
Efficacy:	Response assessment will be performed by the investigator according to the IMWG 2016 criteria. Efficacy will be evaluated by ORR, DOR, and time to response (TTR). Objective response rate is defined as the percentage of patients who achieve sCR, CR, VGPR, or PR.
Pharmacokinetics:	Serum magrolimab concentration will be assessed before the first dose and at specified time points after start of treatment.
Immunogenicity:	Immunogenicity assessments will be conducted before the first dose and at specified time points after start of treatment to detect and measure antidrug antibodies against magrolimab.

Statistical Methods:	Analysis Data Sets: **Full Analysis Set**: The primary analysis set for efficacy analysis is the Full Analysis Set (FAS). The FAS includes all enrolled patients who received at least 1 dose of study treatment with treatment group designated according to the planned treatment assigned at enrollment. **Safety Analysis Set**: The analysis set for safety analyses is the Safety Analysis Set. It includes all patients who received at least 1 dose of study treatment with treatment group designated according to the actual treatment received. This analysis set will be used in the analyses of safety endpoints as well as study treatment administration. All data collected during treatment up to 70 days after treatment discontinuation will be included in the safety summaries. **DLT-Evaluable Analysis Set**: The DLT-Evaluable Analysis Set includes all patients in the Safety Analysis Set who are enrolled in the safety run-in cohorts and fulfill either of the following criteria: • Experienced a DLT after initiation of the first infusion of magrolimab during the DLT assessment period • Completed DLT assessment period and received at least 3 infusions of magrolimab and the following cohort-specific criteria: — Magrolimab in combination with daratumumab cohort: Completed at least 2 doses of daratumumab — Magrolimab in combination with pomalidomide and dexamethasone cohort: Completed at least 10 doses of pomalidomide and 2 doses of dexamethasone — Magrolimab in combination with carfilzomib and dexamethasone cohort: Completed at least 2 doses of carfilzomib and 2 doses of dexamethasone — Magrolimab in combination with bortezomib and dexamethasone cohort: Completed at least 2 doses of bortezomib and 2 doses of dexamethasone **PK Analysis Set**: The PK Analysis Set includes all enrolled patients who received at least 1 dose of magrolimab and have at least 1 measurable posttreatment serum concentration of magrolimab. **Immunogenicity Analysis Set**: The Immunogenicity Analysis Set includes all enrolled patients who received at least 1 dose of magrolimab and have at least 1 evaluable anti-magrolimab antibody test result.

Biomarker Analysis Set: The Biomarker Analysis Set includes all enrolled patients who received at least 1 dose of magrolimab and have the evaluable baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

All Enrolled Set: The All Enrolled Analysis Set includes all patients who received a study patient identification number in the study after screening. This will be the primary analysis set for analyses of patient demographic and baseline characteristics, enrollment, and disposition.

Planned Analyses:

Efficacy analysis: Efficacy analysis will be based on the Full Analysis Set. For the primary efficacy endpoint ORR, the point estimate and the corresponding 2-sided exact 95% CI based on Clopper-Pearson method will be provided for each cohort. Objective response rate will also be tested against the historical control rate of 25% using 1-group Chi-square test for each cohort separately.

The medians, first quartile (Q1), and third quartile (Q3) of DOR will be estimated using the Kaplan-Meier (KM) method along with the corresponding 95% CIs. KM curves will be provided. For DOR, the analysis will include only patients who achieve an objective response.

Safety analysis: All safety data collected on or after the date that any drug in a study treatment regimen was first administered up to the date of the last dose of any drug in a study treatment regimen plus 70 days will be summarized by treatment cohort based on the Safety Analysis Set. Dose limiting toxicities will be summarized based on the DLT-Evaluable Set for safety run-in cohorts. Data for the pretreatment will be included in data listings. For categorical safety data, including incidence of AEs and categorizations of laboratory data, the number and percentage of patients will be summarized. For continuous safety data, including laboratory data, the number of patients, mean, standard deviation, minimum, quartiles, median, and maximum will be summarized.

PK analysis: The PK Analysis Set will be used for summaries of PK concentration of magrolimab versus time. Due to the sparse nature of PK collection, PK parameters will not be calculated. Summary statistics will be presented for magrolimab serum concentrations at each scheduled time point. Descriptive graphical plots of individual serum concentration versus time profiles and mean concentration versus time profiles will be generated.

	Immunogenicity analysis: Immunogenicity will be assessed using a 3-tier–screen, confirmatory, and titer – approach on study samples using a validated immunoassay. The rate and magnitude of anti-magrolimab antibody incidence, prevalence, persistence, and transience will be summarized for the Immunogenicity Analysis Set. CCI [redacted] Sample Size Calculation: For each of the dose-expansion cohorts, a sample size of 30 (24 expansion patients together with the 6 patients from the safety run-in cohort), provides 86.1% power for a 1-group Chi-square test at a 1-sided alpha of 0.1 to detect ORR of $\geq$ 45% for the combination treatment compared with a historical control ORR of 25%. The historical control ORR of 25% is based on outcomes from the MAMMOTH study; the subset of patients treated with any daratumumab-containing regimen, including daratumumab in combination with an IMiD or PI, following at least 1 prior treatment.

This study will be conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ABO	any of the 4 blood groups A, B, AB, and O composing the ABO system
ADA	antidrug antibody
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
CD38	cluster of differentiation 38
CD47	cluster of differentiation 47
CDC	complement-dependent cytotoxicity
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	cutaneous T-cell lymphoma
CYP	cytochrome P450
DAT	direct antiglobulin test
DC	dendritic cell
DEX	dexamethasone
DKd	daratumumab and dexamethasone
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DVd	daratumumab/bortezomib/dexamethasone
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture

ELISA	enzyme-linked immunosorbent assay
EOT	end of treatment
EU	European Union
FACT-MM	Functional Assessment of Cancer Therapy-Multiple Myeloma
FAS	Full Analysis Set
Fc	crystallizable fragment
FcR	Fc receptor
FDA	Food and Drug Administration
FL	follicular lymphoma
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
Gilead	Gilead Sciences
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IFE	immunofixation electrophoresis
Ig	immunoglobulin
IgG4	immunoglobulin G4
IL	interleukin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
INR	international normalized ratio
IRB	institutional review board
IRR	infusion-related reaction
IUD	intrauterine device
IV	intravenous(ly)
IXRS	interactive voice/web response system
K_D	dissociation constant
Kd	Kyprolis and dexamethasone
KM	Kaplan-Meier
KRd	Kyprolis with lenalidomide and dexamethasone

mAb	monoclonal antibody
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma
MOA	mechanism of action
M-protein	monoclonal protein
MR	minimal response
MRD	minimal residual disease
MRI	magnetic resonance imaging
mRNA	messenger RNA
MTD	maximum tolerated dose
MUGA	multigated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
NK	natural killer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PO	orally
POM	pomalidomide alone
POM-DEX	pomalidomide + dexamethasone
PR	partial response
PRO	patient-reported outcome
PS	Patient Safety
PT	prothrombin time
Q1	first quartile
Q3	third quartile
QOL	quality of life
RANKL	receptor activator of nuclear factor kappa-B ligand
RBC	red blood cell

Rd	lenalidomide and dexamethasone alone
REMS	risk evaluation and mitigation strategy
Rh	Rhesus factor
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SC	subcutaneous(ly)
sCR	stringent complete response
SCT	stem cell transplant
SD	stable disease
SFLC	serum free light chain
SIFE	serum immunofixation
SIRPα	signal regulatory protein alpha
SmPC	summary of product characteristics
SOP	standard operating procedure
SPEP	serum protein electrophoresis
SRT	Safety Review Team
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
TNF	tumor necrosis factor
TTR	time to response
UIFE	urine immunofixation
ULN	upper limit of normal
UPEP	urine protein electrophoresis
US	United States
USPI	United States prescribing information
Vd	bortezomib and dexamethasone
VGPR	very good partial response
VMP	bortezomib-melphalan-prednisone
VMPT	bortezomib-melphalan-prednisone-thalidomide
WBC	white blood cell
w/v	weight-to-volume
WGS	whole genome sequencing

1. INTRODUCTION

1.1. Background

Multiple myeloma (MM) is a clonal plasma cell disorder that accounts for 1% of all cancers and approximately 10% of hematological malignancies. Each year over 32,000 cases are diagnosed in the United States (US) and almost 13,000 patients die of the disease {Rajkumar 2020}. Despite the availability of proteasome inhibitors (PIs), immunomodulatory agents, and monoclonal antibodies (mAbs) for MM, most patients will relapse and develop refractory disease. Treatment of patients with relapsed/refractory MM remains challenging despite numerous therapeutic advances. Patients with disease refractory to immunomodulatory drugs, PIs, and anti-CD38 mAbs have a poor prognosis, with newer combination therapies such as selinexor plus dexamethasone resulting in 26% of patients achieving an objective response (median progression-free survival [PFS] of 3.7 months and median overall survival (OS) of 8.6 months) {Chari 2019}. Recently, the DREAMM-2 study reported an objective response rate (ORR) of up to 34% in relapsed/refractory patients treated with belantamab mafodotin who had disease progression after 3 or more lines of therapy and were refractory to immunomodulatory drugs and PIs, and refractory or intolerant (or both) to an anti-CD38 mAb {Lonial 2020}. Therefore, effective novel therapies with acceptable safety profiles are needed to increase the response rates in later lines as well as to enhance the depth and durability of response.

CD47 is a key molecule mediating cancer cell evasion of innate immune surveillance. CD47 expression is a well-characterized mechanism by which cancer cells, including cancer stem cells, overcome phagocytosis due to intrinsic expression of prophagocytic “eat me” signals {Jaiswal 2009, Majeti 2009}. The progression from normal cell to cancer cell involves changes in genes and gene expression that trigger programmed cell death and programmed cell removal {Chao 2012}. Many of the steps in cancer progression subvert the multiple mechanisms of programmed cell death, and the expression of the dominant antiphagocytic signal, CD47, may represent an important checkpoint {Chao 2012}. In mouse xenograft models, CD47-blocking mAbs inhibit human xenograft tumor growth and metastasis by enabling the phagocytosis and elimination of cancer cells from various hematologic malignancies and solid tumors {Chao 2011a, Chao 2010a, Chao 2011b, Edris 2012, Kim 2012, Majeti 2009, Willingham 2012}. Binding of CD47 expressed by cancer cells to signal regulatory protein alpha (SIRPα) expressed on phagocytes leads to inhibition of tumor cell phagocytosis. Thus, blockade of the CD47 SIRPα-signaling pathway by an anti-CD47 antibody leads to phagocytosis and elimination of tumor cells. Selective targeting of tumor cells by an anti-CD47 antibody is due to the presence of prophagocytic signals expressed mainly on tumor cells and not on normal cell counterparts {Chao 2010b}.

There is growing body of evidence that suggests that the overexpression of CD47 contributes to the pathogenesis of MM. A study of 37 MM patient samples demonstrated that myeloma cells express higher levels of CD47 by flow cytometry compared with patient-matched normal bone marrow cells {Kim 2012}. Herein, blocking CD47 with B6H12 antibodies increased phagocytosis of myeloma cells in vitro. In mice engrafted MM models, the anti-CD47 antibody B6H12 inhibited the growth of myeloma cells and led to significant tumor regression and eradication, with a response rate of 72% versus 19% in the control group at 6 weeks. An analysis of patient samples with MM (n = 171 patients) and monoclonal gammopathy of undetermined significance (MGUS) (n = 18 patients) showed that CD47 messenger RNA (mRNA) levels increased with progression from MGUS to MM. A very recent study has reported that MM cells had remarkably higher CD47 expression than other cell populations in the bone marrow and that blocking of CD47 using an anti-CD47 antibody induced immediate activation of macrophages and eliminated MM cells in the 3D-tissue engineered bone marrow model, as early as 4 hours after exposure {Sun 2020}. Taken together, these findings indicate that CD47 is specifically expressed on MM and can be used as a potential therapeutic target.

Magrolimab (GS-4721, formerly Hu5F9-G4 or 5F9) is a recombinant humanized anti-CD47 mAb of the immunoglobulin G4 (IgG4) kappa isotype. There is extensive nonclinical and clinical experience with magrolimab across a range of hematological malignancies and in solid tumors, which is summarized below and in the investigator's brochure (IB). This Phase 2 multi-arm study will investigate the efficacy, safety, and pharmacokinetics (PK) of magrolimab administered intravenously (IV) in combination with other anticancer therapies to patients with relapsed/refractory MM.

1.2. Magrolimab

1.2.1. General Information

Magrolimab is a humanized anti-CD47 mAb that blocks the interaction of CD47 with its receptor and enables phagocytosis of human cancer cells {Liu 2015}. The activity of magrolimab is primarily dependent on blocking CD47 binding to SIRPα and not on the recruitment of crystallizable fragment (Fc)-dependent effector functions, although the presence of the IgG4 Fc domain is required for its full activity. For this reason, magrolimab was engineered with a human IgG4 isotype that is relatively inefficient at recruiting Fc-dependent effector functions that might enhance toxic effects on normal CD47-expressing cells {Liu 2015}. Nonclinical studies using xenograft cancer models provide compelling evidence that magrolimab triggers phagocytosis and elimination of cancer cells from human solid tumors and hematologic malignancies. Based on this mechanism of action (MOA) and its potent nonclinical activity, magrolimab is being developed as a novel therapeutic candidate for solid tumors and hematologic malignancies.

The magrolimab clinical development program represents a novel strategy for the treatment of cancer and is the first therapeutic agent to target the CD47-SIRPα axis. Extensive nonclinical studies have demonstrated activity against both human solid tumors (breast, ovarian, pancreas, colon, leiomyosarcoma, bladder, prostate, and others) and hematologic malignancies (acute myeloid leukemia [AML], acute lymphoblastic leukemia, non-Hodgkin lymphoma [NHL], myeloma, myelodysplastic syndromes [MDS], and others).

For further information on GS-4721 (magrolimab), refer to the current IB.

1.2.2. Nonclinical Pharmacology and Toxicology

1.2.2.1. Pharmacology

In vitro studies of magrolimab activity included protein and cell-based assays using cancer cell lines. Magrolimab showed high binding affinity to monomeric and bivalent human CD47 antigen with a dissociation constant (K_D) of 8×10^{-9} and 8×10^{-12} M, respectively. Magrolimab bound to cynomolgus monkey and human CD47 with high affinity of $K_D = 10$ and 8.0 pM, respectively, but did not bind to mouse CD47. No complement-dependent cytotoxicity (CDC) activity of magrolimab was observed in AML cells, and no antibody-dependent cellular cytotoxicity activity of magrolimab was observed in Raji and HL60 cells. Magrolimab-induced macrophage-mediated phagocytosis in rat myeloma and HL60 cells and did not induce apoptosis in AML cells. Nonclinical experiments in MM cell lines demonstrated that magrolimab inhibits the myeloma cell growth and proliferation both alone and in combination with other agents. (Figure 2).

Expression of CD47 was observed on human peripheral blood cells, and magrolimab did not trigger phagocytosis by human macrophages of normal red blood cells (RBCs) or normal human bone marrow cells in vitro but was a potent inducer of phagocytosis of CD47-expressing AML cells in vitro. Treatment of AML cells with hydroxyurea had no effect on magrolimab-induced phagocytosis, nor did treatment trigger magrolimab-induced phagocytosis of normal bone marrow cells. In contrast, the combination of magrolimab and avelumab effectively enhanced phagocytosis of ovarian cancer cells by human macrophages compared with magrolimab or avelumab alone. Moreover, the combination of magrolimab with cytotoxic agent azacitidine at a clinically relevant concentration enhanced phagocytosis of HL60 cells in vitro when compared with magrolimab or azacitidine alone.

Nonclinical in vivo pharmacology studies using xenograft cancer models provide compelling evidence that magrolimab triggers phagocytosis and elimination of cancer cells from multiple human solid tumors and hematological malignancies. Overall, magrolimab in combination with azacitidine, trastuzumab, rituximab, cetuximab, and panitumumab demonstrated additive effect on eliminating cancer cells, resulting in a long-term remission and increased survival of animals.

Receptor occupancy assays showed that optimal antitumor activity (phagocytosis) in HL60 cells and primary human AML cells could be achieved without full CD47 receptor occupancy. The safety pharmacology evaluations as part of Good Laboratory Practice (GLP) 8-week toxicology study demonstrated no magrolimab-related effects on central nervous system (CNS), cardiovascular, or respiratory function in cynomolgus monkey.

1.2.2.2. Toxicology

In in vitro studies, magrolimab was not hemolytic and there was no evidence of adverse elevations of proinflammatory cytokines.

In the pivotal 8-week repeat-dose toxicology study, magrolimab was administered to cynomolgus monkeys via a 1-hour IV infusion as a priming dose of 5 mg/kg in Week 1 (Day 1), followed by twice-weekly maintenance doses for 7 consecutive weeks at doses ranging from 5 to 100 mg/kg.

Treatment-related findings were limited to changes in hematology and clinical chemistry parameters and erythroid cell morphology.

Hematology changes included decreases in red cell mass associated with decreases in mean corpuscular volume and haptoglobin; increases in mean corpuscular hemoglobin concentration, reticulocytes, and red cell distribution width; red cell morphology changes including spherocytes (microcytes), eccentrocytes, atypical erythrocyte fragments consistent with erythrocyte injury, erythrocyte clumping, and large platelets; and changes associated with increased erythropoiesis consisting of anisocytosis, polychromatophilic macrocytes, and increased total bilirubin.

Changes in blood cell morphology were consistent with previous studies and considered to be associated with accelerated RBC destruction/clearance and increased erythropoiesis.

Additional clinical chemistry changes were observed at the highest dose only (100 mg/kg), which included a slight decrease in albumin, a slight increase in globulin, and a corresponding decrease in albumin:globulin ratio. There was partial to complete recovery for all treatment-related changes, with the exception of increased spleen weights in males and females at 50 and 100 mg/kg at recovery necropsy, which had no macroscopic or microscopic correlate. Based on these results, the highest-non-severely-toxic-dose for this study was considered to be 100 mg/kg, the highest dose evaluated.

Reproductive and developmental toxicology studies have not been conducted, but all the available data (literature, data from knockout mice and limited clinical data) suggests no role for CD47 on embryo-fetal development.

1.2.3. Clinical Background for Magrolimab

1.2.3.1. Summary of Clinical Pharmacology

Clinical PK data have been collected in all ongoing studies of magrolimab conducted to date. Pharmacokinetic data have been analyzed in Phase 1 study (SCI-CD47-001) in patients with solid tumor. In this study, patients were treated with weekly magrolimab doses ranged from 0.1 to 45 mg/kg, with increasing serum concentrations associated with increasing dose. Nonlinear PK consistent with target-mediated clearance was observed over this dose range. However, at maintenance doses of 10 mg/kg and above, target-mediated clearance was saturated within the dosing regimen, and trough levels associated with magrolimab efficacy in nonclinical studies were achieved. Nine of 88 (10%) evaluable patients tested positive for antidrug antibody (ADA) against magrolimab at any time point including baseline; ADA positivity had no impact on PK or clinical safety in these patients.

In the Phase 1 AML study (SCI-CD47-002), similar to the solid tumor Phase 1 study, nonlinear PK consistent with target-mediated clearance was observed. Three of 20 (15%) evaluable patients tested positive for ADA against magrolimab at any time point including baseline; ADA positivity had no impact on PK. Antidrug antibody positivity in either study was not associated with increased adverse events (AEs).

Preliminary PK data of magrolimab from other ongoing studies (5F9003, 5F9004, and 5F9005) of magrolimab indicates similar PK properties across all tumor populations and in the presence of coadministered drugs. Across all studies, 46 of 430 (11%) patients tested positive for ADA against magrolimab at any time point including baseline. Antidrug antibody positivity was not associated with changes in PK or AE profile.

A preliminary population PK analysis of combined magrolimab PK data indicated that results for magrolimab population PK were typical of other nonlinear antibodies. No clinically significant covariates of PK variability were identified.

1.2.3.2. Summary of Clinical Safety

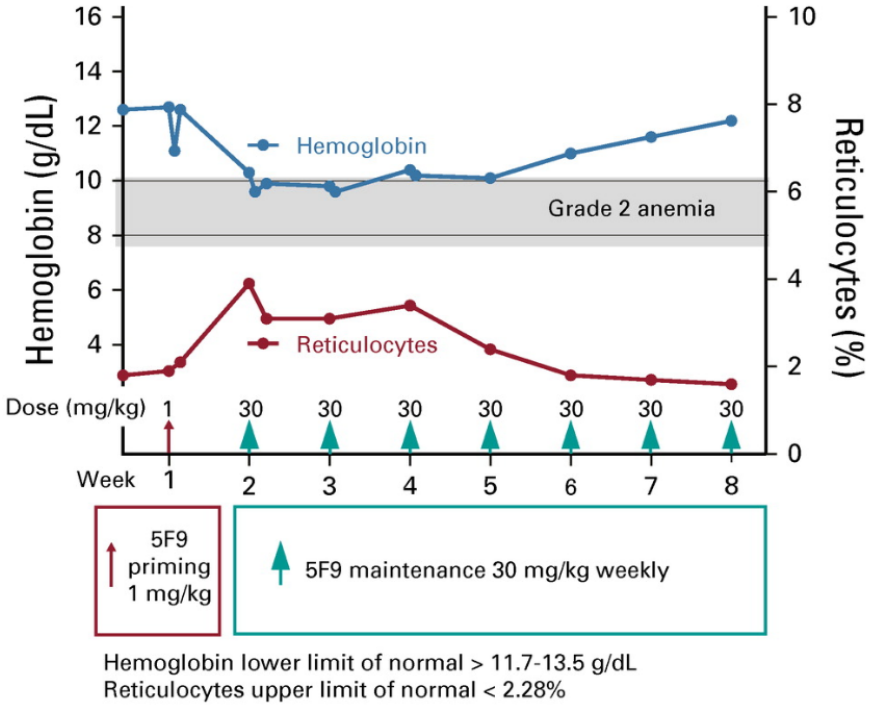
Magrolimab is administered as an IV infusion and it is currently being studied in 6 clinical studies. Two completed single-agent Phase 1 studies include Study SCI-CD47-001 in patients with advanced solid tumors and lymphomas, and Study SCI-CD47-002 in patients with relapsed/refractory AML, along with Phase 1b partnered studies in AML as well as urothelial carcinoma. Four combination studies include the following: Study 5F9003, a Phase 1b/2 study of magrolimab with rituximab in patients with relapsed/refractory NHL; Study 5F9004, a Phase 1b/2 study of magrolimab with cetuximab in solid tumor and colorectal cancer patients; Study 5F9005, a Phase 1b study of magrolimab with azacitidine in AML and MDS patients; and Study 5F9006, a Phase 1b study of magrolimab with avelumab in solid tumor and ovarian cancer patients. As of July 2020, over 500 patients have been treated with magrolimab. Overall, the safety profile has been acceptable with magrolimab as monotherapy or in combination, with no maximum tolerated dose (MTD) reached in any study with dosing up to 45 mg/kg. Two anticipated adverse reactions included on-target

anemia and infusion-related reactions (IRRs), which are expected with mAbs. Importantly, on-target anemia due to CD47 blockade-mediated RBC clearance was mitigated with a priming/maintenance dose strategy. The average hemoglobin declines with the first (priming) dose was between approximately 0.4 to 1.5 g/dL across indications, with many patients improving their hemoglobin on therapy back to baseline with a decrease in RBC transfusion requirements for those patients who were transfusion-dependent at baseline.

Magrolimab has been evaluated as a monotherapy or in combination in multiple solid tumor types. In the Phase 1 Study SCI-CD47-001 of magrolimab monotherapy, 88 patients with advanced solid tumors were treated with magrolimab doses up to 45 mg/kg. No MTD was reached. As per the 2020 IB, across 548 patients treated with magrolimab, which includes both solid tumors and hematologic malignancies, fatigue, anemia, and headache were the 3 most frequently reported AEs (43.0%, 40.8%, and 36.4% of patients, respectively). Patients experienced mostly Grade 1 and 2 fatigue (2.8% of patients reported severe fatigue).

Anemia is the most common treatment-related AE, reported in 35.4% of patients. Approximately 13% of all patients experienced anemia Grade 1 or 2, and 22% severe anemia. Notably many of those patients with severe anemia occurred in patients with AML and MDS, who have severe anemia at baseline. Anemia was typically manifested as a decline in hemoglobin observed within the first 2 weeks of treatment. The initial decrease in hemoglobin after the first dose is on average 0.5 to 2 g/dL. In patients with solid tumors, the fall in hemoglobin was followed by a compensatory reticulocytosis, with many patients experiencing a gradual return to baseline despite continued dosing. The changes in hemoglobin and reticulocytes described with magrolimab treatment are fairly consistent across tumor types and is shown in Figure 1. Hyperbilirubinemia (predominately unconjugated) is indicative of extravascular hemolysis consistent with phagocytic removal of RBCs arising from the blockade of CD47 signaling. Administration of a low priming dose of magrolimab mitigated on-target anemia, an effect that is mostly observed after the first dose.

Figure 1. Effect of Magrolimab on Anemia and Mitigation with a Priming/Maintenance Dosing Regimen



The RBC profile of a solid tumor patient treated with magrolimab monotherapy is shown {Sikic 2019}.

Infusion-related reactions are also a commonly observed AE with magrolimab. In total, 29% of patients reported at least 1 IRR. Most common signs/symptoms of IRRs related to magrolimab included chills, pyrexia, back pain, headache, nausea, vomiting, dyspnea, anemia, and blood bilirubin increase. These IRRs were generally observed during the initial 2 doses of magrolimab. Current recommendations for premedication and IRR management are described in Sections 5.3.1 and 7.8.1.2. Lastly, hemagglutination (RBC agglutination) as observed on the peripheral smear is a common treatment effect and was reported as a treatment-related AE in 11.8% of all patients.

Transient hemagglutination is observed after the initial priming or first maintenance dose of drug, however, it is less common thereafter, and it has not been consistently correlated with any clinical sequelae.

In summary, 568 patients (346 solid tumor/lymphoma patients and 222 AML/MDS patients) have been treated with magrolimab as monotherapy or in combination. Based on this aggregate safety data, magrolimab has an acceptable safety profile both as monotherapy and in combination with other agents (rituximab, gemcitabine, oxaliplatin, cetuximab, avelumab, or azacitidine) across multiple advanced solid tumor and hematological malignancies. Refer to the magrolimab IB for further details.

1.2.3.3. Summary of Clinical Efficacy

In Study 5F9005, 10 relapsed/refractory patients (4 MDS and 6 AML) received magrolimab monotherapy and 68 treatment-naive patients (39 MDS and 29 AML) were enrolled in the magrolimab plus azacitidine cohort. As of May 2020, for patients treated with magrolimab plus azacitidine, 58 untreated MDS/AML patients were evaluable for efficacy. In the AML cohort, 16/25 (64%) patients achieved an objective response, including 56% with complete response (CR) or CR with incomplete blood count recovery. In the MDS cohort, 30/33 (91%) achieved an objective response, including 45% with a CR + partial response (PR). Additionally, 26% of all responders were minimal residual disease (MRD)-negative, as determined by flow cytometry. Patients are continuing to be enrolled in the magrolimab plus azacitidine combination cohorts. In summary, magrolimab plus azacitidine induced a high rate of objective responses in newly diagnosed AML and MDS patients.

In Study SCI-CD47-001, magrolimab was investigated as a monotherapy in 66 solid tumor and lymphoma patients, including 2 patients with refractory diffuse large B-cell lymphoma (DLBCL), 16 patients with ovarian or fallopian tube cancers, and 10 patients with cutaneous T-cell lymphoma (CTCL). No objective responses were observed, although some mixed responses and stable disease (SD) were noted. Study 5F9003 investigated magrolimab plus rituximab in patients with DLBCL and follicular lymphoma (FL) and revealed an ORR of 45%, with 19% achieving a best response of CR. An ongoing Phase 1b/2 study (5F9004) is combining magrolimab with cetuximab in solid tumor and advanced colorectal cancer including both wild-type and mutant-KRAS patients, although efficacy results are not yet available.

For further clinical efficacy and safety information of magrolimab in other indications, please refer to the magrolimab IB.

1.3. Information About Agents Used in Combination With Magrolimab

Where available and allowed by the local regulations, for each of the combination agents (daratumumab, pomalidomide, carfilzomib, bortezomib or dexamethasone), an appropriate approved generic or a biosimilar may be used.

1.3.1. Daratumumab

1.3.1.1. Description of Daratumumab

Daratumumab (DARZALEX®, DARZALEX FASRPO®) is a first-in-class human monoclonal IgG1k antibody directed against the CD38 antigen with a direct on-tumor and immunomodulatory MOA {DARZALEX 2020, DARZALEX FASPRO 2020, Overdijk 2016}. CD38 is a transmembrane glycoprotein expressed on the surface of hematopoietic cells, including MM and other cell types and tissues, and has multiple functions, such as receptor mediated adhesion, signaling, and modulation of cyclase and hydrolase activity. Daratumumab binds to CD38 and inhibits the growth of CD38 expressing tumor cells by inducing apoptosis directly through Fc mediated cross linking as well as by

immune-mediated tumor cell lysis through CDC, antibody-dependent cell-mediated cytotoxicity and antibody-dependent cellular phagocytosis (ADCP). Daratumumab is approved both as a monotherapy and in combination with various regimens for the treatment of relapsed/refractory MM; selected daratumumab-based regimens are approved for newly diagnosed MM patients. Daratumumab is available as both IV and subcutaneous (SC) formulations {DARZALEX 2020, DARZALEX FASPRO 2020}.

1.3.1.2. Clinical Data for Daratumumab

Daratumumab has been extensively studied in MM, both as a single agent and in combination with various regimens. In relapsed/refractory MM patients, daratumumab is indicated: a) in combination with lenalidomide and dexamethasone in patients who are ineligible for autologous stem cell transplant (SCT) and in those patients who have received at least 1 prior therapy; b) in combination with bortezomib (VELCADE®) and dexamethasone in patients who have received at least 1 prior therapy, plus alongside melphalan and prednisone or thalidomide depending on eligibility for autologous SCT; c) in combination with carfilzomib and dexamethasone in patients who have received 1 to 3 prior lines of therapy d) in combination with pomalidomide (POMALYST®) and dexamethasone in patients who have received at least 2 prior therapies including lenalidomide and a PI; and e) as monotherapy in patients who have received at least 3 prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent {DARZALEX 2020, DARZALEX FASPRO 2020}.

Daratumumab monotherapy was evaluated in the SIRIUS study in patients with relapsed/refractory MM who had received at least 3 prior lines of therapy including a PI and an immunomodulatory drug (IMiD) or who were double-refractory to a PI and an IMiD. Daratumumab achieved an ORR of 29.2% (stringent complete response [sCR] 2.8%, very good partial response [VGPR] 9.4% and PR 17%). The CASTOR study demonstrated an improvement in PFS in the DVd (daratumumab/bortezomib/dexamethasone) combination as compared with the Vd (bortezomib/dexamethasone) arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (hazard ratio [HR] [95% CI]: 0.39 [0.28, 0.53]; $P < 0.0001$), representing a 61% reduction in the risk of disease progression or death for patients treated with DVd versus Vd. Similarly, daratumumab in combination with pomalidomide and dexamethasone, achieved an ORR of 59.2% (sCR 7.8%, CR 5.8%, VGPR 28.2%, and PR 17.5%) in the EQUULEUS study, a single-arm study that enrolled a cohort of 103 patients who had been heavily pretreated (median number of 4 therapies; all previously treated with a PI and an IMiD) {DARZALEX 2020, DARZALEX FASPRO 2020}.

The most frequently reported adverse reactions (incidence ≥ 20%) reported in daratumumab studies were infusion reactions, neutropenia, thrombocytopenia, fatigue, asthenia, nausea, diarrhea, constipation, decreased appetite, vomiting, muscle spasms, arthralgia, back pain, pyrexia, chills, dizziness, insomnia, cough, dyspnea, peripheral edema, peripheral sensory neuropathy, bronchitis, pneumonia, and upper respiratory tract infection {DARZALEX 2020, DARZALEX FASPRO 2020}.

1.3.2. Pomalidomide and Dexamethasone

1.3.2.1. Description of Pomalidomide

Pomalidomide is an analog of thalidomide with potent immunomodulatory, antiangiogenic, and antineoplastic properties. Cellular activities of pomalidomide are mediated through its target cereblon, a component of the cullin ring E3 ubiquitin ligase enzyme complex. In vitro, in the presence of drug, substrate proteins (including Aiolos and Ikaros) are targeted for ubiquitination and subsequent degradation leading to direct cytotoxic and immunomodulatory effects. In in vitro cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibited the proliferation of lenalidomide-resistant MM cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhanced T cell and natural killer (NK) cell–mediated immunity and inhibited production of proinflammatory cytokines (eg, tumor necrosis factor [TNF]-α and interleukin [IL]-6) by monocytes {POMALYST 2020}.

1.3.2.2. Description of Dexamethasone

Dexamethasone is widely commercially available. Details regarding the description, supply, and storage instructions for dexamethasone are found in the reference US prescribing information (USPI), summary of product characteristics (SmPC), or applicable local or regional label. Sites are advised to refer to the prescribing information for information that is specific to the brand or formulation of the drug product in use.

1.3.2.3. Clinical Data for Pomalidomide and Dexamethasone

The US Food and Drug Administration (FDA) granted accelerated approval for pomalidomide on the basis of the Phase 2 study (MM-002), which randomized patients with relapsed/refractory disease after at least 2 prior regimens (including lenalidomide and bortezomib) and who had progressed within 60 days of their last therapy to receive either pomalidomide alone (POM) (4 mg/day on Days 1 to 21 of a 28-day cycle; n = 108) or in combination with 40 mg/week dexamethasone (POM-DEX) (n = 113) {POMALYST 2020}. Patients in both arms were comparably refractory to lenalidomide (79%), bortezomib (71%), or both (62%), and 95% had greater than 2 prior therapy regimens. With a median follow-up of 14.2 months, the median PFS was 4.2 versus 2.7 months (HR = 0.68, $P = 0.003$), respectively, for the POM-DEX arm compared with the POM arm. The ORR (PR or better) was 33% versus 18% ($P = 0.013$), median response duration was 8.3 versus 10.7 months, and median OS was 16.5 versus 13.6 months, respectively for the POM-DEX arm compared with the POM arm. The most common hematologic Grade 3/4 AEs were neutropenia (41% vs 48%), anemia (22% vs 24%), and thrombocytopenia (19% vs 22%). The most common nonhematologic AE was pneumonia (22% vs 15%) and fatigue (14% vs 11%) in the POM-DEX arm compared with the POM arm, respectively. The frequency of febrile neutropenia was low (3% vs 5%), as was the incidence of deep vein thrombosis (2% vs 3%). There were no Grade 3 or 4 events of peripheral neuropathy reported.

NIMBUS is a multicenter, open-label, randomized Phase 3 study where relapsed/refractory MM patients who failed at least 2 previous treatments of bortezomib and lenalidomide were randomized to either pomalidomide + low-dose dexamethasone (POM-DEX) or high-dose dexamethasone (DEX) alone. The primary endpoint was PFS. A total of 302 patients received POM plus low-dose DEX and 153 patients received high-dose DEX alone. After a median follow-up of 10 months, median PFS with POM-DEX was 4 months versus 2 months with high-dose DEX alone (HR = 0.48; $P < 0.0001$) {Miguel 2013}. The most common Grade 3/4 hematological AEs in the POM-DEX versus high-dose DEX alone groups were neutropenia (48% vs 16%), anemia (33% vs 37%), and thrombocytopenia (22% vs 26%); and Grade 3/4 nonhematological AEs included pneumonia (13% vs 8%), bone pain (7% vs 5%), and fatigue (5% vs 6%). Treatment-related AEs leading to death were 4% in the POM-DEX group and 5% in the high-dose DEX alone group.

The STRATUS study also assessed safety and efficacy of POM plus low-dose DEX in relapsed/refractory MM. A total of 682 patients who failed treatment with bortezomib and lenalidomide (80% to both) with adequate prior alkylator therapy were enrolled, with safety as the primary endpoint and secondary endpoints including ORR, duration of response (DOR), PFS, and OS. Median number of prior regimens was 5. Median follow-up was 17 months, and median DOR was 5 months. The most frequent Grade 3/4 hematologic AEs included neutropenia (50%), anemia (33%), and thrombocytopenia (24%), and the most frequent Grade 3/4 nonhematologic AEs were pneumonia (11%) and fatigue (6%). The ORR was 33%, and the median DOR was 7 months. Median PFS and OS were 5 months and 12 months, respectively {Dimopoulos 2016}. This study further supports that POM plus low-dose DEX in relapsed/refractory MM patients offers clinically meaningful benefit and is generally well tolerated.

1.3.3. Carfilzomib and Dexamethasone

1.3.3.1. Description of Carfilzomib

Carfilzomib is a tetrapeptide epoxyketone PI that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death.

1.3.3.2. Clinical Data for Carfilzomib and Dexamethasone

Carfilzomib was initially approved in 2012 under the FDA's accelerated approval program for the treatment of patients with MM who have received at least 2 prior therapies, including bortezomib and an IMiD based on the initial Phase 2 Study PX-171-003-A1 in the US.

ASPIRE was a randomized, open-label, multicenter study which evaluated the combination of Kyprolis with lenalidomide and dexamethasone (KRd) versus lenalidomide and dexamethasone alone (Rd) in patients with relapsed/refractory MM who had received 1 to 3 lines of therapy. The 792 patients in ASPIRE were randomized 1:1 to the KRd or Rd arm. Patients in the KRd arm demonstrated improved median PFS compared with those in the Rd arm (26.3 months vs 17.6 months HR = 0.69, $P = 0.0001$) A statistically significant advantage in median OS was also observed in patients in the KRd arm compared with patients in the Rd arm.

ENDEAVOR was a randomized, open-label, multicenter study of Kyprolis and dexamethasone (Kd) versus bortezomib and dexamethasone (Vd) in patients with relapsed/refractory MM who had received 1 to 3 lines of therapy. A total of 929 patients were enrolled and randomized (464 in the Kd arm; 465 in the Vd arm). Randomization was stratified by prior PI therapy (yes versus no), prior lines of therapy (1 versus 2 or 3), current International Staging System stage (1 versus 2 or 3), and planned route of bortezomib administration. Notably, in both arms of the study, > 50% of the patients had previously been treated with bortezomib. The study demonstrated a median PFS of 18.7 months in the Kd arm versus 9.4 months in the Vd arm (HR = 0.53, $P < 0.0001$). Similarly, OS was superior in the Kd arm compared with the Vd arm (47.6 months vs 40 months; HR = 0.79, $P = 0.01$).

Following these approvals, carfilzomib in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for treatment of relapsed/refractory MM. The efficacy of carfilzomib in combination with daratumumab and dexamethasone (DKd) was evaluated in 2 open-label clinical studies (CANDOR and EQUULEUS). CANDOR was a randomized, open-label, multicenter study which evaluated the combination of carfilzomib 20/56 mg/m^2 twice weekly with IV daratumumab and dexamethasone (DKd) versus carfilzomib 20/56 mg/m^2 twice weekly and dexamethasone (Kd) in patients with relapsed/refractory MM who had received 1 to 3 prior lines of therapy. EQUULEUS was an open-label, multicohort study which evaluated the combination of carfilzomib with IV daratumumab and dexamethasone in patients with relapsed/refractory MM who had received 1 to 3 prior lines of therapy. Carfilzomib was administered IV over 30 minutes once weekly at a dose of 20 mg/m^2 on Cycle 1 Day 1 and escalated to a dose of 70 mg/m^2 on Cycle 1, Days 8 and 15; and on Days 1, 8, and 15 of each 28-day cycle. Based on the results of these 2 studies, carfilzomib was approved for the treatment of adult patients with relapsed/refractory MM who have received 1 to 3 lines of therapy in combination with daratumumab and dexamethasone. In the current study, 20/70 mg/m^2 dosing regimen of carfilzomib, as was used in the EQUULEUS study, will be utilized.

Based on the results of ASPIRE and ENDEAVOR, carfilzomib was approved in the US and globally in combination with either lenalidomide and dexamethasone or dexamethasone alone for treatment of relapsed/refractory MM.

Subsequently, the efficacy of carfilzomib in combination with daratumumab and dexamethasone was evaluated in 2 open-label clinical studies (CANDOR and EQUULEUS). Based on the results of these 2 studies, carfilzomib was approved for the treatment of adult patients with relapsed/refractory MM who have received 1 to 3 lines of therapy in combination with daratumumab and dexamethasone.

1.3.4. Bortezomib and Dexamethasone

1.3.4.1. Description of Bortezomib

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells {VELCADE 2019}. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types in vitro. Bortezomib causes a delay in tumor growth in vivo in nonclinical tumor models, including MM. See Section 1.3.2.2 for a description of dexamethasone.

1.3.4.2. Clinical Data for Bortezomib and Dexamethasone

Bortezomib was approved for the treatment of relapsed/refractory MM based on the results of a Phase 3 study (APEX Trial) comparing bortezomib with high-dose dexamethasone as salvage therapy {Richardson 2005, Richardson 2007}. The addition of dexamethasone to bortezomib therapy was shown to add benefit in the Phase 2 SUMMIT Trial {Richardson 2006}. In the recent update of the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for MM, single-agent bortezomib and bortezomib plus dexamethasone are Category 1 and Category 2A recommendations for MM salvage therapy, respectively. Considering the clinical evidence on the effect of bortezomib and more recent data on bortezomib combined with dexamethasone, a treatment regimen of bortezomib combined with low-dose dexamethasone is consistent with the current standard of care in this previously treated MM patient population.

1.4. Rationale for This Study

Multiple myeloma remains incurable. Despite the availability of PIs, immunomodulatory agents, and mAbs for MM, most patients will relapse and develop refractory disease. Strategies directed at improving both the duration and depth of response as well as new treatment options directed at alternative mechanisms are urgently needed for patients with MM. Strong nonclinical rationale exists for the combination of magrolimab with other antimyeloma therapies. There is growing body of evidence to suggest that the overexpression of CD47 contributes to the pathogenesis of MM. A very recent study has reported that MM cells had remarkably higher CD47 expression than other cell populations in the bone marrow. Furthermore, blocking of CD47 using an anti-CD47 antibody induced immediate activation of macrophages and eliminated MM cells in the 3D-tissue engineered bone marrow model, as early as 4 hours after exposure {Sun 2020}. Several early phase studies are currently investigating CD47-targeted therapies for the treatment of MM. Magrolimab, a recombinant humanized anti-CD47 mAb, is currently being studied across many hematological malignancies.

Recent studies have indicated that multiple drug combinations are superior over single- or double-agent combinations in treating MM. The addition of new drugs to available regimens could induce a higher rate of initial CRs, which then improves PFS and OS. Contingent on the premise that the combined agents have nonoverlapping and synergistic MOAs, the immediate and effective targeting of the tumors with multiple agents appears to be a successful strategy in improving the clinical outcome of MM therapy. Such a strategy is consistent with the emerging concept that the genetic signature of MM, and consequently the patient's susceptibility to a specific agent, will be highly heterogeneous, which may lead to drug resistance. Furthermore, nonclinical evidence suggests these drug combinations all have the potential for achieving synergy as discussed in Sections 1.4.1, 1.4.2, and 1.4.3.

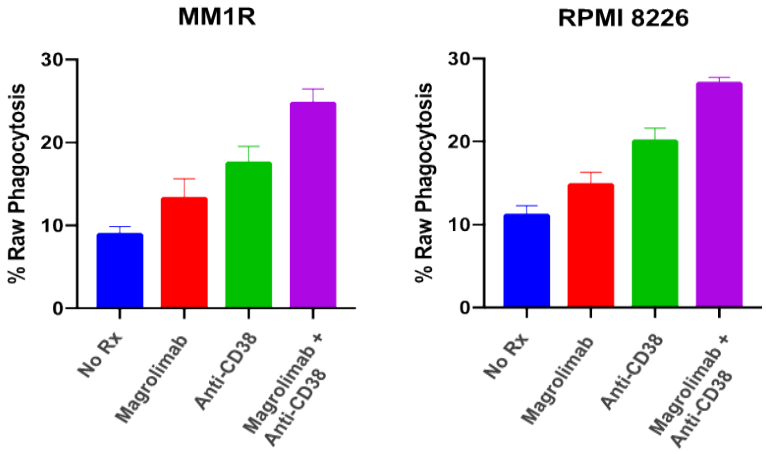
The current study will investigate the combination of magrolimab with other standard of care options used in this setting as the backbones. The study will enroll patients who have previously been treated with at least 3 prior lines of therapy (except for the bortezomib/dexamethasone/magrolimab cohort), including a PI and an IMiD. Although not explicitly specified, these patients are also likely to have been treated with daratumumab. For patients who have been treated with all 3 of the main classes of therapy (PI, IMiD, and an anti-CD38), the options are limited; options are even more limited for those who are refractory to 1 or more classes of drugs. Given the limited treatment options for this patient population, the nonoverlapping MOA for these therapies justifies the selection of the combinations chosen in this study. Carfilzomib has been chosen as the preferred PI given its superiority over bortezomib in patients with relapsed/refractory MM based on the ENDEAVOR study (Section 1.3.3.2). The cohort investigating the bortezomib/dexamethasone/magrolimab combination will only be initiated at the sponsor's discretion based on the preliminary safety and efficacy results of the carfilzomib/dexamethasone/magrolimab combination in patients who have received at least 1 previous line of therapy. In this earlier line of patients, use of bortezomib is justified once the proof-of-concept for the PI class has been generated with carfilzomib.

1.4.1. Magrolimab in Combination With Daratumumab

Nonclinical experiments with MM cell lines, purified MM cells, and mononuclear cell suspensions have demonstrated that daratumumab triggers the lysis of MM cells by a variety of mechanisms. Binding of the antibody to CD38 positions the Fc receptor (FcR) in a way that optimizes interaction with complement resulting in strong complement-dependent lysis {de Weers 2011}. Antibody-dependent lysis with daratumumab has been demonstrated in complement free cell suspensions of MM cells and cell lines with peripheral blood mononuclear cells (PBMCs) enriched for NK cells using both normal and patient PBMCs. Other MOA, including apoptosis triggered by FcR-crosslinking and ADCP, have been demonstrated with daratumumab. In ADCP, effector cells (such as monocytes and macrophages) bind to the Fc tail of the CD38 antibody via their FcγR, leading to opsonization of the target (ie, tumor) cell. ADCP mediated by macrophages has been described as a fast and efficient MOA of daratumumab {Overdijk 2015}. We hypothesize that the daratumumab-induced ADCP can be further enhanced by magrolimab, based on in vitro evidence for synergy between the 2 agents (Figure 2, unpublished data). The highly

significant activity of daratumumab in MM, both in newly diagnosed and relapsed/refractory patients, together with novel nonoverlapping MOA with regard to magrolimab, predict tolerability and efficacy for combination therapy with magrolimab + daratumumab in treatment of patients with relapsed/refractory MM.

Figure 2. In Vitro Assessment of Synergy in MM Cell Lines



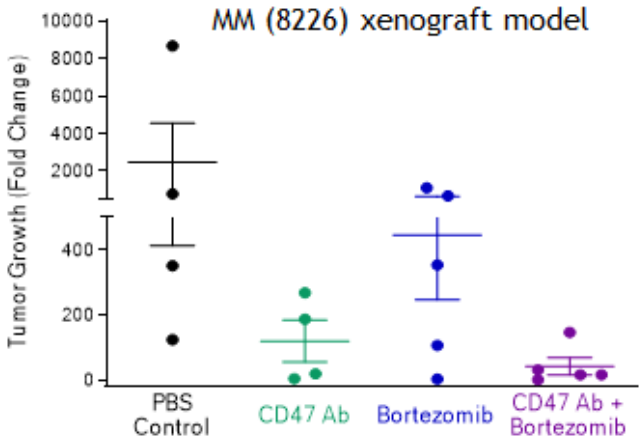
1.4.2. Magrolimab in Combination With Pomalidomide and Dexamethasone

Pomalidomide induces antiproliferative and proapoptotic effects on MM cells {Hideshima 2000, Li 2011}, and modulation of bone marrow microenvironment to inhibit the binding of MM cells to bone marrow stromal cells that mediate the production of growth factors and angiogenic molecules, including vascular endothelial growth factor {Mark 2014}. In addition, pomalidomide improves cellular immunity via the activation of immune effector cells, such as dendritic cells (DCs), NK cells, and T cells {Richardson 2013} and the reduction of immune inhibitory cells, such as regulatory T cells, on tumor microenvironment {Gorgun 2010, Li 2007}. Importantly, in a nonclinical study, pomalidomide displayed significant therapeutic activity against CNS lymphoma with a major impact on the tumor microenvironment with an increase in M1 macrophages and NK cells {Rychak 2016}. In a murine myeloma model, POM-DEX in combination with tumor-antigen loaded DCs resulted in decreased tumor growth, prolonged survival, induced NK cell, and T lymphocytes responses associated with strong antimyeloma activities against myeloma cells and increased numbers of effector cells, including M1 macrophages {Vo 2018}. Based on these observations, we hypothesize that the addition of magrolimab will enhance the efficacy of the POM-DEX combination.

1.4.3. Magrolimab in Combination with Proteasome Inhibitors (Carfilzomib/Dexamethasone and Bortezomib/Dexamethasone)

CD47 ligation with magrolimab induces cell death in a caspase-independent manner; therefore, its effects may be complementary to cytotoxic agents that induce caspase-dependent apoptosis, including carfilzomib and bortezomib. This is supported by the observation that myeloma cells prewashed with PIs are more susceptible to cell death induced by CD47-targeted antibodies compared with either agent given alone (Figure 3, unpublished data). This combinatory effect has been observed with magrolimab as well as other anti-CD47 antibodies when combined with either carfilzomib or bortezomib {Linderoth 2017, Richards 2019}.

Figure 3. In Vitro Assessment of Bortezomib Combined With CD47-targeted Antibodies



Ab = antibody; MM = multiple myeloma; PBS = phosphate-buffered saline

1.5. Rationale for Dose Selection of Magrolimab

The rationale for the magrolimab dose proposed in this study originates from safety, efficacy, and PK/pharmacodynamic data, and modeling and simulation analyses based on data obtained from all ongoing and completed clinical studies with magrolimab in patients with solid tumors, NHL, and AML/MDS.

In the first-in-human study of magrolimab (SCI-CD47-001) in patients with solid tumors and lymphomas, after an initial priming dose of 1 mg/kg on the first day, magrolimab was tested as a monotherapy at weekly doses of up to 45 mg/kg. The use of an initial 1 mg/kg priming dose was integrated into the dosing regimen to mitigate the on-target anemia induced by CD47 blockade. An initial priming dose leads to elimination of aged RBCs that are sensitive to CD47 blockade and triggers reticulocytosis of young RBCs that are not affected by CD47 blockade {Chen 2018}. Utilizing a priming dose leads to an initial, transient, and mild anemia that generally normalizes back to baseline over several weeks, even in the presence

of repeated therapeutic doses of magrolimab {Advani 2018, Liu 2015, Sikic 2019}. The maximum weekly dose of 45 mg/kg has an acceptable safety profile, and no MTD was identified in this study. In Studies SCI-CD47-002 and 5F9005 in patients with AML/MDS, magrolimab was administered as a monotherapy at doses of up to 30 mg/kg twice weekly (60 mg/kg per week cumulative) and in combination with azacitidine at doses of up to 30 mg/kg once weekly in higher-risk MDS patients and up to 60 mg/kg every 4 weeks in lower-risk MDS patients. In these studies, no significant dose-limiting toxicity (DLT) was observed, and magrolimab had an acceptable safety profile over the tested dose range up to a maximum of 30 mg/kg twice a week. In studies 5F9004 (solid tumor and colorectal cancer patients) and 5F9006 (solid tumor and ovarian cancer patients), magrolimab, in combination with cetuximab and avelumab, respectively, was found to have an acceptable safety profile at doses up to 45 mg/kg every week followed by every other week. Taken together, the proposed dosing regimen of magrolimab in this study is expected to have an acceptable safety profile based on the entirety of safety data in multiple oncology populations, both as a monotherapy and in combination with other antimyeloma therapies.

1.5.1. Rationale for Daratumumab, Dexamethasone, Pomalidomide, Carfilzomib, and Bortezomib Dose Selection

Given the lack of dose-related toxicities with magrolimab, the approved doses and the dosing regimens were chosen for daratumumab, pomalidomide (with dexamethasone), and carfilzomib (with dexamethasone). The bortezomib dosing regimen has been modified from a 5-week cycle to a 4-week cycle to align with the magrolimab dosing regimen and to improve patient convenience, which results in a reduced rest period between cycles compared with what is in the approved label (6 days versus 13 days) {POMALYST 2020, VELCADE 2019}. The most common side effect of bortezomib therapy is peripheral neuropathy. In an effort to manage this toxicity, a weekly regimen has been chosen rather than a biweekly regimen, which may result in less neurotoxicity. A study comparing the 2 regimens, bortezomib-melphalan-prednisone (VMP) versus bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide maintenance (VMPT), as up-front therapy for patients > 65 years of age, showed that the weekly infusion of bortezomib significantly reduced the incidence of Grade 3 to 4 peripheral neuropathy (18% in the biweekly vs 9% in the weekly schedule for the VMPT arm, and 12% in the biweekly vs 3% in the weekly schedule for the VMP arm) without adversely influencing the outcome {Palumbo 2008}. Furthermore, the once-weekly schedule of bortezomib resulted in a reduced discontinuation rate and prolonged the time on therapy. Patients will be closely monitored for the development of any dose-related toxicities, in particular, peripheral neuropathy, through regular neurological assessments, and toxicities will be managed with the dose modifications described in Section 7.8.

1.6. Risk/Benefit Assessment for the Study

This study will enroll previously treated patients with relapsed/refractory MM. In each arm, patients will be treated with agents that are considered standard of care in this setting in addition to magrolimab. All these agents, daratumumab, pomalidomide, carfilzomib, bortezomib, and dexamethasone, have been extensively used for the treatment of MM patients and have been approved by the US FDA and European Medicines Agency; their safety profiles have been well characterized. There are guidelines stipulated in the protocol for dose reductions, delays and/or discontinuation of these agents in line with their approved labels. Magrolimab has been investigated in several hematological malignancies and solid tumors. The safety profile has been well documented from these studies and the MTD has not been reached. Although there are no dose-dependent toxicities expected with magrolimab, dose de-escalation option has been included in the protocol as a precautionary measure. No drug-drug interactions between magrolimab and any of the selected combination agents are expected.

During a pandemic, additional potential risks to patients may include adequate study drug availability, interruptions to the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 3 for further details on the risks and risk mitigation strategy.

In summary, based on strong scientific rationale, nonclinical and emerging clinical data, and the risk mitigation measures being implemented for the pandemic, the evaluation of magrolimab in combination with agents that are considered standard of care is anticipated to have an acceptable risk-benefit ratio for patients with MM enrolled in this study.

1.7. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES AND ENDPOINTS

Table 1. Objectives and Endpoints for the Safety Run-in Cohorts

Primary Objective	Primary Endpoint
• To evaluate the safety and tolerability of magrolimab in combination with other anticancer therapies and to determine the recommended Phase 2 dose (RP2D) of magrolimab for the following combinations in patients with relapsed/refractory MM: — Magrolimab in combination with daratumumab — Magrolimab in combination with pomalidomide and dexamethasone — Magrolimab in combination with carfilzomib and dexamethasone — Magrolimab in combination with bortezomib and dexamethasone	• The incidence of dose-limiting toxicities (DLTs), AEs and laboratory abnormalities according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (Appendix 5)

Table 2. Objectives and Endpoints for the Dose-expansion Cohorts

Primary Objective	Primary Endpoint
• To evaluate the efficacy of magrolimab in combination with other anticancer therapies in patients with relapsed/refractory MM as determined by ORR	• ORR, defined as the percentage of patients who achieve sCR, CR, VGPR, or PR[a]
Secondary Objectives	**Secondary Endpoints**
• To evaluate the safety and tolerability of magrolimab in combination with other anticancer therapies	• The incidence of AEs and laboratory abnormalities according to the NCI CTCAE Version 5.0
• To investigate other parameters of efficacy including duration of response	• DOR[a]
• To evaluate the PK and immunogenicity of magrolimab in combination with other anticancer therapies in patients with relapsed/refractory MM	• Magrolimab concentration versus time • Measurements of ADA against magrolimab
CCI	

3. STUDY DESIGN

3.1. Study Design

This is a Phase 2, open-label, multicenter, multiarm study evaluating magrolimab in combination with anticancer therapies for patients with relapsed/refractory MM. This study will include safety run-in cohorts (Section 3.1.1) for the following combination therapies:

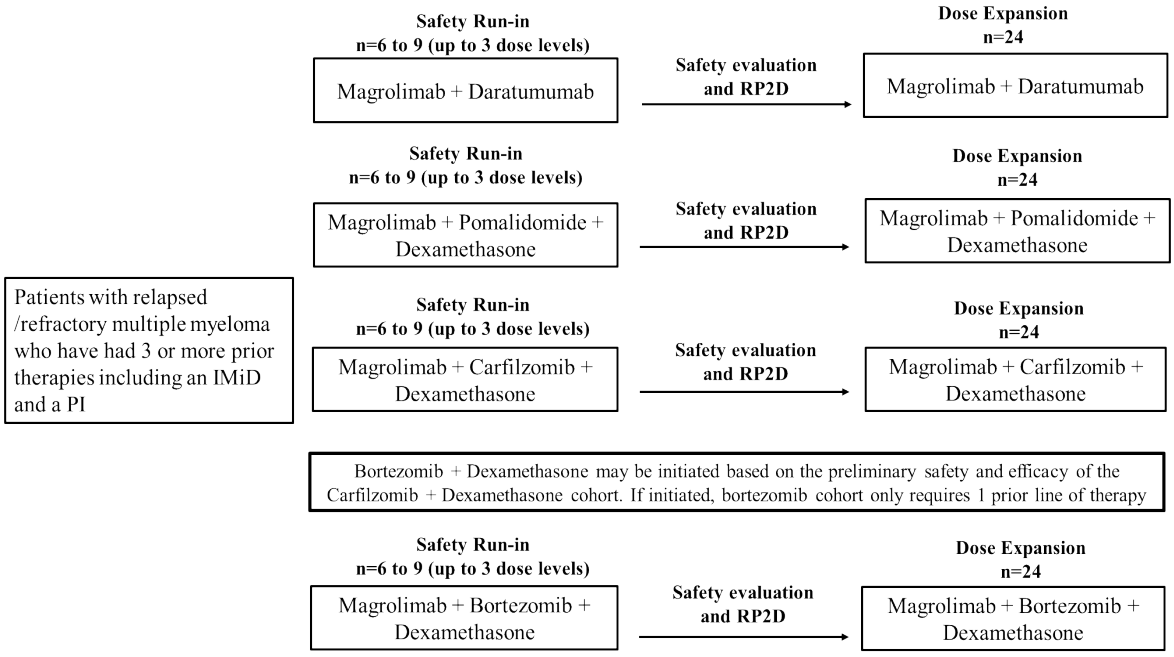
- Magrolimab in combination with daratumumab
- Magrolimab in combination with pomalidomide and dexamethasone
- Magrolimab in combination with carfilzomib and dexamethasone
- Magrolimab in combination with bortezomib and dexamethasone – this cohort will only be initiated at the sponsor's discretion based upon the preliminary safety and efficacy results from the carfilzomib/dexamethasone combination cohort.

After completion of the safety run-in cohorts, dose-expansion cohorts using the same combination therapies will occur as described in Section 3.1.2.

Patient participation will include screening, treatment, and follow-up. Screening will occur up to 30 days before the first dose of study treatment, during which time the patient’s eligibility and baseline characteristics will be determined.

The study schema is presented in Figure 4.

Figure 4. Study Schema



IMiD = immunomodulatory drug; PI = proteasome inhibitor; RP2D = recommended Phase 2 dose

3.1.1. Safety Run-in Cohorts

All safety run-in cohorts may progress concurrently. The DLT assessment period will be the first cycle (35 days). Patients are considered evaluable for assessment of a DLT if either of the following criteria are met in the DLT assessment period:

- The patient experienced a DLT at any time after initiation of the first dose of any study drug
- Completed DLT assessment period and received at least 3 infusions of magrolimab and the following cohort-specific criteria:
  - Magrolimab in combination with daratumumab cohort: Completed at least 2 doses of daratumumab
  - Magrolimab in combination with pomalidomide and dexamethasone cohort: Completed at least 10 doses of pomalidomide and 2 doses of dexamethasone
  - Magrolimab in combination with carfilzomib and dexamethasone cohort: Completed at least 2 doses of carfilzomib and 2 doses of dexamethasone
  - Magrolimab in combination with bortezomib and dexamethasone cohort: Completed at least 2 doses of bortezomib and 2 doses of dexamethasone

Patients who are not evaluable for DLT assessment will be replaced.

The first patient in each safety run-in cohort will be treated for 3 days prior to enrolling additional patients.

In general, no dose-dependent toxicities have been observed with magrolimab, in contrast to the other chemotherapies. To preserve the efficacious doses of the partner drugs, dose de-escalation will take place for magrolimab. The starting magrolimab dose (30 mg), Dose Level −1 (20 mg), and Dose Level −2 (15 mg) are described in Section 5.3.1. Dosing of magrolimab and drugs to be given in combination with magrolimab are described in Section 3.2.

For each of the safety run-in cohorts, a 6 + 3 de-escalation algorithm will be implemented. Six patients will be enrolled in each of the safety run-in cohorts. Dose de-escalation decisions will be made after the first 6 patients in each cohort have completed the Cycle 1 DLT evaluation period and the Safety Review Team (SRT) has reviewed safety and clinical data for the first cycle as follows:

- If no more than 1 patient experienced a DLT in Cycle 1, enrollment into the dose-expansion cohort will begin at this dose level.
- If 2 patients experienced DLTs, 3 additional patients will be enrolled into the cohort at the same dose level. If no additional DLTs occur in these 3 patients, the dose level will be deemed safe by the SRT. If 1 or more DLTs occur in these 3 patients, a lower-dose cohort will be evaluated using the same 6 + 3 de-escalation algorithm to define the recommended dose for the combination regimens.
- If more than 2 patients experienced DLTs, another 6 patients will be enrolled at a lower dose and evaluated in the same manner to define the recommended dose for the combination regimens.

DLT Definition

All toxicities will be graded according to the NCI CTCAE Version 5.0 (Appendix 5). A DLT is defined as any Grade 3 or higher hematologic toxicity or Grade 3 or higher nonhematologic toxicity, that has worsened in severity from pretreatment baseline during the DLT assessment period and, in the opinion of the investigator, the AE is at least possibly related to magrolimab.

The following are exceptions to the DLT definition and are NOT considered a DLT:

- Grade 3 anemia; however, Grade 3 hemolytic anemia that is medically significant, requiring hospitalization or prolongation of existing hospitalization, disabling, or limiting self-care activities of daily life is considered a DLT.
- Grade 3 neutropenia that resolves to Grade 2 or pretreatment baseline with supportive care (including growth factors) within 14 days.

- Grade 3 indirect/unconjugated hyperbilirubinemia that resolves to ≤ Grade 2 with supportive care within 1 week and is not associated with other clinically significant consequences.
- Isolated Grade 3 electrolyte abnormalities that resolve to ≤ Grade 2 with supportive care within 1 week and are not associated with other clinically significant consequences.
- Grade 3 elevation in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase that resolves to ≤ Grade 2 with supportive care within 1 week and is not associated with other clinically significant consequences.
- Grade 3 nausea, vomiting, or diarrhea that resolves to ≤ Grade 2 with supportive care within 72 hours.
- Grade 3 fatigue that resolves to ≤ Grade 2 within 1 week on study.
- Grade 3 magrolimab infusion reactions in the absence of an optimal pretreatment regimen, which is defined as acetaminophen or a comparable nonsteroidal anti-inflammatory agent, plus an antihistamine and corticosteroids.
- Grade 3 tumor lysis syndrome or electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia) that resolves to ≤ Grade 2 or baseline within 72 hours.
- Grade 3 hypomagnesemia, that resolves to ≤ Grade 2 within 1 week.
- Grade 3 or 4 lymphopenia or leukopenia not associated with other clinically significant consequences.

The RP2D will be determined by Gilead in discussion with SRT based on all relevant clinical and PK data from all patients treated in the safety run-in cohorts.

Safety Review Team

An SRT will be established to assess safety of patients in various cohorts.

The SRT will include at least 1 investigator, a Gilead Safety Physician, and the Gilead medical monitor. Others may be invited to participate as members of the SRT if additional expertise is desired (ie, representatives from Patient Safety [PS], Clinical Operations, Biostatistics, Clinical Pharmacology, and Biomarker Sciences, as applicable). The medical monitor serves as the chair of the SRT. An SRT charter (or similar document) will be agreed on by all SRT members prior to the first SRT meeting. The data reviewed at the SRT meeting to make dose de-escalation decisions will be defined in the SRT charter (or similar document). The quality control checks performed on the data reviewed and used for making dose de-escalation decisions will be described in the SRT charter (or similar document).

3.1.2. Dose-expansion Cohorts

Once any of the safety run-in cohorts have been completed and an RP2D is established for that combination, a dose-expansion cohort using the dose level and schedule specified in Table 5 may be initiated. Each dose-expansion cohort may enroll up to 24 patients. Patients may be enrolled simultaneously into the dose-expansion cohorts without an observation period between patients.

3.1.3. Treatment-Related Toxicity Monitoring

The treatment-related toxicity will be monitored at a preset frequency with the stopping boundary listed in Table 3 after the first 10 patients are treated at the dose level for the dose-expansion phase and thereafter when the safety data from every set of 10 patients from the first 3 cycles become available. The frequency of the SRT review is outlined in the SRT charter. This is a Pocock-type boundary {Ivanova 2005, Ivanova 2006} with 80% probability of crossing the boundary when > 25% of patients in the study experience Grade 4 or higher treatment-related AEs or treatment-related deaths occur among > 15% of patients.

Table 3. Stopping Boundary Due to Toxicity for Each Cohort

	N = 10	N = 20	N = 30
Grade 4/5 treatment-related TEAEs	≥ 3	≥ 6	≥ 8
Treatment-related deaths	≥ 2	≥ 3	≥ 5

TEAE = treatment-emergent adverse event

3.2. Study Treatments

Details of on-study treatments administered in this study are described in Section 5. Refer to Section 5.3 for details on planned doses to be administered, timing of doses and any required pre- or postmedication and prophylaxis, Section 5.4 for instructions with regards to dose modifications and delays, and Section 5.5 for information about prior and concomitant medications.

3.3. Duration of Treatment

The length of Cycle 1 will be 35 days; all subsequent cycles will be 28 days. All patients will continue on-study treatment until they meet study treatment discontinuation criteria (Section 3.4).

3.4. Discontinuation Criteria

Reasons for discontinuation of study treatment may include, but are not limited to, the following:

- Disease progression
- Unacceptable toxicity

- Loss of clinical benefit
- Clinically significant change in the patient's status that precludes further treatment (eg, death, pregnancy or other AEs)
- Patient request, with or without a stated reason
- Patient noncompliance
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an institutional review board (IRB) or independent ethics committee (IEC)
- Investigator or treating physician decision in the absence of any of the above

Although disease progression is considered a sufficient reason for discontinuing a patient from study treatment the investigator is advised to continue to treat the patient until the confirmation of disease progression through a subsequent response assessment, or until the investigator considers the study treatment to be no longer clinically beneficial to the patient, or the change of disease state renders the patient unacceptable for further treatment in the judgment of the investigator. All patients must be followed through completion of all study treatment. Refer to Section 6.5.3 for progressive disease (PD) assessments.

Patients who discontinue study treatment are to return for an end of treatment (EOT) visit for evaluation of safety within 7 days of their last dose or the decision to end study treatment, whichever is later. In addition, patients are to have a safety follow-up telephone call 70 days (± 7 days) after their last dose of study treatment. When a serious adverse event (SAE) or treatment-related AE is reported during the telephone call, the patient should come to the clinic for physical examination and blood tests, if clinically needed. Follow-up for ongoing SAEs or treatment-related AEs after the safety follow-up visit/call will stop if a patient begins another anticancer therapy.

The assessments to be performed at each of the posttreatment visits are listed in Appendix Table 3.

3.5. Discontinuation From Study Criteria/End of Study

All Patients: The end of the entire study for all patients is defined as the date on which the last patient remaining on study completes the last study visit/call or when the sponsor decides to end the study. The sponsor reserves the right to terminate the study at any time for any reason (including safety).

Individual Patients: Patients are considered to have completed study participation altogether when they are no longer followed for safety.

Criteria for early discontinuation from study treatment are described in Section 3.4.

3.6. Poststudy Care

Upon withdrawal from study treatment, patients will receive the care upon which they and their physicians agree. Patients will be followed for AEs until the end of the study, as specified in Appendix Table 3.

3.7. Source Data

The source data for this study will be obtained from original records (eg, clinic notes, hospital records, patient charts), patient-reported outcome (PRO) assessments, central laboratory, local laboratory, specialty laboratory (for PK, ADA, and/or pharmacodynamic data) and/or additional biomarker testing, and interactive web/voice response system (IXRS).

The patient identification numbers captured by the IXRS are considered source data.

3.8. Pharmacokinetics/Biomarker Testing

3.8.1. Biomarker Samples to Address the Study Objectives

Peripheral blood and tumor biopsy samples will be collected from all patients who have provided consent to participate in this study. They may be used to evaluate the association of systemic and/or tissue-based biomarkers with study drug response, including efficacy and/or AEs, disease progression, dosage selection, and to better understand the biology of the cancer indications studied, as well as the efficacy and MOA for magrolimab combinations. Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it may not be possible to specify prospectively all tests that may be done on the specimens provided. The specific analyses will include, but may not be limited to, the biomarkers and assays described below. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon new state of the art knowledge.

Blood, bone marrow, and buccal samples will be collected to measure biomarkers which may include but will not be limited to the presence of or changes to immune cell populations, secreted protein factors, the expression of cell surface markers on either tumor cells or cells of the tumor microenvironment, and genetic mutations in tumor cells or subclones of tumor cells at the time points listed in the schedule of assessments (Appendix 2).

Blood and tumor samples will also be used for genomic research. These samples will be used to identify or validate genetic markers that may increase our knowledge and understanding of the biology of the study disease and related diseases, and to study the association of genetic markers with disease pathogenesis, progression and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. These specimens may also be used to develop biomarker or diagnostic assays and establish the performance characteristics of these assays. Genomics research may include sequencing of genetic material derived from both cancer cells and normal cells. Sequencing of genetic material derived from cancer cells will be used to better understand the MOA of magrolimab combinations in this patient population, and potentially to identify subsets of patients who are likely to benefit. Sequencing of genetic material derived from normal cells will be used to define differences in sequence that are cancer specific.

Samples collected for biomarker assessments will be destroyed no later than 15 years after the end of study or per country requirements.

CCI [redacted]

4. PATIENT POPULATION

4.1. Number of Patients and Patient Selection

Approximately 153 patients will be enrolled in the study, with up to 27 in each of the safety run-in cohorts (up to 9 patients at each of the 3 possible dose levels; total up to 81 patients) and approximately 72 patients in the dose-expansion cohorts.

4.1.1. Patient Replacement

Patients may be replaced during the safety run-in period of the study, if not evaluable for DLT assessment as described in Section 3.1.1.

4.2. Inclusion Criteria

All patients must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Patient has been previously diagnosed with MM based on the International Myeloma Working Group (IMWG) 2016 criteria (Appendix 6) and currently requires treatment.

2) Patients must have measurable disease as defined by 1 or more of the following:

   a) Serum monoclonal protein (M-protein) ≥ 0.5 g/dL (≥ 5 g/L)

   b) Urine M-protein ≥ 200 mg/24 h

   c) Serum free light chain (SFLC) assay: involved SFLC level ≥ 10 mg/dL (100 mg/L) with abnormal SFLC ratio

3) Patient has provided informed consent.

4) Patient is willing and able to comply with clinic visits and procedure outlined in the study protocol.

5) Male or female ≥ 18 years of age

6) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (Appendix 7)

7) Life expectancy ≥ 3 months

8) Absolute neutrophil count (ANC) ≥ 1000 cells/μL (1.0 × 109/L); granulocyte colony-stimulating factor (G-CSF) is not permitted within 1 week of screening to meet eligibility criteria.

9) Platelet count ≥ 75,000 cells/μL (75 × 109/L); platelet transfusion is not permitted within 1 week of screening to meet eligibility criteria.

10) Hemoglobin must be ≥ 9 g/dL prior to initial dose of study treatment. NOTE: Transfusions are allowed to meet hemoglobin eligibility (Section 7.8.1.1).

11) Criterion removed.

12) Adequate liver function as demonstrated by the following:

    a) AST ≤ 3.0 × upper limit of normal (ULN)

    b) ALT ≤ 3.0 × ULN

    c) Total bilirubin ≤ 1.5 × ULN (or ≤ 3.0 × ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or genetic equivalent).

13) International normalized ratio (INR) ≤ 1.2; patients receiving anticoagulation treatment may be allowed to participate if INR is within the therapeutic range prior to alternate assignment.

14) Patients must have adequate renal function as demonstrated by a creatinine clearance ≥ 30 mL/min calculated by the Cockcroft-Gault formula (Appendix 8) or measured by 24 hours urine collection.

15) Corrected serum calcium ≤ 2.9 mmol/L (11.5 mg/dL); measures to reduce calcium to acceptable levels, such as a short course of steroids, bisphosphonates, hydration, or calcitonin are acceptable.

16) Pretreatment blood cross-match completed (Section 7.8.1.1).

17) Male and female patients of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception (Appendix 4).

18) Patients must be willing to consent to mandatory pretreatment and on-treatment bone marrow biopsies (trephines).

<u>Magrolimab in Combination With Daratumumab:</u>

In addition to fulfilling the inclusion criteria for all patients, patients who are assigned to receive magrolimab in combination with daratumumab should fulfill the following:

19) Patient must have received at least 3 previous lines of therapy for MM including an IMiD such as lenalidomide and a PI such as bortezomib.

20) Patients must have not had prior anti-CD38 antibody therapy for at least 6 months prior to enrollment.

21) No prior history of discontinuation of daratumumab due to toxicity

Magrolimab in Combination With Pomalidomide and Dexamethasone:

In addition to fulfilling the inclusion criteria for all patients, patients who are assigned to receive magrolimab in combination with pomalidomide and dexamethasone should fulfill the following:

22) Patient must have received at least 3 previous lines of therapy for MM including an IMiD such as lenalidomide and a PI such as bortezomib.

23) Prior treatment with pomalidomide is allowed if the patient achieved at least a PR to the most recent pomalidomide therapy and will have had at least a 6-month treatment-free interval from the last dose of pomalidomide until first study treatment.

24) No prior history of discontinuation of pomalidomide due to toxicity

25) No contraindication to dexamethasone

Magrolimab in Combination With Carfilzomib and Dexamethasone:

In addition to fulfilling the inclusion criteria for all patients, patients who are assigned to receive magrolimab in combination with carfilzomib and dexamethasone should fulfill the following:

26) Patient must have received at least 3 previous lines of therapy for MM including an IMiD such as lenalidomide and a PI such as bortezomib.

27) Prior treatment with a PI, including carfilzomib, is allowed if the patient achieved at least a PR to the most recent prior PI therapy, and will have had at least a 6-month PI treatment-free interval from the last dose until first study treatment.

28) No prior history of discontinuation of carfilzomib due to toxicity.

29) No contraindication to dexamethasone

Magrolimab in Combination With Bortezomib and Dexamethasone:

In addition to fulfilling the inclusion criteria for all patients, patients who are assigned to receive magrolimab in combination with bortezomib and dexamethasone should fulfill the following:

30) Patient must have received at least 1 previous line of therapy.

31) Prior treatment with a PI, including bortezomib, is allowed if the patient achieved at least a PR to the most recent prior PI therapy, and will have had at least a 6 month PI treatment free interval from the last dose until first study treatment.

32) No prior history of discontinuation of bortezomib due to toxicity.

33) No contraindication to dexamethasone.

4.3. Exclusion Criteria

Patients who meet any of the following exclusion criteria are not eligible to be enrolled in this study:

1) Patients with known amyloidosis including myeloma complicated by amyloidosis

2) Multiple myeloma of immunoglobulin M subtype

3) Patients with Waldenstrom's macroglobulinemia

4) Patients with MDS

5) Plasma cell leukemia (defined as either 20% of peripheral blood white blood cell (WBC) count comprised of plasma/CD138-positive cells) or circulating plasma cells $\geq 2 \times 109/L$

6) Patients with solitary bone or extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia

7) POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes)

8) Glucocorticoid therapy (prednisone > 40 mg/day or equivalent) within 14 days prior to enrollment; corticosteroid therapy for hypercalcemia is allowed

9) Chemotherapy with approved or investigational anticancer therapeutics within 28 days prior to enrollment

10) Focal radiation therapy within 7 days prior to enrollment; radiation therapy to an extended field involving a significant volume of bone marrow within 21 days prior to enrollment (ie, prior radiation must have been to less than 30% of the bone marrow)

11) Immunotherapy within 28 days prior to enrollment

12) Major surgery (excluding procedures to stabilize the vertebrae) within 28 days prior to enrollment

13) Positive serum pregnancy test (Appendix 4)

14) Breastfeeding female

15) Known hypersensitivity to any of the study drugs, the metabolites, or formulation excipient

16) Prior treatment with CD47 or SIRPα-targeting agents.

17) Current participation in another interventional clinical study

18) Autologous stem cell transplant < 100 days prior to enrollment

19) Considered eligible to receive autologous or allogeneic SCT at the time of enrollment

20) Allogeneic SCT for the treatment of MM within 6 months of enrollment or active graft-versus-host disease requiring immunosuppression

21) Significant neuropathy (Grade 3 to 4, or Grade 2 with pain) within 14 days prior to enrollment

22) Known inherited or acquired bleeding disorders

23) Known cirrhosis

24) Clinical suspicion or documentation of CNS disease

25) Significant disease or medical conditions, as assessed by the investigator and sponsor, that would substantially increase the risk-benefit ratio of participating in the study. This includes, but is not limited to, acute myocardial infarction within the last 6 months, unstable angina, uncontrolled diabetes mellitus, significant active infections, congestive heart failure, or NYHA Class III or IV heart failure.

26) Acute active infection requiring systemic antibiotics, antiviral (except antiviral therapy directed against reactivation) or antifungal agents within 14 days prior to enrollment

27) Second malignancy, except treated basal cell or localized squamous skin carcinomas, localized prostate cancer, or other malignancies for which patients are not on active anticancer therapies and have had no evidence of active malignancy for at least 1 year. Other exceptions may be considered with sponsor approval. Previous hormonal therapy with luteinizing hormone-releasing hormone agonists for prostate cancer and treatment with bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors are not criteria for exclusion.

28) Known active or chronic hepatitis B or C infection or HIV infection in medical history

29) Active hepatitis B virus (HBV) and/or active hepatitis C virus (HCV), and/or HIV infection following testing at screening:

d) Patients who test positive for hepatitis B surface antigen (HBsAg). Patients who test positive for hepatitis B core antibody (anti-HBc) will require HBV DNA by quantitative polymerase chain reaction (PCR) for confirmation of active disease.

e) Patients who test positive for HCV antibody. Patients who test positive for HCV antibody will require HCV RNA by quantitative PCR for confirmation of active disease.

f) Patients who test positive for HIV

30) Patients who received any live vaccine within 4 weeks prior to initiation of study treatments.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment

Patients who meet eligibility criteria will be enrolled into individual safety run-in cohorts for the specific combination treatment.

An IXRS will be employed to manage the conduct of the study. During the safety run-in and/or dose expansion, the IXRS will be used to maintain a central log documenting enrollment, to manage dose modifications, to assess current inventories of products procured by the sponsor, to initiate any necessary resupply of products procured by the sponsor, and to document discontinuation of study drug and study participation. This is an open-label study in both the safety run-in and the dose-expansion cohorts of the study.

5.2. Description and Handling

5.2.1. Magrolimab

Formulation

Magrolimab is formulated as a sterile, clear to slightly opalescent, colorless to slightly yellow, preservative-free liquid intended for IV administration, containing 10 mM sodium acetate, 5% (weight-to-volume [w/v]) sorbitol, 0.01% (w/v) polysorbate 20 at pH of 5.0. Each vial is manufactured to ensure a deliverable volume of 10 mL containing 200 mg of magrolimab at a concentration of 20 mg/mL.

Packaging and Labeling

Magrolimab is supplied in single-use, 10 mL glass vials with coated elastomeric stoppers and aluminum crimp overseals with a flip-off cap.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, European Union (EU) Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

Storage and Handling

Magrolimab should be stored at 2 to 8 °C (36 to 46 °F). Magrolimab should not be frozen. Protect from light during storage. Do not shake. Storage conditions are specified on the label. Until dispensed to the patients, study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.2.2. Daratumumab

Formulation

Daratumumab is commercially sourced. Information regarding the formulation can be found in the current prescribing information from the reference USPI, SmPC, or applicable local or regional label.

Packaging and Labeling

Commercially available daratumumab will be used for this study.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

Storage and Handling

Commercial product of daratumumab will be used for the study. Further information regarding storage and handling are available in the reference USPI, SmPC, or applicable local or regional label for commercial products.

5.2.3. Pomalidomide

Formulation

Pomalidomide is commercially sourced. Information regarding the formulation can be found in the current prescribing information from the reference USPI, SmPC, or applicable local or regional label.

Packaging and Labeling

Commercially available pomalidomide will be used for this study.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

Storage and Handling

Commercial product of pomalidomide will be used for the study. Further information regarding storage and handling are available in the reference USPI, SmPC, or applicable local or regional label for commercial products.

5.2.4. Carfilzomib

Formulation

Carfilzomib is commercially sourced. Information regarding the formulation can be found in the current prescribing information from the reference USPI, SmPC, or applicable local or regional label.

Packaging and Labeling

Commercially available carfilzomib will be used for this study.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

Storage and Handling

Commercial product of carfilzomib will be used for the study. Further information regarding storage and handling are available in the reference USPI, SmPC, or applicable local or regional label for commercial products.

5.2.5. Bortezomib

Formulation

Bortezomib is commercially sourced. Information regarding the formulation can be found in the current prescribing information from the reference USPI, SmPC, or applicable local or regional label.

Packaging and Labeling

Commercially available bortezomib will be used for this study.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

Storage and Handling

Commercial product of bortezomib will be used for the study. Further information regarding storage and handling are available in the reference USPI, SmPC, or applicable local or regional label for commercial products.

5.2.6. Dexamethasone

Formulation

Dexamethasone is commercially sourced. Information regarding the formulation can be found in the current prescribing information from the reference USPI, SmPC, or applicable local or regional label.

Packaging and Labeling

Commercially available dexamethasone will be used for this study.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

Storage and Handling

Commercial product of dexamethasone will be used for the study. Further information regarding storage and handling are available in the reference USPI, SmPC, or applicable local or regional label for commercial products.

5.3. Dosage and Administration

5.3.1. Magrolimab

The planned dosage and administration schedule for magrolimab in the safety run-in cohorts and dose-expansion cohorts are described in Table 4 and Table 5, respectively.

Table 4. Magrolimab Dose De-escalation and Schedule (All Safety Run-in Cohorts)

Dose Level	Magrolimab Dosing
Starting Dose 30 mg/kg	• Cycle 1: 1 mg/kg IV on Day 1, 30 mg/kg on Days 8, 15, 22, 29 • Cycle 2: 30 mg/kg IV every week on Days 1, 8, 15, 22 • Cycle 3 and onward: 30 mg/kg IV on Days 1, 15
Level −1 20 mg/kg	• Cycle 1: 1 mg/kg IV on Day 1, 20 mg/kg on Days 8, 15, 22, 29 • Cycle 2: 20 mg/kg IV every week on Days 1, 8, 15, 22 • Cycle 3 and onward: 20 mg/kg IV on Days 1, 15
Level −2 15 mg/kg	• Cycle 1: 1 mg/kg IV on Day 1, 15 mg/kg on Days 8, 15, 22, 29 • Cycle 2: 15 mg/kg IV every week on Days 1, 8, 15, 22 • Cycle 3 and onward: 15 mg/kg IV on Days 1, 15

IV = intravenous

Table 5. Magrolimab Dose Level and Schedule (All Dose-expansion Cohorts)

	Dose Schedule (Cycle 1 is 35 Days; All Other Cycles are 28 Days)		
RP2D[a]	Cycle 1	Cycle 2	Cycle 3+
30 mg/kg	1 mg/kg IV Day 1 (priming dose) and 30 mg/kg IV Days 8, 15, 22, 29	30 mg/kg IV Days 1, 8, 15, 22	30 mg/kg IV Days 1, 15
20 mg/kg	1 mg/kg IV Day 1 (priming dose) and 20 mg/kg IV Days 8, 15, 22, 29	20 mg/kg IV Days 1, 8, 15, 22	20 mg/kg IV Days 1, 15
15 mg/kg	1 mg/kg IV Day 1 (priming dose) and 15 mg/kg IV Days 8, 15, 22, 29	15 mg/kg IV Days 1, 8, 15, 22	15 mg/kg IV Days 1, 15

IV = intravenous; RP2D = recommended Phase 2 dose
a RP2D as determined in the safety run-in cohorts.

Instructions for Magrolimab Administration

Magrolimab should be administered as outlined in the Pharmacy Manual for the study. The dose of magrolimab will be calculated based on actual weight enrollment (using weight obtained either at screening or on Day 1) and will remain constant throughout the study, unless there is a > 10% change in weight from baseline. Modifications to the study drug doses administered should be made for a > 10% change in body weight and according to local and regional prescribing standards. Dose modifications for changes in body weight ≤ 10% may be made according to local institutional guidelines.

Magrolimab will be administered by IV infusion. The duration of each magrolimab infusion will be 3 hours (± 30 minutes) for the first 5 doses during Cycle 1 of treatment. From Cycle 2 onward, magrolimab infusions will be 2 hours (± 30 minutes). The reduced infusion time to 2 hours is utilized based on prior data demonstrating majority CD47 receptor occupancy on peripheral blood cells, thus mitigating anticipated RBC toxicities from magrolimab. When magrolimab is given in combination with daratumumab, carfilzomib, or bortezomib on the same day, magrolimab will be administered at least 1 hour after the completion of the other agent.

Magrolimab dosing days may only be adjusted by a maximum of ± 3 days in order to accommodate the administration of other medicines.

Magrolimab Premedication and Prophylaxis

Premedication is required prior to the administration of the first 4 doses of magrolimab and in case of reintroduction with repriming (Section 5.4.1). Premedication should include oral acetaminophen 650 to 1000 mg, oral or IV diphenhydramine 25 to 50 mg, and IV dexamethasone 4 to 20 mg, or comparable regimen. If less than 4 hours has elapsed since a prior dose of acetaminophen has been given, the dose of acetaminophen premedication may be omitted. Premedication can be given 1 to 3 hours prior to the start of infusion. Premedication decisions for subsequent infusions should be based on the treating physician's clinical judgment and the presence/severity of prior IRRs. Guidance is provided in Table 24.

Postinfusion Monitoring

All patients should be monitored for 1 hour after infusion for priming, repriming/re-escalation, and maintenance doses during Cycle 1 (Sections 5.4.1 and 7.8.1). Postinfusion monitoring should begin after the infusion is complete. Postinfusion monitoring is not required for doses after Cycle 1 Day 29. Patients who experience any treatment-emergent AEs during the observation period should be further monitored, as clinically appropriate. Refer to Section 7.8.1.1 for postinfusion hemoglobin monitoring requirements.

Treatment Duration/Discontinuation

Patients may continue study treatment until they show evidence of disease progression, relapse, loss of clinical benefit, or unacceptable toxicity (further details about treatment discontinuation are provided in Section 3.4).

Treatment Delay and Repriming/Re-escalation for Magrolimab

Given the large CD47 antigen sink on normal cells, patients who have a long dose delay of magrolimab are required to be reprimed with magrolimab dosing to resaturate the CD47 antigen sink. Guidelines for repriming/re-escalation for magrolimab after a dose delay are provided in Section 5.4.1.

5.3.2. Daratumumab

Study treatment for daratumumab in combination with magrolimab is shown in Table 6. Magrolimab will be administered as described in Section 5.3.1.

Table 6. Dose Level and Schedule for Daratumumab in Combination With Magrolimab

Drug/Dose/Route	Dose Schedule (Cycle 1 is 35 Days; All Other Cycles are 28 Days)		
	Cycle 1	Cycle 2	Cycle 3+
Daratumumab 16 mg/kg IV or 1800 mg SC	Days 8, 15, 22, 29	Days 1, 8, 15, 22	Days 1 and 15 (every 2 weeks) until Cycle 6 (total of 8 doses) followed by Day 1 (every 4 weeks) for subsequent cycles

IV = intravenous; SC = subcutaneous

Instructions for Daratumumab Administration

Daratumumab will be administered as an IV infusion or as an SC injection.

On days when daratumumab is coadministered with magrolimab, the required administration is as follows:

1) Preinfusion (IV) or preinjection (SC) medications for daratumumab 1 to 3 hours before (premedication)
2) Daratumumab IV infusion or SC injection
3) Postinfusion (IV) or postinjection (SC) medications for daratumumab (postmedication)
4) Preinfusion medications for magrolimab IV (first 4 doses)
5) Magrolimab IV infusion

There will be a minimum 1-hour observation period between the completion of daratumumab infusion/injection and the start of magrolimab infusion.

Instructions on dose modifications and delays are provided in Section 5.4.2. Management of IRRs is described in Section 7.8.2.

Premedication for Daratumumab

Administer the following premedications to reduce the risk of infusion/administration reactions to all patients 1 to 3 hours prior to every dose of daratumumab:

- Methylprednisolone 100 mg, or equivalent, administered IV. Following the second administration, the dose of corticosteroid may be reduced (oral or IV methylprednisolone 60 mg).

- Antipyretics (oral acetaminophen 650 to 1000 mg).
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Postmedication for Daratumumab

Administer postmedication to reduce the risk of delayed infusion/administration reactions to all patients as follows:

- Administer oral corticosteroid (20 mg methylprednisolone or equivalent dose of an intermediate-acting or long-acting corticosteroid in accordance with local standards) on each of the 2 days following each daratumumab administration (beginning the day after the administration).
- In addition, for any patients with a history of chronic obstructive pulmonary disease, consider prescribing postinfusion medications such as short and long-acting bronchodilators, and inhaled corticosteroids. Following the first 4 infusions, if the patient experiences no major infusion reactions, these additional inhaled postinfusion medications may be discontinued.

For the management of IRRs to daratumumab, please refer to Section 7.8.2.

Contraindications for Daratumumab

A contraindication to daratumumab includes those patients with a history of severe hypersensitivity (ie, anaphylactic reactions) to daratumumab or any of the components of the formulation.

Antiviral Prophylaxis for Daratumumab

Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting daratumumab and continue for 3 months following treatment.

5.3.3. Pomalidomide and Dexamethasone

Study treatment for pomalidomide and dexamethasone in combination with magrolimab is shown in Table 7. Magrolimab will be administered as described in Section 5.3.1.

Table 7. Dose Level and Schedule for Pomalidomide and Dexamethasone in Combination With Magrolimab

Drug/Dose/Route	Dose Schedule (Cycle 1 is 35 Days; All Other Cycles are 28 Days)		
	Cycle 1	Cycle 2	Cycle 3+
Pomalidomide 4 mg PO	Days 1 to 21 (daily)	Days 1 to 21 (daily)	Days 1 to 21 (daily)
Dexamethasone 40 mg PO[a]	Days 1, 8, 15, 22, 29	Days 1, 8, 15, 22	Days 1, 8, 15, 22

PO = orally
a Dexamethasone starting dose is 20 mg in patients more than 75 years of age.

Instructions on dose modifications and delays for pomalidomide and dexamethasone are provided in Section 5.4.3 and Section 5.4.6, respectively. Refer to the reference USPIs, SmPCs, or applicable local or regional labels for toxicity management.

Premedication and Prophylaxis for Pomalidomide and Dexamethasone

No premedication is indicated for pomalidomide {POMALYST 2020}.

Pneumocystis jirovecii pneumonia prophylaxis should be considered, as per institutional guidelines, while on dexamethasone.

Contraindications for Pomalidomide

Refer to the reference USPIs, SmPCs, or applicable local or regional labels. Contraceptive requirements are outlined in Appendix 4.

5.3.4. Carfilzomib and Dexamethasone

Study treatment for carfilzomib and dexamethasone in combination with magrolimab is shown in Table 8. Magrolimab will be administered as described in Section 5.3.1.

Table 8. Dose Level and Schedule for Carfilzomib and Dexamethasone in Combination With Magrolimab

Drug/Dose/Route	Dose Schedule (Cycle 1 is 35 Days; All Other Cycles are 28 Days)		
	Cycle 1	Cycle 2	Cycle 3+
Carfilzomib 20/70 mg/m^2 IV[a]	Days 8 (20 mg/m^2), 15 (70 mg/m^2), 22 (70 mg/m^2)	Days 1, 8, 15[b]	Days 1, 8, 15[b]
Dexamethasone 40 mg PO or IV[c]	Days 8, 15, 22, and 29	Days 1, 8, 15, and 22	Days 1, 8, 15, and 22 until Cycle 9 and Days 1, 8, and 15 from Cycle 10 onward

IV = intravenous; PO = orally
a The recommended starting dose of carfilzomib is 20 mg/m^2 on Cycle 1, Day 8. If tolerated, escalate the dose to 70 mg/m^2 on Cycle 1, Day 15, and thereafter.
b From Cycle 2 onwards, carfilzomib will be given on Days 1, 8, and 15 of each cycle.
c Dexamethasone starting dose is 20 mg in patients more than 75 years of age.

Instructions for Carfilzomib Administration

The relevant USPI, SmPC, or applicable local or regional label should be followed for the administration of carfilzomib and dexamethasone.

Carfilzomib will be administered as an IV infusion. Administer dexamethasone either PO or IV 30 minutes to 4 hours before carfilzomib.

On days when carfilzomib is coadministered with magrolimab, carfilzomib will be given first, followed by magrolimab. There will be a minimum 1-hour observation period between the completion of carfilzomib infusion and the start of magrolimab infusion.

Instructions on dose modifications and delays are provided in Section 5.4.4. Management of IRRs is described in Section 7.8.2.

Premedication and Prophylaxis for Carfilzomib and Dexamethasone

No premedication is indicated for carfilzomib.

Pneumocystis jirovecii pneumonia prophylaxis should be considered, as per institutional guidelines, while on dexamethasone.

5.3.5. Bortezomib and Dexamethasone

Study treatment for bortezomib and dexamethasone in combination with magrolimab is shown in Table 9. Magrolimab will be administered as described in Section 5.3.1.

Table 9. Dose Level and Schedule for Bortezomib and Dexamethasone in Combination With Magrolimab

Drug/Dose/Route	Dose Schedule (Cycle 1 is 35 Days; All Other Cycles are 28 Days)		
	Cycle 1	Cycle 2	Cycle 3+
Bortezomib 1.3 mg/m^2 SC or IV[a]	Days 8, 15, 22, 29	Days 1, 8, 15, 22	Days 1, 8 15, 22[b]
Dexamethasone 40 mg PO[c]	Days 1, 8, 15, 22, 29	Days 1, 8, 15, 22	Days 1, 8, 15, 22[d]

IV = intravenous; PO = orally; SC = subcutaneous.
a SC is preferred over IV, where feasible.
b Maximum of 8 cycles in those who have previously received bortezomib.
c Dexamethasone starting dose is 20 mg in patients more than 75 years of age.
d Days 1, 8, 15, and 22 from Cycles 3 to 9 and then Days 1, 8, and 15 from Cycle 10 onward.

The maximum number of cycles is 8 in patients who have previously received bortezomib. On days when bortezomib is coadministered with magrolimab, bortezomib will be given first, followed by magrolimab. Both administrations will be separated by a minimum of 1 hour.

Instructions on dose modifications and delays for bortezomib and dexamethasone are provided in Section 5.4.5 and Section 5.4.6, respectively.

Premedication and Prophylaxis for Bortezomib and Dexamethasone

No premedication is indicated for bortezomib {VELCADE 2019}.

Pneumocystis jirovecii pneumonia prophylaxis should be considered, as per institutional guidelines, while on dexamethasone {DEXAMETHASONE 2015}.

Postdose Monitoring

Refer to Section 7.8.5 for monitoring and dose-adjustment for peripheral neuropathy following administration of bortezomib. Refer to the reference USPI, SmPC, or applicable local or regional label for toxicity management for dexamethasone.

Contraindications for Bortezomib

Bortezomib is contraindicated in patients with acute diffuse infiltrative pulmonary and pericardial disease, plus those patients with hypersensitivity to the active substance or to any of the excipients {VELCADE 2019}.

5.4. Dose Modification and Delays

5.4.1. Magrolimab

Magrolimab dose de-escalation in the safety run-in cohorts is described in Table 4. In the dose-expansion cohorts, magrolimab should not be dose reduced. Clinical safety and PK data from dose finding studies in both solid tumor and hematologic malignancies have not demonstrated any dose-dependent toxicities associated with magrolimab.

Dose reduction/modification may be allowed in certain circumstances (eg, with certain AEs), with approval by the sponsor. Magrolimab may be withheld if treatment-emergent and/or magrolimab-related AEs occur, until clinical resolution or improvement per the treating physician. Refer to Section 7.8.1 for details on management of magrolimab-related toxicities. In the rare event of needing to reduce the magrolimab dose in the dose-expansion cohorts due to toxicity, the schedule described for the safety run-in cohorts in Table 4 may be used in consultation with the sponsor. The magrolimab dose should be increased back to the RP2D when toxicity is resolved.

When the combination drugs (daratumumab, pomalidomide, carfilzomib, bortezomib or dexamethasone) are delayed due to toxicities, magrolimab should continue independently as per magrolimab administration schedule (Table 5). Continuous (every 2 weeks) dosing of magrolimab is needed in order to ensure optimal efficacious exposure. Magrolimab dosing days may only be adjusted by a maximum of ± 3 days in order to accommodate the administration of other medicines as presented in Appendix 2. Magrolimab may be withheld if treatment-emergent and/or related AEs occur, and will require approval by the sponsor if the delay is longer than 3 days.

Magrolimab will be permanently discontinued in patients who experience any Grade 4 nonhematologic AEs related to magrolimab that do not improve to Grade 2 or pretreatment baseline levels within 14 days. Magrolimab will also be permanently discontinued in patients with Grade 4 hemolytic anemia which is defined as anemia with clinical and/or laboratory evidence of hemolysis with life-threatening consequences and/or urgent interventions are indicated. For dose delay criteria, magrolimab may be withheld if treatment-emergent and/or magrolimab-related AEs occur, which include all AEs that constitute a DLT, as defined in Section 3.1.1 of the protocol. Magrolimab may be reintroduced if the severity has recovered to Grade 2 or pretreatment baseline levels with the approval by the medical monitor.

If planned surgical procedures are needed for patients on-study treatment, magrolimab will be delayed and restarted in accordance with Table 10.

Table 10. Magrolimab Dosing Guidance for Planned Surgical Procedures on Study

Planned Surgical Procedure	Magrolimab Dose Guidance
Minimally Invasive Procedure (Examples: Biopsies [Excluding Lung/Liver], Skin/Subcutaneous Lesion Removal, Cataract/Glaucoma/Eye Surgery/Cystoscopy)	Hold magrolimab dose 3 days prior to procedure and restart after 3 days
Moderately Invasive Procedure (Examples: Lung/Liver Biopsy, Hysterectomy, Cholecystectomy, Hip/Knee Replacement, Minor Laparoscopic Procedures, Stent/Angiopathy)	Hold magrolimab dose 3 days prior to procedure and restart after 5 days
Highly Invasive Procedure (Examples: CNS/Spine Surgery, Major Vascular Surgery, Cardiothoracic Surgery, Major Laparoscopic Surgery)	Hold magrolimab dose 3 days prior to procedure and restart after 7 days

CNS = central nervous system

Repriming and Re-escalation Guidelines

Repriming guidelines in Table 11 must be followed for patients with dose delays.

Table 11. Repriming Guidelines

Dose	Dosing Frequency	Minimum Duration of Treatment Gap That Will Lead to Repriming
1 mg/kg	N/A – used at initial priming	2 weeks
15 mg/kg	Weekly	2 weeks
	Every 2 weeks	4 weeks
20 mg/kg	Weekly	2 weeks
	Every 2 weeks	4 weeks
30 mg/kg	Weekly	4 weeks
	Every 2 weeks	4 weeks

The repriming/re-escalation magrolimab dosing regimen and assessments must follow Cycle 1 for magrolimab treatment and magrolimab-specific premedication administration and safety assessments as illustrated in the schedules of assessments and treatment administration (Appendix Table 2), and then switch to the schedule for the assigned cycle number for all assessments and study treatments.

During repriming, cycle numbering, efficacy, biomarker, PK, and immunogenicity assessments should continue as per assigned cycle number. The safety assessment must follow the Cycle 1 safety assessments and switch back to assigned cycle schedule subsequently.

5.4.2. Daratumumab

No dose reductions of daratumumab are allowed. Refer to Section 7.8.2 for details on management of IRRs. If any of the following criteria are met and the event cannot be ascribed to magrolimab, the daratumumab infusion/injection must be held to allow for recovery from toxicity. The criteria for a dose delay are:

- Grade 3 thrombocytopenia with bleeding
- Grade 4 neutropenia, if this is the second occurrence despite growth factor support
- Febrile neutropenia of any grade
- Neutropenia with infection of any grade
- Grade 3 or higher nonhematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for < 7 days after the last administration of daratumumab
  - Grade 3 asthenia that was present at baseline or that lasts for < 7 days after the last administration of daratumumab

If a daratumumab administration does not commence within the prespecified window of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date (Table 12).

Table 12. Management of Daratumumab-related Dosing Delays

Cycle	Frequency	Dose Held	Dosing Restart
1	Weekly Days 8, 15, 22, and 29	> 3 days	Next planned weekly dosing date
2	Weekly Days 1, 8, 15, and 22	> 3 days	Next planned weekly dosing date
3-6	Every 2 weeks (Q2W)	> 1 week	Next planned Q2W dosing date
7+	Every 4 weeks (Q4W)	> 2 weeks	Next planned Q4W dosing date

Q2W = every 2 weeks; Q4W = every 4 weeks

A missed dose will not be made up.

Patients who permanently discontinue daratumumab may continue to receive magrolimab monotherapy in agreement with the sponsor. Patients who discontinue magrolimab will discontinue all other study treatments and will enter follow-up.

No formal studies of daratumumab have been conducted in patients with renal or hepatic impairment. Based on population PK analysis, no dosage adjustment is necessary in these patients. No dose adjustments are considered necessary in elderly patients. No interaction studies have been performed. Due to the high affinity to a unique epitope on CD38, daratumumab is not anticipated to alter drug-metabolizing enzymes, although interference with Indirect Antiglobulin Test (Indirect Coombs Test) and Serum Protein Electrophoresis and Immunofixation Tests have been noted.

5.4.3. Pomalidomide

Recommended dose adjustments for the management of AEs as judged by the investigator to be related to pomalidomide are provided in Table 13. Dose modification decisions for pomalidomide will be at the investigator's discretion per the reference USPI, SmPC, or applicable local or regional label. These documents should be consulted for use in special populations and drug-drug interactions.

To initiate a new cycle of pomalidomide following a dose interruption, the ANC must be ≥ 1000/μL with or without G-CSF, the platelet count must be ≥ 50,000/μL, and nonhematologic AEs must be resolved or improved as outlined in Table 13.

If recovery from toxicities is prolonged and pomalidomide dose withholding is beyond 14 days, then the dose of pomalidomide should be decreased by 1 dose-level when dosing is resumed in the new cycle (Table 14). The minimum permitted dose level for pomalidomide is 1 mg. No dose re-escalation is permitted for pomalidomide.

Patients who permanently discontinue pomalidomide may continue magrolimab with or without dexamethasone in agreement with the sponsor. Patients who discontinue magrolimab will discontinue all other study treatments and will enter follow-up.

Table 13. Pomalidomide Dose Modifications

Toxicity	Dose Modification
Neutropenia Grade 4 Neutropenia (ANC < 500/μL) or Febrile Neutropenia (Fever ≥ 38.5 °C and ANC < 1000/μL)	Withhold the dose for remainder of cycle. If the patient was not receiving G-CSF therapy, G-CSF therapy may be started at the discretion of the Investigator. On Day 1 of the next cycle, the dose of pomalidomide may be maintained if neutropenia was the only pomalidomide-related toxicity requiring a dose modification and G-CSF treatments are continued. Otherwise, decrease by 1 dose-level at start of next cycle. Note, ANC must be ≥ 1000/μL to resume dosing.
Thrombocytopenia Grade 4 Thrombocytopenia (Platelets < 25,000/μL)	Withhold the dose for remainder of cycle. Dosing may resume at 1 dose-level lower once the platelet count has recovered to ≥ 50,000/μL
Grade 3 Rash	Withhold dose for remainder of cycle. Decrease by 1 dose-level when dosing is resumed at next cycle (rash must be resolved or improved to ≤ Grade 1 before dose resumption).
Grade 4 Rash or Skin Exfoliation, Bullae, or any Other Severe Dermatologic Reaction	Permanently discontinue pomalidomide
≥ Grade 3 Constipation	Withhold dose for remainder of cycle. Initiate bowel regimen. Decrease by 1 dose-level when dosing is resumed at next cycle (constipation must be resolved or improved to ≤ Grade 2 before dose resumption)
Venous Thromboembolic Event	Withhold dose for remainder of cycle. Initiate anticoagulation treatment. Maintain dose level when dosing resumed at next cycle at discretion of the investigator.
Other ≥ Grade 3 Pomalidomide-related AEs[a]	Withhold dose for remainder of cycle. Decrease by 1 dose-level when dosing resumed at next cycle (AE must be resolved or improved to ≤ Grade 2 before restarting dosing)

AE = adverse event; ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor
a For Grade 3 or 4 AEs that are not considered to be related to pomalidomide, the investigator should consult with the Gilead medical monitor for dose interruptions and reductions.

Table 14. Pomalidomide Dose Reduction Levels

Dose Level	Oral Pomalidomide Dose (Days 1 to 21 of 28-day Cycle)
Starting Dose	4 mg
Dose Level −1	3 mg
Dose Level −2	2 mg
Dose Level −3	1 mg

5.4.4. Carfilzomib

Table 15 details instructions for carfilzomib dose interruptions and reductions and Table 16 outlines the dose reduction levels for carfilzomib; however, dose modification decisions for carfilzomib will be at the investigator's discretion (in consultation with the medical monitor) per the reference USPI, SmPC, or applicable local or regional label. These documents should be consulted for use in special populations and drug-drug interactions.

Patients who permanently discontinue carfilzomib may continue to receive magrolimab monotherapy with or without dexamethasone in agreement with the sponsor. Patients who discontinue magrolimab will discontinue all other study treatments and will enter follow-up.

Table 15. Carfilzomib Dose Modifications

Hematologic Toxicity	Recommended Action
ANC less than 0.5×10^9/L	Withhold dose: • If recovered to greater than or equal to 0.5×10^9/L, continue at the same dose level For subsequent drops to less than 0.5×10^9/L, follow the same recommendations as above and consider 1 dose-level reduction when restarting carfilzomib
Febrile neutropenia: ANC less than 0.5×10^9/L and an oral temperature more than 38.5 °C or 2 consecutive readings of more than 38.0 °C for 2 hours	Withhold dose • If ANC returns to baseline grade and fever resolves, resume at the same dose level
Platelets less than 10×10^9/L or evidence of bleeding with thrombocytopenia	Withhold dose • If recovered to greater than or equal to 10×10^9/L and/or bleeding is controlled, continue at the same dose level For subsequent drops to less than 10×10^9/L, follow the same recommendations as above and consider 1 dose-level reduction when restarting carfilzomib
Renal Toxicity	**Recommended Action**
Serum creatinine greater than or equal to 2 × baseline, or Creatinine clearance less than 15 mL/min, or creatinine clearance decreases to less than or equal to 50% of baseline, or need for hemodialysis	Withhold dose and continue monitoring renal function (serum creatinine or creatinine clearance) • If attributable to carfilzomib, resume when renal function has recovered to within 25% of baseline; start at 1 dose-level reduction • If not attributable to carfilzomib, dosing may be resumed at the discretion of the healthcare provider For patients on hemodialysis receiving carfilzomib, the dose is to be administered after the hemodialysis procedure
Hepatic Impairment (Mild or Moderate)	**Recommended Action**
For patients with mild (total bilirubin 1 to 1.5 × ULN and any AST or total bilirubin ≤ ULN and AST > ULN) or moderate (total bilirubin > 1.5 to 3 × ULN and any AST) hepatic impairment	Reduce the dose of carfilzomib by 25%
Other Nonhematologic Toxicity	**Recommended Action**
All other severe or life-threatening (Grade 3 or Grade 4) nonhematological toxicities	Withhold until resolved or returned to baseline Consider restarting the next scheduled treatment at 1 dose-level reduction

ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal

Table 16. Carfilzomib Dose Reduction Levels

Dose Level	Carfilzomib dose
Starting Dose	70 mg/m^2
Dose Level −1	56 mg/m^2
Dose Level −2	45 mg/m^2
Dose Level −3	36 mg/m^2

If toxicity persists at 36 mg/m^2, discontinue carfilzomib treatment.
Note: Infusion times remain unchanged during dose reduction(s).

5.4.5. Bortezomib

Table 17 details instructions for bortezomib dose interruptions and reductions and Table 18 outlines the dose reduction levels for bortezomib; however, dose modification decisions for bortezomib will be at the investigator's discretion per the reference USPI, SmPC, or applicable local or regional label. These documents should be consulted for use in special populations and drug-drug interactions.

Patients who permanently discontinue bortezomib may continue to receive magrolimab monotherapy with or without dexamethasone in agreement with the sponsor. Patients who discontinue magrolimab will discontinue all other study treatments and will enter follow-up.

Table 17. Bortezomib Dose Modifications

Toxicity	Bortezomib Dose Modification
≥ Grade 3 Nonhematological Toxicity (excluding neuropathy)	Withhold bortezomib until the symptoms of the toxicity have resolved, bortezomib therapy may be reinitiated at reduced bortezomib dosing by 1 dose-level
Grade 4 Hematological Toxicity	Withhold bortezomib until the symptoms of the toxicity have resolved, bortezomib therapy may be reinitiated at reduced bortezomib dosing by 1 dose-level
Grade 1 Neuropathy Without Pain or Loss of Function	No action
Grade 1 Neuropathy with Pain or Grade 2 Neuropathy	Reduce bortezomib dosing by 1 level
Grade 2 Neuropathy with Pain or Grade 3 Neuropathy	Withhold bortezomib until toxicity resolves, bortezomib therapy may be reinitiated at a reduced dose level of 0.7 mg/m^2 and change treatment schedule to once per week (Days 1 and 8 of a 21-day cycle)
Grade 4 Neuropathy	Permanently discontinue bortezomib

Table 18. Bortezomib Dose Reduction Levels

Dose Level	Bortezomib Dose Level (SC or IV)
Starting Dose	1.3 mg/m^2 on Days 1, 8, 15, and 22 of each cycle from Cycle 2 (Days 8, 15, 22, and 29 of Cycle 1)
Dose Level −1	1.3 mg/m^2 Days 1, 8, and 15 of each cycle from Cycle 2
Dose Level −2	1 mg/m^2 Days 1, 8, and 15 only of each cycle

IV = intravenous; SC = subcutaneous

5.4.6. Dexamethasone

Table 19 and Table 20 detail instructions for low-dose dexamethasone dose interruptions and reductions; however, dose withholding/resumption decision is at the investigator's discretion per the reference USPI, SmPC, or applicable local or regional label.

Table 19. Dose Reductions for Low-Dose Dexamethasone-related Toxicities

Toxicity	Low-Dose Dexamethasone Dose Modification
Dyspepsia (Grade 1 or 2)	Maintain dose and treat with histamine (H2) blockers or equivalent. Decrease by 1 dose-level if symptoms persist
Dyspepsia ≥ Grade 3	Withhold dose until symptoms are controlled. Add H2 blocker or equivalent and decrease 1 dose-level when dosing is resumed
Edema ≥ Grade 3	Use diuretics as needed and decrease dose by 1 dose-level
Confusion or Mood Alteration ≥ Grade 2	Withhold dose until symptoms resolve. When dosing is resumed decrease dose by 1 dose-level
Muscle Weakness (Steroid Myopathy) ≥ Grade 2	Withhold dose until muscle weakness < Grade 1. When dosing is resumed decrease dose by 1 dose-level
Hyperglycemia ≥ Grade 3	Decrease dose by 1 dose-level. Treat with insulin or oral hypoglycemic agents as needed
Acute Pancreatitis	Discontinue dexamethasone from treatment regimen
Other ≥ Grade 3 Dexamethasone-related AEs	Stop dexamethasone dosing until the AE resolves to ≤ Grade 1. Decrease by 1 dose-level when dosing is resumed

AE = adverse event

If recovery from toxicities is prolonged and dexamethasone dose withholding is beyond 14 days, then the dose of dexamethasone will be decreased by 1 dose-level when dosing is resumed in the new cycle.

Table 20. Low-Dose Dexamethasone Dose Reduction Levels

Dose Level	≤ 75 years old	> 75 years old
Starting Dose	40 mg	20 mg
Dose Level −1	24 mg	12 mg
Dose Level −2	16 mg	8 mg

Dexamethasone may be discontinued if the patient is unable to tolerate 16 mg if ≤ 75 years old or 8 mg if > 75 years old. In the event of discontinuation of dexamethasone, other study medications will be continued per protocol.

5.5. Prior and Concomitant Medications

All prior and concomitant medications, including all prescription, over-the-counter, herbal supplements, and IV medications and fluids received within 70 days prior to signing the informed consent form (ICF) through the 70-day safety follow-up visit should be recorded in the electronic case report form (eCRF).

Live vaccines are prohibited during the study, and for 3 months after the last dose of study treatment {Rubin 2014}.

5.5.1. Prohibited Prior Medications

Prohibited medications prior to study enrollment are summarized in Table 21.

Table 21. Prohibited Prior Medications

Medication	Length of Time Prior to Enrollment
Glucocorticoids (Prednisone > 40 mg/day or Equivalent)	14 days
Chemotherapy with Approved or Investigational Anticancer Therapeutics	28 days
Immunotherapy	28 days
CD47 or SIRPα-targeting Agents	None
Magrolimab in Combination with Daratumumab Cohort Only: No Prior Anti-CD38 Antibody Therapy	6 months
Magrolimab in Combination with Pomalidomide and Dexamethasone Cohort Only: No Prior Pomalidomide Therapy	6 months
Magrolimab in Combination with Carfilzomib and Dexamethasone Cohort Only: No Prior PI Therapy	6 months
Magrolimab in Combination with Bortezomib and Dexamethasone Cohort Only: No Prior PI Therapy	6 months

PI = proteasome inhibitor; SIRPα = signal regulatory protein alpha

5.5.2. Prohibited Concomitant Medications

Anticancer therapies including chemotherapy, targeted therapies, and immunotherapy (apart from study drugs) or radiation to large marrow reserves for either a palliative or therapeutic intent are not permitted while patients are on study.

Except for the protocol-specified regimens, long-term corticosteroids for nonmalignant conditions (eg, asthma, inflammatory bowel disease) equivalent to a dexamethasone dose > 4.0 mg/day or prednisone > 20 mg/day are not permitted. Corticosteroids given short-term (up to 2 weeks) for nonmalignant conditions are permitted provided that the cumulative dose is less than 40 mg per week dexamethasone equivalent. Medical monitor should be contacted in the event that short-term corticosteroid use is required greater than 2 weeks or at cumulative dose of more than 40 mg dexamethasone equivalent.

Plasmapheresis is not permitted at any time while the patient is receiving study treatment. For patients requiring plasmapheresis while on-study treatment, every attempt should be made to first document disease status by the IMWG 2016 criteria. Study treatment must be discontinued.

5.5.3. Permitted and Required Concomitant Medications

Use of bisphosphonates, hematopoietic growth factors, hormonal therapy, luteinizing hormone-releasing hormone agonists for prostate cancer, hormonal maintenance therapy for breast cancers, treatment with RANKL inhibitors and other therapies including antibiotics, analgesics, antihistamines, or other medications and transfusions of RBCs, platelets, or fresh-frozen plasma are permitted at the discretion of the investigator. Radiation therapy to a pathological fracture site or to treat bone pain as well as any localized non-CNS therapy is allowed. Premedication and prophylaxis for AEs is permitted while on study treatment. Corticosteroid use is permitted for symptomatic treatment, premedication, pseudoprogression and/or specific patient conditions. Chronic high-dose steroid use is not recommended unless clinically indicated.

Thromboprophylaxis

An anticoagulant (eg, enteric-coated aspirin at standard prophylactic dose or other anticoagulant or antiplatelet medication, such as clopidogrel bisulfate, low molecular weight heparin, or warfarin), is a suggested concomitant medication in patients based on an individual benefit/risk assessment.

Tumor Lysis Syndrome Prophylaxis

An approved uric acid-lowering agent (eg, allopurinol) in patients at high risk for tumor lysis syndrome due to high tumor burden may be prescribed at the investigator's discretion, per the reference USPI, SmPC, or applicable local or regional label.

Bone Health Therapy

Concomitant bone health therapy is strongly recommended for all patients with evidence of lytic destruction of bone or with osteopenia {Gralow 2013, Terpos 2013}. Commercially available therapies are preferred when available, and should be used according to the manufacturer's recommendations, as described in the reference USPI, SmPC, or applicable local or regional label, for patients with osteolytic or osteopenic myelomatous bone disease.

Patients who are using bisphosphonate or mAb therapy when they enter the study should continue the same treatment. Patients with evidence of lytic destruction of bone or with osteopenia who are not using a bisphosphonate or mAb at the time of enrollment should start a bisphosphonate or other bone health medications that have proven efficacy, such as mAbs, as soon as possible during Cycle 1 or 2 of treatment. Investigators should not start bisphosphonate or mAb therapy during the study unless it has been agreed with the sponsor that there is no sign of disease progression.

Antiviral Prophylaxis for Daratumumab

Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting daratumumab and continue for 3 months following treatment.

Refer to the prescribing information in the reference USPI, SmPC, or applicable local or regional label.

Proton-pump Inhibitor Required With Dexamethasone

A proton-pump inhibitor (omeprazole or equivalent) is required while on dexamethasone per the reference USPI, SmPC, or applicable local or regional label {DEXAMETHASONE 2015}.

Prophylaxis for *Pneumocystis jirovecii* Pneumonia With Dexamethasone

Pneumocystis jirovecii pneumonia prophylaxis is recommended, as per institutional guidelines while on dexamethasone {DEXAMETHASONE 2015}.

COVID-19 Vaccine

There are no substantial safety data regarding the concomitant administration of the coronavirus disease 2019 (COVID-19) vaccines and magrolimab. Patients are allowed to receive the COVID-19 vaccine, and study visits should continue as planned if vaccination occurs while the patients is on the study. Investigators should follow local guidelines for concomitant administration of the COVID-19 vaccines with the study drug.

5.6. Accountability for Study Drug(s)

The investigator is responsible for ensuring adequate accountability of all used and unused study drug (kits, vials, etc) This includes acknowledgment of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to patients must be returned to the site.

Each study site must keep accountability records that capture:

- The date received and quantity of study drug kits (kits, vials, etc)
- The date, patient number, and the study lot number dispensed
- The date, quantity of used and unused study drug returned, along with the initials of the person recording the information

5.6.1. Study Drug(s) Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for the electronic trial master file. If study drug is destroyed at the site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

6. STUDY PROCEDURES

The study procedures to be conducted for each patient enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows.

The investigator must document any deviation from the protocol procedures and notify Gilead or the contract research organization.

6.1. Patient Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment onto the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

Patients will be screened within 30 days before enrollment to determine eligibility for participation in the study. Standard-of-care procedures performed before obtaining informed consent may be used for screening.

Patients who are determined to be not eligible after screening may be rescreened once at the discretion of the investigator. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Patients who are determined to be eligible for rescreening must be reconsented with a new screening number assigned.

Patients rescreening within 21 days of the signing of the original informed consent only need to repeat the assessment(s) that did not originally meet the eligibility criteria; all other initial screening assessments do not need to be repeated. Patients rescreening more than 21 days from the signing of the original informed consent must be reconsented, with a new screening number assigned, all screening procedures repeated.

In cases of technical failure, lab samples can be retested during screening period and patient will not be considered a screen failure. Patients who do not enroll within 30 days of screening will be screen failed.

6.2. Pretreatment Assessments

The following will be performed and documented at screening (Appendix Table 1):

- Obtain written informed consent
- Obtain demographics and medical history, including MM history
- Bone marrow sample for % plasma cells, morphology and cytogenetics (FISH) – these will be conducted locally. Additional sample will be sent centrally for biomarker and other correlative studies – refer to Section 6.5.4

- Myeloma frailty score calculation (patients ≥ 65 years of age) (Appendix 10)
- ECOG performance status
- Complete physical examination, including vital signs, body weight, and height
- Peripheral neurological examination for residual neuropathy (patients enrolling onto bortezomib cohort)
- 12-lead electrocardiogram (ECG) (single)
- Echocardiogram (ECHO) or multigated acquisition (scan) (MUGA)
- FACT-MM questionnaire *(as of Protocol Amendment 6, this assessment is not required)*
- Serum/plasma chemistry, hematology, and urinalysis assessments
- Serum pregnancy test (females of childbearing potential)
- Blood phenotyping or genotyping for minor antigens, type, and screen (any of the 4 blood groups A, B, AB, and O composing the ABO system [ABO]/Rhesus factor [Rh]), direct antiglobulin test (DAT)
- Serum protein electrophoresis (SPEP) and 24-hour urine protein electrophoresis (UPEP)
- SFLC
- Serum immunofixation (SIFE)
- Urine immunofixation (UIFE)
- β2-microglobulin and quantitative immunoglobulin (Ig) levels
- Hepatitis B, hepatitis C, and HIV
- C-reactive protein (CRP)
- Skeletal survey
- Computed tomography (CT) (with or without positron emission tomography [PET]) or magnetic resonance imaging (MRI) assessment for extramedullary soft tissue plasmacytoma
- Record all SAEs and any AEs related to protocol-mandated procedures occurring after signing of the ICF
- Record prior and concomitant medications

From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any AEs related to protocol-mandated procedures on the applicable eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be considered medical history. See Section 7, Adverse Events and Toxicity Management, for additional details.

6.2.1. Screening Laboratory Assessments

Analytes and tests to be assessed by the local laboratory or specialty laboratories at screening are presented in Table 22.

Table 22. Laboratory Analyte Listing (to be Performed at Screening)

Chemistry (Serum or Plasma)	Hematology	Urinalysis	Other Laboratory Measurements
Sodium	Red blood cell	Red blood cell	Pregnancy test (serum)
Potassium	Hemoglobin	Glucose	C-reactive protein (CRP)
Chloride	Hematocrit	Protein	Serum free light chain (SFLC)
Bicarbonate	Platelets	Urine pH	Serum protein electrophoresis (SPEP)
Total protein	WBC differential	Ketones	24-hour urine protein electrophoresis (UPEP)
Albumin	Absolute neutrophil count	Bilirubin	Serum immunofixation (SIFE)
Calcium	Eosinophils	Urine specific gravity	Urine immunofixation (UIFE)
Magnesium	Basophils		Blood phenotyping or genotyping for minor antigens, type, and screen (ABO/Rh), direct antiglobulin test
Phosphorus	Lymphocytes		β2-microglobulin and quantitative Ig levels
Glucose	Monocytes		Hepatitis B and hepatitis C assessments: HBsAg, anti-HBc, -HCV antibody; HBV DNA and HCV RNA as required
BUN or urea	Reticulocytes		HIV antibody
Creatinine	Haptoglobin		Peripheral blood smear
Uric acid	Prothrombin time		
Total bilirubin	INR		
Direct bilirubin	aPTT or PTT		
Indirect bilirubin			
Lactate dehydrogenase			
AST			
ALT			
Alkaline phosphatase			

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HBV = hepatitis B virus; HCV = hepatitis C virus; anti-HBc = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; Ig = immunoglobulin; INR = international normalized ratio; PTT = partial thromboplastin time; WBC = white blood cell

6.2.2. Type and Screen and Direct Antiglobulin Test

Magrolimab may interfere with RBC phenotyping due to expected coating of the RBC membrane. Due to the risk of developing anemia, and because magrolimab may make phenotyping difficult, ABO/Rh type, antibody screen, blood phenotyping or genotyping, and DAT need to be performed at screening before exposure to magrolimab, as described in Section 7.8.1.1.

RBC phenotyping/genotyping, ABO type and DAT need not be repeated if results dated before screening are available. Antibody screen need not be repeated if results dated before screening are available unless the patient was transfused since that time.

6.3. Treatment Assessments

On study treatment assessments include evaluations of safety (Section 6.4) efficacy (Section 6.5), PROs (Section 6.6), PK (Section 6.7), immunogenicity (Section 6.8), and pharmacodynamics and biomarkers (Section 6.9). The schedule for on-treatment assessments is provided in Appendix Table 2.

6.4. Safety Assessments

Safety will be evaluated by incidence of AEs, assessment of clinical laboratory test findings (chemistry, hematology, urinalysis), physical examination, 12-lead electrocardiogram, vital signs measurements, and other assessments as presented in Appendix 2.

6.4.1. Adverse Events

At each visit, all AEs observed by the investigator or reported by the patient that occur after the first dose of study treatment through 70 days after the last dose of study treatment are to be reported using the applicable eCRF (Section 7.1.1). Full details on the definitions, assessment and reporting instructions for AEs are provided in Section 7.

6.4.2. Laboratory Assessments

Analytes and tests to be assessed by the local laboratory or specialty laboratories during treatment are presented in Table 23. Refer to Section 7.8.1.1 for hemoglobin testing requirements predose and postdose monitoring for the first 2 magrolimab doses.

Table 23. Laboratory Analyte Listing (to be Performed During Treatment)

Chemistry (Serum or Plasma)	Hematology	Urinalysis	Other Laboratory Measurements
Sodium	Red blood cell	Red blood cell	Pregnancy test (urine)
Potassium	Hemoglobin	Glucose	C-reactive protein (CRP)
Calcium	Platelets	Protein	Pharmacokinetics
Chloride	WBC differential	Urine pH	Serum free light chain (SFLC)
Bicarbonate	Absolute neutrophil count	Ketones	Serum protein electrophoresis (SPEP)
Albumin	Lymphocytes	Bilirubin	24-hour urine protein electrophoresis (UPEP)
Glucose	Reticulocytes	Urine specific gravity	Serum immunofixation (SIFE)
BUN or urea	Haptoglobin		Urine immunofixation (UIFE)
Creatinine			β2-microglobulin and quantitative Ig levels
Uric acid			Antidrug antibodies
Total bilirubin			Receptor occupancy[a]
Direct bilirubin			Peripheral blood smear
Indirect bilirubin			
Lactate dehydrogenase			
AST			
ALT			
Alkaline phosphatase			

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Ig = immunoglobulin; WBC = white blood cell

a Receptor occupancy samples will be collected at selected sites *(as of Protocol Amendment 6, this assessment is not required)*.

6.4.3. Vital Signs

Vital signs should include heart rate, respiratory rate, oxygen saturation, blood pressure, temperature, and weight. Height should be recorded during screening only. Weight should be recorded during screening, on Day 1 of each cycle, and Day 1 and Day 15 for Cycles 3 and up. Vital signs are to be recorded prior to infusion of magrolimab at the visits specified in the schedules of assessments in Appendix 2.

6.4.4. Physical Examination

Complete physical examination should be performed at screening. Thereafter, symptom-directed physical examinations are acceptable and may also include routine examination of the skin (including fingers, toes, and ears) and neurologic system. A comprehensive peripheral neurological exam will be performed for patients receiving bortezomib.

6.4.5. Pregnancy Test

Pregnancy tests are required only for female patients of childbearing potential. Note that a woman is considered to be of childbearing potential following the initiation of puberty (Tanner Stage 2) until becoming postmenopausal, unless permanently sterile or with medically documented ovarian failure. Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female patient of any age. Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of < 54 years with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy. A negative serum pregnancy test is required at screening, and a negative urine pregnancy test is required prior to study treatment administration on Cycle 1 Day 1. The Cycle 1 Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was performed within the 72 hours before study treatment administration. Pregnancy tests will also be required at Day 1 of each subsequent cycle. For patients in the cohort receiving magrolimab in combination with pomalidomide and dexamethasone, the first test should be performed within 10 to 14 days and the second test within 24 hours prior to prescribing pomalidomide therapy and then weekly during the first month. The test should then be performed monthly thereafter in females with regular menstrual cycles, or every 2 weeks in females with irregular menstrual cycles. For further details, refer to Appendix 4.

6.4.6. Performance Status

Performance status will be scored using the ECOG performance status scale index (Appendix 7).

6.4.7. 12-lead Electrocardiogram

A 12-lead ECG will be performed at screening, at Cycle 1, and every other cycle after Cycle 1.

6.4.8. Echocardiogram

All patients will have a baseline transthoracic ECHO (TTE) during screening, including assessments of systolic and diastolic left ventricular function and right ventricular function. Screening ECHO may be done within 30 days prior to enrollment, if performed as a part of standard of care. A MUGA scan is also allowed in lieu of ECHO.

6.4.9. Prior and Concomitant Medications

All concomitant medications taken by the patient while on study are to be documented. All prior and concomitant medications, including all prescription, over-the-counter, herbal supplements, and IV medications and fluids received within 30 days prior to signing the informed consent through the 70-day safety follow-up visit should be recorded in the eCRF. Note that any anticancer therapies after the study treatment period should also be collected per the schedule of assessments (Appendix Table 3).

6.4.10. Peripheral Blood Smear Assessment

Peripheral smears should be collected per the schedule of assessments and assessed for standard cell morphology. These samples should be collected from the arm contralateral to the arm being used for drug infusion/injection, if possible. All other observed findings should be reported according to local laboratory hematopathology standard procedures. Peripheral smears will be assessed locally (see also Section 7.8).

6.5. Efficacy Assessments

Efficacy will be determined using response criteria based on the IMWG 2016 criteria (Appendix 6). Efficacy assessments will be done in conjunction with bone marrow assessments, according to the schedule of assessments on Day 1 of Cycle 2 onward (Appendix Table 2).

Disease response and progression assessments include: SPEP, UPEP, SFLC, SIFE, and UIFE (Section 6.5.1), tumor response and MM disease assessment (Section 6.5.2), PD assessment (Section 6.5.3), bone marrow assessment (Section 6.5.4), MRD assessment (Section 6.5.5), bone lesion assessment (Section 6.5.5), and plasmacytoma evaluation (Section 6.5.7).

6.5.1. Laboratory Assessments for Multiple Myeloma – Serum Protein Electrophoresis, Urine Protein Electrophoresis, Serum Free Light Chain, Serum Immunofixation, and Urine Immunofixation

Serum protein electrophoresis, UPEP, SFLC, SIFE, and UIFE will be conducted at a central or local laboratory (based on investigator preference) during screening and subsequently every 28 ± 7 days (starting from Cycle 1 Day 1) irrespective of cycle duration including dose delays and treatment discontinuation.

1) Serum: SPEP for M protein quantification, total serum protein, SIFE, and quantitative immunoglobulin assay.

    a) SIFE is required at baseline and at suspected CR regardless of whether measurable M-protein was present at baseline

    b) SIFE will also be performed at suspected disease progression or relapse from CR

c) Patients with measurable disease in SPEP will be assessed for response based on SPEP and will not require SIFE routinely

d) All other serum tests will be followed at each tumor assessment

2) Urine: 24-hour urine collection for UPEP, urinary light chains, and UIFE. Twenty-four-hour urine must be collected with each cycle for all patients.

a) UIFE is required at baseline and to confirm CR, regardless of whether measurable M-protein was present at baseline

b) UIFE will also be performed at suspected disease progression or relapse from CR

c) Patients with measurable disease in UPEP will be assessed for response based on UPEP and will not require UIFE routinely

d) All other urine tests will be followed at each tumor assessment

e) Urine M-protein is not needed to document PR or minimal response (MR) if baseline urine M-protein was not measurable; however, it is still required for CR and VGPR.

3) Serum free light chain:

a) Patients without measurable serum M-protein (ie, < 0.5 g/dL) or urine M-protein (ie, < 200 mg/24 hours) and considered oligosecretory must have SFLC assessed at each cycle until progression

b) Patients with measurable disease in both SPEP and UPEP will be assessed for response based on these 2 tests and not by the SFLC assay

c) Serum must be collected at screening and time of SIFE and UIFE negativity to confirm CR and be sent to the central lab for SFLC analysis. This measurement is required to assess for sCR.

During each cycle, blood will be obtained for SFLC, SPEP, and SIFE and 24-hour urine samples will be obtained for UPEP and UIFE. Results for SPEP, UPEP, or SFLC must be available at screening and before enrollment. SPEP, UPEP, and SFLC will be repeated on Cycle 1 Day 1 (unless screening values are within 14 days of Cycle 1 Day 1). For IgA and IgD myelomas, quantitative immunoglobulin measurements are preferred for disease assessments; the same percentage changes apply as for serum M-spike.

6.5.2. Tumor Response and Multiple Myeloma Disease Assessment

Investigator evaluation of disease response assessments will be based on central or local laboratory data (for SPEP, UPEP, SIFE, UIFE and SLFC) obtained every 28 ± 7 days until confirmed PD irrespective of cycle duration, including dose delays and treatment discontinuation. Where indicated, bone marrow samples (biopsy and/or aspirate; Section 6.5.4), bone lesion assessment (Section 6.5.5), and plasmacytoma evaluation (Section 6.5.7) will be analyzed and read locally.

Patients will be evaluated for disease response and progression according to the IMWG 2016 response criteria in Appendix 6. Disease status categories include sCR, CR, VGPR, PR, MR, SD, and PD.

The following considerations should be given to response assessments:

- All response categories require 2 consecutive assessments made at any time before initiation of any new therapy. Two consecutive readings of the applicable disease parameter (SPEP, UPEP, or SFLC), performed at any time (no minimum interval is required, it can be done the same day) are required; however, to confirm response or PD, 2 discrete samples are required; testing cannot be based upon the splitting of a single sample.

- All categories also require no known evidence of progression, including new bone lesions, if radiographic studies were performed.

- Confirmation of CR or sCR requires bone marrow assessment (aspirate or biopsy); bone marrow assessments do not need to be repeated for confirmation.

- Extramedullary plasmacytoma evaluation (if present at screening) (refer to Section 6.5.7)

- Whenever more than 1 parameter is used to assess response, the overall assigned level of response is determined by the lower or lowest level of response.

- Patients should be categorized as SD until they meet criteria for any response category or have documented PD.

- Patients will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status; patients cannot move to a lower response category.

- If alternate therapy is started before confirming PD any additional testing during subsequent therapy can be used to confirm PD.

- The lowest confirmed value before suspected progression will be used as baseline for calculation of progression; if a serum and/or urine spike is considered too low to quantitate, this value can be assigned as zero as a baseline for documentation of subsequent PD.

- Any soft tissue plasmacytoma documented at baseline must undergo serial monitoring; otherwise, the patient is classified as not evaluable.

- In patients with 2 M-protein bands at the start of therapy, the sum of the 2 spikes should be used for monitoring of disease.

- Careful attention should be given to new positive immunofixation results appearing in patients who have achieved a CR, when the isotype is different, it probably represents oligoclonal immune reconstitution and should not be confused with relapse; these bands typically disappear over time.

For patients with daratumumab interference on SIFE, a second reflex assay using the anti-idiotype mAb will be used to label daratumumab migration on the immunofixation electrophoresis (IFE) {Kumar 2016}. Patients that meet all other IMWG 2016 criteria for CR (Appendix 6), and whose positive IFE is confirmed to be daratumumab, will be considered complete responders. Similarly, for patients with magrolimab interference on SIFE, a second reflex assay using the anti-idiotype mAb rhCD47 may be used to mitigate this effect. As daratumumab and magrolimab are monoclonal IgG kappa antibodies, additional serum samples may be utilized to monitor for potential interference with the IFE.

6.5.3. Progressive Disease Assessment

Confirmation of PD using 2 consecutive assessments will be required per the IMWG 2016 criteria. The assessments outlined in Appendix 6 are required for PD. Patients will be considered to have PD if they meet the criteria for progression by a variable that was not considered measurable at baseline; however, for patients who had a measurable serum or urine M-spike at baseline, progression cannot be defined by increases in SFLC alone.

6.5.4. Bone Marrow Assessments

Bone marrow assessments (including aspirate and core/trephine biopsy specimens) are required for response assessments (for the confirmation of CR and sCR; refer to Section 6.5.2), including conventional cytogenetic analysis per local institutional standards at each time point according to the schedules of assessments in Appendix 2.

CCI [redacted] Details for preparation and distribution of aspirate and biopsy/trephine specimens to the testing laboratories will be provided in the laboratory manual for this study.

Priority of samples for bone marrow aspirate testing will be as follows:

1) Response assessment (including PD)

2) Other clinical reasons (which may take priority over MRD)

3) MRD assessment

4) Other biomarkers/genomic research *(as of Protocol Amendment 6, these assessments are not required)*

A bone marrow sample (aspirate slides and/or biopsy) will be obtained at the following time points:

5) A baseline bone marrow sample (aspirate and biopsy) will be obtained within 14 days prior to the first dose (baseline) on Cycle 1 Day 1 and will be used to quantify the percent (%) of myeloma cell involvement. A bone marrow sample obtained as standard of care may be used as baseline if taken within 45 days prior to enrollment and are sent to the central laboratory for processing. If a fresh aspirate and/or biopsy is obtained, in addition to baseline assessment of myeloma involvement, it will also be made available for biomarker studies.

6) Within 7 days prior to Cycle 2 Day 1 (before dose) for first response assessment and for biomarker studies.

7) From Cycle 3 onwards, it will be repeated as clinically indicated at suspected CR or sCR, and to confirm CR or sCR. A sample obtained at either suspected or confirmed CR/sCR will also be made available for MRD assessment.

6.5.5. Minimal Residual Disease

Sequencing-based assays can identify MM cells to a frequency of below 1×10^{-5} of total WBCs. These rare myeloma cells are termed MRD, and their presence or absence following treatment is an independent prognostic factor for disease progression and relapse in all MM treatment paradigms.

Minimal residual disease in bone marrow is a biomarker measurement in this study. MRD will be measured by a next-generation sequencing (NGS)-based assay at multiple time points to further understand the efficacy and MOA of magrolimab combinations. For each screened, consenting patient, bone marrow aspirates will be collected before the first dose, within 7 days prior to Cycle 2 Day 1, at Cycle 12 (± 2 weeks), and at suspected CR. The bone marrow aspirates will be processed and stored according to a protocol that is provided to the central lab. The samples will be analyzed centrally by the NGS-based MRD assay.

6.5.6. Skeletal Survey

Skeletal survey will include lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri. Low-dose whole body CT or fluorodeoxyglucose-PET/CT may be used in place of the skeletal survey. Bone lesion assessment (all patients) will be conducted at screening (may be within 30 days prior to enrollment) and will be repeated if worsening clinical symptoms suggest PD or as clinically indicated (development of compression fracture does not exclude response). The same method of assessment used at baseline will be used throughout the study. These imaging studies will be read locally. The number and location of skeletal lesions and whether they are lytic should be recorded on the eCRF. An on-treatment survey should record whether there is an increase in the number or size of lytic lesions.

6.5.7. Extramedullary Plasmacytoma Assessment

Extramedullary plasmacytoma evaluation will be conducted at screening in all patients. The evaluation may be done within 30 days prior to enrollment if performed as a part of standard of care. If an extramedullary plasmacytoma is detected, evaluation will be repeated during treatment to confirm a response of SD or better, or to confirm PD or as clinically indicated. Assessment of measurable sites of extramedullary disease will be performed and evaluated locally every cycle (by physical examination) for patients with plasmacytomas or as clinically indicated during treatment for other patients until confirmed CR or confirmed disease progression. In addition, radiological evaluation of extramedullary plasmacytomas will be conducted every 12 weeks (or every 3 cycles) in patients with radiological evidence of extramedullary plasmacytoma at baseline. The same technique, which may include CT (with or without PET) or MRI should be employed for each measurement of plasmacytoma dimensions as clinically appropriate (Appendix 6). A plasmacytoma that has been radiated is not suitable for response assessment; however, it must be monitored to assess for PD.

A sum of the products of the longest diameters and longest perpendicular diameter for all measurable lesions will be calculated at screening. This sum will be used as the reference for on-study assessments by which to characterize the objective tumor response. All tumor measurements must be made in millimeters. All documented measurable and nonmeasurable lesions are to be followed throughout the study. All assessments to be used for tumor response evaluation, including the baseline assessment, must be performed using the same method for repeat assessment.

Measurable disease are lesions that can be accurately measured in 2 dimensions and both diameters must be ≥ 20 mm when evaluated by standard CT scanning or ≥ 10 mm when evaluated by spiral CT scanning or MRI. The minimum diameter size should be at least twice the slice thickness.

Nonmeasurable disease are all other lesions (or sites of disease), including those that are too small (ie, do not meet above criteria), occur within a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion (exception for effusions documented by cytology as not malignant or present at baseline without progression), lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques, and cystic lesions.

Bidimensional lesion measurements must be performed and recorded in the designated eCRF.

6.6. Patient-Reported Outcome Assessments

6.6.1. FACT-MM Questionnaire

Health-related quality of life (QOL) and potential for improvement over the course of the study will be assessed by the FACT-MM PRO questionnaire specific to the MM patient population {Facit.org 2009}. The FACT-MM consists of 41 questions (items) and reports on a 5-point Likert-type scale on physical well-being, social/family well-being, emotional well-being, functional well-being, MM subscale (Appendix 9). The recall period is 7 days (past 7 days) and will take approximately 15 minutes to complete.

The QOL questionnaire should be completed preferably before patients undergo any study-related procedures, including other study-related evaluations, discussions with medical personnel, physician and study treatment administration.

As of Protocol Amendment 6, the FACT-MM assessment is not required.

6.7. Pharmacokinetic Assessments

Magrolimab serum concentration will be measured by a validated enzyme-linked immunosorbent assay (ELISA) immunoassay method.

Blood samples for PK assessment will be collected before dosing at multiple time points according to the schedule of assessments in Appendix 2. CCI [redacted] CCI [redacted]

6.8. Immunogenicity

Peripheral blood for immunogenicity assessments for ADA against magrolimab will be collected as described in the schedule of assessments in Appendix 2 in all patients. When collected on the day of study drug dosing, the ADA blood sample must be collected at the same time as the pre-dose PK sample. The presence of anti-magrolimab antibodies will be determined by a validated immunoassay method.

Serum from venous blood samples collected from patients receiving daratumumab will be assessed for the generation of antibodies to daratumumab. Daratumumab concentration is also evaluated at all immunogenicity time points to ensure appropriate interpretation of immunogenicity data. When both serum concentration and immunogenicity analyses are specified, they are performed on aliquots from the same blood draw and no additional sampling is required. Procedures for sample collection, preparation, identification, storage, and shipment will be provided in the laboratory manual or equivalent document.

A blood sample should be drawn, if possible, for determination of antibodies to daratumumab any time an infusion reaction is observed or reported during the study.

Daratumumab serum concentration will also be determined from the same infusion reaction sample for the purpose of interpreting immunogenicity data.

6.9. Pharmacodynamic and Biomarker Assessments

Biomarker samples will be collected to assess the pharmacodynamic, MOA, and treatment response biomarkers, and to define correlates of clinical efficacy and/or safety, as outlined in Section 3.8. Pharmacodynamic and biomarker assessments will be conducted as indicated in Appendix 2.

For additional details and instructions regarding sample requirements and procedures for sample collection, storage, and shipment, refer to the study laboratory manual.

As of Protocol Amendment 6, biomarker assessments are not required.

6.9.1. Analyses of Peripheral Blood

Whole blood will be collected from participating patients at screening, Cycle 1 Day 15, Cycle 3 Day 1, and Cycle 6 Day 1 to explore the relationship between serum- and plasma-based biomarkers and patient response to treatment. Plasma collected at study start will be analyzed by ELISA for the determination of biomarkers including, but not limited to, soluble CD38 protein.

6.9.2. Cancer Mutation Profiles and Mutation Burden

The pathogenesis of all cancers, including MM, has a basis in their acquired genetic mutations. The particular genetic mutations present in a patient's cancer may render it sensitive or resistant to anticancer therapies, including magrolimab-based combinations. In some cases, if strongly associated with clinical benefit or the MOA of a drug, these genetic mutations can be used to select patients who are eligible for a given treatment. In other cases, the total number of mutations present in the genome of a given cancer (eg, rather than the specific genes mutated) can correlate with likelihood of response, such as is the case with some T cell checkpoint therapies. The myeloma cells in this study will be assessed by whole genome sequencing (WGS) at multiple time points before and after treatment, and the data will be compared to WGS of normal cells, in order to identify cancer-specific mutations and to understand the efficacy profile and the MOA for magrolimab across different genetic subtypes. Clonal evolution of MM cells will also be tracked while on treatment and at the time of relapse, in order to understand mechanism of resistance to magrolimab combinations.

6.9.3. Changes in Immune Effector Cell Composition

Magrolimab is an immunotherapy, which exerts its anticancer effects through modulation of the patient's immune cells. Nonclinical evidence suggests that magrolimab can induce macrophages to attack cancer cells, and that it can enhance cross-presentation of cancer neoantigens to adaptive immune cells, including T cells. Activation of the immune system can be associated with changes in immune cell frequency or localization to the tumor

microenvironment. In order to explore changes in the composition of immune cells as both pharmacodynamic biomarker and to inform MOA, MM patients in this study will be assessed by methods including, but not limited to, multiplex immunofluorescence and single cell RNA sequencing at multiple time points before and after treatment.

6.9.4. Changes in Immune Effector Cell Signaling Molecules

Activation of the immune system can be associated with changes in expression or secretion of immune-regulatory molecules, including cytokines, chemokines, and others. Release of such molecules, and their concentration in the peripheral blood or tumor microenvironment, may serve as both pharmacodynamic biomarker and can inform MOA. MM patients in this study will be assessed for soluble protein factors in the peripheral plasma and/or bone marrow by methods potentially including, but not limited to, multiplex ELISA or aptamer-based measurement.

6.9.5. Expression of Prophagocytic and Antiphagocytic Signals by Cancer Cells

Nonclinical studies suggest that the efficacy of magrolimab depends on the balance of pro- and antiphagocytic signals expressed by cancer cells. Magrolimab combination therapies, including those investigated as part of this clinical study, may derive their efficacy from the simultaneous blockade of antiphagocytic signals by magrolimab, and the increased expression of prophagocytic signals by the companion drug. In order to better define the efficacy and MOA of magrolimab combinations in MM, the surface profile of known pro- and antiphagocytic signals will be assessed on cancer cells at multiple time points before and after treatment using methods that include, but not limited to, flow cytometry and multiplex immunofluorescence.

6.10. Posttreatment Assessments

Posttreatment assessments are presented in Appendix Table 3.

Patients who discontinue study treatment are to return for an EOT visit for evaluation of safety within 7 days of their last dose or the decision to end study treatment. In addition, patients are to have a safety follow-up telephone call 70 days (± 7 days) after their last dose of study treatment. When an SAE or treatment-related AE is reported during the telephone call, the patient should come to the clinic for physical examination and blood tests, if clinically needed. Follow-up for ongoing SAEs or treatment-related AEs after the safety follow-up visit/call will stop if a patient begins another anticancer therapy. Pregnancy tests will continue at monthly intervals until end of contraception requirements outlined in Appendix 4. Testing may be done at home and the result self-reported by the patient.

6.11. End of Study

All Patients: The end of the entire study for all patients is defined as the date on which the last patient remaining on study completes the last study visit/call or when the sponsor decides to end the study. The sponsor reserves the right to terminate the study at any time for any reason (including safety).

Individual Patients: Patients are considered to have completed study participation altogether when they are no longer followed for safety.

6.12. Poststudy Care

Upon withdrawal from study treatment, patients will receive the care upon which they and their physicians agree. Patients will be followed for AEs until the end of study as specified in Appendix Table 3.

6.13. Sample Storage

The stored biological samples may be used by Gilead or its research partner for CCI [redacted]. CCI [redacted]. If patients provide additional specific consent, residual PK samples may be destroyed no later than 15 years after the end of study or per country requirements.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study patient administered a study drug that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. AEs may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.3).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (Section 7.1.3)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented as medical history.
- Preexisting events that increase in severity or change in nature after study drug initiation or as a consequence of participation in the clinical study will also be considered AEs.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death
- A life-threatening situation (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: Such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.1.2.1. Protocol-Specific Adverse Event/Serious Adverse Event Clarifications

Given the primary and secondary endpoints of the study, in order to maintain study integrity, the following events that are assessed as unrelated to study drug will not be considered AEs/SAEs:

- Progression of MM
- Deaths related to progression of MM

Events that are considered to represent progression of the underlying MM should not be recorded as AEs/SAEs. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE/SAE.

Death that is attributed by the investigator as solely due to progression of MM and that occurs during the protocol-specified AE reporting period should be recorded only on the Death eCRF (ie, not collected as an SAE or an AE on the AE eCRF).

7.1.2.1.1. Deaths Not Related to Progression of Multiple Myeloma

All other deaths (ie, deaths that are not due to MM progression) occurring during the protocol-specified AE reporting period, regardless of attribution, will be recorded on the AE eCRF and reported within 24 hours of awareness and no later than the next business day.

When recording a death on the eCRF, the event or condition that is considered the primary cause of death should be the AE term, and the outcome should be fatal. A patient can only have 1 AE (SAE) with outcome of death and severity of CTCAE Grade 5.

7.1.3. Study Drugs and Gilead Concomitant Therapy Special Situations Reports

Special situation reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit or falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of a study drug while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a patient.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the reference USPI, SmPC, or applicable local or regional label.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively that is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the patient in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the patient has taken the excess dose(s). Overdose cannot be established when the patient cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the patient has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead study drug.

Counterfeit or falsified medicine is defined as any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes**: There is reasonable possibility that the AE may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.

- **Yes:** The AE occurred as a result of protocol procedures (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the NCI CTCAE Version 5.0. For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale (Appendix 5).

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study medication, the following types of events must be reported on the applicable eCRFs: all SAEs and AEs related to protocol-mandated procedures.

7.3.2. Adverse Events

Following initiation of study medication, all AEs, regardless of cause or relationship, will be collected until 70 days after last administration of study drug and reported on the eCRFs as instructed.

All AEs should be followed up until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the patient first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported on the applicable eCRFs and to Gilead PS as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the ICF is signed.

Any SAEs and deaths that occur after the posttreatment follow-up visit but within 70 days of the last dose of study drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if the investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to Gilead PS.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead PS (Section 7.4.2). AEs and SAEs resulting from SSRs must be reported in accordance to the AE and SAE reporting guidance (Section 7.4).

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situation reports involving a Gilead concomitant therapy (not considered study drug), that occurs after the patient first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead PS utilizing the paper SSR form (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Therapy Report

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situation Reports

7.4.1. Serious Adverse Event Reporting Process

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal patient identification, maintaining the traceability of a document to the patient identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the patient's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

- Site personnel will record all SAE data on the applicable eCRFs and from there transmit the SAE information to Gilead PS within 24 hours of the investigator's knowledge of the event from ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

- If it is not possible to record and transmit the SAE information electronically, record the SAE on the paper SAE reporting form and transmit within 24 hours:

  Gilead PS
  Email: Safety_fc@gilead.com
  or
  Fax: 1-650-522-5477

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to Gilead PS.

7.4.2. Special Situations Reporting Process

7.4.2.1. Paper Special Situations Reporting Process for Study Drug

- All SSRs will be recorded on the special situations report form and transmitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead PS from study drug initiation throughout the duration of the study, including the protocol required posttreatment follow-up period.

Gilead PS
Email: Safety_fc@gilead.com
or
Fax: 1-650-522-5477

7.4.2.2. Reporting Process for Gilead Concomitant Medications

- Special situations that involve concomitant medications manufactured by Gilead that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to Gilead PS utilizing the paper SSR form to:

Gilead PS
Email: Safety_fc@gilead.com
or
Fax: 1-650-522-5477

- Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

- Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs due to a non-Gilead concomitant medication, must be reported as an AE.

7.4.2.3. Pregnancy Reporting Process

- The investigator should report pregnancies in female patients who are identified after initiation of study drug and throughout the study, including the poststudy drug follow-up period, to Gilead PS using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Contact details for transmitting the pregnancy report form are as follows:

Gilead PS
Email: Safety_fc@gilead.com
or
Fax: 1-650-522-5477

- The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.
- All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.
- A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome after study must be reported to the Gilead PS.

- The patient should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy should be reported to Gilead PS using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PS. Gilead PS contact information is as follows: email: Safety_FC@gilead.com and fax: +1 (650) 522-5477.

- Refer to Appendix 4 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs which may be in the form of line-listings, serious adverse drug reactions, or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local or regional label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the NCI CTCAE Version 5.0. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.7. Abnormal Liver Function Tests

Liver toxicity will be evaluated for all patients.

In the absence of an explanation for increased liver function tests, such as viral hepatitis, preexisting or acute liver disease, or exposure to other agents associated with liver injury, the patient may be discontinued from the study treatment if the investigator determines that it is not in the patient's best interest to continue. Discontinuation of treatment should be considered if there is an indication of severe liver injury according to Hy's Law, defined by FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation {U.S. Department of Health & Human Services (DHHS) 2009}, as follows:

- Treatment-emergent ALT or AST elevation (≥ 3 × ULN), AND
- Treatment-emergent total bilirubin elevation (> 2 × ULN), and absence of cholestasis (defined as alkaline phosphatase < 2 × ULN), AND
- No other good explanation for the injury (hepatitis A, B, C, or other viral hepatic injury, alcohol ingestion, congestive heart failure, worsening liver metastases).

7.8. Toxicity Management

7.8.1. Magrolimab

7.8.1.1. Anemia, Blood Cross-matching, and Packed Red Blood Cell Transfusion Procedures

Magrolimab binds to RBCs and leads to erythrophagocytosis. CD47 is a member of the Rh complex in the RBCs membrane. Therefore, when magrolimab binds to CD47, it is likely to interfere with routine blood bank tests needed in case of transfusion. Notify blood transfusion centers/blood banks of this interference with blood bank testing and inform them that a patient will receive magrolimab.

In clinical studies, anemia is the most common treatment-related AE and is typically manifested as a decline in hemoglobin of about 0.5 g/dL to 1.5 g/dL observed in the first 1 to 2 weeks of treatment. This decrease in hemoglobin level is acceptable in patients with no other significant diseases or medical conditions. However, for patients with significant diseases or medical conditions, such as unstable angina, ischemic heart disease, or uncontrolled diabetes mellitus, treatment-related anemia could be life-threatening or fatal. Significant drops (up to 3 g/dL) have been observed in early doses.

Within 24 hours prior to each of the first 2 doses of magrolimab infusion during initial treatment, *all patients* must have a documented hemoglobin ≥ 9 g/dL. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet 9 g/dL prior to each of the first 2 doses of magrolimab.

Patients with a low baseline hemoglobin level, especially those with cardiac history or risk factors, must be monitored closely after initial administrations of magrolimab as preexisting anemia could be exacerbated. Red blood cell transfusions are permitted prior to study treatment to ensure adequate hemoglobin level as per investigator's clinical judgment. The need for RBC transfusions and anemia from other causes in patients with cancer, means that care has to be taken with RBC cross-matching and packed RBC transfusions.

Prior to initiation of magrolimab, ABO/Rh type, antibody screen, DAT, and extended RBC phenotyping (minor antigens such as CcDEe, Cw, MNSs, Kk, FyaFyb, and JkaJkb) will be performed for each patient. RBC genotyping instead of extended RBC phenotyping is acceptable for any patient. RBC genotyping (instead of an extended RBC phenotyping) must be performed if a patient received any RBC or whole blood transfusion within the previous 3months (unless laboratory has availability for special techniques for performing phenotyping for patients with recent transfusion). Results must be available before the first dose of magrolimab.

For patients after exposure to magrolimab:

An additional hemoglobin must be checked 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment. The patient should be transfused as clinically appropriate. Investigators should consider additional hemoglobin monitoring during the first week of treatment in patients with symptoms of anemia or at increased risk for complications of anemia.

For all elective RBC and platelet transfusions, use leukocyte-reduced and gamma-irradiated units per institutional guidelines.

For RBC transfusions, phenotype/genotype matched units are preferred. However, CMV-seronegative units for CMV-seronegative patients will not be required for this study.

In case ABO/Rh type cannot be resolved, use pretreatment (historical) phenotype/genotype matched units for minor RBC antigens (CcDEe and Kk, to the feasible extent). Regarding the ABO type, institution can use historical blood group or O type as per the institutional guidelines.

For emergency transfusions, the transfusion centers may consider using emergency Group O red cells if phenotype/genotype matched units are not available.

Whenever possible, blood plasma therapy should be blood type specific. Platelets should be blood type compatible whenever possible and, if not, should have been tested and found not to have high titer anti-A or anti-B. Otherwise, plasma and platelet products can be provided as per the institutional policy.

A recent report has suggested that cross-match interference by RBCs due to treatment with magrolimab may be resolved by use of gamma-clone anti-IgG and multiple alloadsorptions with papain-treated RBC samples, pooled single donor apheresis platelets or commercial H.P.C product if required {Troughton 2018, Velliquette 2019}.

Blood components for transfusion

- For all elective RBC transfusions, leukocyte-reduced units matched for the phenotype of the patients (as described above) will be used. Where exact matching for all the specified blood groups proves impractical (eg, for MNS blood group), local sites will decide on the best matched donor units to be used. Cytomegalovirus (CMV) matching (ie, CMV-seronegative units for CMV-seronegative patients) will not be required for this study because it will limit the inventory for antigen matching.

- If the cross-match is incompatible, the RBC units that are Coombs cross-match-incompatible will be selected (eg, phenotype-matched or least incompatible) for issue at the discretion of the local site's transfusion service medical director or equivalent person, where available.

- For emergency transfusions, the transfusion laboratory may consider using emergency Group O Rh negative units if phenotyped units are not available.

- Blood plasma therapy will be blood type specific. Platelets will be blood type compatible whenever possible and, if not, will have been tested and found not to have high titer anti-A or anti-B.

- A recent report has suggested that cross-match interference by RBCs due to treatment with magrolimab may be resolved by use of multiple alloadsorptions with papain-treated cells or pooled platelets {Velliquette 2019}. This strategy can be considered.

7.8.1.2. Management of Infusion-related Reactions

Infusion-related reactions are defined by the NCI CTCAE, Version 5.0 (under the category "General disorders and administration site conditions") as "a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances" (Appendix 5). For the purposes of this study, the time frame for IRR assessment is the 24-hour period beginning from the start of the infusion. Premedication use described in Section 5.3.1 will be used to manage IRRs pre-emptively.

Recommendations for the management of IRRs are provided in Table 24:

Table 24. Management of Infusion-Related Reactions

Infusion-related Reactions	
CTCAE Grade	**Management**
Grade 1 Mild transient reaction.	Remain at bedside and monitor patient until recovery from symptoms. Patients who experience IRRs with the first 4 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion.
Grade 2 Requiring symptomatic treatment and prophylactic medications for ≤ 24 hours.	Interrupt magrolimab therapy per protocol and begin an IV infusion of normal saline and consider treating the patient with diphenhydramine 50 mg IV (or equivalent) and/or 500 to 750 mg of oral acetaminophen. Remain at bedside and monitor patient until resolution of symptoms. Corticosteroid therapy may also be given at the discretion of the investigator. If the infusion is interrupted, wait until symptoms resolve, then restart the infusion at 50% of the original infusion rate. If no further complications occur after 1 hour (± 10 minutes), the rate may be increased to 100% of the original infusion rate. Monitor the patient closely. If symptoms recur, stop infusion and disconnect patient from the infusion apparatus. No further magrolimab will be administered at that visit. Patients who experience IRRs with the first 4 doses of magrolimab should continue premedication with corticosteroids prior to subsequent doses at the investigator's discretion. The amount of magrolimab infused must be recorded on the eCRF. Patients who experience a Grade 2 IRR during the postinfusion observation period that does not resolve to ≤ Grade 1 during that time should be observed until the AE resolves or stabilizes, with vital sign measurements as medically indicated for the management of the AE.
Grade 3-4 Grade 3: Prolonged reactions or recurrence of symptoms following initial improvement, or where hospitalization is indicated for other clinical sequelae. Grade 4: Life-threatening consequences, where urgent intervention is indicated.	Immediately discontinue infusion of magrolimab. Begin an IV infusion of normal saline, and consider treating the patient as follows: administer bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for SC administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. The patient should be monitored until the investigator is comfortable that the symptoms will not recur. Patients who experience Grade 3 IRRs must be given premedication prior to subsequent doses. In this setting, premedication with oral acetaminophen (650 to 1000 mg), oral or IV diphenhydramine (25 to 50 mg), and IV dexamethasone (4 to 20 mg), or a comparable regimen, is recommended for the subsequent 2 doses. Continued premedication with corticosteroids beyond these 2 doses may be administered at the discretion of the treating physician. Patients who receive premedication and still experience a recurrent Grade 3 IRR or patients who experience a Grade 4 IRR at any time should be permanently discontinued from the study treatment. For anaphylaxis, investigators should follow their institutional guidelines for treatment. All patients with a Grade 3 or higher IRR will be observed until the AE resolves or stabilizes, with vital sign measurements and additional evaluations as medically indicated for the management of the AE.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic case report form; IRR = infusion-related reaction; IV = intravenous; SC = subcutaneous

7.8.1.3. Thromboembolic Events

Thromboembolic events, including deep vein thromboses and pulmonary embolisms, have been reported in some patients receiving magrolimab, sometimes early in therapy. Available data for magrolimab do not support a clear or consistent relationship between clinical thromboembolic events and magrolimab use. Patients should be closely monitored for the symptoms of thromboembolic events and treated accordingly.

7.8.1.4. Severe Neutropenia

Severe neutropenia and febrile neutropenia have been reported in patients treated with magrolimab. Close monitoring of hematologic parameters (Appendix Table 2) including neutrophils is required for all patients treated with magrolimab. Prophylactic antibiotics and/or antimycotics should be considered. Administer G-CSF if clinically indicated.

Recommendations for magrolimab dose delay in case of severe neutropenia:

- For Grade 3 neutropenia without fever or infection, delay of magrolimab dosing is not recommended.
- For Grade 4 neutropenia (ANC < 500/μL) without fever or infection, or Grade 3 or higher neutropenia with fever or infection, magrolimab dose delay should be considered. Upon resolution to Grade ≤ 2, resuming magrolimab at the same dose should be considered.
- For persistent severe neutropenia or febrile neutropenia (> 2 occurrences), discontinuation of magrolimab can be considered.

7.8.1.5. Serious Infections

Patients (with or without neutropenia) should be regularly monitored for signs and symptoms of infection. For patients with prolonged neutropenia or patients at risk, consider infection prophylaxis including antibiotics (eg, fluoroquinolone) or antifungal agents (eg, oral triazoles or parenteral echinocandin) in accordance with current guidelines.

For serious infections, hold magrolimab until the infection has resolved clinically. For serious infections that remain active for ≥ 14 days, consider discontinuation of magrolimab.

7.8.1.6. Management of Pneumonitis

Pneumonitis has been infrequently observed in patients receiving magrolimab. Generally, immune-related AEs have not been observed in clinical use with magrolimab. In contrast to T-cell checkpoint inhibitors, magrolimab primarily exerts its antitumor efficacy through macrophage-mediated phagocytosis of tumor cells. Nonspecific T-cell or other host immune responses that are seen with T-cell checkpoint inhibitors have not been observed with magrolimab in nonclinical studies. Additionally, no events of macrophage activation syndrome or hemophagocytic lymphohistiocytosis have been reported in clinical studies.

In instances of suspected pneumonitis, first rule out noninflammatory causes (eg, infections). If a noninflammatory cause is identified, treat accordingly and continue therapy per protocol. Evaluate with imaging (eg, chest x-ray or computed tomography) and pulmonary consultation.

Management of potential pneumonitis is detailed in Table 25 and follows the American Society of Clinical Oncology (ASCO) guidelines for immune-related AEs {Brahmer 2018}. Patients who experience Grade 3-4 pneumonitis will be permanently discontinued from study treatment.

Table 25. Pneumonitis Management Algorithm

Pneumonitis		
CTCAE Grade of Pneumonitis	**Management**	**Follow-Up**
Grade 1 Radiographic changes (CXR or CT) only.	Monitor for signs and symptoms weekly and consider monitoring with CXR. Consider pulmonary and infectious disease consults.	Consider reimaging with CT in 3-4 weeks as clinically indicated. May resume magrolimab with radiographic evidence of improvement or resolution. If no clinical improvement or worsening, treat as Grade 2.
Grade 2 Mild to moderate new symptoms.	Interrupt magrolimab therapy per protocol. Pulmonary and infectious disease consults. Consider empirical antibiotics. Monitor signs and symptoms every 2-3 days; consider hospitalization. 1 mg/kg/day oral prednisone or IV equivalent. Consider bronchoscopy, lung biopsy.	Re-image every 1-3 days. If improving to baseline, taper corticosteroids over 4-6 weeks and resume magrolimab therapy per protocol. If no clinical improvement after 48-72 hours or worsening, treat as Grade 3-4.
Grade 3-4 Severe new symptoms; new/worsening hypoxia; life-threatening.	Discontinue magrolimab therapy. Hospitalize. Pulmonary and infectious disease consults. 1-2 mg/kg/day methylprednisolone IV or IV equivalent. Add empirical antibiotics and consider prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy.	If improving to baseline, taper corticosteroids over 4-6 weeks. If no clinical improvement after 48 hours or worsening, consider additional immunosuppression (eg, infliximab, cyclophosphamide, IV immunoglobulin, mycophenolate mofetil).

CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; CXR = chest x-ray; IV = intravenous.

7.8.1.7. Management of Other Nonhematologic Adverse Events

Magrolimab will be permanently discontinued in patients who experience any Grade 4 nonhematologic AEs related to magrolimab that do not improve to Grade 2 or pretreatment baseline levels within 14 days. Magrolimab will also be permanently discontinued in patients with Grade 4 hemolytic anemia which is defined as anemia with clinical and/or laboratory evidence of hemolysis with life-threatening consequences and/or urgent interventions are indicated. For dose delay criteria, magrolimab may be withheld if treatment-emergent and/or magrolimab-related AEs occur, which include all AEs that constitute a DLT, as defined in Section 3.1.1 of the protocol. Magrolimab may be reintroduced if the severity has recovered to Grade 2 or pretreatment baseline levels with the approval by the medical monitor.

7.8.2. Daratumumab

Management of Infusion-related Reactions

Both systemic and administration-related reactions, including severe of life-threatening reactions and local injection-site reactions can occur with both IV and SC formulations of daratumumab. Severe reactions included hypoxia, dyspnea, hypertension and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension {DARZALEX 2020, DARZALEX FASPRO 2020}.

- Monitoring: signs and symptoms for systemic administration-related reactions, especially following first and second infusions/injections.
  - For Grades 1, 2, or 3: the infusion rate should be reduced when restarting the infusion (for IV formulations).
  - For Grade 4 (anaphylactic reaction or other life-threatening reaction): immediately and permanently discontinue daratumumab.
  - Consider administering corticosteroids and other medications after the administration of daratumumab depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.
  - For local reactions: the most frequent (> 1%) injection-site reaction was injection-site erythema. These local reactions occurred a median of 7 minutes (range: 0 minutes to 4.7 days) after starting administration of daratumumab. Monitor for local reactions and consider symptomatic management.

7.8.3. Pomalidomide

Refer to the reference USPI, SmPC, or applicable local or regional label for instructions on monitoring, toxicity management, and potential drug interactions during administration of pomalidomide.

7.8.4. Carfilzomib

Refer to the reference USPI, SmPC, or applicable local or regional label for instructions on monitoring, toxicity management, and potential drug interactions during administration of carfilzomib.

7.8.5. Bortezomib

Refer to the reference USPI, SmPC, or applicable local or regional label for instructions on monitoring, toxicity management, and potential drug interactions during administration of bortezomib.

Monitoring and Dose Adjustment for Peripheral Neuropathy

Bortezomib treatment causes a peripheral neuropathy that is predominantly sensory. However, cases of severe sensory and motor peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including ≥ Grade 3) during treatment with bortezomib {VELCADE 2019}.

Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require change in the dose and schedule of bortezomib.

Following dose adjustments, improvement in or resolution of peripheral neuropathy was reported in 51% of patients with ≥ Grade 2 peripheral neuropathy in the relapsed MM study. Improvement in or resolution of peripheral neuropathy was reported in 73% of patients who discontinued due to Grade 2 neuropathy or who had ≥ Grade 3 peripheral neuropathy in the Phase 2 MM studies. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

7.8.6. Dexamethasone

Refer to the reference USPI, SmPC, or applicable local or regional label for instructions on monitoring and toxicity management following administration of dexamethasone.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Study Objectives

The study objectives and endpoints are provided in Section 2. Additional details are provided in Sections 8.1.2, 8.1.3, and 8.1.4.

8.1.2. Primary Endpoints

The primary endpoint for the safety run-in cohorts is as follows:

- Incidence of DLTs, AEs and laboratory abnormalities according to the NCI CTCAE Version 5.0 (Appendix 5).

The primary endpoint for the dose-expansion cohorts is as follows:

- Objective response rate, defined as the percentage of patients who achieve sCR, CR, VGPR, or PR

8.1.3. Secondary Endpoints for Dose-expansion Cohorts

The secondary endpoints are as follows:

- Incidence of AEs and laboratory abnormalities according to the NCI CTCAE Version 5.0 (Appendix 5).
- Duration of response: DOR is measured from the earliest date of sCR, CR, VGPR, or PR, whichever is first recorded, until the earliest date of documented PD, documented relapse, or death from any cause, whichever occurs first. Those who are not observed to have documented relapse, documented PD, or death will be censored at the date of their last response assessment.
- Magrolimab concentration versus time
- Measurements of ADA against magrolimab

CCI [redacted]

[redacted]

[redacted]

8.2. Planned Analyses

The final analysis will be performed after all patients have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Efficacy

The primary analysis set for efficacy analysis is the Full Analysis Set (FAS). The FAS includes all enrolled patients who took at least 1 dose of study treatment with treatment group designated according to the planned treatment assigned at enrollment.

8.3.1.2. Safety

The primary analysis set for safety analyses is the Safety Analysis Set. It includes all patients who took at least 1 dose of study treatment with treatment group designated according to the actual treatment received. This analysis set will be used in the analyses of safety endpoints as well as study treatment administration. All data collected during treatment up to 70 days after treatment discontinuation will be included in the safety summaries.

The DLT-Evaluable Analysis Set includes all patients in the Safety Analysis Set who are enrolled in the safety run-in cohorts and fulfill either of the following criteria:

- Experienced a DLT after initiation of the first infusion of magrolimab during the DLT assessment period (Section 3.1.1)
- Completed DLT assessment period and received at least 3 infusions of magrolimab and the following cohort-specific criteria:
  - Magrolimab in combination with daratumumab cohort: Completed at least 2 doses of daratumumab
  - Magrolimab in combination with pomalidomide and dexamethasone cohort: Completed at least 10 doses of pomalidomide and 2 doses of dexamethasone
  - Magrolimab in combination with carfilzomib and dexamethasone cohort: Completed at least 2 doses of carfilzomib and 2 doses of dexamethasone
  - Magrolimab in combination with bortezomib and dexamethasone cohort: Completed at least 2 doses of bortezomib and 2 doses of dexamethasone

The recommended dose for the expansion cohorts will be based on the DLT-Evaluable Analysis Set.

8.3.1.3. Pharmacokinetics

The PK Analysis Set includes all enrolled patients who received at least 1 dose of magrolimab and have at least 1 measurable posttreatment serum concentration of magrolimab.

8.3.1.4. Immunogenicity

The Immunogenicity Analysis Set includes all enrolled patients who received at least 1 dose of magrolimab and have at least 1 evaluable anti-magrolimab antibody test result.

8.3.1.5. Biomarker

The Biomarker Analysis Set includes all enrolled patients who received at least 1 dose of magrolimab and have the evaluable baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

8.3.1.6. Demographic and Baseline Characteristics

The All Enrolled Analysis Set includes all patients who received a study patient identification number in the study after screening. This will be the primary analysis set for analyses of patient demographic and baseline characteristics, enrollment, and disposition.

8.3.2. Data Handling Conventions

By-patient listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in analysis set), n (number with data), mean, standard deviation, 95% CIs for the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 95% CIs for the percentage. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided. Data will be described and summarized by treatment cohort.

The baseline value used in each analysis will be the last (most recent) pretreatment value before or on the first dosing date of study treatment. As appropriate, changes from baseline to each subsequent time point will be described and summarized. Similarly, as appropriate, the maximum change from baseline during the study will also be described and summarized. Graphical techniques (ie, waterfall plots, Kaplan-Meier [KM] curves, line plots) may be used when such methods are appropriate and informative. Analyses will be based on observed data unless methods for handling missing data are specified. If there is a significant degree of nonnormality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods. Demographic summaries will include sex, race/ethnicity, and age. Baseline data will include a summary of body weight, height, body mass index, ECOG performance status, and MM status.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

For the primary efficacy endpoint ORR, the point estimate and the corresponding 2-sided exact 95% CI using Clopper-Pearson method will be provided for each cohort. Objective response rate will also be tested against the historical control rate of 25% using 1-group Chi-square test for each cohort separately.

8.5.2. Secondary Analyses

The medians, first quartile (Q1), and third quartile (Q3) of DOR will be estimated using the KM method along with the corresponding 95% CIs, respectively. KM curves will be provided. For DOR, the analysis will include only patients who achieve objective response.

CCI [redacted]

[redacted].

8.6. Safety Analysis

All safety data collected on or after the date that any drug in a study treatment regimen was first administered up to the date of the last dose of any drug in a study treatment regimen plus 70 days will be summarized by treatment cohort based on the Safety Analysis Set. Dose-limiting toxicities will be summarized based on the DLT-Evaluable Set for safety run-in cohorts. Data for the pretreatment will be included in data listings. For categorical safety data, including incidence of AEs and categorizations of laboratory data, the number and percentage of patients will be summarized. For continuous safety data, including laboratory data, the number of patients, mean, standard deviation, minimum, quartiles, median, and maximum will be summarized.

8.6.1. Extent of Exposure

A patient's extent of exposure to study drug data will be generated from the study drug administration data. Exposure data will be summarized for each drug separately by treatment cohort.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the MedDRA. System organ class, high-level group term, high-level term, preferred term, and lower-level term will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of any study drug up to the date of last dose of any study drug plus 70 days.

Summaries (number and percentage of patients) of treatment-emergent AEs (by system organ class, and preferred term) will be provided by treatment cohort.

AEs that occurred before exposure to study treatment will be reported in data listings and appropriately identified as nontreatment-emergent AEs

8.6.3. Laboratory Evaluations

Selected laboratory data (using conventional units) will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme in Appendix 5.

Incidence of treatment-emergent laboratory abnormalities, defined as posttreatment results that increase at least 1 toxicity grade from baseline to the date of last dose of any study drug plus 70 days, will be summarized by treatment cohort. If baseline data are missing, then any graded abnormality (ie, at least Grade 1) will be considered a treatment-emergent abnormality.

Laboratory abnormalities that occur before the first dose of any study drug or 70 days after the last dose of any study drug will be included in a data listing.

8.6.4. Other Safety Evaluations

Vital signs and physical examination findings will be summarized at select time points. Details will be provided in the statistical analysis plan.

8.7. Pharmacokinetic Analysis

The PK Analysis Set will be used for summaries of PK concentration of magrolimab versus time. Due to the sparse nature of PK collection, PK parameters will not be calculated.

Summary statistics will be presented for magrolimab serum concentrations at each scheduled time point. Descriptive graphical plots of individual serum concentration versus time profiles and mean concentration versus time profiles will be generated.

Missing concentration values will be reported as is in data listings. Concentration values below lower limit of quantitation will be handled as zero in summary statistics and reported as is in data listings.

All data from this study may be combined with PK data from other Gilead clinical studies and analyzed using a population PK model. Such an analysis would be reported separately.

8.8. Immunogenicity Analysis

Immunogenicity will be assessed using a 3-tier—screen, confirmatory, and titer—approach on study samples using a validated immunoassay. The rate and magnitude of anti-magrolimab antibody incidence, prevalence, persistence, and transience will be summarized for the Immunogenicity Analysis Set. Titer summaries may also be generated, if relevant. CCI [redacted].

8.9. Sample Size

For each of the dose-expansion cohorts, a sample size of 30 (24 expansion patients together with the 6 patients from the safety run-in cohort), provides 86.1% power for a 1-group Chi-square test at a 1-sided alpha of 0.1 to detect an ORR of $\geq$ 45% for the combination treatment compared with a historical control ORR of 25%.

The historical control ORR of 25% is based on outcomes from the MAMMOTH study; the subset of patients treated with any daratumumab-containing regimen, including daratumumab in combination with an IMiD or PI, following at least 1 prior treatment {Gandhi 2019}.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the International Council for Harmonisation (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Gilead or proprietary interests in the study drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last patient completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study patient activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the patient after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study patients.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved ICF for documenting written informed consent. Each ICF (or assent as applicable) will be appropriately signed and dated by the patient or the patient's legally authorized representative, the person conducting the consent discussion, and an impartial witness (if required by IRB or IEC or local requirements).

The ICF will inform patients about genomic testing and/or planned sample retention. In addition to the study-specific ICF to be signed by each patient participating in the study, patients will be required to document agreement to provide additional samples or to allow the use of the remainder of their already-collected specimens for CCI [redacted], in accordance with applicable regulations. In addition to the study-specific ICF to be signed by each patient participating in the study, patients will be required to document agreement to provide additional samples for CCI [redacted]. The results of the tests done on the samples will not be given to the patient or the investigator.

9.1.5. Confidentiality

The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB/IEC, or the laboratory. Laboratory specimens must be labeled in such a way as to protect patient identity while allowing the results to be recorded to the proper patient. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log with details for all patients screened and enrolled in the study, in accordance with the site procedures and regulations. Patient data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, case report forms (CRFs)/eCRFs, study drug information, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Case Report Forms

For each patient consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the electronic data capture (EDC) system. The eCRF casebook will only capture the data required per the protocol schedules of events and procedures. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the CRF Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or Gilead staff who routinely review the data for completeness, correctness, and consistency. The site investigator or site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. At a minimum, prior to any interim time

points or database lock (as instructed by Gilead), the investigator will use his/her login credentials to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.7.

9.1.7. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, CRFs/eCRFs, IRB/IEC and governmental approval with correspondence, the ICF, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each patient:

- Patient identification
- Documentation that patient meets eligibility criteria, ie, medical history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented patient is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medication (start and end date; dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the patient, appropriate copies should be made for storage away from the site.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications may be made only by the sponsor.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) when applicable and in accordance with local regulatory requirements. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases. For studies with sites in countries following the EU Regulation No. 536/2014, a CSR will be submitted within 1 year (6 months for pediatric studies, in accordance with Regulation [EC] No. 1901/2006) after the global end of study (as defined in Section 6.11).

Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Gilead clinical trial agreement.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries in the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on-site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the patients, appropriate regulatory authority, IRB, and IEC. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the patients' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGMENT

A Phase 2 Multi-Arm Study of Magrolimab Combinations in Patients With Relapsed/Refractory Multiple Myeloma

GS-US-558-5915 Protocol Amendment 6; 02 November 2023

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD	*[See appended electronic signature]*
Name (Printed) Medical Monitor	Signature
[See appended electronic signature]	
Date	

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)	Signature
Date	Site Number

Appendix 2. Schedules of Assessments

Appendix Table 1. Schedule of Assessments – Screening

	Study
Assessment	**Day −30 to −1**
Informed Consent[a]	X
Demographics	X
Medical History, Including MM History	X
Bone Marrow Sample[b]	X
Myeloma Frailty Score Calculation (Patients ≥ 65 Years of Age)[c]	X
ECOG Performance Status	X
Vital Signs, Height, and Weight[d]	X
Complete Physical Examination	X
Peripheral Neurological Examination for Residual Neuropathy (Patients Enrolling onto Bortezomib Cohort)[e]	X
12-lead ECG	X
Echocardiogram/MUGA Scan	X
Serum or Plasma Chemistry[f]	X
Hematology[f]	X
Urinalysis[f]	X
Pregnancy Test[g]	X
Blood Phenotyping or genotyping for minor antigens, Type, and Screen (ABO/Rh), DAT	X
Serum Protein Electrophoresis (SPEP)	X
24-Hour Urine Protein Electrophoresis (UPEP)	X
Serum Free Light Chain (SFLC)	X
Serum Immunofixation (SIFE)	X
Urine Immunofixation (UIFE)	X
β2-microglobulin and Quantitative Ig Levels	X
Hepatitis B, Hepatitis C, and HIV	X
C-Reactive Protein (CRP)	X
Skeletal Survey	X
CT (± PET) or MRI Assessment for Extramedullary Soft Tissue Plasmacytoma	X
SAEs and AEs Related to Protocol-mandated Procedures	X
Prior and Concomitant Medications	X

ABO = any of the 4 blood groups A, B, AB, and O comprising the ABO system; AE = adverse events; CT = computed tomography; DAT = direct antiglobulin test; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FSH = follicle-stimulating hormone; Ig = immunoglobin; MM = multiple myeloma; MRI = magnetic resonance imaging; MUGA = multigated acquisition (scan); PET = positron emission tomography; Rh = Rhesus factor; SAE =serious adverse events

a Screening must be completed prior to enrollment. Enrollment must occur within 30 days of signing informed consent.

b A baseline bone marrow sample (aspirate slides and biopsy) will be obtained within 14 days prior to first dose (baseline) on Cycle 1 Day 1 and will be used to quantify the percent of myeloma cell involvement. A bone marrow sample obtained as standard of care may be used as baseline if taken within 45 days prior to enrollment and are sent to the central laboratory for processing.
c This is applicable to patients ≥ 65 years of age (Appendix 10).
d Height should be recorded during screening only.
e Patients should be assessed for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness.
f Specific analytes listed in Table 22.
g Serum pregnancy test will be conducted at screening. Screening pregnancy test may be used as the Cycle 1 Day 1 test if performed within 72 hours of first dose; additional guidance is provided in Section 6.4.5. For patients in the cohort receiving magrolimab in combination with pomalidomide and dexamethasone, the first test should be performed within 10 to 14 days and the second test within 24 hours prior to prescribing pomalidomide therapy. FSH test is required for female patients who are < 54 years old who are not on hormonal contraception and who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure.

Appendix Table 2. Schedule of Assessments – Treatment Period

	Cycle 1 lasts for 35 days; all other Cycles last for 28 days																
	1[a]					2				3				4+			
Visit Window (Days)	None		± 3[b]			± 3[b]				± 3[b]				± 3[b]			
Cycle Day	**1**	**8**	**15**	**22**	**29**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Serum or Plasma Chemistry[b]	X	X	X			X		X		X		X		X		X	
Hematology[b]	X[aa]	X[aa]	X			X	X	X		X		X		X		X	
Haptoglobin	X	X				X											
Peripheral smear	X	X	X														
Urinalysis[b]	X	X	X			X		X		X		X		X		X	
Pregnancy Test[c]	X					X				X				X			
C-Reactive Protein (CRP)						X				X				X			
Antidrug Antibodies[b]	X					X				X				X[d]			
Pharmacokinetics[e]	X			X		X				X				X[d]			
Serum Protein Electrophoresis (SPEP)						X				X				X			
24-Hour Urine Protein Electrophoresis (UPEP)						X				X				X			
Serum Free Light Chain (SFLC)						X				X				X			
β2-microglobulin and Quantitative Ig Levels[f]														X			
Serum Immunofixation (SIFE)[g]						X				X				X			
Urine Immunofixation (UIFE)[h]						X				X				X			
Skeletal Survey						X[i]											
Buccal Swab[j]	X																

	Cycle 1 lasts for 35 days; all other Cycles last for 28 days																
	1[a]					2				3				4+			
Visit Window (Days)	None		± 3[b]			± 3[b]				± 3[b]				± 3[b]			
Cycle Day	**1**	**8**	**15**	**22**	**29**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Bone Marrow Sample[k]						X											
IMWG Response Assessment						X				X				X			
MRD Assessment[l]														X			
CT (± PET) or MRI Assessment for Extramedullary Soft Tissue Plasmacytoma[m]														X			
Vital Signs[n]	X	X	X	X	X	X	X	X		X		X		X		X	
12-lead ECG[o]	X									X				X[o]			
Symptom-directed Physical Examination	X	X	X			X				X				X			
Peripheral Neurological Examination (Bortezomib Cohort)[p]	X	X	X	X		X	X	X	X	X		X		X		X	
ECOG Performance Status	X	X	X			X				X				X			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Premedication for Magrolimab[q]	X	X	X	X													
Magrolimab[r]	X[y]	X[y]	X	X	X	X	X	X	X	X		X		X		X	
Daratumumab[s] IV or SC[t]		X	X	X	X	X	X	X	X	X		X		X		X	
Pomalidomide[t]	Days 1 to 21					Days 1 to 21				Days 1 to 21				Days 1 to 21			
Carfilzomib IV[t,u]		X	X	X		X	X	X		X	X	X		X	X	X	
Bortezomib SC or IV[t,v]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Cycle 1 lasts for 35 days; all other Cycles last for 28 days																
	1[a]					2				3				4+			
Visit Window (Days)	None		± 3[b]			± 3[b]				± 3[b]				± 3[b]			
Cycle Day	**1**	**8**	**15**	**22**	**29**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Dexamethasone[w,x]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; Ig = immunoglobulin; IV = intravenous; IMWG = International Myeloma Working Group; MRD = minimal residual disease; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; PD = progressive disease; PET = positron emission tomography; PRO = patient-reported outcome; SC = subcutaneous; sCR = stringent complete response; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis

a In cases of magrolimab repriming following a treatment delay (Section 5.4.1), efficacy, biomarker, PK, and immunogenicity assessments should follow the schedule of the assigned cycle number. Magrolimab dosing and the safety assessment must follow Cycle 1, and then subsequently switch back to the next assigned cycle schedule. Magrolimab should not be given on consecutive days. Refer to footnote (t) for premedication requirement.

b Pretreatment assessments are to be collected within 24 hours prior to any study treatment administration for assessments listed in Appendix Table 1; specific analytes for serum or plasma chemistry, hematology, and urinalysis are listed in Table 23

c Urine pregnancy test. Screening pregnancy test may be used if performed within 72 hours of first dose; pregnancy tests will be conducted on Day 1 of every cycle; additional guidance is provided in Section 6.4.5. For patients in the cohort receiving magrolimab in combination with pomalidomide and dexamethasone, the first test should be performed within 10 to 14 days and the second test within 24 hours prior to prescribing pomalidomide therapy, and then weekly during the first month, then monthly thereafter in females with regular menstrual cycles, or every 2 weeks in females with irregular menstrual cycles.

d Should be collected Cycle 5 Day 1, Cycle 7 Day 1, Cycle 10 Day 1, and Cycle 13 Day 1.

e Samples will be collected within 72 hours before the first dose of magrolimab and within 12 hours before subsequent doses of magrolimab.

f To be performed for patients with IgA and IgD myelomas and when clinically indicated eg, recurrent infections.

g Serum immunofixation is performed if SPEP shows no measurable protein, at suspected CR and at suspected PD.

h Urine immunofixation is performed if UPEP shows no measurable protein and at suspected CR.

i Skeletal survey will be repeated if worsening clinical symptoms suggest PD or as clinically indicated.

j Buccal swab sample collected from enrolled patient before or at Cycle 1 Day 1, predose. If the sample is missed, it can be taken later on in the study.

k Bone marrow samples will be obtained within 14 days prior to the first dose (baseline) on Cycle 1 Day 1 and within 7 days prior to Cycle 2 Day 1 (before dose). From Cycle 3 onwards, it will be repeated as clinically indicated for response assessment at suspected CR or sCR and to confirm CR or sCR. A sample obtained at either suspected or confirmed CR/sCR may also be made available for MRD assessment.

l Only in patients with suspected or confirmed CR or sCR and during specific landmark analyses – refer to Section 6.5.4.

m CT/MRI/CT-PET for extramedullary soft tissue plasmacytoma is performed every 12 weeks or every 3 cycles starting from Cycle 4 Day 1 for patients who were found to have extramedullary soft tissue plasmacytoma at screening/baseline.

n Vital signs prior to infusion/injection of any study treatment. Weight at Day 1 of each cycle, and Day 1 and 15 for Cycles 3 and up. Details are provided in Section 6.4.3.

o 12-lead ECGs will be performed at Cycle 1, and every other cycle thereafter (Cycle 3, Cycle 5 etc.).

p Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness.

q Premedication with acetaminophen, diphenhydramine, and corticosteroids is required prior to the administration of the first 4 doses of study treatment and in case of reintroduction with repriming.

r Monitor patients for 1-hour after infusion during Cycle 1.

s Daratumumab can be given as IV or SC during Days 8, 15, 22 and 29 of Cycle 1, Days 1, 8, 15 and 22 of Cycle 2, Days 1 and 15 from Cycle 3 through to Cycle 6 and then Cycle 7 onwards Day 1 of each cycle.
t Daratumumab, pomalidomide, carfilzomib and bortezomib are only given to patients assigned to the individual cohorts for these drugs.
u 20 mg/m^2 on Cycle 1 Day 8 and 70 mg/m^2 for all subsequent doses.
v Bortezomib is given on Days 8, 15, 22, and 29 during Cycle 1 and Days 1, 8, 15, and 22 during subsequent cycles. The maximum number of cycles is 8 in patients who have previously received bortezomib; SC is preferred over IV, where feasible.
w For carfilzomib and bortezomib cohorts only, given weekly until Cycle 9 and then Days 1, 8, and 15 from Cycle 10 onwards.
x Dexamethasone is administered to patients in the pomalidomide, carfilzomib, and bortezomib cohorts as part of myeloma treatment and may be administered in the daratumumab cohort as part of pre- and/or postmedication. Refer to each cohort-specific dosing for dexamethasone.
y Within 24 hours prior to each of the first 2 doses of magrolimab infusion during initial treatment, all patients must have a documented hemoglobin ≥ 9 g/dL. Patients who do not meet these criteria must be transfused and have their hemoglobin rechecked to meet 9 g/dL prior to each of the first 2 doses of magrolimab. An additional hemoglobin must be checked 3 to 6 hours after the initiation of the first and second doses of magrolimab during initial treatment (as described in Section 7.8.1.1).

Appendix Table 3. Schedule of Assessments – Posttreatment

	EOT Visit	Safety Follow-up Visit/Call (Telephone)[a]
	Within 7 Days After Last Dose or EOT Decision	70 Days After Last Dose
Visit Window	**± 7 Days**	**± 7 Days**
Serum or Urine Pregnancy Test	Q4W[b] →	→
CBC with Differential, Platelet Count, Reticulocytes	X	
Serum or Plasma Chemistry	X	
Pharmacokinetics	X	
Antidrug Antibodies	X	
CCI [redacted]	CCI [redacted]	
Serum Protein Electrophoresis	X	
24-Hour Urine Protein Electrophoresis (UPEP)	X	
Serum Free Light Chain (SFLC)	X	
Serum Immunofixation (SIFE)	X	
Urine Immunofixation (UIFE)	X	
β2-microglobulin and Quantitative Ig Levels	X	
Skeletal Survey	X	
Vital Signs	X	
Symptom Driven Physical Examination	X	
ECOG Performance Status	X	
IMWG Response Assessment[c]	X	
Minimal Residual Disease Assessment[d]	X	

	EOT Visit	Safety Follow-up Visit/Call (Telephone)[a]
	Within 7 Days After Last Dose or EOT Decision	70 Days After Last Dose
Visit Window	**± 7 Days**	**± 7 Days**
CT (± PET) or MRI Assessment of Extramedullary Soft Tissue Plasmacytoma[e]	X	
Adverse Events[f]	X	X
Concomitant Medications	X	X
New Anticancer Therapy[g]	X	X

AE = adverse event; CBC = complete blood count; CR = complete response; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; Ig = immunoglobulin; IMWG = International Myeloma Working Group; MRI = magnetic resonance imaging; PET = positron emission tomography; Q4W = every 4 weeks; SAE = serious adverse event.

a If the patient experiences a treatment-related AE or an SAE (regardless of attribution), the patient must be asked to come to the site.
b Pregnancy tests should be taken at monthly intervals until end of contraception requirement.
c Response assessment at EOT visit not required if performed within the last 30 days or progressive disease has been documented.
d In patients with suspected or confirmed CR only.
e Only in patients who were found to have extramedullary soft tissue plasmacytoma at screening/baseline or during the study.
f Report all AEs through the safety follow-up visit/call, and any treatment-related SAEs thereafter.
g Collect new anticancer therapy data following the last dose of study treatment.

Appendix 3. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with patients being unable to attend study visits have been identified for this study.

These potential risks and mitigation plans can be summarized as follows:

1) Schedule of assessments:

    a) Physical examination:

        i) In order to limit a patient's time in the clinic, a virtual visit may be conducted for the physical examination assessment. Vital signs may be omitted. However, dosing and biological sample collection should occur per protocol in the clinic.

    b) Dosing:

        i) Patients may be unable to return to the site for a number of visits to receive the study drug, or the site may be unable to accept any patient visits. Without study drugs, the patient would not be able to stay on the study drug as planned per protocol.

        Mitigation plan: If permitted by local regulations and ethics committee (EC)/institutional review boards (IRBs), combination agents (ie, daratumumab, carfilzomib, or bortezomib) may be administered at a clinic closer to the patient, under the supervision of a physician specializing in the treatment of multiple myeloma (MM) provided that all facilities for managing infusion-related reactions, anaphylaxis and other acute emergencies are available. If necessary, a dosing delay for magrolimab must be discussed with the sponsor in this instance. A virtual study visit, via phone or video conferencing, must be performed prior to remote dosing. At the earliest opportunity, the site will schedule in person patient visits and return to the protocol's regular schedule of assessments. A qualified courier may be considered to ship the drug from sites to the alternate clinic.

    c) General patient selection guidance:

        i) To minimize patients receiving red blood cell transfusions, we recommend selecting patients with higher hemoglobin thresholds at baseline and use intravenous iron and/or erythropoietin where clinically indicated.

2) Study drug supplies to patients and sites:

    a) Patients may be unable to return to the site for a number of visits to get the study drug, or the site may be unable to accept any patient visits. Without study drugs, the patient would not be able to stay on the study drug as planned per protocol.

Mitigation plan: If permitted by local EC/IRB/regulatory authority as applicable, and with sponsor's approval, study drug supplies may be provided to the patient from the site without a clinic visit. It must be confirmed that the patient may safely continue on study drug as determined by the principal investigator. A virtual study visit, via phone or video conferencing, must be performed prior to remote study drug resupply. At the earliest opportunity, the site will schedule in-person patient visits and return to the protocol's regular schedule of assessments. A qualified courier may be utilized to ship the study drug from sites to study patients, and a qualified vendor may be utilized to perform infusions in the patients' local vicinity.

b) Shipments of study drug could be delayed from the sponsor to the investigational site because of transportation issues. Without study drug patient would not be able to stay on the study drug as planned per protocol.

Mitigation plan: The sites' study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and study sites. Manual shipments will be triggered as necessary.

3) Patient safety monitoring and follow-up:

a) Patients may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol.

Mitigation plan: For patients who may be unable or unwilling to visit the study site for their scheduled study visits as required per protocol, the principal investigator or qualified delegate will conduct a virtual study visit, via phone or video conferencing, to assess the patient within target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

i) Confirm if patient has experienced any AEs/SAEs/special situations (including pregnancy) and follow-up on any unresolved AE/SAEs.

ii) Review current list of concomitant medications and document any new concomitant medications.

iii) If applicable, confirm patients study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed it will be provided as described above in (2).

iv) If applicable, remind patient to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit.

b) Patients may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be analyzed at the site laboratory and/or sent for central laboratory analyses.

Mitigation plan: Accredited local laboratories that are not affiliated with the site may be utilized as appropriate to monitor patient safety until the patient can return to the site for their regular follow-up per protocol. Any laboratory assessments conducted at a local lab due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local lab pregnancy testing is not feasible. Alternative sample handling and storage may be possible for samples routinely sent to the central laboratory; sites should refer to the study laboratory manual and discuss with the sponsor for further guidance.

c) Patients may be unable or unwilling to attend the study visit to sign an updated ICF version if there is an update.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local EC/IRB and national laws and regulations. Remote consent will be allowed if has been approved by the local EC/IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

4) Protocol and monitoring compliance:

a) Protocol deviations may occur, in case scheduled visits cannot occur as planned per protocol.

Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed patient visits or deviation to the protocol due to the pandemic must be reported in the eCRF and described in the clinical study report. Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

b) Monitors may be unable to carry out source data review or source data verification, or study drug accountability or assess protocol and GCP compliance. This may lead to delays in source data verification, an increase in protocol deviations, or under-reporting of AEs.

Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or patients on site, must be tracked centrally and updated on a regular basis.

5) Missing data and data integrity:

    a) There may be an increased amount of missing data due to patients missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

    Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternative methods that will ensure the evaluation and assessment of the safety of patients who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of study drugs in study patients remains unchanged.

Appendix 4. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a) Definition of Childbearing Potential

For the purposes of this study, a female born patient is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal, unless the patient is permanently sterile or has medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of < 54 years of age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their FSH level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female patient of any age.

b) Definition of Male Fertility

For the purposes of this study, a male born patient is considered fertile after the initiation of puberty unless the patient is permanently sterile by bilateral orchidectomy or medical documentation.

2) Cohort Receiving Magrolimab in Combination With Daratumumab

a) Study Drug Effects on Pregnancy and Hormonal Contraception

Magrolimab is contraindicated in pregnancy as a higher incidence of total pregnancy loss has been observed in and embryo-fetal development toxicity study in cynomolgus monkeys and there is a strong suspicion of human fetotoxicity in early pregnancy based on the nonclinical data. For magrolimab, there is no anticipated PK interaction with progestin or other steroids based on the distinct clearance pathways.

Based on the MOA and findings in animal studies, daratumumab (DARZALEX® FASPRO and DARZALEX®) can cause fetal harm when administered to a pregnant woman {DARZALEX 2020, DARZALEX FASPRO 2020}. Due to the high affinity to a unique epitope on CD38, daratumumab is not anticipated to alter drug-metabolizing enzymes.

Refer to the latest version of the magrolimab IB for additional information. Refer to the reference USPI, SmPC, or applicable local or regional label for information on the potential risks of treatment with daratumumab.

b) Contraception Requirements for Female Patients of Childbearing Potential

The inclusion of female patients of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of < 1% per year. They must have a negative serum pregnancy test at screening and a negative pregnancy test is required prior to study treatment administration on Cycle 1 Day 1. The Cycle 1 Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was performed within 72 hours before study treatment administration. Pregnancy tests will be performed at the beginning of each cycle thereafter (described in the protocol) until the end of contraception requirement.

Duration of required contraception for female patients in this clinical study cohort should start from screening visit until 3 months after the last dose of the latest administered study drug.

Female patients must agree to 1 of the following contraceptive methods:

Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the patient's preferred and usual lifestyle.

Or

Consistent and correct use of 1 of the following methods of birth control listed below:

- Hormonal or nonhormonal intrauterine device (IUD)
- Subdermal contraceptive implant
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

Or

Female patients who wish to use a hormonally based method must use it in conjunction with a barrier method, preferably a male condom. Hormonal methods are restricted to those associated with the inhibition of ovulation. Hormonally based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods (each method must be used with a barrier method, preferably male condom)
  - — Oral contraceptives (either combined or progesterone only)
  - — Injectable progesterone
  - — Transdermal contraceptive patch
  - — Contraceptive vaginal ring

- Barrier methods (each method must be used with a hormonal method)
  - Male condom (with or without spermicide)
  - Female condom (with or without spermicide)
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Sponge with spermicide

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Female patients must also refrain from egg donation, cryopreservation of cells, and in vitro fertilization during treatment and until the end of contraception requirement. If needed, female patients should be advised to seek advice about egg donation and cryopreservation prior to treatment.

c) Contraception Requirements for Male Patients

Male patients with female partners of childbearing potential must use condoms during treatment and until 3 months after last dose of the latest administered study drug. If the female partner of childbearing potential is not pregnant, use of any locally approved contraceptive measure should also be considered.

Male patients must also refrain from sperm donation and cryopreservation of cells during treatment and until the end of contraception requirement. If needed, male patients should be advised to seek advice about sperm donation and cryopreservation prior to treatment.

d) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

e) Procedures to be Followed in the Event of Pregnancy

Female patients will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study to 3 months after last study drug dose. Study drug must be discontinued immediately. Male patients whose partner has become pregnant or suspects she is pregnant from the start of the study to 3 months after the last study drug dose must also report the information to the investigator.

Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.4.2.3.

3) Cohort Receiving Magrolimab in Combination With Pomalidomide and Dexamethasone

a) Study Drug Effects on Pregnancy and Hormonal Contraception

Magrolimab is contraindicated in pregnancy as a higher incidence of total pregnancy loss has been observed in and embryo-fetal development toxicity study in cynomolgus monkeys and there is a strong suspicion of human fetotoxicity in early pregnancy based on the nonclinical data. For magrolimab, there is no anticipated PK interaction with progestin or other steroids based on the distinct clearance pathways.

For magrolimab, there is no anticipated PK interaction with progestin or other steroids based on the distinct clearance pathways.

Based on the MOA and findings from animal studies, pomalidomide (POMALYST®) can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy {POMALYST 2020}. Advise females of reproductive potential that they must avoid pregnancy while taking pomalidomide. Based on findings in animals, female fertility may be compromised by treatment with pomalidomide. Pomalidomide does not inhibit or induce cytochrome P450 (CYP) enzymes or transporters in vitro.

Based on findings from clinical and animal reproduction studies, corticosteroids, including dexamethasone, can cause fetal harm when administered to a pregnant woman {DEXAMETHASONE 2015}. Coadministration of dexamethasone with contraceptives that are CYP3A4 substrates may decrease the concentration of these drugs. This may result in loss of efficacy of these drugs.

Refer to the latest version of the magrolimab IB for additional information.

Because of the embryo-fetal risk, pomalidomide is available only through a restricted program under a risk evaluation and mitigation strategy (REMS), the “POMALYST REMS” program in the US. Refer to the current prescribing information from the reference USPI, SmPC, or applicable local or regional label for information on the potential risks of treatment with pomalidomide and dexamethasone.

b) Contraception Requirements for Female Patients of Childbearing Potential

The inclusion of female patients of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of < 1% per year. Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10 to14 days and the second test within 24 hours prior to prescribing pomalidomide therapy. Tests should be performed weekly during the first month and monthly thereafter in females with regular menstrual cycles, or every 2 weeks in females with irregular menstrual cycles. Pregnancy tests will be performed at the beginning of each cycle (described in the protocol) until the end of contraception requirement.

Duration of required contraception for female patients in this clinical study cohort should start 4 weeks prior to initiating treatment, during therapy, during dose interruptions, and continuing until 3 months after the last dose of the latest administered study drug.

While taking pomalidomide, female patients must agree to 1 of the following contraceptive methods:

Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the patient's preferred and usual lifestyle.

Or

Consistent and correct use of 2 methods of birth control including 1 of the following:

- Nonhormonal IUD
- Hormonal IUD
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

And

- A barrier method
  - Male condom (with or without spermicide)
  - Female condom (with or without spermicide)
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Sponge with spermicide

The following hormonal methods may not be used during dexamethasone administration and for 4 weeks after the last dose of dexamethasone. If the patient continues on study, hormonal methods may be used 4 weeks after discontinuation of dexamethasone.

Female patients who wish to use a hormonally based method must use it in conjunction with a barrier method, preferably a male condom. Hormonal methods are restricted to those associated with the inhibition of ovulation. Hormonally based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods (each method must be used with a barrier method, preferably male condom)
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring
  - Subdermal contraceptive implant

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Female patients must also refrain from egg donation, cryopreservation of cells, and in vitro fertilization during treatment and until the end of contraception requirement. If needed, female patients should be advised to seek advice about egg donation and cryopreservation prior to treatment.

c) Contraception Requirements for Male Patients

Male patients with female partners of childbearing potential must use condoms during treatment and until 3 months after last dose of the latest administered study drug. If the female partner of childbearing potential is not pregnant, use of any locally approved contraceptive measure should also be considered.

Male patients must also refrain from sperm donation and cryopreservation of cells during treatment and until the end of contraception requirement. If needed, male patients should be advised to seek advice about sperm donation and cryopreservation prior to treatment.

d) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

e) Procedures to be Followed in the Event of Pregnancy

Female patients will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study to 3 months after the last study drug dose. Study drug must be discontinued immediately. Male patients whose partner has become pregnant or suspects she is pregnant from the start of study to 3 months after the last study drug dose must also report the information to the investigator.

Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.4.2.3.

4) Cohort Receiving Magrolimab in Combination With Carfilzomib and Dexamethasone

a) Study Drug Effects on Pregnancy and Hormonal Contraception

Magrolimab is contraindicated in pregnancy as a higher incidence of total pregnancy loss has been observed in and embryo-fetal development toxicity study in cynomolgus monkeys and there is a strong suspicion of human fetotoxicity in early pregnancy based on the nonclinical data. For magrolimab, there is no anticipated PK interaction with progestin or other steroids based on the distinct clearance pathways.

For magrolimab, there is no anticipated PK interaction with progestin or other steroids based on the distinct clearance pathways.

Carfilzomib (Kyprolis) is contraindicated in pregnancy as a malformative effect has been demonstrated/suspected or is unknown taking into consideration class effects or a strong suspicion of human teratogenicity/fetotoxicity in early pregnancy based on nonclinical data {KYPROLIS 2021}. Carfilzomib has demonstrated/suspected or has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. Therefore, hormonal contraception is not recommended as a contraceptive method either solely or as a part of a contraceptive regimen.

Based on findings from clinical and animal reproduction studies, corticosteroids, including dexamethasone, can cause fetal harm when administered to a pregnant woman {DEXAMETHASONE 2015}. Coadministration of dexamethasone with contraceptives that are CYP3A4 substrates may decrease the concentration of these drugs. This may result in loss of efficacy of these drugs.

Refer to the latest version of the magrolimab IB for additional information. Refer to the regional prescribing information from the reference USPI, SmPC, or applicable local or regional label for information on the potential risks of treatment with carfilzomib and dexamethasone.

b) Contraception Requirements for Female Patients of Childbearing Potential

The inclusion of female patients of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of < 1% per year. They must also not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at screening and a negative pregnancy test is required prior to study treatment administration on Cycle 1 Day 1. The Cycle 1 Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was performed within the 72 hours before study treatment administration. Pregnancy tests will be performed at the beginning of each cycle thereafter (described in the protocol) until the end of contraception requirement.

Duration of required contraception for female patients in this clinical study should start from the screening visit until 6 months after the last dose carfilzomib or 3 months after the last dose of magrolimab, whichever is later.

Female patients must agree to 1 of the following contraceptive methods:

Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the patient's preferred and usual lifestyle.

Or

Consistent and correct use of 1 of the following methods of birth control listed below:

- Nonhormonal IUD
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Female patients must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement.

c) Contraception Requirements for Male Patients

Male patients with female partners of childbearing potential must use condoms during treatment and until 3 months after the last dose of the latest administered study drug. If the female partner of childbearing potential is not pregnant, use of any locally approved contraceptive measure should also be considered.

Male patients must also refrain from sperm donation and cryopreservation of cells during treatment and until the end of contraception requirement. If needed, male patients should be advised to seek advice about sperm donation and cryopreservation prior to treatment.

d) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

e) Procedures to be Followed in the Event of Pregnancy

Female patients will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study to 6 months after the last dose of carfilzomib or 3 months after the last dose of magrolimab, whichever is later. Study drug must be discontinued immediately. Male patients whose partner has become pregnant or suspects she is pregnant from the start of study to 3 months after the last study drug dose must also report the information to the investigator.

Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.4.2.3.

5) Cohort Receiving Magrolimab in Combination With Bortezomib and Dexamethasone

a) Study Drug Effects on Pregnancy and Hormonal Contraception

Magrolimab is contraindicated in pregnancy as a higher incidence of total pregnancy loss has been observed in and embryo-fetal development toxicity study in cynomolgus monkeys and there is a strong suspicion of human fetotoxicity in early pregnancy based on the nonclinical data. For magrolimab, there is no anticipated PK interaction with progestin or other steroids based on the distinct clearance pathways.

For magrolimab, there is no anticipated PK interaction with progestin or other steroids based on the distinct clearance pathways.

Based on the MOA and findings in animals, bortezomib (VELCADE®) can cause fetal harm when administered to a pregnant woman {VELCADE 2019}. Based on the MOA and findings in animals, bortezomib may have an effect on female fertility. In vitro studies indicate that bortezomib is a weak inhibitor of the CYP isozymes 1A2, 2C9, 2C19, 2D6, and 3A4.

Based on findings from clinical and animal reproduction studies, corticosteroids, including dexamethasone, can cause fetal harm when administered to a pregnant woman {DEXAMETHASONE 2015}. Coadministration of dexamethasone with contraceptives that are CYP3A4 substrates may decrease the concentration of these drugs. This may result in loss of efficacy of these drugs.

Refer to the latest version of the magrolimab IB for additional information. Refer to the regional prescribing information from the reference USPI, SmPC, or applicable local or regional label for information on the potential risks of treatment with bortezomib and dexamethasone.

b) Contraception Requirements for Female Patients of Childbearing Potential

The inclusion of female patients of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of < 1% per year. They must have a negative serum pregnancy test at screening and a negative pregnancy test is required prior to study treatment administration on Cycle 1 Day 1. The Cycle 1 Day 1 pregnancy test does not need to be repeated if the screening pregnancy test was performed within the 72 hours before study treatment administration. Pregnancy tests will be performed at the beginning of each cycle thereafter (described in the protocol) until the end of contraception requirement.

Duration of required contraception for female patients in this clinical study should start from the screening visit until 7 months after the last dose bortezomib or 3 months after the last dose of magrolimab, whichever is later.

Female patients must agree to 1 of the following contraceptive methods:

Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the patient's preferred and usual lifestyle.

Or

Consistent and correct use of 1 of the following methods of birth control listed below:

- Nonhormonal IUD
- Hormonal IUD (must be used in conjunction with a barrier method)
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

The following hormonal methods may not be used during dexamethasone administration and for 4 weeks after the last dose of dexamethasone. If the patient continues on study, hormonal methods may be used 4 weeks after discontinuation of dexamethasone.

Female patients who wish to use a hormonally based method must use it in conjunction with a barrier method, preferably a male condom. Hormonal methods are restricted to those associated with the inhibition of ovulation. Hormonally based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods (each method must be used with a barrier method, preferably male condom)
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring
  - Subdermal contraceptive implant
- Barrier methods (each method must be used with a hormonal method)
  - Male condom (with or without spermicide)
  - Female condom (with or without spermicide)
  - Diaphragm with spermicide

- Cervical cap with spermicide
- Sponge with spermicide

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Female patients must also refrain from egg donation, cryopreservation of cells, and in vitro fertilization during treatment and until the end of contraception requirement. If needed, female patients should be advised to seek advice about egg donation and cryopreservation prior to treatment.

c) Contraception Requirements for Male Patients

Male patients with female partners of childbearing potential must use condoms during treatment and until 4 months after the last dose of the latest administered study drug. If the female partner of childbearing potential is not pregnant, use of any locally approved contraceptive measure should also be considered.

Male patients must also refrain from sperm donation and cryopreservation of cells during treatment and until the end of contraception requirement. If needed, male patients should be advised to seek advice about sperm donation and cryopreservation prior to treatment.

d) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

e) Procedures to be Followed in the Event of Pregnancy

Female patients will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study to 7 months after the last dose of bortezomib or 3 months after the last dose of magrolimab, whichever is later. Study drug must be discontinued immediately. Male patients whose partner has become pregnant or suspects she is pregnant from the start of study to 4 months after the last study drug dose must also report the information to the investigator.

Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.4.2.3.

Appendix 5. Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Appendix 6. Disease Response Criteria Based on International Myeloma Working Group (IMWG) 2016 Criteria

Appendix Table 4. IMWG 2016 MRD Criteria

Response	MRD Criteria
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)[a]
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF[b] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells[c] or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue

CT = computed tomography; IMWG = International Myeloma Working Group; MFC = multicolor flow cytometry; MM = multiple myeloma; MRD = minimal residual disease; NGF = next-generation flow; NGS = next-generation sequencing; PET = positron emission tomography; SUV = standard uptake value

a Sustained MRD negativity when reported should also annotate the method used (eg, sustained flow MRD-negative, sustained sequencing MRD-negative).

b Bone marrow multicolor flow cytometry should follow NGF guidelines. The reference NGF method is an 8-color 2-tube approach, which has been extensively validated. The 2-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The 8-color technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete 8-color method is most efficient using a lyophilized mixture of antibodies which reduces errors, time, and costs. Five million cells should be assessed. The MFC method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells.

c DNA sequencing assay on bone marrow sample should use a validated assay such as LymphoSIGHT (Sequenta).

Appendix Table 5. Standard IMWG 2016 Response Criteria

Response	IMWG Criteria
Stringent Complete Response (sCR)	Complete response as defined below, plus normal FLC ratio[a] and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤ 4:1 or ≥ 1:2 for κ and λ patients, respectively, after counting ≥ 100 plasma cells)
Complete Response (CR)	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow aspirates
Very Good Partial Response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h
Partial Response (PR)	≥ 50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥ 90% or to < 200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥ 30%. In addition to these criteria, if present at baseline, a ≥ 50% reduction in the size (sum of products of 2 longest perpendicular diameters [SPD])[b] of soft tissue plasmacytomas is also required
Minimal Response (MR)	≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50 to 89%. In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size (SPD)[b] of soft tissue plasmacytomas is also required
Stable Disease (SD)	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease

Progressive Disease (PD) [c,d]	Any 1 or more of the following criteria:
	• Increase of 25% from lowest confirmed response value in 1 or more of the following criteria:
	  • Serum M-protein (absolute increase must be ≥ 0.5 g/dL);
	  • Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥ 5 g/dL;
	  • Urine M-protein (absolute increase must be ≥ 200 mg/24 h);
	  • In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL);
	  • In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥ 10%);
	• Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD[b] of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion > 1 cm in short axis; ≥ 50% increase in circulating plasma cells (minimum of 200 cells/μL) if this is the only measure of disease

Response	IMWG Criteria
Clinical Relapse	Clinical relapse requires 1 or more of the following criteria: • Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥ 1 cm) increase as measured serially by the SPD[b] of the measurable lesion; • Hypercalcemia (> 11 mg/dL); • Decrease in hemoglobin of ≥ 2 g/dL not related to therapy or other nonmyeloma-related conditions; • Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; • Hyperviscosity related to serum paraprotein
Relapse from Complete Response (to be Used Only if the Endpoint is Disease-free Survival)	Any 1 or more of the following criteria: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis; • Development of ≥ 5% plasma cells in the bone marrow; • Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia see above)
Relapse from MRD Negative (to be Used Only if the Endpoint is Disease-free Survival)	Any 1 or more of the following criteria: • Loss of MRD-negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); • Reappearance of serum or urine M-protein by immunofixation or electrophoresis; • Development of ≥ 5% clonal plasma cells in the bone marrow; • Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

CR = complete response; CRAB = Calcium, Renal Failure, Anemia, Bone Lesions; CT = computed tomography; FLC = free-light chain; IMWG = International Myeloma Working Group; MR = minimal response; MRD = minimal disease residue; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography; PR = partial response; sCR = stringent complete response; SD = stable disease; SFLC = serum free light chain; SPD = sum of products of 2 longest perpendicular diameters; UK = United Kingdom; VGPR = very good partial response

a All recommendations regarding clinical uses relating to SFLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).

b Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

c Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

d In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

Appendix Table 6. Required Baseline and Follow-up Tests for Response Assessment Using IMWG 2016 Criteria

	Every Response Assessment Time Point (Every Cycle)	If Electrophoresis Shows No Measurable Protein	At Suspected CR	At Suspected Progression (Clinical or Biochemical)
Serum Electrophoresis (Serum M-spike ≥ 1 g/dL)[a]	X		X	X
Serum Immunofixation (Any)		X	X	X
Urine Electrophoresis (Urine M-spike ≥ 200 mg/24 h)	X		X	X
Urine Immunofixation		X	X	
SFLC				
Serum M-spike < 1 g/dL, Urine M-spike < 200 mg/24 h, but Involved Ig FLC is ≥ 10 mg/dL	X		X	X
Any	–		X	X
Bone Marrow Aspirate/Biopsy				
Serum M-spike, Urine M-spike, or Involved Ig FLC not Meeting Above Criteria but Bone Marrow Plasma Cell Percentage ≥ 30%	X[b]		X	
Any	–		X	
Extramedullary plasmocytoma assessment				
Serum M-spike, Urine M-spike, Involved Ig FLC or Bone Marrow not Meeting Above Criteria, but at Least One Lesion that has a Single Diameter of ≥ 2 cm	X[b]		X	
Any	-		X	
Hemoglobin, Serum Calcium, Creatinine (Any)	X			X

CR= complete response; FLC = free light chain; Ig = immunoglobulin; IMWG = International Myeloma Working Group; SFLC = serum free-light chain; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; X = test performed; – = test not performed

a A baseline M-spike of ≥ 0.5 g/dL is acceptable if very good partial response or higher is the response endpoint to be measured and in situations where progression-free survival or time to progression are the endpoints of interest.

b To be done every 3 or 4 cycles till a plateau or CR, or as clinically indicated and then at suspected progression.

c Source: {Kumar 2016}

Appendix 7. Eastern Cooperative Oncology Group Performance Status

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655. Available online: http://ecog-acrin.org/resources/ecog-performance-status. Accessed 18 February 2020.

Appendix 8. Cockcroft-Gault Method for Estimating Creatinine Clearance

Formulas for calculating the estimated creatinine clearance (eC_{cr}) are provided in Appendix Table 7. The formula appropriate to the units in which serum creatinine was measured and the patient's gender should be used.

Appendix Table 7. Cockcroft-Gault Formula for Predication of Creatinine Clearance

Serum Creatinine Units	Gender	Formula
mg/dL	Males	eC_{cr} [mL/min] = $\frac{(140 - \text{patient age [years]}) \times \text{patient weight [kilograms]} \times 1}{72 \times \text{patient serum creatinine [mg/dL]}}$
	Females	eC_{cr} [mL/min] = $\frac{(140 - \text{patient age [years]}) \times \text{patient weight [kilograms]} \times 0.85}{72 \times \text{patient serum creatinine [mg/dL]}}$
µM/dL	Males	eC_{cr} [mL/min] = $\frac{(140 - \text{patient age [years]}) \times \text{patient weight [kilograms]} \times 1.23}{\text{Patient serum creatinine [mg/dL]}}$
	Females	eC_{cr} [mL/min] = $\frac{(140 - \text{patient age [years]}) \times \text{patient weight [kilograms]} \times 1.04}{\text{Patient serum creatinine [mg/dL]}}$

eCcr = estimated creatinine clearance
Source: {Cockcroft 1976}

Appendix 9. FACT-MM (Version 4) {Facit.org 2009}

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
HI 12	I feel weak all over	0	1	2	3	4
BMT 6	I get tired easily	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU 3	I feel discouraged about my illness	0	1	2	3	4
LEU 4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4
LEU 6	I worry that I might get new symptoms of my illness	0	1	2	3	4
BRM 9	I have emotional ups and downs	0	1	2	3	4
BP1	I have bone pain	0	1	2	3	4
An 14	I need help doing my usual activities	0	1	2	3	4
MM 1	I have trouble walking because of pain	0	1	2	3	4
HI7	I feel fatigued	0	1	2	3	4
ES 10	I have gained weight	0	1	2	3	4

Appendix 10. Myeloma Frailty Score Calculator

The Myeloma Frailty score on this study will be calculated using the Myeloma Frailty score calculator: available at http://www.myelomafrailtyscorecalculator.net/ {Palumbo 2015}.

The myeloma frailty score calculator was developed by International Myeloma Working Group for the prognosis of myeloma patients ≥ 65 years of age. This frailty score predicts mortality and the risk of toxicity in elderly myeloma patients. The International Myeloma Working group proposes this score for the measurement of frailty in the treatment decision-making process and in designing future clinical trials.

Appendix 11. Amendment History

A high-level summary of this amendment is provided in tabular form in Appendix Table 8. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

Separate summary of change documents for earlier amendments are available upon request.

A separate tracked change (red-lined) document comparing Amendment 5 with this amendment will be made available upon the publication of this protocol.

Appendix Table 8. Amendment 6 (02 November 2023)

Rationale for Key Changes Included in Amendment 6	Affected Sections
Removal of posttreatment follow-up for disease progression and survival follow-up assessments and secondary endpoints for progression-free survival (PFS) and overall (OS) as efficacy data will no longer be collected after the end-of-treatment (EOT) visit.	Synopsis, Sections 2, 3.5, 3.6, 6.10, 6.11, 6.12, 6.13, 6.5.2, 8.1.3, 8.5.2, and Appendix Table 3
CCI [redacted] CCI	Sections 2, 8.1.4, and 8.5.3
CCI [redacted]	Synopsis, Sections 2, 6.5.4, 6.9, 8.1.4, 8.9, Appendix Table 2, and Appendix Table 3
Guidance for the use of corticosteroids as premedication for the first few infusions of magrolimab has been incorporated to align with the information in Edition 12 of the Investigator's Brochure..	Section 5.3.1
Clarification of standard of care procedure language incorporated from Administrative Amendment 1 for Protocol Amendment 5.	Section 6.1
Removal of receptor occupancy assessment.	Section 6.4.2, Table 23 and Appendix Table 2
Removal of the requirement for multiple myeloma, tumor response, and bone marrow assessments to be performed by a central laboratory. These assessments may now be performed by a central or local laboratory based on investigator preference.	Sections 6.5.1, 6.5.2, 6.5.3 and 6.5.4
Removal of FACT-MM questionnaire assessment as patient-reported outcome data are no longer required.	Synopsis, Sections 2, 6.6.1, 8.1.4, 8.5.3 Appendix Table 1, Appendix Table 2, Appendix Table 3
Guidance for the management of infusion-related reactions has been updated to incorporate the use of corticosteroids as premedication during the first few infusions of magrolimab, and to incorporate guidance for discontinuation of magrolimab in certain cases. This was done to align with the information in Edition 12 of the Investigator's Brochure.	Section 7.8.1.2, Table 24

Rationale for Key Changes Included in Amendment 6	Affected Sections
Toxicity management section for magrolimab has been updated to include guidelines for dose delay and discontinuation in case of severe neutropenia and serious infections to align with the information in Edition 12 of the Investigator's Brochure.	Sections 7.8.1.4 and 7.8.1.5
Removal of primary analysis as final analysis will occur sooner than originally planned; therefore, primary analysis is no longer required.	Section 8.2.1
Clarification that assessment of quantitative Ig levels is to be performed for patients with IgA and IgD myelomas to align with Section 6.5.1.	Appendix Table 2
Contraception appendix has been updated to reflect the latest nonclinical embryo-fetal development toxicity data.	Appendix 4
Global Patient Safety (GLPS) has been updated to Patient Safety (PS) to reflect the new department name.	Throughout the protocol, as required

Prot GS-US-558-5915 amd-6

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Development eSigned	02-Nov-2023 20:44:50