Janssen Research & Development *

Clinical Protocol

A Phase 3 Study Comparing Daratumumab, VELCADE (bortezomib), Lenalidomide, and Dexamethasone (D-VRd) with VELCADE, Lenalidomide, and Dexamethasone (VRd) in Subjects with Untreated Multiple Myeloma and for Whom Hematopoietic Stem Cell Transplant is Not Planned as Initial Therapy

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Protocol 54767414MMY3019; Phase 3
Amendment 6
JNJ-54767414 (daratumumab)

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Studies conducted at sites in the United States (US) will be conducted under US Food and Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).
Studies conducted at sites in the European Economic Area (EEA) will be conducted under Regulation [EU] No 536/2014.

EU TRIAL NUMBER: 2023-507312-13

Status: Approved
Date: 14 March 2024
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-160761684; 9.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 6	14 March 2024
Amendment 5	24 March 2022
Amendment 4	1 October 2020
Amendment 3	19 November 2019
Amendment 2	18 January 2019
Amendment 1	10 September 2018
Original Protocol	17 July 2018

Amendment 6 (14 March 2024)

Overall Rationale for the Amendment: The overall rationale is to continue the study with limited data collection after the planned final PFS analysis. Subjects who are benefitting from treatment with daratumumab will have continued access to study treatment after the end of data collection. Additionally, this amendment harmonizes changes previously included in Protocol Amendment 5/EEA-1. Specifically, this amendment includes text to address country-specific changes for France and Czech Republic within this global amendment. As a result, the Protocol Amendment 5/EEA-1 will be retired.

The changes made to the clinical protocol 54767414MMY3019 as part of Protocol Amendment 6 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.22 Appendix 22: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
1.1 SYNOPSIS 1.3 Schedule of Activities (SoA) 4.1 Overall Study Design 4.4 End of Study Definition 8.1.1 Overview 9.2 Sample Size Determination	Text was updated to specify that investigator-assessed long term PFS, PFS2 and OS will continue to be collected after the final PFS analysis until the end of data collection, defined as 7 years after the last subject was randomized into the study, or earlier as per sponsor discretion.	To continue with limited data collection after the planned final PFS analysis until the end of data collection.
1.3 Schedule of Activities (SoA) 6.6.2.2 Daratumumab-Related Toxicity Management 8.1.1 Overview 8.1.4 End-of-Treatment Visit 8.6 Pharmacokinetics and Immunogenicity 8.6.1 Evaluations 8.6.4 Immunogenicity Assessments	Text was updated to specify that pharmacokinetic and immunogenicity sampling will no longer be required for subjects in Treatment Arm B after the planned final PFS analysis.	To continue with limited data collection after the planned final PFS analysis.
4.4 End of Study Definition	Text was updated to clarify the definition of 'end of study' and 'end of data collection' so that subjects who are benefitting from treatment with daratumumab can continue to receive study treatment after the end of data collection.	To ensure that subjects continue to have drug access after end of data collection and end of study.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA) 8.2.1 Response Categories 8.2.2 Myeloma Protein Measurements in Serum and Urine 8.2.3 Albumin and Serum Calcium Corrected for Albumin 8.3.6 Clinical Safety Laboratory Assessments 10.20 Appendix 20: Interpretation of The SEBIA Hydrashift 2/4 Daratumumab IFE Interference test	Text was updated to clarify that after the planned final PFS analysis, disease evaluations will be performed by the local laboratory instead of the central laboratory.	To continue to monitor investigator assessed PFS and OS for the subjects in the study after the planned final PFS analysis.
8.2.1 Response Categories	Text was updated to clarify that after the final PFS analysis, disease progression and response according to IMWG criteria will be determined by the investigator and the computer algorithm will not be used.	To continue with limited data collection after the planned final PFS analysis.
7.2 Discontinuation of Study Treatment	Text was updated to clarify that if a subject becomes pregnant, lenalidomide must be discontinued. Additionally, text was added to clarify that discontinuation of all study treatment is also acceptable if mandated by local regulations.	To clarify pregnancy requirements with respect to study treatment; to harmonize protocol text with respect to EU CTR requirements.
8.3.8.1 HBV Screening Serology Testing	Text was updated to clarify that if required by local regulations, if the hepatitis B serologic status of a subject in Arm B is unknown, HBsAg, Anti-HBs, and Anti-HBc testing is recommended if the subject is still receiving daratumumab.	To harmonize protocol text with respect to EU CTR requirements.
1.1 SYNOPSIS 5.3 Restrictions During Study Participation (Criterion 4)	The brand name (Revlimid®) has been replaced by the generic drug name lenalidomide and references to the lenalidomide Global Pregnancy Prevention plan have been included.	To accommodate the use of generic lenalidomide in countries when and if needed.
7.4 Lost to Follow-up	Information has been added on the actions that must be taken if a subject fails to return to the study site for a required study visit.	To align with information included in the ICF.
8.4.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information 10.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Information for reporting of SAEs has been updated.	To clarify the current safety reporting process for clinical studies.
1.3 Schedule of Activities (SoA) 6.1.2 Daratumumab Administration 10.1 Appendix 1: Abbreviations	Reference to the IPPI has been replaced by reference to the daratumumab SmPC, USPI, local prescribing information, or equivalent documentation.	Commercial prescribing information to be used for additional guidance on treatment preparation and administration.
6.2.2 Injection-related Reactions	Text was updated to clarify that if ocular symptoms occur, daratumumab has to be	Added upon Health Authority request.

Section Number and Name	Description of Change	Brief Rationale
	interrupted and immediate ophthalmologic evaluation has to be sought prior to restarting daratumumab.	
6.6.2.2 Daratumumab-Related Toxicity Management 7.2 Discontinuation of Study Treatment	Text was updated to clarify that if a subject's dose is held for more than 28 days, the Sponsor has to be consulted to review safety, and efficacy, and to discuss continuation on study.	To clarify treatment continuation following daratumumab delay.
1.3 Schedule of Activities (SoA) 8.2.4 Bone Marrow Examination	The window of yearly bone marrow sampling was extended from +/-1 month to +/-3 months.	To allow more flexibility in the window for sites to collect bone marrow for MRD assessments.
8.4.5 Disease-Related Events and Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events	Text was updated to clarify reporting of disease-related events and outcomes not qualifying as AEs or SAEs.	To align with the clinical protocol template.
6.8.3 Prohibited Therapies 11 REFERENCES	Removed medications used for other indications that have anti-myeloma properties from the list of prohibited therapies.	Amended to reflect the latest research/data in the field.
7.2 Discontinuation of Study Treatment	Deleted "the subject initiates treatment with a prohibited medication" as reason to discontinue a subject's study treatment.	Amended to reflect the latest research/data in the field.
	Clarified that for subjects who experience a second primary malignancy that cannot be treated by surgery alone, this scenario should be discussed with the Sponsor.	Amended to reflect the latest research/data in the field.
8.3.6 Clinical Safety Laboratory Assessments	Text amended to refer serum chemistry and hematology to schedule of activities and to clarify that additional chemistry and hematologic laboratory assessment supporting the start and end dates of an AE should be reported in the eCRF.	Amended to reflect the latest research/data in the field.
Title page; 1.1 SYNOPSIS	Added EU Trial Number	To align with EU CTR requirements.
1.1 SYNOPSIS	Added text for benefit/risk.	To align with EU CTR requirements.
6 STUDY DRUG	Added table (Table 3) providing designations of the study medicinal products (Investigational Medicinal Product[s]/Non-investigational Medicinal Product[s]/Auxiliary Medicinal Products).	To align with EU CTR requirements.
4.2.1 Study-Specific Ethical Design Considerations 5.1 Inclusion Criteria 7.2 Discontinuation of Study Treatment 8.3.2 Adverse Events 10.3 Appendix 3: Regulatory, Ethical, and Study Oversight Considerations	The term "legally acceptable representative" has been replaced by "legally designated representative".	To align with ICF v12.
7.3.1 Withdrawal from the Use of Study Samples 8.1.1 Overview	The term "research sample" has been replaced with the term "study sample".	To align with ICF v12.

Section Number and Name	Description of Change	Brief Rationale
10.3 Appendix 3: Regulatory, Ethical, and Study Oversight Considerations	Revised text regarding publication by Investigator and disclosure of results by the sponsor.	To align with the clinical protocol template.
10.3 Appendix 3: Regulatory, Ethical, and Study Oversight Considerations	Recording of the AE assessment and related follow-ups by the investigator should be kept as source documents.	To clarify the current safety reporting process for clinical studies.
10.3 Appendix 3: Regulatory, Ethical, and Study Oversight Considerations	Added text regarding record retention under EU regulation.	Update per EU CTR requirement.
Title Page	Added text on EU regulation; added EU Trial number; removed EudraCT number.	Updates per EU CTR requirement and local requirements.
8.4.3. Regulatory Reporting Requirements for Serious Adverse Events	Updated safety reporting text to use broader language (“safety information” and “Regulatory Authorities/IECs/IRBs”)	Update per EU CTR requirement.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

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1. PROTOCOL SUMMARY

1.1. SYNOPSIS

A Phase 3 Study Comparing Daratumumab, VELCADE (bortezomib), Lenalidomide, and Dexamethasone (D-VRd) with VELCADE, Lenalidomide, and Dexamethasone (VRd) in Subjects with Untreated Multiple Myeloma and for Whom Hematopoietic Stem Cell Transplant is Not Planned as Initial Therapy

EU TRIAL NUMBER: 2023-507312-13

BENEFIT-RISK ASSESSMENT

The bortezomib, lenalidomide, and dexamethasone (VRd) backbone regimen to be used in this study is now considered a standard of care regimen for newly diagnosed patients with multiple myeloma. Based on the results of nonclinical studies, the mechanism of action, the route of administration, and results from participants treated in daratumumab studies, the potential safety risks for daratumumab are systemic administration-related reactions, cytopenia, and infections. Given the potential advantages of subcutaneous (SC) administration, SC daratumumab will be used in this study. The safety and tolerability of SC daratumumab has been demonstrated.

The addition of daratumumab to the VRd backbone regimen may improve initial disease control and long-term outcomes. Additionally, daratumumab has been successfully combined with VRd, lenalidomide and dexamethasone (Rd), and bortezomib and dexamethasone (Vd) in previous studies in various treatment settings. Considering the measures taken to minimize risk to participants of this study, including an Independent Data Monitoring Committee, the potential risks associated with the addition of daratumumab to the VRd backbone are justified by the anticipated benefits for this patient population. Taken together, there is a strong rationale for evaluating SC daratumumab in combination with VRd for the treatment of patients with previously untreated multiple myeloma for whom initial transplant is not planned. More detailed information about the known and expected benefits and risks of daratumumab may be found in the Investigator's Brochure.

OBJECTIVES AND ENDPOINTS

Objectives

Primary Objective

The primary objective is to determine if the addition of daratumumab to VELCADE® (bortezomib), lenalidomide, and dexamethasone (VRd) will improve overall minimal residual disease (MRD) negativity rate compared with VRd alone.

Secondary Objectives

Key secondary objectives are:

- To determine if the addition of daratumumab to VRd will improve clinical outcome as measured by:
  - Progression-Free Survival (PFS)
  - Durability of MRD negativity
  - Rate of complete response (CR) or better
- To assess the safety profile of daratumumab + VRd (D-VRd)

OVERALL DESIGN

This is a randomized, open-label, multicenter, Phase 3 study evaluating subjects with newly diagnosed multiple myeloma and for whom transplant is not planned. Approximately 360 subjects (180/arm) will be randomized 1:1. Subjects in Arm A will receive VRd alone for eight 21-day cycles followed by lenalidomide and dexamethasone (Rd) until disease progression or unacceptable toxicity. Subjects in Arm B will receive D-VRd for eight 21-day cycles followed by daratumumab, lenalidomide, and dexamethasone (DRd) therapy until disease progression or unacceptable toxicity. Subjects will be stratified at randomization by International Staging System (ISS) Stage and age/transplant eligibility.

DOSAGE AND ADMINISTRATION

Bortezomib will be given as a subcutaneous (SC) injection (1.3 mg/m^2) on Days 1, 4, 8, 11 for 8 cycles. Subjects will not receive bortezomib after Cycle 8. Lenalidomide will be administered PO at 25 mg on Days 1 to 14 on a 21-day cycle for Cycles 1-8 and then Days 1 to 21 on a 28-day cycle for Cycle 9 and beyond, until disease progression or unacceptable toxicity. Dexamethasone will be administered PO at 20 mg on Days 1, 2, 4, 5, 8, 9, 11, 12 during Cycles 1-8 and 40 mg Days 1, 8, 15, and 22 during Cycle 9 and beyond.

Daratumumab 1800 mg SC will be administered to subjects in Arm B once every week for Cycles 1 to 2, then every 3 weeks for Cycles 3-8. For Cycle 9 and beyond, subjects will receive daratumumab 1800 mg SC once every 4 weeks until documented disease progression or unacceptable toxicity.

Individual dose modification of daratumumab is not permitted, either a dose interruption or a dose delay is recommended for managing daratumumab-related toxicities. Bortezomib, lenalidomide and dexamethasone doses may be reduced, or the treatment schedule may be modified for the management of study treatment-related toxicities.

EFFICACY EVALUATIONS

Assessment of tumor response and disease progression will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria. Efficacy evaluations will include measurements of tumor burden/residual disease, myeloma proteins, bone marrow examinations, skeletal surveys, extramedullary plasmacytomas, and serum calcium corrected for albumin.

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Samples will be collected from all subjects in Arm B to assess both the serum concentration (pharmacokinetics) of daratumumab and generation of anti-daratumumab antibodies (immunogenicity) according to the Schedule of Activities. Samples will also be collected from all subjects in Arm B to evaluate the immunogenicity of recombinant human hyaluronidase (rHuPH20) according to the Schedule of Activities. After the planned final PFS analysis, pharmacokinetic and immunogenicity sampling will no longer be required for subjects in Treatment Arm B.

BIOMARKER EVALUATIONS

Bone marrow samples will be collected from all subjects in both arms to evaluate MRD and high-risk cytogenetics anomalies as outlined in the Schedule of Activities. Whole blood samples will be collected from subjects as specified in the Schedule of Activities for processing to plasma and peripheral blood mononuclear cells and may be used to evaluate mechanism of action of daratumumab in combination with VRd.

SAFETY EVALUATIONS

Safety evaluations will include adverse event (AE) monitoring, physical examinations, electrocardiogram (ECGs) monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status. All toxicities will be graded

according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.

Based on the previous experience with daratumumab in humans, in vitro studies, and animal toxicological findings, injection-related reactions (IRRs)/allergic reactions, hemolysis, and thrombocytopenia will be closely monitored. As daratumumab is a biologic agent, immunogenicity also will be monitored.

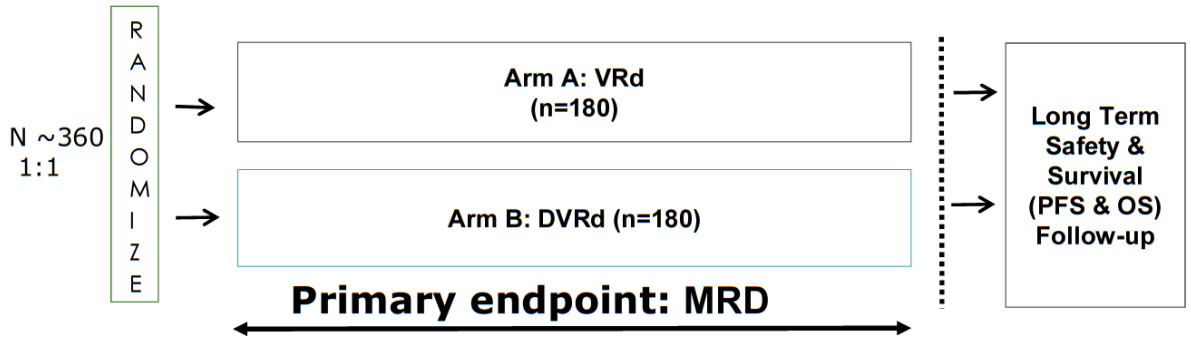
STATISTICAL METHODS

The primary endpoint of the study is overall MRD negativity rate. The study is powered to test the assumption that the addition of daratumumab will increase the overall MRD negativity rate by 15%.

The primary analysis of the overall MRD negativity rate will be performed approximately 18 months after the last subject is administered his/her first dose of study treatment. The final PFS analysis will take place when approximately 162 PFS events have been observed. An interim analysis for PFS is planned, when 98 PFS events (60% of total planned PFS events) are expected to have been accumulated.

1.2. Schema

Figure 1: Schematic Overview of the Study



Abbreviations: D-VRd=daratumumab in combination with bortezomib, lenalidomide, and dexamethasone; OS=overall survival; PFS=progression-free survival; VRd=bortezomib, lenalidomide, and dexamethasone.

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities – Treatment and Follow-Up Phases

	Notes	Screening Phase	Treatment Phase					Follow-up Phase	
		within 28 days before randomization	Cycles 1-8 (21d cycles) Day 1 to Day 21			Cycle 9 and beyond (28d cycles) Day 1 to Day 28	EOT Within 30d after last dose	Prior to PD[b]	Post PD (Q16wks) ± 2 wks
			D1	D8	D15	D1			
Screening/Administrative									
Study treatment should be initiated within 3 days after randomization. The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. After EOT, and prior to PD, subjects in both treatment arms will continue to return for disease evaluations. After PD is documented, subjects will be followed for survival, PFS2, second primary malignancy, subsequent anticancer therapy, PRO assessments, and medical resource utilization									
Informed consent	Subjects must sign the informed consent form must be signed before any study-related procedures are performed	X							
Eligibility criteria		X							
Demographics/Medical History		X							
Height		X							
Chest x-ray (or full dose chest CT scan)[a]	Acceptable for screening if performed as part of SOC within 42 days before randomization	X							
Pulmonary function test (PFT)	For subjects with COPD only. FEV1 must be measured within 42d before randomization	X							
ECOG	See Appendix 7 (Section 10.7)	X	D1 of Cycle 4, 8, 11, 14 for Year 1; every 6th cycle thereafter until PD. For subjects who discontinue treatment prior to PD, every 3 months in Year 1, then every 6 months thereafter. Post PD, collect at 8 and 16 weeks post PD						
Myeloma Frailty Index		X							
12-lead ECG	Acceptable for screening if performed as part of SOC within 42 days before randomization	X	As clinically indicated						
Physical exam	Including neurological exam[c]	X	Symptom and disease directed exam as clinically indicated						
Vital signs (heart rate, temperature, and blood pressure)	For Arm A, vital signs are required only on Day 1 of every cycle. For Arm B, on C1D1, vital signs are required immediately before Daratumumab SC administration; at end of Daratumumab SC administration; and at 0.5 and 1 hour after end of	X	X	Arm B C1-C2 only	Arm B only	X			

Table 1: Schedule of Activities – Treatment and Follow-Up Phases

	Notes	Screening Phase	Treatment Phase					Follow-up Phase	
		within 28 days before randomization	Cycles 1-8 (21d cycles) Day 1 to Day 21			Cycle 9 and beyond (28d cycles) Day 1 to Day 28	EOT Within 30d after last dose	Prior to PD[b]	Post PD (Q16wks) ± 2 wks
			D1	D8	D15	D1			
	Daratumumab SC administration. For all other Daratumumab SC administrations, immediately prior to administration and immediately following completion of administration Clinically significant abnormalities will be reported as AEs.								
Weight	If a subject's weight changes by more than 10% from baseline, the weight used for drug calculations should be adjusted and the dose of bortezomib should be re-calculated[e]	X	X			X			
Patient-reported outcome (PRO) assessments (EORTC QLQ-C30, EORTC QLQ-MY20 module, and the EQ-5D-5L)	PRO measures should be completed before any other study procedures are performed on the day of the visit.		X			every 3rd cycle until PD			Every 16 wks (EQ-5D-5L only). And start of subsequent therapy and 4 weeks after start of subsequent therapy
Medical resource utilization (MRU)	For additional details, see Section 8.9.		X			X	X	X	
Study drug accountability review			X			X	X		
Laboratory Assessments									
Blood type and indirect IAT	ABO, Rh, and IAT to be assessed locally once randomization to D-VRd is known, and prior to dosing with daratumumab. A wallet card with the subject's blood type will be provided to subjects randomized to D-VRd.	Prior to first dose of daratumumab, D-VRd arm only							
Pregnancy test (Section 8.3.6)	D1 all cycles. For women of childbearing potential only. During Screening, within 10-14 days prior to first dose and again within 24 hrs prior to first dose. Minimum testing requirements during study: Weekly during Cycle 1 and then monthly in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Refer to Section 8.4.4 for details.						X[e]		
Hematology	May be performed up to 3 days before study drug administration day. Results must be evaluated before each study drug administration. At Cycle 1 Day 1, tests do not need to be repeated if they were performed within the previous 5 days	X	X	C1-2[d]	C3-8[d]	X	X		
Serum chemistry		X	X		X	X	X		

Table 1: Schedule of Activities – Treatment and Follow-Up Phases

	Notes	Screening Phase	Treatment Phase					Follow-up Phase	
		within 28 days before randomization	Cycles 1-8 (21d cycles) Day 1 to Day 21			Cycle 9 and beyond (28d cycles) Day 1 to Day 28	EOT Within 30d after last dose	Prior to PD[b]	Post PD (Q16wks) ± 2 wks
			D1	D8	D15	D1			
Creatinine Clearance	Calculation of Creatinine Clearance (Refer to Section 10, Appendix 10.8)	X	X			X			
Hepatitis B (HBV) serology	Local testing for hepatitis B surface antigen (HbsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc). Refer to Section 8.3.8.1	X							
HBV-DNA	For subjects with serologic evidence of resolved HBV infection (ie, positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. Refer to Section 8.3.8.2.	X	Every 6 weeks (±1 week with the exception of C1D1).			Q12W (±1 month) during treatment, at the End of Treatment Visit, and Q12W for up to 6 months after the last dose of study treatment.			
Whole Blood	Same day pre-administration collections of whole blood for PBMCs and plasma		Predose Day 1 of Cycle 1 and Cycle 3 and at PD						
Disease Evaluations: Every effort should be made to conduct disease evaluations as per schedule (window± 7 days). Refer to Section 8.2 for details on efficacy evaluations									
Serum disease evaluations (SPEP)	Sample to be sent to central laboratory up until the final PFS analysis, then to local laboratory. IFE and FLC when CR is suspected or maintained. FLC every cycle for subjects with light chain only myeloma. C1D1 can be skipped if performed in screening within 14 days of starting therapy.	X	Every 3 weeks for Cycles 1-8			Every 4 weeks for 30 months then every 8wks until PD			
Urine disease evaluations (UPEP)	Sample to be sent to central laboratory up until the final PFS analysis, then to local laboratory. Urine IFE when CR is suspected or maintained. C1D1 can be skipped if performed in screening within 14 days of starting therapy. If the 24-h urine collection (UPEP) began before informed consent was obtained as part of routine patient care, the sample can be used in this study as long as it was sent to the central lab for analysis after the informed consent was obtained.	X	Every 3 weeks for Cycles 1-8			Every 4 weeks for 30 months then every 8wks until PD			
Serum Free Light Chain (FLC) Assay	Required at Screening and whenever sCR is suspected or maintained for all subjects. For FLC-only subjects, without measurable disease in the serum or urine, FLC must be done every cycle of treatment. C1D1 can be skipped if performed in screening within 14 days of starting therapy.	X	Every 3 weeks for Cycles 1-8			Every 4 weeks for 30 months then every 8 wks until PD			

Table 1: Schedule of Activities – Treatment and Follow-Up Phases

	Notes	Screening Phase	Treatment Phase					Follow-up Phase	
		within 28 days before randomization	Cycles 1-8 (21d cycles) Day 1 to Day 21			Cycle 9 and beyond (28d cycles) Day 1 to Day 28	EOT Within 30d after last dose	Prior to PD[b]	Post PD (Q16wks) ± 2 wks
			D1	D8	D15	D1			
Calcium, albumin, β2-microglobulin	Sample to be sent to central laboratory up until the final PFS analysis, then to local laboratory. B2-microglobulin at Screening only. ISS Stage to be based upon central laboratory data at Screening. C1D1 can be skipped if performed in screening within 14 days of starting therapy.	X	Every 3 weeks for Cycles 1-8			Every 4 weeks for 30 months then every 8 wks until PD			
Quantitative Immunoglobulins (Q Igs)	Sample to be sent to central laboratory	X							
Bone marrow aspirate/biopsy	For screening, fresh aspirate required (archived samples will not be accepted). See Section 8.2.4 (Table 13) for required testing to confirm diagnosis of multiple myeloma, to confirm CR/sCR and for MRD testing. If a sample is unevaluable, every effort should be taken to repeat BM assessment if not within 2 months of another pre-specified collection.	X	At suspected CR. For subjects who achieve CR and remain on study, at 12,18, 24, 30, and 36 months post Day 1 Cycle 1 (±1 month) and yearly (±3 months) thereafter until PD						
FISH for t (4;14); t (14;16), del17p and amp(1q21)	Performed at central labs for screening within 42 days before randomization	X							
Flow cytometry or Immunohistochemistry or immunofluorescence (2-4 color flow) or immunohistochemistry/ immunofluorescence with kappa/lambda)	Performed locally to confirm diagnosis of myeloma and at time of CR to measure sCR	X	At time of suspected CR						
Assessment of lytic disease	Acceptable for screening if performed as part of SOC within 42 days before randomization	X	As clinically indicated using the same method as used at screening						
Extramedullary plasmacytomas	Subjects with history of plasmacytoma; acceptable for screening if performed as part of SOC within 42 days before randomization	X	If applicable, by physical exam every 4 wks, by radiologic exam (if required) every 12 wks using same methodology as used at screening; for subjects with history of plasmacytoma assessed by physical exam, repeat assessment on Day 1 Cycle 1 if not done within 14 days prior to randomization						
Pre-Administration Medications for Daratumumab									
Dexamethasone 20 mg (Cycles 1-8) 40 mg (Cycle 9 and beyond) IV or PO see Section 6.6.5.	Administer approximately 1-3 hours before daratumumab administration		X	C1-2 only	C1-2 only	X			
Antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent)			X	C1-2 only	C1-2 only	X			
Paracetamol (Acetaminophen) 650-1000 mg IV or PO			X	C1-2 only	C1-2 only	X			

Table 1: Schedule of Activities – Treatment and Follow-Up Phases

	Notes	Screening Phase	Treatment Phase					Follow-up Phase	
		within 28 days before randomization	Cycles 1-8 (21d cycles) Day 1 to Day 21			Cycle 9 and beyond (28d cycles) Day 1 to Day 28	EOT Within 30d after last dose	Prior to PD[b]	Post PD (Q16wks) ± 2 wks
			D1	D8	D15	D1			
Montelukast 10 mg (or equivalent) (recommended up to 24 hours prior to administration)	As clinically needed		C1 only						
Study Treatment: Arms A and B									
Bortezomib 1.3 mg/m^2 SC	Administer by SC injection (Section 6.3)		(Days 1, 4, 8, and 11 of Cycles 1-8)						
Lenalidomide 25 mg PO daily	Dispense on Day 1 for Cycles 1-8 for self-administration (Section 6.4)		(Day 1-14 of 21-day cycle (Cycles 1-8)			(25 mg PO daily Day 1-21)			
Dexamethasone 20 mg PO	Dispense on Day 1 for self-administration. (On daratumumab dosing days, dexamethasone premedication for daratumumab injection will replace the daily dose of dexamethasone). For subjects, older than 75 years or underweight (BMI <18.5), see Section 6.5		(Days 1, 2, 4, 5, 8, 9, 11, 12)			(40 mg PO Days 1, 8, 15, 22)			
Study Drug Administration – Arm B Only									
Daratumumab 1800 mg SC	Refer to the sIPPM and the SmPC, USPI, local prescribing information, or equivalent documentation for additional guidance on study treatment handling, administration, and storage.		(Days 1, 8, 15 for Cycles 1-2 [weekly] then Day 1 of Cycles 3-8 [every 3 weeks])			(Day 1 of each cycle)			
Follow-up									
Survival, PFS2, second primary malignancy, subsequent anticancer therapy.			Continuous from first dose of study drug until end of data collection						
Ongoing Subject Review									
Adverse events	See Section 8.3.2 for detailed instructions.	Continuous from the time of signing of ICF until 30 days after last dose of last study drug						Treatment-related serious adverse events	
Concomitant Medications	See Section 6.8 for detailed instructions.	Continuous from the time of signing of ICF until 30 days after last dose of last study drug							

Abbreviations: BMI=body mass index; C=cycle; COPD=chronic obstructive pulmonary disease; CR=complete response; CT=computed tomography; D=day; Dara=daratumumab; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L=EuroQol Five Dimension Questionnaire; ECG=electrocardiogram; EOT=End-of-Treatment; FEV1=Forced Expiratory Volume (in 1 second); FISH=Fluorescence in situ hybridization; FLC=free light chain; hrs=hours; IAT=indirect antiglobulin test; ICF=informed consent form; IFE=immunofixation; Ig=immunoglobulin; ISS=International Staging System; IV=intravenous; MRD=minimal residual disease; PBMC=peripheral blood mononuclear cell; PFT=pulmonary function test; PFS2=time from randomization to progression on the next line of therapy or death, whichever comes first; PD=progressive disease; PO=per oral; PRO=patient-reported outcomes; Q(3)(6)mo=every (3)(6) months; Q16wk=every 16 weeks; SAE=serious adverse event; SC=subcutaneous; sCR=stringent complete response; sIPPM=Site Investigational Product Procedures Manual (or equivalent document); SmPC= Summary of Product Characteristics; SPEP=serum M-protein quantitation by electrophoresis; SOC=standard of care; UPEP=urine M-protein quantitation by electrophoresis; USPI=Unite States Product Information; Wk=week.

Table 1: Schedule of Activities – Treatment and Follow-Up Phases

	Notes	Screening Phase	Treatment Phase					Follow-up Phase	
		within 28 days before randomization	Cycles 1-8 (21d cycles) Day 1 to Day 21			Cycle 9 and beyond (28d cycles) Day 1 to Day 28	EOT Within 30d after last dose	Prior to PD[b]	Post PD (Q16wks) ± 2 wks
			D1	D8	D15	D1			

A Low-dose full body CT used for skeletal disease evaluation cannot be used for baseline lung evaluation.
B For subjects who discontinue study treatment before PD, disease evaluations should continue at the frequency specified until confirmed PD, death, withdrawal of consent to study participation, or end of study whichever occurs first.
C Subject's neurological examination should be performed during the Screening phase by the treating physician (a neurologic specialist is not required).
D The visit window for these evaluations is **4** days instead of 3 days.
E A pregnancy test is required at the End-of-Treatment visit and 28 days following the last dose of lenalidomide for women with regular menstrual cycles or 14 and 28 days following the last dose of lenalidomide for women with irregular menstrual cycles.

Table 2: Schedule of Activities – Pharmacokinetic/Immunogenicity Sample Collection Times – Arm B ONLY

	Cycle 1		Cycle 3		Cycle 9	Cycle 12	Post-treatment
Day	1	4	1	4	1	1	Post-treatment Week 8
Visit window d=days, w=weeks	0[a]	±1d	0 [a]	±1d	0 [a]	0 [a]	±1w
Daratumumab pharmacokinetics (serum)[a, c]	X predose[a]	X	X predose[a]	X	X predose[a]	X predose[a]	X
Daratumumab immunogenicity (serum)[b, c]	X predose[a]				X predose[a]	X predose[a]	X
rHuPH20 immunogenicity (plasma)[a, c]	X predose[a]				X predose[a]	X predose[a]	X

Abbreviations: rHuPH20=recombinant human hyaluronidase; PK=pharmacokinetics: IRR=injection-related reaction

[a] Samples collected on daratumumab dosing days (i.e. C1D1, C3D1, C9D1, and C12 D1) Day 1 of a cycle) should be collected on the actual day of study drug administration; sample collection on these days may occur up to 2 hours before (but not after) the start of daratumumab administration.

[b] No additional sample needed; will be taken from PK sample. In addition, when an IRR occurs associated with the second or later daratumumab administration, 2 separate blood samples should be obtained, if possible, for determination of anti-daratumumab antibodies and anti-rHuPH20 antibodies.

[c] After the planned final PFS analysis, pharmacokinetic and immunogenicity sampling will no longer be required for subjects in Treatment Arm B.

2. INTRODUCTION

Daratumumab has multiple mechanisms of action, including the direct targeting of tumor cells by selectively binding to cluster of differentiation 38 (CD38) molecules, immune mediated activity with antibody-dependent cellular cytotoxicity, antibody dependent cellular phagocytosis and complement-dependent cytotoxicity, decreased immunosuppression and CD38 enzymatic inhibition. CD38 is highly expressed on myeloma cells but is expressed at relatively low levels on normal lymphoid and myeloid cells and in some tissues of non-hematopoietic origin, making it a relevant target for the treatment of multiple myeloma.

For the most comprehensive nonclinical and clinical information regarding daratumumab, refer to the latest version of the Investigator's Brochure (IB) for daratumumab. The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

2.1. Background

2.1.1. Multiple Myeloma

Multiple myeloma is characterized by uncontrolled and progressive proliferation of a plasma cell clone. Patients with multiple myeloma produce a monoclonal protein (paraprotein) comprising monoclonal protein (M-protein) and free light chain (FLC), which is an immunoglobulin (Ig) or a fragment of one that has lost its function. The proliferation of myeloma cells causes displacement of the normal bone marrow. Normal Ig levels are compromised, leading to susceptibility to infections. Hypercalcemia, renal insufficiency or failure, and neurological complications are frequently reported signs and symptoms of the disease.

2.1.2. Treatment Options for Patients with Newly Diagnosed Multiple Myeloma

Treatment choices for multiple myeloma vary with age, performance status, comorbidity, the aggressiveness of the disease, and related prognostic factors.[35] Newly diagnosed patients with multiple myeloma are typically categorized into 2 subpopulations usually defined by their age and suitability for intensive treatment. Younger patients (ie, <65 years of age) typically receive an induction regimen followed by treatment with high-dose chemotherapy and autologous stem cell transplantation (ASCT), followed by consolidation therapy and maintenance treatment. For those not considered suitable for high-dose chemotherapy and ASCT, longer-term treatment with multi-agent combinations including alkylators, high-dose steroids, and novel agents are currently considered standards of care.

The current standard of care combinations for nontransplant patients include lenalidomide-dexamethasone (Rd),[4] bortezomib-melphalan-prednisone (VMP),[43] bortezomib-cyclophosphamide-dexamethasone (VCD),[26] melphalan-prednisone-thalidomide (MPT),[16] and bortezomib-lenalidomide-dexamethasone (VRd)[2,13]

The Rd registration study (Front-line Investigation of Revlimid and Dexamethasone versus Standard Thalidomide [FIRST]) is a large, randomized Phase 3 study (MM-020/IFM 07-01)

comparing 2 active-treatment arms consisting of different durations of Rd to a third active control arm of MPT in subjects newly diagnosed with multiple myeloma.[14] In this study, 1,623 subjects who were ineligible for ASCT were randomized to receive continuous Rd until disease progression (Arm A); Rd for eighteen 28-day cycles (72 weeks) (Arm B); or MPT for up to twelve 42-day cycles (72 weeks) (Arm C). Continuous treatment with Rd (Arm A) significantly improved the primary endpoint of progression-free survival (PFS) versus fixed treatment duration of 18 months with Rd (Arm B) (HR 0.70; 95% confidence interval [CI] 0.60-0.81) and versus MPT (Arm C) (HR 0.69; 95% CI 0.59-0.79; p>0.00001).[15] Based on this study, the paradigm of treatment until disease progression was established.

2.1.3. VRd Followed by Lenalidomide as a Front-line Treatment Option for Multiple Myeloma

Richardson and colleagues[42] studied the use of VRd for subjects with newly diagnosed multiple myeloma. Subjects were enrolled regardless of their eligibility for high-dose therapy and ASCT. Sixty-six subjects were treated on this single-arm study. All subjects achieved a partial response (PR) or better. Complete Response (CR) was achieved in 19 subjects (29%) with an additional 7 subjects (11%) in near CR (nCR). Importantly, this study showed that VRd was a feasible induction regimen prior to ASCT.

A Phase 3 study conducted by the *Intergroupe Francophone du Myélome* (IFM) cooperative group evaluated the VRd regimen in 700 newly diagnosed subjects with multiple myeloma who were transplant eligible. All subjects received induction with 3 cycles of VRd and were then randomized to receive either standard of care ASCT followed by 2 additional cycles of VRd or 5 additional cycles of VRd alone. All subjects were given maintenance with lenalidomide for 1 year. The median PFS was significantly improved in the subjects with transplant as part of their initial therapy (50 months versus 36 months, HR 0.65, 95% CI 0.53-0.8; p value <0.001). However, overall survival (OS) at 4 years did not differ between the 2 groups, 82% in VRd alone versus 81% in the VRd transplant group. The CR rate was 48% in the VRd alone arm versus 59% in the VRd transplant arm. The minimal residual disease (MRD) negativity rate as measured by 7-color flow cytometry was 65% in the VRd alone arm versus 79% VRd transplant arm.[2] This study showed the depth of response with the VRd regimen with or without ASCT. Further, there was no difference in OS between the 2 arms, suggesting that use of ASCT as salvage therapy is an appropriate alternative approach to treatment.

The Southwest Oncology Group (SWOG) and the National Clinical Trial Network conducted a randomized, open-label, Phase 3 study (SWOG S0777) "Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in subjects with newly diagnosed myeloma without intent for immediate autologous stem cell transplant."[13] In this study, 525 subjects were randomized 1:1; 264 to VRd and 261 to Rd. In the 242 subjects in the VRd arm and 229 subjects in the Rd arm, the median PFS was significantly improved in the VRd group (43 months versus 30 months, HR 0.712, 95% CI 0.56-0.906; p=0.0018). The median OS was also significantly improved in the VRd group (75 months versus 64 months; HR 0.709, 95% CI: 0.524-0.959; p=0.025). The rate of the overall response rate (ORR) was 82% in the VRd arm versus 72% in the Rd group. The CR rate was 15.7% in the VRd arm versus 8.4% in the Rd arm.

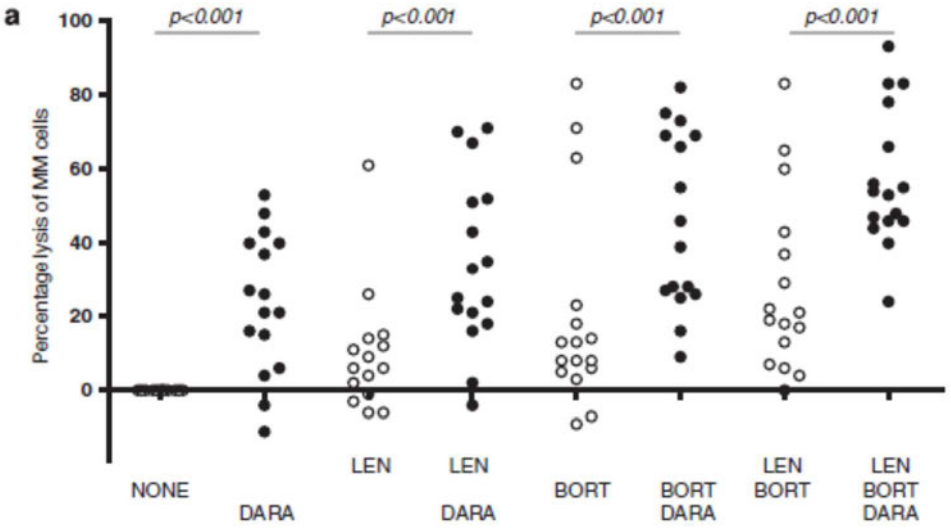
Grade 3 or higher treatment-emergent adverse event (TEAEs) were experienced by 169 subjects (75%) in the Rd arm and 198 subjects (82%) in the VRd arm. This study utilized IV bortezomib treatment that likely resulted in a higher incidence of neurological toxicity for VRd versus Rd alone (33% versus. 11% Grade 3 or worse neurological toxic effects), as well as premature discontinuations during induction therapy (Cycles 1-8) (approximately 25% versus. 10%). This study included a mixed age population (57% of subjects, <65 years of age). The improvement in PFS and OS for the VRd arm versus the Rd arm showed a similar trend in subjects greater than 65 years of age.[13] As such, this study demonstrates the benefit of the VRd regimen for treatment of all newly diagnosed patients with multiple myeloma.

Based on the observed PFS benefit in both the Phase 3 IFM study and the SWOG 0777 study and the OS benefit and tolerable safety profile observed in the SWOG077 study, the VRd regimen was established as a standard care option for all patients with newly diagnosed multiple myeloma.[27,33]

2.1.4. Nonclinical Studies of Daratumumab in combination with lenalidomide and bortezomib

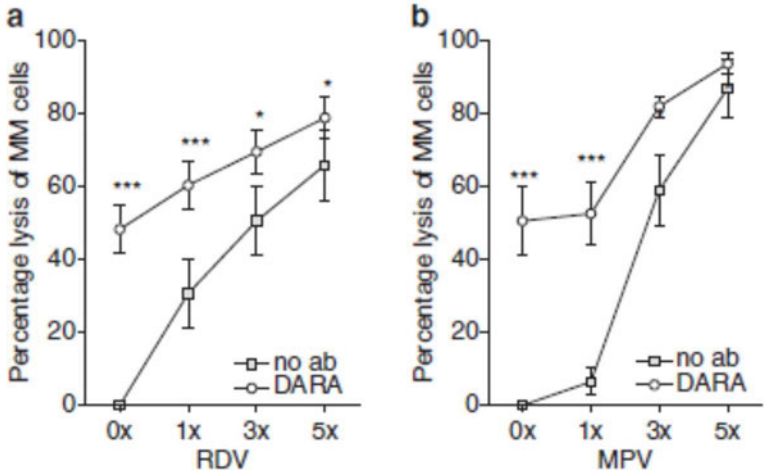
In preclinical studies (GMB3003-070), the potential benefit of combining daratumumab with multi-drug chemotherapy regimens was evaluated in fresh tumor cells from subjects with multiple myeloma (data on file). Lysis of primary tumor cells was measured directly in bone marrow mononuclear cell (BM-MNC) isolates obtained from subjects with multiple myeloma. Synergistic tumor cell lysis was demonstrated when daratumumab was combined with lenalidomide or bortezomib or both, even in samples from subjects who were refractory to lenalidomide and bortezomib treatment. Treatment of BM-MNC with lenalidomide or bortezomib resulted in 10% and 18% lysis, respectively. A combination of lenalidomide and bortezomib resulted in 25% lysis of BM-MNC. When daratumumab was added to either lenalidomide or bortezomib, a 2-fold increase in lysis was observed compared with lenalidomide or bortezomib alone. When daratumumab was added to combinations of dexamethasone, lenalidomide and bortezomib or to bortezomib, prednisone, and dexamethasone, the cell lysis was significantly increased ($p<0.001$) compared with the triple combination alone (no daratumumab).[45] Refer to Figure 2 and Figure 3.

Figure 2: Daratumumab-Enhanced Multiple Myeloma Cell Killing by Key Multiple Myeloma Chemotherapeutic Agents



BORT = bortezomib; DARA = daratumumab; LEN = lenalidomide; MM = multiple myeloma.

Figure 3: Dose-dependent Lysis of Multiple Myeloma Cells in Triple Chemotherapy Treatments



DARA = daratumumab; RDV= combination lenalidomide, bortezomib, and dexamethasone; MM = multiple myeloma; MPV = bortezomib, prednisone, and dexamethasone.
P-values were calculated by a paired t-test. *P<0.05, ***P<0.001.

In conclusion, preclinical data, both from the literature and the sponsor's ex vivo studies, support the combination of daratumumab with bortezomib and lenalidomide in the treatment of multiple myeloma.

2.1.5. Clinical Studies

Daratumumab was initially developed as a treatment for multiple myeloma. There is a comprehensive development plan across various hematologic malignancies.

In the EU, daratumumab is approved for the following indications:

- As monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor (PI) and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.
- In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

In the US, daratumumab is approved for the following indications:

- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.
- In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant.
- In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy.
- As monotherapy, in patients who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and an immunomodulatory agent.
- In combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.
- In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant.

2.1.5.1. Combination Therapy Studies

Two Phase 3 studies examined the safety and efficacy of intravenous (IV) daratumumab in combination with bortezomib and lenalidomide containing therapies in the treatment of relapsed multiple myeloma:

- In Study MMY3003, subjects with multiple myeloma received IV daratumumab in combination with lenalidomide and dexamethasone (DRd). At the time of the first interim analysis, treatment with DRd resulted in a 63% reduction in the risk of disease progression or death compared with Rd alone. The median PFS was not reached in the daratumumab group; median PFS was 18.4 months in the Rd group. The ORR were 93% for the DRd group and 76% for Rd group. The safety profile was consistent with the known safety profile of daratumumab and the backbone regimen. No new safety signals were identified.

- In Study MMY3004, subjects with multiple myeloma received IV daratumumab in combination with daratumumab, bortezomib, and dexamethasone (DVd). At the time of the first interim analysis, treatment with DVd resulted in a 61% reduction in the risk for disease progression or death compared with bortezomib-dexamethasone (Vd) alone. The median PFS was not estimable in the DVd group; median PFS was 7.2 months in the Vd group. The ORRs were 83% for the DVd group and 63% for the Vd group. The safety profile was consistent with the known safety profile of daratumumab and the backbone regimen. No new safety signals were identified.

Three Phase 3 studies examine the safety and efficacy of IV daratumumab in combination with other therapies in previously untreated multiple myeloma:

- In Study MMY3007, subjects with multiple myeloma received intravenous daratumumab (Dara-IV) in combination with bortezomib, melphalan and dexamethasone (D-VMP). At the time of the first interim analysis, treatment with D-VMP showed a 50% reduction in the risk for disease progression or death compared with the combination of bortezomib, melphalan and dexamethasone (VMP). The median PFS was not reached for the D-VMP group and was 18.1 months for the VMP group (HR=0.50, 95% CI: 0.38-0.65; p<0.0001). The ORRs were 91% for the D-VMP group and 75% for the VMP group. The safety profile was consistent with the known safety profile of daratumumab and the backbone regimen. No new safety signals were identified.
- In Studies MMY3006 and MMY3008, subjects with multiple myeloma received IV daratumumab in combination with VTd and DRd, respectively. Results of these studies are not yet available.

Collectively, data from MMY3003, MMY3004, and MMY3007 demonstrate a favorable benefit-risk profile of the triplet DVd and DRd regimens for the treatment of subjects with relapsed or refractory multiple myeloma who have received at least 1 prior therapy and the quadruplet regimen of daratumumab and VMP in transplant ineligible subjects with newly diagnosed multiple myeloma.

Experience with daratumumab in combination with VRd

In Study MMY2004 (NCT02874742), IV daratumumab in combination with VRd, (D-VRd) is being compared with VRd alone in subjects with newly diagnosed multiple myeloma eligible for high-dose chemotherapy and ASCT. The primary endpoint of this study is stringent complete response (sCR) rate post-consolidation. Subjects will receive 4 cycles of VRd induction therapy followed by ASCT and 2 cycles of VRd consolidation therapy followed by maintenance therapy until disease progression or unacceptable toxicity.

Sixteen subjects were enrolled in the safety run-in portion of the study and data for all 16 subjects who completed 4 cycles of induction therapy is presented below.[46] During Cycle 1, 3 subjects experienced the following AEs that met the protocol-specified dose limiting criteria (DLT) criteria: 1 subject with Grade 3 fatigue on Day 15, 1 subject with Grade 3 gastroenteritis on Day 21, and 1 subject with Grade 3 pneumonitis (due to infection) and Grade 3 hypotension on Day 5. No DLTs resulted in treatment discontinuation. All 16 subjects experienced at least 1 TEAE during Cycles 1 to 4. Three subjects (19%) had at least 1 serious adverse event (SAE) and 2 subjects (13%) had SAEs that were considered by the investigator to be related to daratumumab

(gastroenteritis and pneumonitis). Eight subjects (50%) had Grade 3 or Grade 4 TEAEs, for 6 subjects (38%) these events were considered by the investigator to be related to daratumumab. The most commonly reported Grade 3 or Grade 4 TEAEs were neutropenia and thrombocytopenia (19% each), and lymphopenia and leukopenia (13% each). Six subjects (38%) experienced infections, including 1 Grade 3 SAE of gastroenteritis. There were no adverse events (AEs) of febrile neutropenia. No subject died or discontinued treatment due to TEAEs during the safety run- in. Daratumumab IRRs (all Grade ≤2) were reported in 31% of subjects.

The safety profile was consistent with that previously reported for daratumumab as monotherapy and the regimen of VRd. No new safety signals were identified with the addition of daratumumab to VRd during the first 4 cycles of treatment in these 16 subjects with newly diagnosed multiple myeloma. As per protocol, the study proceeded to the randomized phase and enrolled approximately 200 subjects randomized 1:1 to D-VRd versus VRd. A pre-specified interim analysis for safety after at least 50 subjects completed 4 cycles of induction treatment and stem cell mobilization occurred on 04 April 2018, the Independent Data Monitoring Committee (IDMC) recommended that the study continue without modification. Emerging data from this study will be communicated to the IDMC (Section 9.8).

2.2. Overall Rationale for the Study

The treatment of newly diagnosed patients with multiple myeloma is evolving. Induction therapy followed by transplant is not feasible in all patients due to age or patient frailty. Due to the effectiveness of triplet and quadruplet therapies, some patients are deferring initial transplant. The superiority of the VRd regimen has been established by the results of the Phase 3 study by Durie and colleagues.[13] This study demonstrated both increased PFS and OS in the VRd arm compared with Rd alone. Further, the Phase 3 study by Attal and colleagues[2] showed that a deep level of response, CR and MRD negative status can be achieved with the VRd regimen without transplant.

While the treatment of newly diagnosed patients with multiple myeloma continues to improve, patients still are not cured. The most active combination to date is the VRd regimen described above. The sponsor has observed compelling clinical data with daratumumab in combination with either bortezomib or lenalidomide in the relapsed/refractory setting, and bortezomib in the frontline setting. The addition of daratumumab with VRd is anticipated to improve the response rates and the depth of response and may lead to improved long-term outcomes in newly diagnosed patients with multiple myeloma. Based upon the initial safety and efficacy observed in the ongoing Phase 2 Study MMY2004 and continued positive results with daratumumab in various disease settings in combination with both lenalidomide and bortezomib the Phase 3 D-VRd study will proceed prior to completion of the Phase 2 D-VRd study. The initial PK of SC daratumumab administration shows similar exposure to IV and improved safety with a lower IRR rate compared with the IV formulation. The Phase 3 study of D-VRd will utilize the subcutaneous (SC) formulation of daratumumab instead of the IV formulation utilized in the Phase 2 VRd study, which is expected to provide similar exposure and is expected to limit additional toxicity to patients treated with this quadruplet regimen, as injection-related reaction (IRR) is the primary toxicity for daratumumab, and this toxicity is limited with the SC formulation.

2.3. Benefit/Risk Assessment

The combination of VRd with subcutaneously administered daratumumab is anticipated to have a positive benefit-risk profile when used for the treatment of patients with previously untreated multiple myeloma and for whom transplant is not planned as frontline therapy, as proposed for investigation in Study MMY3019. This assessment is based upon the following:

- The VRd backbone regimen to be used in this study is now considered a standard of care (SOC) regimen for newly diagnosed patients with multiple myeloma. Further details of studies conducted using this regimen, which has demonstrated a positive benefit-risk profile, are outlined in Section 2.1.3.
- The addition of daratumumab to the VRd backbone regimen may improve initial disease control and long-term outcomes. Daratumumab has been successfully combined with either Rd or Vd in multiple myeloma patients. In Study MMY3003 (daratumumab + Rd) and MMY3004 (daratumumab + Vd) a significant improvement was seen in PFS in the DRd and DVd arms of the studies in relapsed/refractory subjects. In the newly diagnosed transplant ineligible setting, Study MMY3007 (studying the combination of daratumumab with VMP versus VMP) also showed a statistically significant improvement in PFS in the D-VMP arm of the study (see Section 2.1.5.1 for further details). All 3 studies demonstrated that the safety profiles were consistent with the known safety profile of daratumumab and the respective backbone regimen and no new safety signals were identified. Preclinical synergism has also been observed with daratumumab in combination with bortezomib and lenalidomide.
- Data available from Study MMY2004 suggest that daratumumab can be combined safely with VRd (see Section 2.1.5.1). The initial safety profile was consistent with that previously reported for daratumumab as monotherapy and the regimen of VRd with the exception of lower neurotoxicity due to use of SC bortezomib.
- Given the potential advantages of SC administration, SC daratumumab will be used in this study. As presented in Section 4.2, and in the current daratumumab IB, the safety and tolerability of SC daratumumab has been demonstrated. Previous exposure-response analyses have demonstrated a strong correlation between ORR and the maximum daratumumab C_{trough}. Analysis of the preliminary pharmacokinetic data indicated the 1800 mg Dara-SC dose achieved maximum C_{trough} values comparable with, or higher than, those observed for Dara-IV 16 mg/kg. Details are provided in Section 4.2.
- The potential risks for the study will be mitigated with monitoring by the IDMC and the sponsor's medical monitor during the conduct of the study, as described throughout the protocol (see Section 9.8).

In light of the above, there is a strong rationale for evaluating SC daratumumab in combination with VRd for the treatment of patients with previously untreated multiple myeloma for whom initial transplant is not planned. More detailed information about the known and expected benefits and risks of daratumumab may be found in the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

3.1. Objectives and Endpoints

3.1.1. Objectives

The primary objective is to determine if the addition of daratumumab to VRd will improve overall MRD negativity rate compared with VRd alone.

Secondary Objectives

The secondary objectives are:

- To determine if the addition of daratumumab to VRd will improve clinical outcome as measured by:
  - PFS
  - MRD negativity rate at 1 year
  - Durability of MRD negativity (defined in Section 3.1.2)
  - ORR, rate of very good partial response (VGPR) or better, and rate of CR or better
  - Time to response
  - Duration of response
  - Time to next treatment
  - Progression-free survival on the next line of therapy (PFS2; defined as time from randomization to progression on the next line of therapy or death, whichever comes first)
  - OS
- To evaluate medical resource utilization
- To evaluate the pharmacokinetics (PK) of daratumumab
- To determine the immunogenicity of daratumumab and recombinant human hyaluronidase PH20 (rHuPH20)
- To assess the safety profile of daratumumab + VRd (D-VRd)
- To evaluate clinical efficacy (ie, overall MRD negativity rate and PFS) of daratumumab when added to VRd in cytogenetic high-risk subgroups
- To evaluate patient-reported outcomes (PROs).

Exploratory Objectives

The exploratory objectives are to determine:

- Time to MRD negativity
- Correlation of MRD negative status and clinical outcomes such as PFS and OS.

3.1.2. Endpoints

Primary Endpoint

The primary endpoint of this study is:

- Overall MRD negativity rate, which is defined as the proportion of subjects who have achieved MRD negative status (at 10^{-5}) by bone marrow aspirate after randomization and prior to progressive disease (PD) or subsequent anti-myeloma therapy. Subjects who have achieved MRD negative status on or after PD or after the switch to subsequent anti-myeloma therapy before PD, will not be considered MRD negative in the primary endpoint analysis.

Secondary Endpoints

Secondary efficacy endpoints are:

- PFS defined as the duration from the date of randomization to either progressive disease (PD) or death, whichever comes first. Disease progression will be determined according to the International Myeloma Working Group (IMWG) criteria (Table 11).[12,40] For subjects who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.
- MRD negativity rate at 1 year.
- Durable MRD negativity rate is defined as the proportion of subjects who have achieved MRD negative status (at 10^{-5}) at 2 bone marrow aspirate examinations that are a minimum of 1 year apart, without any examination showing MRD positive status in between.
- Overall response rate is defined as the proportion of subjects who achieve PR or better responses prior to subsequent anti-myeloma therapy in accordance with the IMWG criteria, during or after the study treatment.
- VGPR or better rate is defined as the proportion of subjects achieving VGPR and CR (including sCR) prior to subsequent anti-myeloma therapy in accordance with the IMWG criteria during or after the study treatment.
- CR or better rate is defined as the proportion of subjects achieving CR or sCR prior to subsequent anti-myeloma therapy in accordance with the IMWG criteria during or after the study treatment.
- Progression-free survival on the next line of therapy is defined as the time from randomization to progression on the next line of treatment or death, whichever comes first. Disease progression will be based on investigator judgment. Subjects who are still alive and not yet progressed on the next line of treatment will be censored on the last date of follow-up.
- Overall survival is measured from the date of randomization to the date of the subject's death due to any cause. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive.
- Time to response is defined as the time between the randomization and the first efficacy evaluation at which the subject meets all criteria for PR or better.

- Duration of response is calculated from the date of initial documentation of a response (PR or better) to the date of first documented evidence of PD, as defined in the IMWG evaluation before the start of any subsequent anti-myeloma therapy.
- Clinical efficacy (ie, overall MRD negativity rate and PFS) of D-VRd in high-risk molecular subgroups compared with VRd alone.
- Pharmacokinetic concentrations of daratumumab.
- Incidence of anti-daratumumab antibodies.
- Prevalence and incidence of anti-rHuPH20 antibodies.
- Mean change from baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) core 3-item (EORTC QLQ-C30) and the multiple myeloma 20-item (EORTC QLQ-MY20), and EuroQol Five Dimension Questionnaire (EQ-5D-5L) scales.

Refer to Section 8.2, Efficacy Assessments for evaluations related to endpoints.

3.1.3. Hypothesis

The primary hypothesis is that daratumumab added to VRd regimen will improve the overall MRD negativity rate compared with VRd alone in subjects with newly diagnosed multiple myeloma for whom hematopoietic stem cell transplant is not planned as initial therapy.

4. STUDY DESIGN

4.1. Overall Study Design

This is a randomized, open-label, multicenter, Phase 3 study evaluating subjects with newly diagnosed multiple myeloma for whom hematopoietic stem cell transplant is not planned as initial therapy. At randomization, subjects will be stratified by International Staging System (ISS) Stage (I, II, or III, based on β-2 microglobulin and albumin by central laboratory), and age/transplant eligibility (<70 years ineligible, or age <70 years and refusal to transplant, or age ≥70 years). Approximately 360 subjects (180/arm) will be randomized in a 1:1 ratio in 2 arms. Subjects in Arm A will receive VRd alone for eight 21-day cycles followed by Rd alone until disease progression or unacceptable toxicity. Subjects in Arm B will receive D-VRd for eight 21-day cycles and will continue to receive DRd therapy until disease progression or unacceptable toxicity.

The study will consist of 3 phases: A Screening Phase, a Treatment Phase (Intervention Phase), and a Follow-up Phase (Postintervention Phase). The Screening Phase will be up to 28 days before randomization. Subjects will receive either D-VRd or VRd for 8 cycles. No subject will receive bortezomib after completion of the first 8 cycles of VRd. After completing 8 cycles of therapy, subjects will continue with DRd or Rd until disease progression or unacceptable toxicity. Subjects who discontinue treatment with any one component of study treatment (bortezomib, lenalidomide, dexamethasone, or daratumumab) may continue to receive treatment with the other components of study treatment, as assigned. Subjects will enter the Follow-up Phase once they have documented disease progression, or unacceptable toxicity and all treatment is discontinued. In the Follow-up Phase, subjects who discontinued before disease progression must continue to have

disease evaluations according to the Schedule of Activities until confirmed PD, death, withdrawal of consent, lost to follow-up, or the end of data collection. After disease progression is documented, follow-up will be obtained at least every 16 weeks until the final PFS analysis. Subsequent anticancer treatment, PFS2 (per investigator judgment), second primary malignancies, and survival will also be recorded.

The primary analysis of the overall MRD negativity rate will be performed approximately 18 months after the last subject is administered his/her first dose of study treatment. The final PFS analysis will take place when approximately 162 PFS events have been reached. An interim analysis for PFS is planned, when 98 PFS events (60% of total planned PFS events) are expected to have been accumulated. After the cut-off for the final PFS analysis, sponsor confirmation of disease response and progression will no longer be required and will be based on investigator assessment. Investigator-assessed long-term PFS, PFS2, and OS will continue to be collected until end of data collection, which will be 7 years after the last subject is randomized into the study, or earlier at sponsor discretion. Updates to the final Clinical Study Report for both efficacy and safety will be provided in an addendum to the Clinical Study Report at study closure.

Assessment of tumor response and disease progression will be conducted in accordance with the IMWG response criteria. An assessment of MRD will be conducted on bone marrow samples. Safety evaluations will include AE monitoring, physical examinations, electrocardiogram (ECG) monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status. Blood samples will be drawn for assessment of pharmacokinetic and immunogenicity parameters.

An IDMC will be commissioned for this study to review safety and efficacy results before the final analysis of PFS. After each review at the primary MRD analysis and the interim analysis of PFS, the IDMC will make recommendations regarding the unblinding and the continuation of the study. The IDMC will also review cumulative safety data after the first 100 subjects have been treated for at least 1 cycle or discontinued, and thereafter every 6 months. Refer to Section 9.8, for details.

When data from the study are available, the benefit-risk assessment of D-VRd versus VRd will be conducted by comparing between-treatment differences of key efficacy and safety endpoints. Efficacy endpoints may include overall MRD negativity rate, durable MRD negativity rate, PFS, duration of response, and improvement in PRO measures. Safety endpoints may include serious infections (eg, pneumonia, lower respiratory tract infection), atrial fibrillation, diarrhea, infusion reactions and other SAEs or events of special interest. Safety endpoints that show no between-treatment differences will be noted but may be excluded from the benefit-risk analyses. Adverse events (AEs) not in this list, but that show a clinically meaningful between-treatment difference may be included. More detailed information about the known and expected benefits and risks of daratumumab can be found in the daratumumab IB. A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Rationale for Study Design

The VRd regimen in this study is based upon the SWOG S0777 study in newly diagnosed subjects with multiple myeloma for whom transplant is not planned as frontline therapy, which utilized eight 21-day cycles of induction therapy with VRd followed by Rd continuous therapy until PD.[13] Continuous therapy with Rd until disease progression was demonstrated to be superior to a fixed 18-month duration of therapy in the FIRST study.[4,41] In the current study, treatment with Rd will continue until disease progression or unacceptable toxicity in Arms A and B. The SWOG S0777 study utilized IV bortezomib which resulted in 33% Grade 3 or higher neurologic toxicity in the VRd arm compared with the Rd arm. For this study, bortezomib will be given via SC administration which has been shown to decrease neurotoxicity versus IV administration.[28]

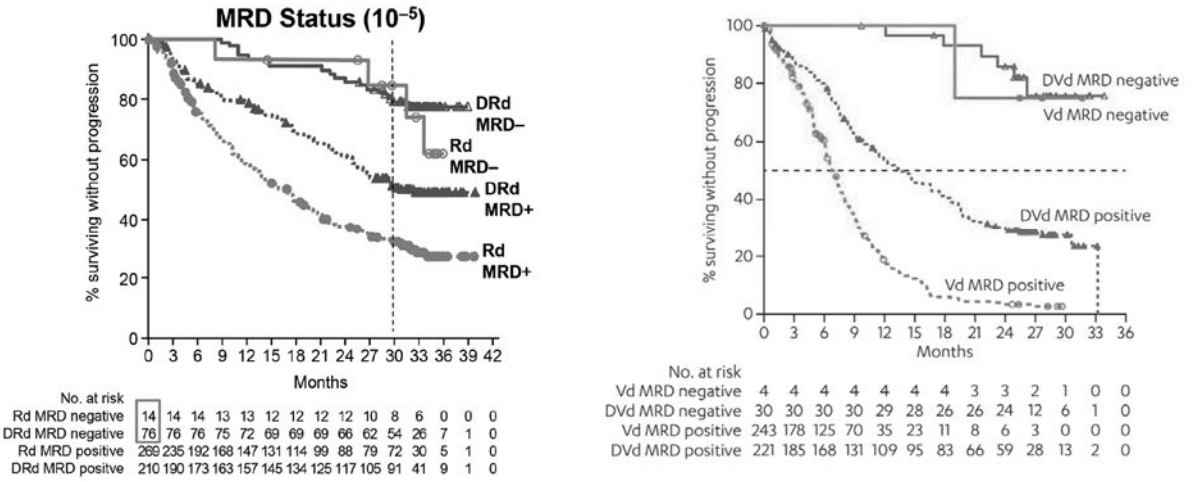
Rationale for MRD as a Primary Endpoint

Achievement of MRD negativity by flow or next generation sequencing (NGS) at a cutoff of both 10^{-4} and 10^{-5} has been correlated with improvement of both PFS and OS.[20,21,30] These meta-and pooled analyses of MRD data have demonstrated that MRD negative status is the strongest independent prognostic biomarker for PFS and OS in newly diagnosed multiple myeloma. Based upon the strength of these early analyses, the acceptance of MRD as a validated, clinical endpoint may be achieved in the near future.

Furthermore, data from 2 studies utilizing daratumumab in combination with either Rd (MMY3003) or Vd (MMY3004) in subjects with relapsed/refractory multiple myeloma have shown over a 3-fold increase in the number of subjects who achieved MRD negative status (Figure 4).[3] Subjects achieving MRD negative status demonstrated improved PFS (Figure 4). These studies utilized the FDA-approved clonoSEQ v2.0 MRD assay (Adaptive Biotechnologies®) that is an analytically validated NGS assay. The use of the clonoSEQ assay allows for centralized analysis and the consistent, accurate evaluation of MRD status that will support the primary endpoint.

Figure 4: Progression-free Survival According to MRD Status 10^{-5} in Studies MMY3003 and MMY3004

Study MMY3003 **Study MMY3004**



In this study, minimal residual disease (MRD) initially will be evaluated at suspected CR when a subject has achieved a deep clinical response. For subjects who achieve CR, have not progressed, and remain on the study, additional landmark bone marrow aspirate samples will be obtained to allow for the statistical analysis of the association of MRD with PFS/OS and to evaluate the durability of MRD negativity in these subjects.

The primary endpoint will evaluate the overall MRD negativity rate in both arms thus capturing the best overall MRD negativity rate between the 2 arms. Further secondary endpoints will assess the durability of MRD negativity, thus assessing whether subjects who obtain MRD negativity are able to maintain that depth of response. The sponsor will assess the impact of this durability of MRD negativity on the long-term outcome of PFS. Further, the sponsor will assess whether fixed-timepoints for evaluation of MRD negativity are as predictive of long-term outcome as the overall MRD negative rate. The primary analysis for MRD at the 18-month timepoint was chosen in order to mitigate the impact of Coronavirus Disease 2019 (COVID-19) on MRD sample collection, and to ensure the maturity of MRD negativity at the primary analysis.

Rationale for Subcutaneous Daratumumab

A new formulation of daratumumab for subcutaneous (SC) administration has been developed to avoid the long infusion time that frequently requires hospitalization with IV administration of daratumumab and to lessen the rate and severity of infusion-related reactions observed with IV daratumumab. Further, an enzyme rHuPH20 was used in the SC formulation in order to facilitate the high-volume SC administration.

This SC formulation of daratumumab is currently being evaluated in Study MMY1004, an open-label, multicenter, dose escalation Phase 1b Study. This study assessed the safety, pharmacokinetics, and efficacy of SC administration of daratumumab plus rHuPH20 (DARA-PH20) in subjects with relapsed or refractory multiple myeloma. After a median treatment duration of 5.6 months (clinical cutoff date of 13 Dec 2017), 25 subjects received at least 1 dose

of 1800 mg Dara-SC in Study MMY1004.[8] The infusion-related reaction rate was 16% and consisted of Grade 1 or 2 chills, dyspnea, sneezing and allergic rhinitis, and two Grade 3 events of hypertension. None of the IRR events led to treatment discontinuation. Injection-site reactions occurred in 12% of subjects, all were Grade 1. The events were discoloration/injection-site induration, hematoma, and erythema. The ORR was 52% with 28% VGPRs. Median PFS has not been reached. The efficacy and AE profile are consistent with that of IV daratumumab with a lower rate of infusion-related reactions. Based on this clinical data and supported by the pharmacokinetic profile of Dara-SC, the safety and efficacy of Dara-SC appear equivalent to and may be better than Dara-IV. The SC formulation is currently being further tested in Study, MMY3012, a Phase 3 study of Dara-IV versus Dara-SC in subjects with relapsed or refractory multiple myeloma.

Rationale for rHuPH20 Concentration

In this study, the concentration of rHuPH20 in Dara-SC will be 2000 U/mL; this is the same concentration and total amount of rHuPH20 administered in Part 2 of Study MMY1004 with the co-formulated drug product (Dara-CF). Products approved for commercial use, such as Herceptin SC (trastuzumab) and MabThera SC (rituximab), also contain 2000 U/mL of rHuPH20. Two studies in minipigs support the use of this concentration of rHuPH20 in SC daratumumab (Dara-SC). In the first study, 20 mg/mL of human IgG in daratumumab formulation buffer was formulated with 200, 500, or 800 U/mL of rHuPH20 and infused SC into the abdomen of sedated animals at a rate of 2 or 4 mL/min using a syringe pump. The higher infusion rate (4 mL/min) resulted in less local swelling and erythema. Erythema, when present, was mild and subsided by the next day. Infusion pressures were similar for all concentrations of rHuPH20 at both infusion rates (~40 to 60 mm Hg or 1 PSI). The second study evaluated 100 mg/mL daratumumab formulated with 50, 500, 2000, or 5000 U/mL of rHuPH20. Sixteen (16) mL of each formulation was infused SC into the abdomen of sedated animals at a rate of 3 mL/minute. Infusion pressures showed a dose-dependent trend where pressures were reduced as the concentration of rHuPH20 increased. Formulations with ≥500 U/mL of rHuPH20 showed relatively small areas of local swelling that was mainly soft to the touch with mild to no erythema. These all resolved by the following day, with many resolving within an hour.

Rationale for Fixed Daratumumab Dose

Dara-IV exhibits a wide therapeutic window with no apparent relationship between drug exposure in the therapeutic dose range and AEs of interest, which supports the feasibility of utilizing a fixed dose approach. Simulations based on preliminary PK data from Part 1 of the MMY1004 study where a mix-and-deliver SC presentation (Dara-MD) of the currently approved daratumumab IV formulation was used indicated that across weight quartiles, similar exposure and variability was predicted for each dosing approach (either Dara-MD 1800 mg or daratumumab IV 16 mg/kg). Based on these simulations and the safety, efficacy, and PK data in Study MMY1004, fixed dosing for SC administration is a feasible approach and will be used in this study.

Rationale for Daratumumab Dose Regimen

Previous exposure-response analyses have demonstrated a strong correlation between ORR and the maximum daratumumab lowest drug concentration reached before the next dose is administered (C_{trough}) which occurs at the end of weekly dosing (Cycle 3 Day 1 in the monotherapy

schedule). These analyses have also demonstrated the lack of relationship between daratumumab concentrations and AEs in the therapeutic dose range. Therefore, the dose of Dara-SC selected is intended to achieve a similar or greater maximum C_{trough} compared with 16 mg/kg IV administration.

As 03 Aug 2017, 18 subjects were evaluable for PK in Study MMY1004 Part 2. Analysis of the preliminary pharmacokinetic data indicated the 1800 mg Dara-SC (co-formulated) dose achieved maximum C_{trough} values comparable with, or higher than, those observed for Dara-IV 16 mg/kg. The maximum C_{trough} mean value was 904.42 µg/mL for the 1800 mg Dara-SC cohort (n=18), compared with 617.17 µg/mL in Study GEN501 Part 2 (n=27), and 573.49 µg/mL in Study MMY2002 (n=73). The range of maximum C_{trough} observations for the SC cohort is contained within the range observed following 16 mg/kg IV dosing and variability was similar with a % coefficient of variance (CV) of 46 to 58% across the SC and IV doses. The observed mean maximum observed concentration (C_{max}) values following the last (8^{th}) weekly dose for the Dara-SC cohort was 1012.4 µg/mL, similar to the mean C_{max} of 914.9 µg/mL observed after the 9^{th} dose for Dara-IV in Study MMY2002. The observed C_{max} values from the Dara-SC cohort is within the range observed for Dara-MD and 16 mg Dara-IV.

Study MMY1004 Part 2 also showed that 1800 mg Dara-SC can be administered subcutaneously by manual injection with a median of 5 minutes (ranging from 2 to 11 minutes) and it is associated with low incidence of IRRs, as noted above. The overall safety profile for the Dara-CF cohort is consistent with previously reported safety profiles for daratumumab with daratumumab IV administration and subcutaneous administration with Dara-MD. There are no new safety signals with the Dara-SC administration. Therefore, based on the available safety and PK data, the dose of 1800 mg Dara-SC is selected for study in Phase 3 studies, including this study.

The schedule utilized for this study begins with two 21-day cycles of weekly daratumumab dosing to quickly achieve effective daratumumab concentrations, which is the same initial dosing schedule (6 weeks of weekly dosing) as used in the MMY3007 study of daratumumab (16 mg/kg IV) + VMP. The results from MMY3007 showed that the maximal trough concentration was similar following the D-VMP dose regimen in subjects with newly diagnosed multiple myeloma and the approved dose regimens in previous monotherapy and combination therapy studies in subjects with relapsed or relapsed and refractory multiple myeloma, indicating 6 weeks of weekly dosing in newly diagnosed multiple myeloma subjects is sufficient to achieve effective concentrations. For Cycles 3-8 daratumumab will be given every-3-weeks and then every-4-weeks for Cycle 9 and beyond; this progression to every-3-week and every-4-week dosing intervals is similar to other approved daratumumab dosing schedules and is intended to maintain target saturation.

Rationale for Pharmacokinetics and Immunogenicity Assessments

Data obtained from this study will provide information about the PK profile of Dara-SC in combination with VRd in subjects with multiple myeloma. Therefore, samples will be obtained from all subjects for PK assessments. Data may also be used for a population PK analysis to

estimate additional PK parameters and provide information about the determinants of inter-subject variability in this population.

Immunogenicity to daratumumab or rHuPH20 is possible. Therefore, the presence of anti-daratumumab antibodies and anti-rHuPH20 antibodies (immunogenicity) will be determined from PK samples collected from all subjects in Arm B.

Rationale for DNA and Biomarker Collection

Biomarker samples will be collected to evaluate the depth and durability of clinical response to daratumumab through evaluation of MRD, using DNA sequencing of immunoglobulin genes (FDA-approved clonoSEQ v2.0, Adaptive Biotechnologies®). Emerging data suggest that the evaluation of circulating tumor DNA may be a less invasive method to identify biomarkers of response than a bone marrow aspirate.

Rationale for Medical Resource Utilization

Medical resource utilization (MRU) data will be collected to determine the medical cost impact of D-VRd and VRd treatment regimens. The data collected will be used to conduct exploratory analyses that may be used to support the value story and cost-effectiveness modeling for market access.

Rationale for Patient-reported Outcome Evaluations

The PRO data complements data collected by clinical and laboratory findings to describe the subject experience, directly reported by the subject. Patient-reported outcome data is supportive of the clinical endpoints and captures inputs required for cost-effectiveness modeling. In addition, the PRO data provides the patient perspective to communicate the value of treatment to patients, clinicians, regulators, and payers.

4.2.1. Study-Specific Ethical Design Considerations

This study is designed to provide a highly efficacious regimen for the treatment of multiple myeloma for subjects who are either transplant eligible or ineligible. VRd is established as a standard treatment option for newly diagnosed myeloma. The improved outcomes of daratumumab in combination with either of the components (DRd or DVd) in Phase 3 studies MMY3003 and MMY3004 and the preclinical synergy observed with the combination indicates the potential for improved outcome for daratumumab in combination with VRd. The safety profile of daratumumab primarily consists of infusion-related reactions. This study will utilize SC daratumumab administration, which demonstrated a lower IRR rate compared with IV daratumumab administration. Based on the mode of action of daratumumab, infection could be a potential risk; therefore, the protocol requires the review of hematological laboratory results prior to daratumumab administration. CD38 is distributed in erythrocytes and platelets. Routine safety laboratory measurement of red blood cells (RBC) and platelets will be closely monitored in this study. An IDMC will be established to review safety data on a regular basis throughout the duration of the study, and review both safety and efficacy results at primary analysis of the overall MRD negativity rate and the interim analysis for PFS. Based on the data presented in Section 2.1.5 and the addition of daratumumab to VRd is anticipated to provide benefit to subjects in this study.

Potential subjects will be fully informed of the risks and requirements of the study, and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled. Note that as specified in Appendix 3 (Section 10.3) a legally designated representative may provide consent on behalf of the subject.

Blood volumes drawn for all phases of the study are provided in Section 8.1.1. The total blood volume to be collected is considered to be acceptable for subjects with multiple myeloma participating in a clinical study and reasonable over the time frame of the study.

4.3. Measures to Minimize Bias: Randomization and Blinding

Eligible subjects will be stratified by ISS (Stage I, II, or III, based on β-2 microglobulin and albumin by central laboratory), and age/transplant eligibility (<70 years ineligible, or age <70 years and refusal to transplant, or age ≥70 years), and then assigned randomly to 1 of 2 treatment groups in a 1:1 ratio based on an algorithm implemented in the interactive web response system (IWRS) before the study. The randomization will be balanced by using randomly permuted blocks. Based on the randomization code, the IWRS will assign a unique intervention code, which will dictate the intervention assignment and matching study drug kit for the subject.

As this is an open study, blinding procedures are not applicable.

4.4. End of Study Definition

The end of data collection is defined as 7 years after the last subject is randomized, or earlier at sponsor discretion. The sponsor will notify sites of the end of data collection, after which point no additional eCRF data will be collected and the clinical database will be closed. Data collected in the eCRF following the final PFS analysis up until the end of data collection will be reported in an addendum to the Clinical Study Report. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

The sponsor will ensure that subjects who are still receiving treatment with daratumumab at the end of data collection can continue to receive study treatment until and after the end of the study.

The end of study is defined as when one of the following occurs (whichever comes first):

- When all subjects who are still receiving study treatment at the end of data collection have access through another source such as a commercial availability, continued access through a dedicated long-term extension study, or a patient access program.
- When all subjects have discontinued daratumumab treatment.
- By 31 October 2028.

5. STUDY POPULATION

Screening for eligible subjects will be performed within 28 days before randomization. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures is allowed. The inclusion and exclusion criteria for enrolling subjects in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed. For a discussion of the statistical considerations of subject selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Newly diagnosed and not considered candidate for high-dose chemotherapy with stem cell transplantation (SCT) due to:
   - Being age ≥65 years

     or
   - age 18-65 years with presence of comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with SCT or who refuse high-dose chemotherapy with SCT as initial treatment.
2. Diagnosis of multiple myeloma as documented per IMWG criteria: Monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma and documented multiple myeloma satisfying at least one of the CRAB (calcium, renal, anemia, bone) criteria or biomarkers of malignancy criteria:

   <u>CRAB criteria:</u>

   1. Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than upper limit of normal (ULN) or >2.75 mmol/L (>11 mg/dL)
   2. Renal insufficiency: creatinine clearance <40mL/min or serum creatinine >177 µmol/L (>2 mg/dL)
   3. Anemia: hemoglobin >2 g/dL below the lower limit of normal or hemoglobin <10 g/dL
   4. Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography (PET)-CT

   <u>Biomarkers of Malignancy:</u>

   a. Clonal bone marrow plasma cell percentage ≥60%
   b. Involved: uninvolved serum free light chain (FLC) ratio ≥100
   c. >1 focal lesion on magnetic resonance imaging (MRI) studies
3. Must have measurable disease, as assessed by central laboratory, defined by any of the following:

- IgG, IgA, IgM, IgD, or IgE multiple myeloma: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
- Light chain multiple myeloma without measurable disease in serum or urine: Serum Ig FLC ≥10 mg/dL and abnormal serum Ig kappa lambda FLC ratio.

4. ECOG performance status score of 0, 1, or 2 (Appendix 7 [10.7])

5. Criterion modified per Amendment 2.

5.1 Criterion modified per Amendment 3

5.2 Clinical laboratory values meeting the following criteria during the Screening Phase:

a. hemoglobin ≥7.5 g/dL (≥5 mmol/L) (without prior RBC transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted);
b. absolute neutrophil count (ANC) ≥1.0 x10^9/L (granulocyte colony stimulating factor [G-CSF] use is permitted);
c. platelet count ≥70 x10^9/L for subjects in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count >50 ×10^9/L (transfusions are not permitted within 7 days);
d. aspartate aminotransferase (AST) ≤2.5 x ULN;
e. alanine aminotransferase (ALT) ≤2.5 x ULN;
f. total bilirubin ≤1.5 x ULN, except in subjects with congenital bilirubinemia, such as Gilbert syndrome (direct bilirubin ≤2.0 x ULN);
g. Estimated creatinine clearance (CrCl) ≥30 mL/min. Creatinine clearance can be calculated using the Cockcroft-Gault formula[9] (Appendix 8 [Section 10.8]) or eGFR (MDRD; Appendix 9 [Section 10.9]), or CKD-epi formula, or for subjects with over- or underweight, CrCl may be measured from a 24-hours urine collection using the formula provided in Appendix 8 [Section 10.8]). If Cockcroft-Gault formula is used and body mass index (BMI) is ≥30 kg/m^2 then adjusted body weight should be used in calculation (Appendix 8 [Section 10.8]);
h. corrected serum calcium ≤13.5 mg/dL (≤3.4 mM/L); or free ionized calcium ≤6.5 mg/dL (≤1.6 mM/L) (Appendix 10 [Section 10.10])

Note: For criteria 6 to 11, contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

6. Female subjects of reproductive childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously during the Treatment Period, during any dose interruptions, and for 3 months after the last dose of any component of the treatment

regimen. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. This birth control method must include one highly effective form of contraception (tubal ligation, intrauterine device, hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy (Appendix 5 [Section 10.5]).

7. A woman of childbearing potential must have 2 negative serum or urine pregnancy tests at Screening, first within 10 to 14 days prior to dosing and the second within 24 hours prior to dosing. For requirements during the Treatment Phase, refer to Section 5.3.

8. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 3 months after receiving the last dose of any component of the treatment regimen.

9. Male subjects of reproductive potential who are sexually active with females of reproductive potential must always use a latex or synthetic condom during the study and for 3 months after discontinuing study treatment (even after a successful vasectomy).

10. Male subjects of reproductive potential must not donate sperm during the study or for 3 months after the last dose of study treatment.

11. Criterion modified per Amendment 6

    11.1 Must sign an informed consent form (ICF) or their legally designated representative must sign indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

12. Able to adhere to the prohibitions and restrictions specified in this protocol.

5.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Frailty index of ≥2 according to Myeloma Geriatric Assessment score.[31,35]

2. Criterion modified per Amendment 3.

    2.1 Prior therapy for multiple myeloma other than a short course of corticosteroids (not to exceed 40 mg of dexamethasone, or equivalent per day, total of 160 mg dexamethasone or equivalent).

3. Prior or concurrent invasive malignancy (other than multiple myeloma) within 5 years of date of randomization (exceptions are adequately treated basal cell or squamous cell

carcinoma of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years).

4. Peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.

5. Criterion modified per Amendment 3.

   5.1 Focal radiation therapy within 14 days of randomization with the exception of palliative radiotherapy for symptomatic pain management. Radiotherapy within 14 days prior to randomization on measurable extramedullary plasmacytoma is not permitted even in the setting of palliation for symptomatic management.

6. Plasmapheresis within 28 days of randomization.

7. Clinical signs of meningeal involvement of multiple myeloma.

8. Chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted. (FEV1 testing is required for subjects suspected of having COPD).

9. Moderate or severe persistent asthma within the past 2 years (see Appendix 11 [Section 10.11]), uncontrolled asthma of any classification. (Subjects who have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).

10. Criterion modified per Amendment 2.

    10.1 Criterion modified per Amendment 3

    10.2 Subject is:

    a. Known to be seropositive for human immunodeficiency virus (HIV).
    b. seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to total hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.
    c. Known to be seropositive for hepatitis C virus (HCV; anti-HCV antibody positive or HCV-RNA quantitation positive), except in the setting of a sustained

virologic response (SVR), defined as aviremia at least 12 weeks after completion of antiviral therapy.

11. Concurrent medical or psychiatric condition or disease (such as but not limited to, systemic amyloidosis, POEMS, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard if enrolled in the study.

12. Has clinically significant cardiac disease, including:

    - Myocardial infarction within 6 months before signing the ICF, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV; Appendix 18 [Section 10.18])
    - Uncontrolled cardiac arrhythmia or clinically significant ECG abnormalities
    - Screening 12-lead ECG showing a baseline QT interval as corrected by Frederica's formula (QTcF) >470 msec.

13. Received a strong CYP3A4 inducer within 5 half-lives prior to randomization.[17]

14. Allergy, hypersensitivity, or intolerance to boron or mannitol, corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to the Investigator's Brochure), or sensitivity to mammalian-derived products or lenalidomide.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 3 (Section 10.3) Regulatory, Ethical, and Study Oversight Considerations.

5.3. Restrictions During Study Participation

Potential subjects must be willing and able to adhere to the following restrictions during the study to be eligible for participation:

1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. A woman of childbearing potential must remain on a highly effective method of birth control (see inclusion criteria). Contraception must begin 4 weeks before initiating treatment with daratumumab and lenalidomide, and continue during the Treatment

Phase, during dose interruptions and continuing for at least 4 weeks after the last dose of lenalidomide and 3 months following of the last dose of daratumumab. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. In addition, women must not donate ova during the study, for 4 weeks after the last dose of lenalidomide, and for 3 months after the last dose of daratumumab. All women must not breastfeed while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

4. Criterion modified per Amendment 6

   4.1 During the Treatment Phase, pregnancy tests are required weekly during Cycle 1 and then monthly in subsequent cycles in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. A pregnancy test is also required at the End-of-Treatment Visit and 28 days following the last dose of lenalidomide for women with regular menstrual cycles or 14 and 28 days following the last dose of lenalidomide for women with irregular menstrual cycles. Additional pregnancy tests may be required, as specified in the local lenalidomide Risk Evaluation and Mitigation Strategy (REMS) (where lenalidomide is supplied locally) or the Lenalidomide Global Pregnancy Prevention Plan (where lenalidomide is supplied centrally and no local lenalidomide REMS program exists).

   - In order to mitigate the risk of embryo-fetotoxicity associated with exposure to lenalidomide, all investigators will prescribe lenalidomide according to the following requirements:
   - All investigators at study centers will comply with either CELGENE's Global Lenalidomide Pregnancy Prevention Plan for subjects in clinical trials, or the Lenalidomide Global Pregnancy Prevention Plan. This applies to countries where study drug will be dispensed as Investigational Medicinal Product.
   - All investigators at study centers will comply with either the respective CELGENE country-specific Revlimid Risk Minimization Program (ie, pregnancy prevention program) as implemented in the post-marketing setting, or the Lenalidomide Global Pregnancy Prevention Plan. This applies to countries where study drug will be dispensed as Non-Investigational Medicinal Product.

5. A man who has not had a vasectomy and who is sexually active with a pregnant woman or a woman of childbearing potential must agree to use a barrier method of birth control eg, condom with spermicidal foam/gel/film/cream/suppository during the study and for at least 4 weeks after the study, All men must not donate sperm during the study, during dose interruptions, or for at least 4 weeks after the last dose of lenalidomide, and for 3 months after the last dose of daratumumab. The exception to this restriction is that if the subject's female partner is surgically sterile, a second method of birth control is not required.
6. Because of the embryo-fetal risk of lenalidomide all subjects must adhere to the local lenalidomide REMS program (when lenalidomide is supplied locally), or the

Lenalidomide Global Pregnancy Prevention Plan (when lenalidomide is supplied centrally and no local lenalidomide REMS program exists).

7. Subjects must not donate blood during therapy, during dose interruptions and for at least 4 weeks following discontinuation of lenalidomide.
8. Typically, IV contrast is not used in CT scanning of subjects with secretory multiple myeloma because of the risk to the kidney. If administration of IV contrast is necessary, then adequate precautions including hydration are indicated.

5.4. Screen Failures

Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and age at initial informed consent.

In cases where the subject is not randomized into the study, the date seen and age at initial informed consent will be used.

Subjects who fail to meet the inclusion criteria or who fulfill any of the exclusion criteria (ie, screen failures) may be rescreened once if their condition changes. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Subjects who are determined to be eligible for the study after rescreening must sign a new ICF and then will be assigned a new screening number.

6. STUDY DRUG

The study medicinal products and their designations are listed in Table 3.

Table 3: Designations of Medicinal Products Used in the Study

<table>
<tr><th>Designation</th><th>Product</th></tr>
<tr><td>Investigational Medicinal Product(s)</td><td>Daratumumab SC

Authorization status in the EU/EEA
<table><tr><td>Authorized</td><td>Daratumumab SC</td></tr><tr><td>Unauthorized</td><td>None</td></tr></table></td></tr>
<tr><td>Non-investigational Medicinal Product(s) (NIMP)/Auxiliary Medicinal Product(s) (AxMP)</td><td>Bortezomib, Lenalidomide, Dexamethasone

Authorization status in the EU/EEA</td></tr>
</table>

Table 3: Designations of Medicinal Products Used in the Study

Designation	Product	
	Authorized	Bortezomib, Lenalidomide, Dexamethasone
	Unauthorized	None

6.1. Daratumumab

6.1.1. Daratumumab Subcutaneous Preparation

Dara-SC will be provided as a fixed-dosed (1800 mg), combination drug product containing rHuPH20 drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial. Manuals with detailed descriptions for preparation and administration of daratumumab will be supplied to each pharmacy and site.

6.1.2. Daratumumab Administration

Daratumumab (1800 mg) will be administered by SC injection by manual push over approximately 3-5 minutes in the abdominal subcutaneous tissues in left/right locations, alternating between individual doses. The volume of the SC solution will be 15 mL for the 1800 mg dose. Refer to the SmPC, USPI, local prescribing information, or equivalent documentation for additional guidance on study treatment handling, administration, and storage. All subjects will be observed for at least 6 hours after the end of the SC injection during Cycle 1 Day 1 and, if deemed necessary by the investigator, after subsequent injections. Reasons for continued observation on subsequent daratumumab injections may include but are not limited to the following: subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with COPD who have an FEV1 <80% at screening or developed FEV1 <80% during the study without any medical history), subjects with IRR with first injection of study drug, subject with a decreased condition on day of dosing compared to prior dosing day. The dose of daratumumab will remain constant throughout the study.

Daratumumab will be administered weekly in Cycles 1-2, every 3 weeks in Cycles 3-8, and every 4 weeks in Cycle 9 and beyond until the subject has progression or unacceptable toxicity. Every effort should be made to keep subjects on the planned dosing schedule see Schedule of Activities (Section 1.3) for acceptable window for treatment. However, doses given within 3 days of the scheduled dose are permitted. Cycles 1-8 are 21 days and Cycle 9 and beyond are 28 days.

All daratumumab administrations will be in an outpatient setting. Subjects will receive pre-injection medications and post-injection medications as outlined in Sections 6.1.3.1 and 6.1.3.2, respectively.

As noted in the Schedule of Activities (Section 1.3), vital signs should be monitored extensively on Cycle 1 Day 1 before, and after the first administration of daratumumab. For all other administrations, vital signs should be measured before the start of injection and at the end of the injection. If the subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a SAE.

On dosing days where the VRd combination is given with daratumumab they should be administered in the following order:

- Lenalidomide, dexamethasone, daratumumab, and bortezomib.
- If preference is to administer lenalidomide at night, the order should be: dexamethasone, daratumumab, bortezomib, and lenalidomide.

Daratumumab will be manufactured and provided under the responsibility of the sponsor. Refer to the daratumumab IB for a list of excipients.

6.1.3. Guidelines for Prevention and Management of Injection Reactions

6.1.3.1. Pre-administration Medication

To decrease the risk of IRRs, all subjects will receive the following medications 1 to 3 hours prior to each study drug administration:

- Paracetamol (acetaminophen) 650-1000 mg IV or orally (PO).
- An antihistamine: diphenhydramine 25-50 mg IV or PO, or equivalent (see Appendix 12 [Section 10.12]) for list of antihistamines that may be used). Avoid IV promethazine.
- Dexamethasone 20 mg Cycles 1-8 and 40 mg for Cycle 9 and beyond IV or PO on injection days. For subjects older than 75 years or underweight (body mass index [BMI] <18.5), dexamethasone 20 mg may be administered as appropriate (see Section 6.5). An equivalent intermediate-acting or long-acting corticosteroid may substitute (see Appendix 13 (Section 10.13 for conversion table).
- Montelukast 10 mg (or equivalent) is recommended on Cycle 1 Day 1 only up to 24 hours prior to daratumumab injection.

If necessary, due to timing constraints, all PO pre-injection medications may be administered outside of the clinic on the day of the injection, provided they are taken within 3 hours before the injection.

6.1.3.2. Post-administration Medication

For subjects with a higher risk of respiratory complications (e.g., subjects with mild asthma or subjects with COPD who have an FEV1 <80% at screening or developed FEV1 <80% during the study without any medical history), the following post-injection medications should be considered:

- Antihistamine
- Short-acting β2 adrenergic receptor agonist such as salbutamol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with COPD).

In addition, subjects at-risk for respiratory complications may be hospitalized for monitoring for up to 2 nights after an injection after daratumumab administration. If subjects are hospitalized, then their FEV1 should be measured before discharge. If these subjects are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after all injections. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a SAE. Investigators may prescribe bronchodilators, antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event that bronchospasm occurs after a subject is released from the hospital/clinic. If, after 4 full doses, an at-risk subject experiences no major IRR, then these post-injection medications may be stopped.

6.2. Management of Injection-site and Injection-related Reactions

6.2.1. Local Injection-site Reactions

In Study MMY1004 Part 1, SC administration of daratumumab in abdominal SC tissue was associated with local injection-site reactions, such as induration and erythema, in some subjects. The reactions usually resolved within 60 minutes. Local injection-site reactions should be managed per institutional standards.

6.2.2. Injection-related Reactions

Subjects should be observed carefully during daratumumab administrations. Trained study staff at the clinic should be prepared to intervene in case of any IRRs, and resources necessary for resuscitation (e.g., agents such as epinephrine and aerosolized bronchodilator, medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

If an IRR develops, then daratumumab administration should be temporarily interrupted. Subjects who experience AEs during daratumumab administration must be treated for their symptoms. Subjects should be treated with paracetamol (acetaminophen), antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors. If ocular symptoms (including choroidal effusion, acute myopia, and acute angle closure glaucoma) occur, interrupt daratumumab and seek immediate ophthalmologic evaluation prior to restarting daratumumab. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or an anaphylactic reaction, daratumumab should be discontinued.

6.2.2.1. Injection-related Reactions of Grade 1 or Grade 2

If the investigator assesses a Grade 1-2 IRR AE to be related to administration of study drug, then the daratumumab administration should be paused. When the subject's condition is stable, daratumumab administration may be restarted at the investigator's discretion. Refer to the sIPPM for further details regarding continuation of daratumumab administration.

If the subject experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the subject must be permanently discontinued from daratumumab treatment.

6.2.2.2. Injection-related Reactions of Grade 3 or Higher

For IRR AEs (other than laryngeal edema or bronchospasm) that are Grade 3, the daratumumab administration must be stopped and the subject must be observed carefully until resolution of the AE or until the intensity of the event decreases to Grade 1, at which point the daratumumab administration may be restarted at the investigator’s discretion. Refer to the sIPPM for further details regarding continuation of daratumumab administration.

If the intensity of the AE returns to Grade 3 after restart of the daratumumab administration, then the subject must be permanently discontinued from daratumumab treatment.

For IRR AEs that are Grade 4, the daratumumab administration must be stopped and the subject permanently discontinued from daratumumab treatment.

6.2.2.3. Recurrent Injection-related Reactions

If a Grade 3 IRR (or Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm) recurs during or within 24 hours after a subsequent daratumumab administration, the subject must be permanently discontinued from daratumumab treatment.

6.3. Bortezomib (Arms A and B)

The amount (in mg) of bortezomib to be administered will be determined by body surface area, calculated per a standard nomogram, there is no maximum dose (Appendix 14 ([Section 10.14]). The calculated dose of bortezomib may be rounded to the nearest tenth of a mg (or as per institutional practice).

Subjects will receive 1.3 mg/m^2 bortezomib as a subcutaneous injection twice weekly on Days 1, 4, 8, and 11 of each 21-day cycle for Cycles 1-8. For subjects who experience injection-site reactions at the subcutaneous administration site, bortezomib may be administered by IV injection (see local prescribing information). Subjects will not receive bortezomib after the first 8 cycles of treatment. On treatment days when both bortezomib and daratumumab are administered, bortezomib must be administered after the daratumumab administration.

If a subject's weight changes by more than 10% from baseline, the weight used for drug calculations should be adjusted and the dose of bortezomib will be re-calculated. Bortezomib dosing may be delayed up to 48 hours, however subsequent doses must be adjusted to account for the delay. Note that there should be approximately 3 days between doses of bortezomib. Skipped doses of bortezomib will not be made up later in the cycle.

For subjects with unacceptable toxicity at the local injection-site despite dose modifications or change in injection concentration, bortezomib can be administered intravenously as a 3 to 5 seconds bolus injection. Refer to local prescribing information for further details on either SC or IV administration.

6.4. Lenalidomide (Arms A and B)

In Cycles 1 through 8, lenalidomide will be self-administered at a dose of 25 mg orally each day on Days 1 through 14 of each 21-day cycle for subjects with CrCl ≥60 mL/min. During Cycles 9 and beyond, lenalidomide 25 mg will be administered daily on Days 1-21 of each 28-day cycle. Lenalidomide will be continued until disease progression or unacceptable toxicity whichever occurs first. See Section 6.6.3.1, Renal Impairment for lenalidomide dose adjustments in subjects with renal impairment.

On daratumumab administration days, it is recommended that lenalidomide should be administered either prior to or at the same time (preferred) as pre-injection medication. If a daily lenalidomide dose is missed, it may be taken if <12 hours have elapsed since the time that it should have been taken. Otherwise, the missed lenalidomide dose should be skipped.

Lenalidomide should be taken as a single dose at the same time daily. Lenalidomide can be taken with or without food. Breaking or dividing the lenalidomide capsule is strongly discouraged.

6.5. Dexamethasone (Arms A and B)

Dexamethasone (or equivalent in accordance with local standards; see Appendix 13 (Section 10.13) for conversion table) will be self-administered orally, 20 mg on Days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle for Cycles 1-8. For subjects older than 75 years or underweight (BMI <18.5), the dexamethasone dose may be administered at a dose of 20 mg on days 1, 4, 8, and 11. For subjects in Arm B, the dexamethasone 20 mg oral or IV dose administered as a pre-injection medication on daratumumab injection days, replaces the oral dexamethasone dose for that day.

In Cycle 9 and beyond dexamethasone, will be self-administered orally at a total dose of 40 mg on Days 1, 8, 15, 22 of each 28-day cycle. For subjects older than 75 years or underweight (BMI <18.5), the dexamethasone dose may be administered at a dose of 20 mg weekly. For subjects in Arm B, the dexamethasone 40 mg oral or IV dose administered as a pre-injection medication on daratumumab infusing days Day 1 of each cycle replaces the oral/IV dexamethasone dose for that day. Dexamethasone will be administered until the subject experiences' disease progression or unacceptable toxicity during the treatment phase.

If a weekly dexamethasone dose is missed, it may be taken if <4 days have elapsed since the time that it should have been taken. If the next dose is scheduled to be taken within 3 days, the missed dexamethasone dose should be skipped.

Dexamethasone tablets are to be taken with or immediately after a meal or snack, preferably in the morning.

6.6. Dose Delays and Dose Modification

Any dose/dosage adjustment should be overseen by medically-qualified study site personnel (principal or sub investigator unless an immediate safety risk appears to be present).

Study drug administration must be captured in the source documents and the electronic case report form (eCRF).

6.6.1. Cycle Delay

On the first day of each new treatment cycle and before each daratumumab dose, the subject will be evaluated by the treating physician for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to NCI-CTCAE, Version 5. Dose modifications or delays will be made based on the toxicity experienced during the previous cycle of therapy or newly encountered on Day 1 of a cycle. For any neurological deficits that develop, it is strongly recommended that these be evaluated by the same physician who performed the neurological assessment at baseline. The parameters in Table 4 must be met on the first day of a new cycle (ie, the following represent baseline inclusion criteria levels):

Table 4: Re-treatment criteria before the start of Cycles 1-8[a]

Laboratory parameter	Requirements before each study agent administration
ANC	≥1.0 x10^9/L
Platelet count	≥70 x10^9/L
Hemoglobin	≥7.5 g/dL (≥4.96 mmol/L)

[a] Refer to Table 10 or management of neurotoxicity.

Retreatment criteria before the start of Cycle 9 and beyond are provided in Table 5.

Table 5: Re-treatment criteria before the start of Cycle 9 and beyond

Laboratory parameter	Requirements before each study agent administration
ANC	≥1.0 x10^9/L
Platelet count	≥50 x10^9/L
Hemoglobin	≥7.5 g/dL (≥4.96 mmol/L)

If the above parameters are not met, the start of the next cycle will be held for a minimum of 1 week from the planned start of a new cycle and a maximum of 28 days until recovery to the specified levels. Supportive care medications including transfusions should be administered at the investigator discretion. During the cycle delay, daratumumab, bortezomib, dexamethasone and lenalidomide, (all applicable) must be held.

If there is a delay in the start of a new cycle (ie, none of the study medications are given during this period) for more than 28 days due to insufficient recovery from toxicity, subjects will discontinue taking the study drugs permanently unless continuation is approved by the medical monitor. If the PRO assessment is completed and then the cycle is delayed, the PRO data does not need to be collected again when the drugs are resumed. If subject permanently discontinues therapy procedures should be performed as outlined in the Schedule of Activities (Section 1.3).

6.6.2. Daratumumab

6.6.2.1. Daratumumab Dose Modification

Individual dose modification of daratumumab is not permitted. Dose delay is recommended as the primary method for managing daratumumab-related toxicities.

6.6.2.2. Daratumumab-Related Toxicity Management

Refer to Section 6.1.3 for details on management of IRRs. If any of the following criteria are met and the toxicity is more than expected for the backbone therapy (lenalidomide, bortezomib, dexamethasone), or underlying multiple myeloma, the daratumumab injection must be held to allow for recovery from toxicity as noted below. If attribution is unclear, then daratumumab should be held until recovery from toxicity as noted below.

The criteria for a dose delay are:

- Grade 4 hematologic toxicity, except for Grade 4 lymphopenia
- Grade 3 thrombocytopenia with bleeding
- Febrile neutropenia of any grade
- Neutropenia with infection, of any grade
- Grade 3 or higher non-hematologic 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 or asthenia that was present at baseline and lasts for <7 days after the last administration of daratumumab
  - Grade 3 or 4 electrolyte disturbances which can be managed with replacement therapy
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered.

Other than on Day 1 of a cycle, if daratumumab administration does not commence within the pre-specified window (Table 6) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date.

Table 6: Daratumumab-Related Toxicity Management

Cycles	Frequency	Missed Dose	Dosing Resumption
1-2	Weekly (every 1 week)	>3 days	Next planned weekly dosing date
3-8	Every cycle (every 3 weeks)	>7 days	Next planned every 3-week dosing date
9+	Every cycle (every 4 weeks)	>14 days	Next planned every 4-week dosing date

A missed dose will not be made up. If a dose delay occurs, then pharmacokinetic blood samples should be collected on the actual day of study drug administration, not on the original scheduled administration day. After the planned final PFS analysis, pharmacokinetic and immunogenicity sampling will no longer be required for subjects in Treatment Arm B.

If a dose is delayed, the dose schedule within cycle should be maintained. If an AE deemed to be related to daratumumab requires a dose hold of more than 28 days, consult with the Sponsor to review safety, and efficacy, and to discuss continuation on study. If not approved, the subject should be discontinued from daratumumab and proceed to End-of-Treatment Visit. If daratumumab is held or discontinued, treatment with bortezomib, lenalidomide, and dexamethasone may continue.

6.6.3. Lenalidomide

Dose adjustments of lenalidomide will follow the approved labeling as noted in Table 7.

Table 7: Dose Modification for Lenalidomide

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction	Fourth Dose Reduction	Fifth Dose reduction
Lenalidomide 25 mg	Lenalidomide 20 mg	Lenalidomide 15 mg	Lenalidomide 10 mg	Lenalidomide 5 mg	Discontinue Lenalidomide

Dose adjustments should be based on the highest grade of toxicity that is ascribed to lenalidomide as noted in Table 10. If lenalidomide is held or discontinued, treatment with daratumumab (Arm B only), bortezomib, and dexamethasone may continue.

6.6.3.1. Renal Impairment

Adjustments to the dose of lenalidomide is recommended to provide appropriate drug exposure in subjects with moderate or severe renal impairment, because lenalidomide is primarily excreted unchanged by the kidney. Lenalidomide dose adjustment should be instituted for subjects with a CrCl <60 mL/min. The recommended doses for subjects with multiple myeloma and renal impairment are shown in Table 10. To be enrolled in the study, subjects must have CrCl ≥30 mL/min. If during treatment a subject's renal status changes, the dose should be adjusted as shown in Table 10. In the event of a dose adjustment, lenalidomide doses may be re-escalated at the investigator's discretion.

6.6.4. Bortezomib

Dose adjustments should be based on the highest grade of toxicity that is ascribed to bortezomib. Bortezomib therapy should be withheld at the onset of any Grade 3 or Grade 4 non-hematological or Grade 4 hematological toxicities excluding neuropathy as discussed in Table 10.

Once the symptoms of the toxicity have resolved, bortezomib therapy may be reinitiated at a 25% reduced dose per approved labeling, as follows (Table 8):

Table 8: Dose Modification for Bortezomib

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Bortezomib 1.3 mg/m^2	Bortezomib 1.0 mg/m^2	Bortezomib 0.7 mg/m^2	Discontinue bortezomib

A dose of bortezomib may be delayed up to 48 hours; however, subsequent doses must be adjusted as all bortezomib doses should be approximately 3 days apart. Doses that are delayed >48 hours or need to be withheld are skipped and will not be made up later in the cycle. Dose adjustments for toxicity should be followed as outlined in Table 10. If bortezomib is held or discontinued, treatment with daratumumab (Arm B only), lenalidomide, and dexamethasone may continue.

6.6.5. Dexamethasone

Dexamethasone may be reduced, if necessary, according to Table 9. For other Grade 3 or 4 non-hematologic and non-renal toxicities judged by the investigator to be related to dexamethasone alone, treatment with dexamethasone should be interrupted and restarted at the next lower dose level once the toxicity has resolved to Grade 2 or less. Treatment with daratumumab (Arm B only), bortezomib, and lenalidomide may continue. For complete details on dexamethasone, refer to the most current local product prescribing information.

If weekly dexamethasone dosing has been reduced below 10 mg due to AEs during study, a minimum of dexamethasone 10 mg IV or PO should continue to be administered prior to daratumumab injections.

Dexamethasone will be reduced or discontinued according to the guidelines presented in Table 9.

Table 9: Dose Reductions for Dexamethasone

First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Reduce dexamethasone by 50% from starting dose	Skip dexamethasone on days when daratumumab is not given in Arm B, or corresponding days for Arm A.	Discontinue dexamethasone

6.6.6. Dose Modification Guidelines

Dose modification guidelines for bortezomib, lenalidomide, and dexamethasone are provided in Table 10.

Note that the dose modifications in Table 10 are suggested, but physician discretion and clinical judgment should prevail.

Table 10: Dose modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib	Lenalidomide	Dexamethasone
Allergic reactions	Allergic reaction or hypersensitivity Grade 2 OR 3	Hold all therapy. If the toxicity resolves to ≤ Grade 1, restart VRd. Reduce by 1 dose-level the suspected medication(s) AND implement appropriate anti-allergic prophylaxis therapy. If the reaction was anaphylactic in nature, do not resume VRd. NOTE: If the reaction was cutaneous in nature, refer to the cutaneous category below.		
	Allergic reaction or hypersensitivity Grade 4	Discontinue VRd.		
Cardiovascular	Fluid Retention (ie, edema) >Grade 3 (limiting function and unresponsive to therapy or anasarca)			Administer diuretics as needed and decrease dexamethasone dose by 1 dose-level; if edema persists despite above measures, decrease dose another dose-level. Permanently discontinue dexamethasone if symptoms persist despite second dose reduction.
Constitutional	Fatigue[a] ≥ Grade 3 (ie, severe fatigue interfering with activities of daily living)	Hold the dose until resolved to Grade ≤2. Consider reduction of lenalidomide or bortezomib by 1 dose-level or change to bortezomib dosing once per week.		

Table 10: Dose modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib	Lenalidomide	Dexamethasone
Cutaneous	Non-blistering rash Grade 2	Hold bortezomib therapy. Begin treatment with antihistamines and/or low-dose steroids as per institutional practice. If the toxicity resolves to ≤ Grade 1, reduce dose by 1 level and restart bortezomib. Restart with lower concentration formulation. If recurrent consider IV bortezomib.	Consider holding lenalidomide.	
	Non-blistering rash ≥ Grade 3 or 4	Hold bortezomib therapies. Begin treatment with antihistamines and/or low-dose steroids as per institutional practice. If the toxicity resolves to ≤ Grade 1, reduce dose by 1 level and restart bortezomib and lenalidomide and continue antihistamines and/or low-dose steroids as per institutional practice. Restart with lower concentration formulation. If recurrent consider IV bortezomib. For Grade 4 toxicity permanently discontinue bortezomib and lenalidomide permanently.		
	Desquamating (blistering) rash- any grade or erythema multiform ≥ Grade 3	Discontinue bortezomib and lenalidomide permanently. Hold other therapies. Begin treatment with antihistamines and/or low-dose steroids as per institutional practice. If the toxicity resolves to ≤ Grade 1, restart other medications.		
Gastrointestinal	Constipation[b] ≥ Grade 3	Hold bortezomib therapy. Upon recovery to ≤ Grade 1, restart bortezomib at 1 dose-reduced level.		
	Diarrhea[c] ≥ Grade 3	Hold bortezomib and consider loperamide therapy. Upon recovery to ≤ Grade 1, restart bortezomib at 1 dose-reduced level.		
	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)			Treat with histamine-2 blockers, sucralfate, or proton pump inhibitor. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose-level.

Table 10: Dose modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib	Lenalidomide	Dexamethasone
	Dyspepsia, gastric or duodenal ulcer, gastritis ≥ Grade 3 (requiring hospitalization or surgery)			Hold dexamethasone and consider treatment with histamine-2 blockers, sucralfate, or proton pump inhibitor. Restart and reduce dexamethasone by 1 dose level if symptoms are adequately controlled. If symptoms persist despite above measures, permanently discontinue dexamethasone.
	Acute Pancreatitis			Permanently discontinue dexamethasone.
Hematological	Neutropenia Grade 3 (without complications)	No dose reduction required of bortezomib. Consider treatment with G-CSF.	Hold therapy with lenalidomide until recovery to baseline OR ≤ Grade 2. Consider G-CSF support. Upon recovery if isolated neutropenia, maintain lenalidomide at current dose level. If other hematologic toxicities present reduce lenalidomide by 1 dose level. Maintain bortezomib at current dose. If recurrent episode, reduce lenalidomide by 1 dose-level.	
	Neutropenia associated with fever (≥38.5ºC): Grade 3 or neutropenia Grade 4	Hold therapy with all drugs until recovery to baseline OR ≤ Grade 2. Consider G-CSF support. Upon recovery if isolated neutropenia, maintain lenalidomide at current dose level. If other hematologic toxicities present reduce lenalidomide by 1 dose level. Maintain bortezomib at current dose. If recurrent episode, reduce lenalidomide and bortezomib by 1 dose-level.		
	Thrombocytopenia Grade 3 (without complications)	No dose reduction required for bortezomib.	Reduce lenalidomide by 1 dose-level for the remainder of the cycle.	

Table 10: Dose modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	NCI-CTC Adverse Event and or Symptom and Category		Bortezomib	Lenalidomide	Dexamethasone
	Platelet count ≤30 x 10^9/L or ANC ≤0.75 x 10^9/L on a bortezomib dosing day		Hold bortezomib dose.		
	Platelet count <25,000/μL (ie, Grade 4) or Grade 3 thrombocytopenia with bleeding		Hold therapy with all drugs until recovery to baseline OR ≤Grade 2. Upon recovery, reduce bortezomib 1 dose level, hold lenalidomide for remainder of the cycle and decrease by 1 dose level at start of next cycle.		
Infection	Herpes Zoster[d] activation or reactivation ANY grade		Hold ALL therapies until lesions are dry. If not already underway, begin antiviral treatment Once the infection is resolved all medications can be restarted without a dose reduction; however, continued antiviral prophylaxis is required.		
Musculoskeletal	Muscle weakness >Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)				Decrease dexamethasone dose by 1 dose-level. If weakness persists despite above measures, decrease dose by 1 *further* dose-level. If symptoms *still* persist, permanently discontinue dexamethasone.
Metabolic	Hyperglycemia ≥ Grade 3				Treatment with insulin or oral hypoglycemics. If uncontrolled despite above measures, decrease dose by 1 dose-level until levels are satisfactory.
Neurological[e]	Peripheral Neuropathy (Sensory or Motor) and/or Neuropathic Pain	Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action required.		
		Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Change schedule to once per week; if recurrence Reduce bortezomib by 1 dose-level		
		Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Hold bortezomib until toxicity resolves to <Grade 2. When toxicity resolves, reinitiate with a reduction by 1 dose-level and change bortezomib treatment schedule to once per week		

Table 10: Dose modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	NCI-CTC Adverse Event and or Symptom and Category		Bortezomib	Lenalidomide	Dexamethasone
		Grade 4 (permanent sensory loss that interferes with function) and/or severe autonomic neuropathy	Discontinue bortezomib permanently.		
Neuro-psychological	Confusion or mood alteration >Grade 2 (interfering with function ± interfering with activities of daily living)				Hold dexamethasone until symptoms resolve. Restart with 1 dose-level reduction. If symptoms persist despite above measures, permanently discontinue dexamethasone.
Thromboembolic	Venous and /or pulmonary thrombo-embolism ≥ Grade 3 [Deep vein thrombosis or cardiac thrombosis intervention indicate; eg: anticoagulation, lysis, filter, invasive procedure.]			Stop until toxicity resolves and, if not already given, start anticoagulation therapy. Restart lenalidomide and dexamethasone at full dose after adequate anticoagulation.	
Renal Impairment	Moderate renal impairment-CrCl[f] 30-59 mL/min			Lenalidomide should be given at a dose of 10 mg daily	
	Severe renal impairment-CrCl[f] <30 mL/min (not requiring dialysis)			Lenalidomide should be given at a dose of 15 mg every 48 hrs	
	End-stage renal disease- CrCl[f] <30 mL/min (requiring dialysis)			Lenalidomide should be given at a dose of 5 mg daily. Administer dose after dialysis.	
Other toxicities	Any reported ≥ Grade 3		Determine drug attribution of the toxicity and hold the therapy(ies) as appropriate. If toxicity resolves to ≤ Grade 1, resume therapy with 1 level of dose reduction for suspect drug.		

Abbreviations: ANC=absolute neutrophil count; CrCl=creatinine clearance; hrs=hours; IV=intravenous; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; G-CSF=Granulocyte colony stimulating factor; VRd=VELCADE, lenalidomide, and dexamethasone

[a] Determine if fatigue is possibly not medication-related but due to an underlying cause (eg, infection, progression of disease, diarrhea, anemia, depression) and treat these symptoms/causes as appropriate.

[b] Prior to dose reduction of medications, consider/eliminate other possible causes of constipation.

[c] Prior to dose reduction of medications, consider/eliminate other possible causes (ie, bacterial or viral infections) of diarrhea.

[d] In the event that a subject is already receiving antiviral treatment at the time of the Herpes Zoster activation, consider switching to or adding another antiviral agent.

Table 10: Dose modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib	Lenalidomide	Dexamethasone

[e] The neurotoxicity-directed questionnaire is a useful tool for determining the presence and intensity of neuropathic pain and/or peripheral neuropathy from the subject's perspective. Neuropathic symptoms are more prominent than abnormalities on the clinical examination. After the subject completes the neurotoxicity-directed questionnaire, the questionnaire should be reviewed to assist with the evaluation of the onset and intensity of peripheral neuropathy and other neurotoxicities that may require intervention or dose modification.

[f] CrCl = creatinine clearance. Estimated by creatinine clearance as calculated by the Cockcroft-Gault formula and adjusted for body weight in subjects with a body mass index >30 kg/m^2. The eGFR (MDRD) or CKD-epi formulas can also be utilized to assess renal function.

6.7. Study Drug Compliance

Study drug (daratumumab) and the components of the backbone regimens (VRd) will be administered or prescribed by qualified site staff, and the details of study drug and the components of VRd administration will be recorded in the eCRF. Study drug accountability and additional study drug additional details are provided in the sIPPM or equivalent document.

6.8. Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.8.3. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

For subjects who may need stem cell transplant at a later time, stem cell harvest following mobilization with G-CSF or plerixafor or cyclophosphamide or any combination of the 3 is permitted after Cycle 4 while on study treatment. Autologous stem cell transplantation cannot be initiated as part of initial therapy.

Routine systemic use of concomitant medications will be collected in the eCRF and recorded in the source documents beginning with signing of the ICF to 30 days after the last dose of the last study treatment or until the start of subsequent anticancer treatment, if earlier. Concomitant medications to manage AEs and SAEs will be recorded as per Appendix 4 (Section 10.4).

6.8.1. Recommended Therapies

6.8.1.1. Prevention of Deep Vein Thrombosis and Pulmonary Embolism

Lenalidomide has been associated with an increased risk of deep vein thrombosis and pulmonary embolism. Therefore, prophylaxis of venous thromboembolism for all subjects is recommended according to IMWG guidelines (Appendix 19 [Section 10.19]).[38] Both individual and myeloma-related risks of venous thromboembolism should be considered in determining the type of thromboprophylaxis.

In summary:

- Individual and Myeloma-related Risk factors:
  - If no risk factor, or any one risk factor is present, then aspirin 81-325 mg once daily is recommended or dose per institutional standards.
  - If 2 or more risk factors are present, low molecular weight heparin (equivalent of enoxaparin 40 mg once daily) or full dose warfarin, a target international normalized ratio of 2-3, is recommended until the risk factors are resolved.

6.8.1.2. Bisphosphonate Therapy and Denosumab

Bisphosphonate therapy is strongly recommended for all subjects with evidence of lytic destruction of bone or with osteopenia. Bisphosphonate therapy should be continued per treatment guidelines.[29,32] Commercially available IV bisphosphonates (pamidronate and zoledronic acid) are preferred when available, and should be used according to the manufacturer's prescribing information, for subjects with osteolytic or osteopenic myelomatous bone disease. Oral bisphosphonates may be used as alternatives if IV bisphosphonates are not available at the study site. It is preferred that investigators should use the same route of bisphosphonate therapy for all subjects at their sites.

Subjects who are currently using bisphosphonate therapy when they enter the study should continue the same treatment. Subjects with an indication for bisphosphonates who are not using it at the time of randomization should start a bisphosphonate as soon as possible during Cycle 1 or 2 of treatment. Investigators should not start a bisphosphonate later during the study, unless it has been agreed with the sponsor that there is no sign of disease progression.

Denosumab is permitted as an alternative to bisphosphonate therapy and should be started as soon as possible during Cycle 1 or 2 of treatment. Investigators should not start denosumab later during the study, unless it has been agreed with the sponsor that there is no sign of disease progression.

6.8.1.3. Therapy for Tumor Lysis Syndrome

Subjects should be monitored for symptoms of tumor lysis syndrome. Management of tumor lysis syndrome, including increasing hydration and treating hyperkalemia, hyperuricemia, and hypocalcemia, is highly recommended. It is also recommended that high-risk subjects, ie, those with a high tumor burden, be treated prophylactically in accordance with local standards (eg, increased hydration; allopurinol 300 mg daily and medication to increase urate excretion). Subjects are to be provided prophylactic therapy to manage injection reactions during the Treatment Phase, as described in Section 6.1.3.1.

6.8.1.4. Prophylaxis for Bacterial Pneumonia and *Pneumocystis Carinii* Pneumonia

Antibacterial prophylaxis for bacterial pneumonia should be considered, as per institutional guidelines, especially in patients with a history of respiratory disorders.

Pneumocystis carinii pneumonia prophylaxis should be considered, as per institutional guidelines.

6.8.1.5. Prophylaxis for Herpes Zoster Reactivation

Prophylaxis for herpes zoster reactivation is recommended during the Treatment Phase and continue for 3 months following treatment with daratumumab. Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting study treatment and continue for 3 months following study treatment. Acceptable antiviral therapy includes acyclovir (eg, 400 mg given orally 3 times a day, or 800 mg given orally 2 times a day or per institutional standards), famcyclovir (eg, 125 mg given, twice a day or per institutional standards), or valacyclovir (eg, 500 mg given orally, twice a day or per institutional standards).

6.8.1.6. Prevention of Steroid Induced Gastritis

Dexamethasone and other corticosteroids may induce gastritis. Medications to prevent gastritis are permitted per institutional guidelines. For eg, proton pump inhibitors (omeprazole or equivalent) or sucralfate, or H2 blockers (ranitidine or equivalent) may be used.

6.8.1.7. Management of Hepatitis B Virus Reactivation

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation see Section 8.3.8.

For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.

6.8.2. Permitted Therapies

Subjects are to receive full supportive care during the study. The following medications and supportive therapies are examples of support therapies that may be used during the study:

- Colony stimulating factors, erythropoietin, and transfusion of platelets and red cells
- Loperamide is recommended for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose and regimen is according to institutional guidelines. Prophylactic loperamide is not recommended
- Prevention of constipation (e.g., adequate hydration, high-fiber diet, and stool softeners, if needed)
- Adequate hydration is recommended for prevention of myeloma-related kidney disease
- Prophylactic antiemetics, except for corticosteroids
- An emergency short course of corticosteroid (equivalent of dexamethasone 40 mg/day for a maximum 4 days) is permitted before treatment
- G-CSF/plerixafor for mobilization of stem cells
- Single dose of cyclophosphamide for mobilization of stem cells
- Vaccination is recommended per local guidelines (including annual influenza and inactivated SARS CoV-2 vaccines); however, some types of vaccines (eg, live, attenuated or with suspected replication capabilities) are not permitted. mRNA-based vaccines are permitted. Note that antibody responses to vaccines may be suboptimal during study treatment.[1]

Other symptoms may be managed according to institutional guidelines provided prohibited therapies are not administered (see Section 6.8.3).

6.8.3. Prohibited Therapies

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. Use of the treatments listed below is prohibited during the study:

- Concomitant administration of strong CYP3A4 inducers is prohibited with the use of bortezomib. Administration of strong CYP3A4 inhibitors (eg, ketoconazole, ritonavir) should be avoided and is not recommended in subjects receiving bortezomib. If a strong CYP3A4 inhibitor must be given in combination with bortezomib, monitor subjects for signs of bortezomib toxicity and consider a bortezomib dose reduction. For an ongoing list of CYP3A inhibitors and inducers, see Flockhart et al.[17]
- Other agents that target CD38.
- Approved or investigational treatments for multiple myeloma (including but not limited to conventional chemotherapies, immunomodulatory drugs, or PIs.
- Concomitant administration of investigational agents is prohibited, including administration of commercially available agents with activity against or under investigation for multiple myeloma.
- Systemic corticosteroids (>10 mg dexamethasone per day or equivalent, or a total maximum dose of 140 mg dexamethasone or equivalent in 14 days) other than those given for IRRs as described in Section 6.2.2.
- Non-steroidal anti-inflammatory agents should be avoided as they may exacerbate myeloma-related kidney disease.

In the absence of disease progression, should a subject require emergency orthopedic surgery or radiotherapy, upon recovery the subject may continue treatment after consultation with, and approval by, the sponsor's medical monitor. Such emergency radiotherapy may consist of localized radiotherapy for pain control or for stabilization of an extensive bone lesion at high-risk of pathologic fracture or damage to surrounding tissues in a subject in whom delay of systemic therapy is not appropriate. Such radiotherapy is to occur within the first 2 cycles of treatment and the absence of evidence of disease progression is to be reviewed and approved by the sponsor.

6.8.4. Subsequent Therapies

It is not permissible to start other anti-myeloma therapy until disease progression is confirmed by IMWG criteria. Subjects who discontinue study treatment for reasons other than disease progression should not start subsequent treatment until documented disease progression; following study treatment discontinuation, these subjects should be monitored for disease progression according to the Schedule of Activities (Section 1.3).

After confirmation of disease progression, subsequent therapy is left to the investigator's discretion. Subsequent therapy for multiple myeloma (including start and end date and best response) should be documented in the appropriate section of the CRF.

6.9. Long-term Follow-up

The Follow-up Phase will begin once a subject permanently discontinues treatment with study medications. See Section 6.8.4 above regarding subsequent therapy for multiple myeloma.

Telephone contact will be made to determine survival as per the schedule of events table until the study end unless the subject has died, is lost to follow-up, or has withdrawn consent. If the information on safety or survival is obtained via telephone contact, written documentation of the

communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and documented on the CRF. Investigators may contact the subject to obtain long-term follow-up information regarding the subject's safety or survival status as noted in the ICF (refer to Informed Consent in Appendix 3 [Section 10.3]), Regulatory, Ethical, and Study Oversight Considerations).

7. DISCONTINUATION OF STUDY DRUG AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Completion

A subject will be considered to have completed the study if he or she has finished all protocol specified procedures before the end of the study, has not been lost to follow-up, and has not withdrawn consent for study participation before the end of the study.

7.2. Discontinuation of Study Treatment

Subjects who need to discontinue treatment with any component of study treatment (bortezomib, lenalidomide, dexamethasone, or daratumumab) may continue to receive treatment with the other components of study treatment, as assigned.

A subject will not be automatically withdrawn from the study if he or she must discontinue study treatment before the end of the treatment regimen; instead, the subject will enter the Follow-up Phase. The End-of-Treatment Visits and Follow-up visit assessments should continue as specified in the Schedule of Activities (Section 1.3).

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, AE, IRR as described in Section 6.2) it is in the best interest of the subject to discontinue study drug.
  - If the subject’s dose is held for more than 28 days, or if 3 consecutive planned doses of daratumumab are missed for reasons other than toxicity, consult with the Sponsor to review safety, and efficacy, and to discuss continuation on study. If not approved, the subject should be discontinued from study treatment and proceed to End of Treatment visit.
- The subject becomes pregnant, unless the subject (or the subject's legally designated representative), investigator, and sponsor agree the benefits outweigh the risks to the fetus and continuation of study treatment is in the best interests of the subject, except for lenalidomide (which must be permanently discontinued if a subject becomes pregnant). Refer to Appendix 5 (Section 10.5 Contraceptive Guidance and Collection of Pregnancy Information. Discontinuation of all study treatment is also acceptable if mandated by local regulations.
- The subject (or the subject’s legally designated representative) withdraws consent for administration of study treatment.
- The subject received concurrent (non-protocol) treatment for multiple myeloma prior to disease progression.
- The subject experiences unacceptable toxicity, including IRR described in Section 6.2.

- The subject experiences disease progression (as outlined below).
- The subject experiences a second primary malignancy that cannot be treated by surgery alone. This scenario should be discussed with the Sponsor. However, a subject who develops a malignancy that can be cured surgically may continue to receive the assigned study treatment and should continue to be followed for subsequent progression of multiple myeloma.

The primary reason for discontinuation of study treatment is to be recorded in the eCRF.

Study treatment will continue until confirmation of disease progression. Before subjects are discontinued from study treatment because of suspected disease progression:

1. The investigator (or designee) will provide documentation of disease progression (for example, by completing a disease progression form or by contacting the IWRS) as soon as possible and within 48 hours of confirmation of disease progression.
2. The sponsor's medical monitor will review the provided documentation and confirm disease progression has occurred per IMWG criteria (see Section 8.2.1, Response Categories) and that study treatment should be discontinued.
3. After confirmation of disease progression by the sponsor, the subject will discontinue study treatment and enter the Follow-up Phase.

7.3. Subject Discontinuation/Withdrawal from the Study

A subject will not be automatically withdrawn from the study if they discontinue study drug before the end of the treatment regimen.

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent for study participation
- Death
- The study investigator or sponsor, for any reason, stops the study or stops the subject's participation in the study

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Additional subjects will not be entered to ensure the protocol-specified number of subjects complete the study. If a subject discontinues study treatment and withdraws from the study before the end of the Treatment Phase, End-of-Treatment assessments should be obtained. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

7.3.1. Withdrawal from the Use of Study Samples

The subject may withdraw consent for use of study samples (refer to Appendix 3 [Section 10.3]). In such a case, samples will be destroyed after they are no longer needed for the clinical study.

Details of sample retention are presented in the ICF.

7.4. Lost to Follow-up

A subject will be considered lost to follow-up if the subject repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A subject cannot be deemed lost to follow-up until all reasonable efforts made by the study site personnel to contact the subject are deemed futile. The following actions must be taken if a subject fails to return to the study site for a required study visit:

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

- Before a subject is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the subject (where possible, 3 telephone calls, emails, fax, and, if necessary, a certified letter to the subject's last known mailing address, or local equivalent methods). Locator agencies may also be used as local regulations permit. These contact attempts should be documented in the subject's medical records.

- Should the subject continue to be unreachable, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Study Procedures

8.1.1. Overview

The Schedule of Activities summarize the frequency and timing of assessments applicable to this study. Study assessments will be performed only after written informed consent is obtained. Every effort should be made to keep subjects on the study schedule as planned from Cycle 1 Day 1. At each visit, study assessments should be completed before the administration of any treatment. Any missed visits, tests not performed, or examinations that are not conducted must be reported as such in the eCRF.

During the treatment phase and prior to PD, the PRO measures will be completed using an electronic tablet (ePRO), unless the subject is unable to complete the visit in-person. Site-assisted, telephone-based collection of the PRO responses can be done if the subject is unable to come to the site due to the coronavirus pandemic, and paper PRO assessments can be completed as part of the home health care visits. All visit-specific PRO assessments should be completed before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions. If the subject is unable to complete the PRO assessments, the reason for not completing the questionnaires will be documented (ie, too ill, subject refused, etc). Refer to Section 8.10 for details.

Urine and blood collections should be kept as close to the specified time as possible. Other measurements may be done earlier than specified, if needed. Additional pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

The total blood volume for the study is estimated at approximately 50 mL during screening, approximately 360 mL in the Treatment Phase (Cycles 1-8). In Cycle 9 and beyond, the blood volume is estimated to be approximately 600 mL during the first two and a half years, then approximately 180 mL per year until disease progression, and approximately 10 mL per visit in the pre-PD Follow-up Phase. This includes laboratory assessments associated with safety, efficacy, and pharmacokinetic evaluations, as well as scientific study samples. At the End-of-Treatment Visit, approximately 10 mL of blood will be collected and approximately 10 mL will be collected for pharmacokinetic testing in the Post-treatment Phase. After the planned final PFS analysis, pharmacokinetic and immunogenicity samples will no longer be collected from subjects in Treatment Arm B. Unscheduled samples may be taken for safety reasons (eg, IRR) or repeat samples may be taken due to technical issues with the samples. After the planned final PFS analysis, pharmacokinetic and immunogenicity samples will no longer be collected from subjects in Treatment Arm B for safety reasons.

8.1.2. Screening Phase

The signed ICF must be obtained before any study-specific procedures are performed. The Screening Phase begins when the first screening assessment is conducted. During the Screening Phase, eligibility criteria will be reviewed by the investigator or the delegate and a complete clinical evaluation will be performed as specified in the Schedule of Activities (Section 1.3). Screening procedures will be performed within 28 days before randomization; however, results of tests such as hematology or chemistry to document CRAB criteria, skeletal survey or other radiologic tests (eg, CT scans or MRI) to document baseline lytic lesions or size of known or suspected extramedullary plasmacytomas, ECG, chest x-rays or full chest CT scans, spirometry, or bone marrow aspirate/biopsy performed within 6 weeks (42 days) before randomization as routine SOC for the subject’s disease can be used. A negative pregnancy test for women of childbearing potential must be documented within 10 to 14 days and again within 24 hours before the first dose of any component of the treatment regimen. If approved by the sponsor, subjects who are screen failures may be rescreened if their condition changes (see Section 5.4 for details).

8.1.3. Treatment Phase

Details of the procedures performed during the Treatment Phase are outlined in the Schedule of Activities. The Treatment Phase begins on Cycle 1 Day 1 and continues until disease progression or for the other reasons outlined in Section 7.3. Subjects will be monitored closely for AEs, laboratory abnormalities, and clinical response. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. If disease progression is diagnosed, then the subject will discontinue the study drugs, complete the End-of-Treatment Visit, and enter the Follow-up Phase.

8.1.4. End-of-Treatment Visit

Unless a subject withdraws consent for study participation, or is lost to follow-up, an End-of-Treatment Visit should be performed within 30 days after the last dose of all components of the treatment regimen have been discontinued. Every effort should be made to conduct the End-of-Treatment Visit before the subject starts subsequent therapy. Posttreatment PK and immunogenicity samples from subjects in Arm B still should be collected, even if a subsequent therapy has been initiated. After the planned final PFS analysis, pharmacokinetic and immunogenicity samples will no longer be collected from subjects in Treatment Arm B. If a subject is unable to return to the site for the End-of-Treatment Visit, then the subject should be contacted to collect AEs and concomitant therapies that occur within 30 days after the last dose of any component of the treatment regimen. Additional information on reporting of AEs can be found in Appendix 4 (Section 10.4).

8.1.5. Follow-up Phase

The Follow-up Phase begins when a subject permanently discontinues treatment with study medications. For all subjects who complete or discontinue study drug without disease progression, disease evaluations should continue to be performed as specified in the Schedule of Activities until documented disease progression. Thereafter subsequent anticancer treatment and response to treatment including date of subsequent progression (PFS2) will be recorded and survival status will be obtained. In accordance with the 2016 IMWG consensus recommendations for the purposes of the study a line of subsequent therapy is defined as one or more cycles of a planned treatment program. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of a disease progression, relapse, or toxicity.[40]

If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, then the date and cause of death will be collected and documented in the eCRF.

8.1.6. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the Schedule of Activities for the timing and frequency of all sample collections. Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

8.1.7. Study-specific Materials

The investigator will be provided with the following supplies:

- Study protocol
- IWRS Manual
- Investigational Product Manual

- Investigator Brochure for daratumumab
- Site Investigational Product Procedures Manual
- Laboratory manual and laboratory kits
- PRO questionnaires and completion guidelines
- Sample ICF
- Trial Center File, and corresponding site-specific documentation
- Subject study tools (including emergency ID card etc, as required)
- Investigator study tools and quick reference cards, as required.

8.2. Efficacy Assessments

Assessment of tumor response and disease progression will be conducted in accordance with the IMWG response criteria. Efficacy evaluations will include measurements of tumor burden/residual disease, myeloma proteins, bone marrow examinations, skeletal surveys, extramedullary plasmacytomas, and serum calcium corrected for albumin.

8.2.1. Response Categories

Disease evaluations must be performed as outlined in the Schedule of Activities (Section 1.3) on the scheduled assessment day (±7 days). Disease evaluations scheduled for treatment days should be collected before study drug is administered. Disease evaluations will be performed by a central laboratory until the final PFS analysis (unless otherwise specified). In exceptional circumstances up to the final PFS analysis, the local laboratory results of blood and urine M-protein measurements may be used to determine disease response and progression. After the final PFS analysis, disease evaluations will no longer be performed by the central laboratory, and local laboratory results of blood and urine M-protein measurements should be used by investigators to determine disease response and progression.

This study will use the IMWG consensus recommendations for multiple myeloma treatment response criteria[40] presented in Table 11. For quantitative immunoglobulin at baseline, M-protein, and immunofixation measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory until the final PFS analysis, after which time the investigator will use local results. The criteria for loss of CR without disease progression is presented in Table 12. During the time period when results are provided by the central laboratory, subjects with suspected daratumumab interference on serum M-protein quantitation by electrophoresis (SPEP) and immunofixation, a Hydrashift interference test will be performed (Section 8.2.2; Appendix 20 [Section 10.20). Subjects with confirmed daratumumab interference who meet all other clinical criteria for CR or sCR will be considered CR/sCR.

Table 11: IMWG Consensus Recommendations for Multiple Myeloma Treatment Response Criteria

Response	Response Criteria
Stringent complete Response (sCR)	• CR as defined below, *plus* • Normal FLC ratio, *and* • Absence of clonal PCs by immunohistochemistry, immunofluorescence[a] or 2- to 4-color flow cytometry
Complete response (CR)*	• Negative immunofixation on the serum and urine, *and* • Disappearance of any soft tissue plasmacytomas, *and* • <5% PCs in bone marrow
Very good partial Response (VGPR)*	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or* • ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours
Partial response (PR)	• ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours • If the serum and urine M-protein are not measurable, a decrease of ≥50% 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 not measurable, and serum free light assay is also not measurable, ≥50% reduction in bone marrow PCs is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% • In addition to the above criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR, or PD
Progressive disease (PD)†	• Increase of 25% from lowest response value in any one of the following: • Serum M-component (absolute increase must be ≥0.5 g/dL) • Urine M-component (absolute increase must be ≥200 mg/24 hours) • Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute increase must be ≥10%) • Bone marrow plasma cell percentage: the absolute increase must be >10% • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the PC proliferative disorder

Abbreviations: CR=complete response; FLC=free light chain; PC=plasma cell; PR=partial response; VGPR=Very good partial response; SD=stable disease.

All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither.

Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

* Clarifications to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such subjects requires a >90% decrease in the difference between involved and uninvolved FLC levels.

† Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in subjects without measurable disease by M-protein and by FLC levels; "25% increase" refers to M-protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value.

[a] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of >4:1 or <1:2.

Reference: Rajkumar 2011[40]

Table 12: Criteria for Loss of Complete Response not Meeting Criteria for Disease Progression (per Table 11)

Loss of CR	One or more of the following criteria: • Reappearance of serum M-protein by immunofixation or electrophoresis • Reappearance of urine M-protein by immunofixation or electrophoresis • Development of ≥5% plasma cells in the bone marrow
Abbreviation: CR=complete response.	

For continuation of treatment, the IMWG response will be determined on an ongoing basis by the investigator. For data analysis and reporting up to the final PFS analysis, however, the sponsor will use a validated computer algorithm that has been shown to provide consistent review of the data necessary to determine disease progression and response according to the IMWG criteria. After the final PFS analysis, the disease progression and response according to IMWG criteria will be determined by the investigator and the computer algorithm will not be used.

8.2.2. Myeloma Protein Measurements in Serum and Urine

Blood and 24-hour urine samples for M-protein measurements will be sent to and analyzed by a central laboratory until the final PFS analysis. After the final PFS analysis, blood and 24-hour urine samples for M-protein measurements should be sent to and analyzed by a local laboratory.

- Serum M-protein quantitation by electrophoresis (SPEP)
- Serum immunofixation (SIFE) at screening and thereafter when M-protein is non-quantifiable up to confirmation of CR
- 24-hour urine M-protein quantitation by electrophoresis (UPEP)
- Urine immunofixation (UIFE) at screening and thereafter when a M-protein is non-quantifiable up to confirmation of CR
- Free light chain assessment for subjects with light chain only myeloma AND for all subjects to confirm sCR
- Serum QIgs: All subjects will be evaluated for IgG, IgA, IgM, IgE, and IgD at Screening.

Blood and 24-hour urine samples will be collected as specified in the Schedule of Activities (Section 1.3) until the development of confirmed disease progression. Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation. Disease evaluations will continue until disease progression or unacceptable toxicity is confirmed. Serum and urine immunofixation tests will be performed at screening and thereafter when serum or 24-hour urine M-protein electrophoresis [by SPEP or UPEP] is negative or non-quantifiable. For subjects with light chain multiple myeloma, both serum and urine immunofixation tests will be performed at every cycle.

As an IgG1 kappa immunoglobulin, daratumumab has been shown to interfere with serum protein electrophoresis (SPE) and immunofixation (IFE).[25] During the period of central laboratory analysis, subjects with daratumumab interference on serum immunofixation (IFE), the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test (Appendix 20 [Section 10.20]) will be used to distinguish a positive SPEP/IFE due to the presence of daratumumab versus the presence of the

underlying (endogenous) monoclonal protein. This assay will be implemented as part of response criteria by central laboratory assessment. For those subjects who meet all other clinical criteria for CR/sCR, with confirmed daratumumab interference on SPE/IFE, will be considered CR/sCR.

Note: All attempts should be made to determine eligibility of the subject based on the central laboratory results of screening blood and urine M-protein measurements. In exceptional circumstances, the local laboratory results of blood and urine M-protein measurements may be used to determine eligibility, but only if the results are clearly (eg, 25% or more) above the thresholds for measurability. In such cases, central laboratory results are still required to be obtained in order to establish baseline values and confirm the results from the local laboratory.

8.2.3. Albumin and Serum Calcium Corrected for Albumin

Blood samples for calculating serum calcium corrected for albumin will be collected and analyzed at the central laboratory up until the final PFS analysis, and at local laboratories after this timepoint, as specified in the Schedule of Activities until the development of confirmed disease progression. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L) may indicate disease progression or relapse if it is not attributable to any other cause (see disease response criteria in Table 11). Calcium binds to albumin and only the unbound (free) calcium is biologically active; therefore, the serum calcium level must be adjusted for abnormal albumin levels ("corrected serum calcium"). The formula for adjustment is presented in Appendix 10 (Section 10.10).

Measurement of free ionized calcium is an acceptable alternative to corrected serum calcium for determining hypercalcemia. Free ionized calcium levels greater than the ULN (local laboratory reference ranges) are hypercalcemic for purposed of safety and efficacy reporting in this study.

8.2.3.1. β2-microglobulin and Albumin

Blood samples for β2 microglobulin and albumin are to be collected at Screening and will be analyzed by the central laboratory and used for the assessment of ISS staging at study entry.

8.2.4. Bone Marrow Examination

Bone marrow aspirate, or bone marrow biopsy, or both will be performed at screening for clinical staging (morphology, central fluorescence in situ hybridization (FISH) evaluation of high-risk cytogenetic anomalies (del17p, t[4;14]) and t[14;16]), and immunohistochemistry [IHC] or immunofluorescence or flow cytometry), to establish baseline multiple myeloma clonality, to monitor for MRD, and to perform molecular subtyping. FISH evaluation of amp(1q21) may be performed as an exploratory risk anomaly. Clinical staging will be performed locally; however, a portion of the bone marrow aspirate/biopsy must be sent to the central lab for analysis of MRD and molecular subtyping. Morphology and IHC or immunofluorescence or flow cytometry will be performed locally. A fresh bone marrow aspirate at screening is required to be sent to the central laboratory (archived samples will not be accepted) for MRD and cytogenetic evaluation. A core bone marrow biopsy/aspirate will be performed to confirm sCR and CR. If a bone marrow core biopsy cannot be obtained or is not available, morphologic review of the bone marrow aspirate

smear may be reviewed by the local laboratory for confirmation of CR. Bone marrow aspirates are acceptable for determination of loss of CR (IHC or immunofluorescence) and to monitor for MRD (Table 13).

While archived samples will not be accepted for MRD or cytogenetic evaluation at screening, archived samples may be requested to be sent to the central laboratory, if available, in cases in which there is difficulty in establishing baseline clonality for MRD or if screening baseline cytogenetics are not evaluable.

Table 13: Bone Marrow Testing

	Local Testing	**Central Testing**
Screening	Disease characterization (morphology, and either immunohistochemistry, immunofluorescence, or flow cytometry).	A fresh bone marrow aspirate will be collected at Screening and sent to a central laboratory to use for MRD index clone identification, while a second portion of the bone marrow aspirate will be used for cytogenetic analysis by conventional FISH.
During Treatment	At time of suspected CR/sCR: Evaluate Plasma cell percentage in the bone marrow to confirm CR Evaluate clonality of plasma cells (by flow cytometry, IHC or IF)[a] in the bone marrow to confirm sCR *(If sCR criteria are not met, repeat local testing for sCR with subsequent bone marrow testing.)*	A portion of bone marrow aspirates collected at time of suspected CR and for subjects who achieve CR, have not progressed, and remain on study, additional bone marrow aspirate will be obtained for MRD at 12,18, 24, 30 and 36 months post Cycle 1 Day 1 (± 1 month) and yearly thereafter (±3 months)[b]

Abbreviations: CR=complete response; FISH=fluorescence in situ hybridization; IHC=immunohistochemistry; IF= immunofluorescence; MRD=minimal residual disease; sCR=stringent complete response

[a] Immunohistochemistry or immunofluorescence (both require kappa/lambda ratio from analysis of ≥100 cells) or 2-to 4-color flow cytometry are acceptable methods to evaluate plasma cell clonality.
[b] If one of these time points occurs within 1 month of suspected CR/sCR, a repeat bone marrow will not be requested. These bone marrow tests will only be required if subject's response is near CR or better by blood and urine evaluations.

8.2.5. Minimal Residual Disease Assessment

Bone marrow samples will be collected when a bone marrow aspirate is performed at Screening and at the subsequent timepoints outlined in Table 13 and Schedule of Activities (Section 1.3). If a sample is unevaluable, every effort should be taken to repeat BM assessment if not within 2 months of another pre-specified collection.

8.2.6. Assessment of Lytic Disease

A complete skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease) is to be performed and evaluated by the local radiologist. An alternative (eg low-dose CT) may be used in accordance with local SOC. Note that the same methodology used at Screening should be used throughout the study for comparison purposes. During the Treatment Phase and before disease progression is confirmed, imaging should be performed whenever clinically indicated based on

symptoms, to document response or progression. Magnetic resonance imaging may be included as an additional assessment at the discretion of the investigator; however, focal lesions identified by MRI alone cannot be counted as lytic disease unless they meet IMWG diagnostic criteria (SLiM [S=≥Sixty-percent (≥60%) clonal BM plasma cells; Li=serum free Light chain ratio involved: uninvolved ≥100; M=>1 focal lesion (≥5 mm each) detected by MRI studies] criteria) for MRI bone lesions. If a radionuclide bone scan was used at Screening in addition to the complete skeletal survey, then both methods must be used to document disease status. These tests must be performed at the same time. However, a radionuclide bone scan does not replace a complete skeletal survey.

Some subjects present with disease progression manifested by symptoms of pain due to bone changes. In this case, disease progression may be documented, in these cases, by skeletal survey or other imaging tests, depending on the symptoms that the subject experiences. If the diagnosis of disease progression is obvious by imaging investigations, then no repeat confirmatory imaging is necessary. In instances when changes are subtler, repeat imaging should be performed in 1 to 3 weeks.

8.2.7. Assessment of Extramedullary Plasmacytomas

Sites of known extramedullary plasmacytomas must be documented during the Screening Phase. Clinical examination or MRI may be used to document extramedullary sites of disease. Computed tomography scan evaluations are an acceptable alternative if there is no contraindication to the use of IV contrast. Positron emission tomography scan or ultrasound tests are not acceptable to document the size of extramedullary plasmacytomas.

Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at Screening, by clinical examination or radiologic imaging. Assessment of measurable sites of extramedullary disease will be performed and evaluated locally every 4 weeks (by physical examination) for subjects with a history of plasmacytomas or as clinically indicated during treatment for other subjects until development of confirmed CR or confirmed disease progression. If assessment can only be performed using imaging, then evaluation of extramedullary plasmacytomas should be done every 12 weeks. For every subject, the methodology used for evaluation of each disease site should be consistent across all visits. Irradiated or excised lesions will be considered not measurable and will be monitored only for disease progression.

To qualify for PR, the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have decreased by at least 50%, and new plasmacytomas must not have developed (see the disease response criteria in Table 11). To qualify for disease progression, either the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have increased by at least 50% or a new plasmacytoma must have developed. In the cases where not all existing extramedullary plasmacytomas are reported, but the sum of products of the perpendicular diameters of the reported plasmacytomas have increased by at least 50%, this will also qualify as disease progression.

8.3. Safety Assessments

Safety evaluations will include AE monitoring, physical examinations, ECGs monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and ECOG performance status. All toxicities will be graded according to the NCI-CTCAE Version 5. Clinically relevant changes occurring during the study must be recorded on the AE section of the CRF. Clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

Adverse events will be reported and followed by the investigator as specified in Section 8.4, Adverse Events and Serious Adverse Events and Appendix 4 (Section 10.4), Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Based on the previous experience with daratumumab in humans, in vitro studies, and animal toxicological findings, IRRs/allergic reactions, hemolysis, and thrombocytopenia will be closely monitored. As a biologic agent, immunogenicity also will be monitored. Any of the safety monitoring assessments may be performed more frequently, and AEs should be evaluated by the investigator according to the standard practice, if clinically indicated.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities (Section 1.3).

8.3.1. Home Health Care and Tele-Health Visits

In exceptional circumstances, home health care (with approval from the sponsor) and tele-health visits may be implemented per the clinical judgement of the investigator, where feasible and permissible by local policy and regulations.

Subjects for whom there is no safety concern may have home health care and tele-health (conducted via phone or video conference) visits.

Study procedures such as subject reconsenting, PRO collection, Eastern Cooperative Oncology Group assessment, AE and concomitant medication reporting, review of body systems, and collection of information on the subject’s current health status (as outlined per the SoA in Section 1.3) may be performed with home health care and tele-health visits. Protocol-specified laboratory assessments for efficacy (central laboratory) and safety (central and local laboratories) may be collected during home health care visits. All assessments should be followed with in-person examination, as applicable.

Where local laboratories are used, it is important to ensure appropriate documentation of laboratory reference ranges. Source documentation and if applicable the appropriate case report forms should be completed and detail how each assessment was collected (eg, remote vs on-site, central vs local laboratory, vital signs taken at home by delegated in-home nursing, etc.).

8.3.2. Adverse Events

Adverse events (with the exception of progression of multiple myeloma) will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally designated

representative) from the time a signed and dated informed consent is obtained until 30 days following the last dose of any component of the treatment regimen. Expected progression of disease should not be considered an AE (or SAE).

8.3.3. Physical Examination

A complete physical examination (including neurological examination) should be performed during the Screening Phase. Height will be measured at screening only; weight will be measured regularly as specified in the Schedule of Activities. Thereafter, only a symptom and disease directed physical examination is required. Abnormalities will be recorded in the appropriate sections of the eCRF.

8.3.4. Vital Signs

Vitals signs (heart rate, temperature, blood pressure) will be assessed as specified in the Schedule of Activities (Section 1.3). It is recommended that blood pressure (sitting) and heart rate measurements be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

The measurements of vital signs at Screening and Cycle 1 Day 1 will be recorded in the eCRF. Adverse events associated with monitoring of vital signs while on treatment will be recorded as AEs in the eCRF. All measurements of vital signs (except Screening and Cycle 1 Day1) will be recorded in the source documents.

8.3.5. Electrocardiogram

12-lead ECGs will be performed as specified in the Schedule of Activities (Section 1.3). When possible, ECGs should be taken immediately before chemistry and PK assessments. During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, it is recommended that the procedures are performed in the following order: ECG(s), vital signs, blood draw.

8.3.6. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in SoA. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Any additional chemistry and hematologic laboratory assessment supporting the start and end dates of an AE should be reported in the eCRF.

The following tests will be performed by the local laboratory unless otherwise noted.

- Hematology Panel

-hemoglobin
-white blood cell count
-platelet count
-absolute neutrophil count
-absolute lymphocyte count

- Serum Chemistry Panel

During Cycles 1-8

-blood urea nitrogen or urea
-creatinine
-glucose
-ALT
-AST
-creatinine clearance (calculated or measured)
-alkaline phosphatase
-lactic acid dehydrogenase (LDH)
-uric acid
-total protein
-sodium
-potassium
-total bilirubin; direct bilirubin (not required except in case of congenital bilirubinemia, such as Gilbert disease)

During Cycle 9 and beyond

-AST
-ALT
- total bilirubin (direct bilirubin if total bilirubin abnormal)
-creatinine clearance (calculated or measured)
-blood urea nitrogen or urea

Serum or Urine Pregnancy Testing

For women of childbearing potential only. Lenalidomide is a thalidomide analog and is contraindicated for use during pregnancy. Birth defects have been observed in preclinical studies of lenalidomide similar to thalidomide in humans. Therefore, strict monitoring for pregnancy must be conducted during Screening and throughout the Treatment Phase as per the Schedule of Activities (Section 1.3). Pregnancy testing is only required for women of childbearing potential. Any subject who becomes pregnant during the study must be discontinue study treatment immediately and the subject should be referred to an obstetrician experienced in reproductive toxicity for further evaluation and counseling (Section 8.4.4)

Calcium and Albumin Adjusted Calcium:

These parameters will be part of the efficacy evaluations as specified in Section 8.2.3, and will be analyzed by the central laboratory until the final PFS analysis (local laboratory assessments may be accepted prior to the final PFS analysis in exceptional circumstances if central laboratory is not evaluable). After the final PFS analysis, local laboratory assessments should be used. Measurement of calcium and albumin should follow the schedule for disease assessments. Measurement of free ionized calcium is an acceptable alternative to corrected serum calcium for determining hypercalcemia.

Daratumumab Interference with Indirect Antiglobulin Test Results:

Blood type, Rh, and Indirect Antiglobulin Test (IAT) should be done before the first dose of daratumumab. Subject RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first daratumumab administration.

Daratumumab interferes with the IAT, which is a routine pre-transfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT

(Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT) determined before the first injection of daratumumab along with information on the IAT interference for health care providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab IAT interference by treating reagent RBCs with dithiothreitol (DTT).[6,7]

Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include:

a) Providing ABO/RhD compatible, phenotypically or genotypically matched units

b) Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using dithiothreitol (DTT)-treated reagent RBCs

Un-crossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice.

Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant hemolysis has been observed in daratumumab studies. For additional details, refer to the Daratumumab IB.

8.3.7. Pulmonary Function Test

Subjects with known or suspected COPD must have a FEV1 test during screening. Refer to Section 6.1.3.2 for details on subjects with higher risk of respiratory complications.

8.3.8. HBV Serology and DNA Testing

8.3.8.1. HBV Screening Serology Testing

All subjects will be tested locally for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) at Screening. Additionally, subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment when Protocol Amendment 2 is implemented will be required to have HBV serology performed locally upon signing the updated ICF. If required by local regulations, if the hepatitis B serologic status of a subject in Arm B (D-VRd) is unknown, HBsAg, Anti-HBs, and Anti-HBc testing is recommended if the subject is still receiving daratumumab (or is within 6 months after the last dose).

HBV serology is not required at Screening or for subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment if this was performed as part of standard of care within 3 months prior to first dose.

8.3.8.2. HBV DNA Serial Testing

Subjects who are positive for Anti-HBc and/or Anti-HBs will undergo testing for hepatitis B DNA by PCR. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. During and following study treatment, subjects who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the Schedule of Activities (Table 1). Where required by local law, the result of HBV testing may be reported to the local health authorities.

8.3.9. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status will be used to evaluate the effect of the disease status on the activities of daily living. When scheduled, ECOG Performance Status assessments should be obtained prior to any other study procedures planned for the same day whenever possible.

8.4. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Appendix 4 (Section 10.4), Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related treatment, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of any component of the treatment regimen, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol. The sponsor will evaluate treatment-related SAEs during the Follow-up Phase of the study.

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study site personnel immediately, but no later than 24 hours after their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site and transmitted to the sponsor immediately, but no later than 24 hours after their knowledge of the event. The initial and follow-up reports of a SAE should be made by facsimile (fax).

8.4.2. Follow-up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 4 (Section 10.4), Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.4.3. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of safety information to the regulatory authorities/IECs/IRBs. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual SAEs the sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the treatment caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the institute where required). The sponsor assumes responsibility for appropriate reporting of anticipated events to the regulatory authorities according to requirements of the countries in which the studies are conducted. The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

8.4.4. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue study treatment immediately and the subject should be referred to an obstetrician experienced in reproductive toxicity for further evaluation and counseling. Pregnancies in partners of male subjects included in the study will be reported as noted above, because the effect of the study drug on sperm is unknown. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.4.5. Disease-Related Events and Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

Expected progression of disease, which is part of the natural course of the disease under study, should not be considered or reported as an adverse event (or serious adverse event).

Death or hospitalization that is attributed by the investigator to progression of disease should not be considered nor reported as an adverse event (or serious adverse event).

Of note, worsening of disease (and associated hospitalization or death) determined by the investigator to be caused by the study treatment should be reported per the usual reporting requirements (refer to Adverse Event Definitions and Classifications in Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

Progression of disease and death due to disease progression should be documented on the appropriate eCRF forms (eg, the Disease Progression form and the Death form).

Signs or symptoms of disease progression that are of clinical significance, such as spinal cord compression, vena cava superior syndrome, major vessel rupture, efflux obstruction or organ failure, should be documented on the appropriate eCRF forms (eg, the Symptomatic Progression Form).

Known consequences of the underlying disease under investigation (eg, symptoms) and events common in the study population independent of drug therapy are AEs. If they are considered drug-related they will be recorded and reported (if appropriate) as per current legislation to Health Authorities and Ethics Committees. If they are considered disease-related or not related to the study drugs they will be exempt from expedited reporting.

8.5. Treatment of Overdose

No MTD has been reached for daratumumab. However, if the dose exceeds the maximum tested dose of 2000 mg, then it will be considered as an overdose in this study.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately.
- Closely monitor the subject for AE/SAE and laboratory abnormalities until daratumumab can no longer be detected systemically (at least 3 months).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the subject.

8.6. Pharmacokinetics and Immunogenicity

Serum samples will be used to evaluate the PK and immunogenicity of daratumumab. Plasma samples will be used to evaluate the immunogenicity of rHuPH20. Samples collected for PK and immunogenicity analysis may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained. After the final PFS analysis, pharmacokinetic and immunogenicity samples will no longer be collected from subjects in Treatment Arm B.

8.6.1. Evaluations

Samples will be collected from all subjects in Arm B to assess both the serum concentration (pharmacokinetics) of daratumumab and generation of anti-daratumumab antibodies (immunogenicity) according to the Schedule of Activities (Section 1.3). At specified time points, venous blood samples (5 mL per sample) will be collected and the serum will be divided into 3 aliquots (1 aliquot for pharmacokinetic analysis, 1 aliquot for immunogenicity assessment [when appropriate], and 1 aliquot as a back-up). Samples will also be collected from all subjects in Arm B to evaluate the immunogenicity of rHuPH20 according to the Schedule of Activities (Section 1.3). After the final PFS analysis, pharmacokinetic and immunogenicity samples will no longer be collected from subjects in Treatment Arm B.

The exact dates and times of blood sampling must be recorded. Refer to the Laboratory Manual or equivalent document for sample collection requirements. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the Laboratory Manual. Samples collected for determining serum concentrations/immunogenicity of daratumumab or immunogenicity of rHuPH20 in this study may be retained to address questions about drug characteristics.

8.6.2. Analytical Procedures

Pharmacokinetics

Serum samples will be analyzed to determine concentrations of daratumumab or generation of anti-daratumumab or anti-rHuPh20 antibodies using a validated, specific, and sensitive immunoassay method by or under the supervision of the sponsor.

Immunogenicity

For the daratumumab immunogenicity assessments, serum samples will be screened for antibodies binding to daratumumab and serum titer will also be determined from confirmed positive samples. Other immunogenicity analyses (eg, assessment of neutralizing capabilities) may be performed to further characterize the immune responses that are generated.

For the rHuPH20 immunogenicity assessments, plasma samples will be screened for antibodies binding to rHuPH20 and will be assessed in confirmatory and titer assays as necessary. Neutralizing antibody assessments may also be performed to further characterize immune responses that are generated.

8.6.3. Pharmacokinetic Parameters and Evaluations

Pharmacokinetic samples to determine serum concentration of daratumumab will be obtained from subjects in Arm B. The pharmacokinetic parameters are defined as:

C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration

The pharmacokinetic evaluations include C_{min} and C_{max} which will be determined based on the assigned collection timepoints. If there are sufficient data, population pharmacokinetic analysis of serum concentration-time data of daratumumab may be performed and may include data from other clinical studies. If performed, details will be provided in a population pharmacokinetic analysis plan and results of the analysis will be presented in a separate report.

8.6.4. Immunogenicity Assessments

Serum from venous blood samples collected from all subjects in Arm B will be assessed for the generation of anti-daratumumab antibodies (immunogenicity) according to the Schedule of Activities. Daratumumab concentration will be evaluated at all immunogenicity time points to ensure appropriate interpretation of immunogenicity data. When both daratumumab serum concentration and immunogenicity analyses are specified, they will be performed on aliquots from the same blood draw and no additional sampling is required. Plasma samples will also be collected from all subjects receiving daratumumab (Arm B) and assessed for anti-rHuPH20 antibodies. Procedures for sample collection, preparation, identification, storage, and shipment will be provided in the Laboratory Manual or equivalent document.

When an IRR occurs associated with the second or later daratumumab administration, 2 blood samples should be obtained, if possible, for determination of antibodies to daratumumab and antibodies to rHuPH20. No unscheduled samples need to be collected for injection reactions associated with the first administration of daratumumab. Daratumumab serum concentration will also be determined from the daratumumab injection reaction sample for interpreting immunogenicity data. If the injection reaction results in treatment discontinuation, then subjects should undergo all scheduled safety and efficacy evaluations. Procedures for sample collection, preparation, identification, storage, and shipment will be provided in the Laboratory Manual or equivalent document. Samples collected for the analysis of daratumumab immunogenicity/serum concentration or rHuPH20 immunogenicity may be used to evaluate safety or efficacy questions that arise during or after the study period or for the evaluation of relevant biomarkers by the sponsor or sponsor's designee.

Subjects who discontinue treatment or withdraw from the study before confirmation of PD should have samples collected at the time of early discontinuation. Subjects who discontinue treatment will also be asked to return for immunogenicity evaluation during the Follow-up Phase. After the final PFS analysis, pharmacokinetic and immunogenicity samples will no longer be collected from subjects in Treatment Arm B. These samples will be tested by the sponsor or sponsor's designee.

8.7. Pharmacokinetic/Pharmacodynamic Evaluations

If sufficient data are available, then other pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of daratumumab and endpoints of clinical efficacy and safety. If these analyses are performed, then the details and results will be presented in a separate report.

8.8. Biomarkers

As permitted by local rules and regulations, bone marrow aspirates in the D-VRd and VRd cohorts will be collected at screening and following treatment as outlined in the Schedule of Activities (Section 1.3) for MRD monitoring. Baseline fresh bone marrow aspirate samples will be subjected to DNA sequencing to establish a multiple myeloma clone for MRD monitoring (calibration) and for cytogenetic evaluation by the central laboratory. A fresh bone marrow aspirate at screening is required (archived samples will not be accepted). Fresh bone marrow aspirates will be utilized for assessment of MRD by NGS of immunoglobulin (Ig) heavy and light chains as specified. For this study only the FDA-approved next generation sequencing (NGS) clonoSEQ v2.0 (Adaptive Biotechnologies®) methodology will be employed for assessing MRD. A portion of the screening bone marrow aspirate will be evaluated by central lab fluorescent in situ hybridization for high-risk cytogenetic anomalies of t (4;14); t (14;16); and del17p. amp(1q21) will be evaluated as an exploratory risk marker.

Whole blood samples will be collected from subjects as specified in the Schedule of Activities for processing to plasma and peripheral blood mononuclear cells. These samples may be used to evaluate the impact of VRd on daratumumab's immunomodulatory mechanism of action where specific subsets of immune cells such as cytotoxic T cells, regulatory T cells, and activated natural killer cells may be evaluated by flow cytometry or cytometry/time-of-flight mass spectrometry and T-cell receptor sequencing. Proteomic or genomic analysis may also be used to evaluate baseline and changes in proteins or tumor associated DNA in circulation to evaluate potential biomarkers of response and resistance.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

Additional Collections

If it is determined at any time before study completion that additional material is needed from a formalin-fixed, paraffin-embedded (FFPE) tumor sample for the successful completion of the protocol-specified analyses, the sponsor may request that additional material be retrieved from existing samples. Also, based on emerging scientific evidence, the sponsor may request additional material from previously collected tumor samples during or after study completion for a retrospective analysis. In this case, such analyses would be specific to research related to the study drug(s) or diseases being investigated.

8.9. Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected in the eCRF by the investigator and study site personnel for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. Data collected will include:

- Number and characteristic of diagnostic and therapeutic tests and procedures (inpatient and outpatient)
- Number and duration of hospitalization (total days length of stay [days], including duration by each hospital unit (intensive care unit)
- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Outpatient medical encounters and treatments (including physician, nurse practitioner, emergency room visits, tests and procedures, and medications)

Refer to the eCRF completion guidelines.

8.10. Patient-reported Outcomes

Subject's HRQoL, symptoms, functioning, and general well-being will be captured using 3 PRO measures: the EORTC QLQ-C30 (Appendix 15 [Section 10.15]), EORTC QLQ-MY20 (Appendix 16 [Section 10.16]), and the EQ-5D-5L (Appendix 17 [Section 10.17]). The PRO measures will be electronically (ePRO) collected to understand the change in PRO endpoints. These measures will be administered according to the Schedule of Activities to understand how subjects self-reported health state changes over time and the difference between treatment arms during treatment, maintenance, and post-progression.

The PRO measures will be provided in the local language. If a subject requires assistance completing the PRO, a study coordinator may assist but should not prompt the subject in selecting their response. At completion, the study coordination should check that the questionnaires are completed or document why they are missing. Full training documentation will be provided to site coordinators before the start of data collection.

The EORTC QLQ-C30 includes 30 items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 Global Health Status (GHS) scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The recall period is 1 week ("past week") and responses are reported using a verbal rating scale. Item and scale scores are transformed to a 0 to 100 scale. A higher score represents greater HRQoL, better functioning, and more (worse) symptoms. The EORTC QLQ-C30 has been widely used among cancer patients. Reliability, validity, and clinically meaningful change have been demonstrated in multiple myeloma patients.[47,48] The EORTC Multiple Myeloma Module (QLQ-MY20) has been designed to use alongside the EORTC QLQ-C30 to address issues of more relevance to myeloma patients.[10] The 20-items make up 4 scales: disease symptoms, side effects of treatment, future perspective, and body image. Recall, response options, and interpretation is similar to the EORTC QLQ-C30. Together the EORTC QLQ-C30 and the EORTC QLQ-MY20

administration time is approximately 30 minutes. Key PRO endpoints include the GHS, Physical Functioning, Fatigue, and Pain subscales from the EORTC QLQ-C30 and the Disease Symptoms from the EORTC QLQ-MY20.

The EQ-5D-5L is a generic measure of health status. For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost-effectiveness analyses. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale rating "health today" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).[18] The scores for the 5 separate questions are categorical and are cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. The EQ-5D-5L asks respondents to select their response based on their current health ("today") and takes less than 5 minutes to complete.

The EQ-5D-5L will be performed until death or study end. Following disease progression, sites should attempt to administer the EQ-5D-5L every 16 weeks, unless death or study end occurs first. Subjects who visit the site for the follow-up assessments should complete the EQ-5D-5L questionnaire at that time. If the EQ-5D-5L is conducted via a telephone call with the subject, then the subject's questionnaire responses will be read over the telephone to the site staff who will record the data in the EQ-5D-5L. If the subject is unable to complete the EQ-5D-5L during the Long-Term Follow-up Phase, the reason for not completing the questionnaire will be documented (i.e., too ill, subject refused).

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

9.1. Statistical Hypotheses

The null hypothesis is that there is no difference in overall MRD negativity rate between daratumumab in combination with VRd and VRd alone in subjects with newly diagnosed multiple myeloma who are not intended for initial transplant.

9.2. Sample Size Determination

Based on the available data from CASTOR, POLLUX, and ALCYONE, approximately 64% of MRD negative subjects at a threshold of 10^{-4} were also MRD negative at 10^{-5}. The IFM2009-TE NDMM study showed a 49% overall MRD negativity rate at 10^{-4} for all the VRd subjects without transplant. Thus, the anticipated overall MRD negative rate (10^{-5}) for the control arm in this study is estimated to be at most 35%. This study assumes a 15% absolute increase in overall MRD negativity rate (50% daratumumab plus VRd versus. 35% VRd alone). A sample size of 360 subjects (180 each arm) is needed to achieve a power of 80% to detect such a treatment difference at a 2-sided alpha of 0.05.

The final PFS analysis will take place when approximately 162 PFS events have been observed, which will provide approximately 80% power to detect a 37% reduction in the risk of progression or death (HR=0.63, translating to an improvement in median PFS from 43 months to 68 months) with a log-rank test at a 2-sided alpha of 0.05. To ensure adequate power for PFS, an adaptive approach may be used to determine the timing of the final PFS analysis. If the observed HR for PFS at the interim analysis (ie, 60% of events) is higher than expected (eg, 0.7 or higher), the final analysis of PFS may be delayed until approximately 205 events have been observed (roughly 3 years later). To control the overall type I error rate, the inverse normal test with the same fixed weights as originally planned will be used to combine the log-rank statistics before and after the interim analysis. Investigator-assessed long-term PFS, PFS2, and OS will continue to be collected after the final PFS analysis until the end of data collection, using local disease assessments. Updates to the final Clinical Study Report for both efficacy and safety will be provided in an addendum to the Clinical Study Report at study closure.

9.3. Populations for Analyses

The primary analysis population will be the intent-to-treat (ITT) population, which will include all randomized subjects. Safety will be evaluated for the population of all treated subjects. Pharmacokinetic analyses will be performed on the pharmacokinetic-evaluable population.

9.4. Statistical Analyses

9.4.1. General Analysis

Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, and range. Categorical variables will be summarized using frequency tables. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries.

9.4.2. Efficacy Analyses

Response to study treatment and PD will be evaluated by a validated computer algorithm that has been used in the previously reported Phase 2 and Phase 3 studies.[11,23,37]

Primary Endpoint

The primary endpoint, overall MRD negativity rate, will be compared between the 2 treatment groups using the stratified Cochran Mantel Haenszel test based on the ITT population (ISS staging and age/transplant eligibility as stratification factors). A Mantel-Haenszel odds ratio, along with its 2-sided 95% CI, will be calculated.

Secondary Endpoints

If the primary endpoint of overall MRD negativity rate is statistically significant, the key secondary endpoints (ie, CR or better rate, PFS, and durable MRD negativity rate) will be sequentially tested, each with an overall two-sided alpha of 0.05, by utilizing a hierarchical testing approach as proposed by Tang and Geller (1999)[44] that strongly controls family wise Type I error rate.

Time-to-event efficacy endpoints, including PFS, PFS2 and OS will be compared between the 2 treatment groups using a stratified log-rank test. The Kaplan-Meier method will be used to

estimate their distribution in each treatment group. Hazard ratio and its 95% CI will be estimated based on a stratified Cox's regression model with treatment as the sole explanatory variable.

For the binary secondary endpoints, including durable MRD negativity rate, rate of CR or better, rate of VGPR or better and ORR, will be analyzed similarly to overall MRD negativity rate. The time to response will be provided descriptively for each treatment arm without formal statistical comparison.

9.4.3. Safety Analyses

Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are AEs with onset during the Treatment Phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue study drug due to an AE, or who experience a severe or a serious AE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

9.4.4. Other Analyses

Pharmacokinetic Analytical Procedures

Pharmacokinetic analyses will be performed on the pharmacokinetic-evaluable population, defined as subjects assigned to Arm B who have received at least 1 dose of daratumumab and have at least one pharmacokinetic sample concentration value after the first administration of daratumumab.

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics.

Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point. The PK parameters C_{min}, and C_{max} will be defined by planned timepoint.

If sufficient data are available, then population pharmacokinetic analysis of serum concentration-time data of daratumumab may be performed using nonlinear mixed effects modeling and may include data from other studies. If the population pharmacokinetic analysis is conducted, details will be given in a population pharmacokinetic analysis plan and the results of the analysis will be presented in a separate report.

Immunogenicity Analyses

The incidence of anti-daratumumab antibodies will be summarized for all subjects who receive at least 1 dose of daratumumab and have daratumumab at least 1 sample obtained after the first dose of daratumumab. The prevalence and incidence of anti-rHuPH20 antibodies will be summarized for all subjects who receive a dose of daratumumab and have at least 1 sample for detection of anti-rHuPH20 antibodies obtained after the first dose of daratumumab. A listing of subjects who are positive for anti-daratumumab antibodies or anti-rHuPH20 antibodies will be provided.

Biomarkers Analyses

MRD negativity rate is the primary endpoint and the analysis method is described in Section 9.4.2. Baseline bone marrow aspirate samples will be evaluated by the FDA-approved clonoSEQ v2.0 MRD assay to establish the myeloma clone (calibration) and for MRD monitoring. MRD assessment by NGS is an emerging tool in the assessment of patients with multiple myeloma and for cytogenetics evaluations.[19] Several studies have demonstrated that MRD status is correlated with PFS and OS.[24] In this study, bone marrow samples will be collected when a bone marrow aspirate is performed at Screening and at the subsequent timepoints outlined in Table 13 and Schedule of Activities (Section 1.3). Whole blood sample will be collected from subjects as outlined in the Time and Events Schedule and processed to plasma and PBMCs and may be used to evaluate daratumumab's immunomodulatory mechanism of action.

Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of daratumumab and endpoints of clinical efficacy or safety. Details and results of any analysis performed will be presented in a separate report.

9.5. Medical Resource Utilization Analyses

Medical resource utilization will be descriptively summarized by treatment group. Additional analyses may be conducted; details and results of any additional analyses will be presented in a separate report.

9.6. Patient-reported Outcomes Analyses

The EORTC QLQ-C30 and EORTC QLQ-MY20 scale scores, and EQ-5D-5L utility and visual analog scores will be descriptively summarized by treatment group at each time point. Within-group and between-group treatment effects of the PRO endpoints will be assessed by

change from baseline using mixed models for repeated measures for exploratory purpose. Full details of statistical analyses will be provided in the SAP.

Benefit-risk Analyses

For benefit-risk (B-R) analyses, between treatment differences will be shown with absolute rate or other difference measures and corresponding 95% CIs. Both continuous and dichotomized versions of continuous endpoints will be shown. Results will be displayed in tabular and forest plot form. Additional details will be provided in the separate benefit-risk SAP.

9.7. Interim Analysis

There is no interim analysis planned for the overall MRD negativity rate. After the primary analysis of MRD negativity rate, disease assessment will continue for the secondary endpoint PFS, for which one interim analysis is planned after approximately 98 events (ie, 60% of the total 162 events) have been accumulated. The significance levels at this interim analysis of PFS to establish the superiority (or declare the futility) of daratumumab plus VRd over VRd alone will be determined based on the observed number of PFS events at this analysis using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha- and beta-spending method.

9.8. Independent Data Monitoring Committee

An IDMC will be established according to regulatory agency guidelines. The IDMC will start the safety review after the first 100 subjects have been treated for at least 1 cycle or discontinued, and subsequently perform a periodic safety review every 6 months. At the primary analysis of the overall MRD negativity rate and the interim analysis for PFS, the IDMC will review both safety and efficacy results and make recommendations regarding the unblinding and continuation of the study. More details are specified in a separate IDMC charter. Emerging data from all ongoing daratumumab studies will be communicated to the IDMC, where applicable.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
Anti-HBc	hepatitis B core antigen
Anti-HBs	hepatitis B surface antigen
ARC	Anticipated Event Review Committee
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
BMI	body mass index
BM-MNC	bone marrow mononuclear cell
B-R	benefit-risk
CD38	cluster of differentiation 38
CDC	Centers for Disease Control
CI	confidence interval
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CR	complete response
CRAB	calcium, renal, anemia, bone
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography
C_{trough}	concentration at the end of a dosing interval at steady state
CV	coefficient of variance
Dara-CF	co-formulated product of daratumumab and rHuPH20
Dara-IV	intravenous daratumumab
Dara-MD	mix-and-deliver formulation of daratumumab
Dara-SC	subcutaneous daratumumab
DLT	dose limiting criteria
DRd	daratumumab + lenalidomide + dexamethasone
DVd	daratumumab + bortezomib
D-VMP	dara-IV in combination with bortezomib, melphalan and dexamethasone
D-VRd	daratumumab, bortezomib, lenalidomide, and dexamethasone
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core 3-item
EORTC QLQ-MY20	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire multiple myeloma 20-item
EOT	end of treatment
EQ-5D-5L	EuroQol Five Dimension Questionnaire
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 second
FFPE	formalin-fixed, paraffin-embedded
FIRST	Front-line Investigation of Revlimid and Dexamethasone versus Standard Thalidomide
FISH	fluorescence in situ hybridization
FLC	free light chain

G-CSF	granulocyte colony stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFE	Immunofixation electrophoresis
IFM	*Intergroupe Francophone du Myélome*
Ig	immunoglobulin
IHC	immunohistochemistry
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IRR	Injection-related reaction
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
M-protein	monoclonal protein
MPT	melphalan-prednisone-thalidomide
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRU	medical resource utilization
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
nCR	near complete response
NGS	next generation sequencing
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PFS2	progression-free survival on the next line of therapy
PI	proteasome inhibitor
PO	orally
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
RBC	red blood cell
Rd	lenalidomide-dexamethasone
REMS	Risk Evaluation and Mitigation Strategy
rHuPH20	recombinant human hyaluronidase
SAC	Safety Assessment Committee
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
sCR	stringent complete response
SCT	stem cell transplantation
sIPPM	site Investigator Product Procedures Manual

SLiM	S=≥Sixty-percent (≥60%) clonal BM plasma cells; Li=serum free Light chain ratio involved:uninvolved ≥100; M=>1 focal lesion (≥5 mm each) detected by MRI studies
SmPC	Summary of Product Characteristics
SOA	Schedule of Activities
SOC	standard of care
SPE	serum protein electrophoresis
SPEP	serum M-protein quantitation by electrophoresis
SVR	sustained virologic response
SWOG	Southwest Oncology Group
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UPEP	24-hour urine M-protein quantitation by electrophoresis
USPI	Unite States Product Information
US	United States
VCd	bortezomib + cyclophosphamide + dexamethasone
Vd	bortezomib + dexamethasone
VGPR	very good partial response
VMP	bortezomib + melphalan + dexamethasone
VRd	bortezomib + lenalidomide + dexamethasone
VTd	Bortezomib + thalidomide + dexamethasone

Definition of Study Terms
Daratumumab = study drug
daratumumab+VRd = study treatment

10.2. Appendix 2: Anticipated Events

Anticipated Event

An anticipated event is an AE (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

- Bleeding
- Bone diseases
- Hypercalcemia
- Hyperuricemia
- Hyperviscosity syndrome
- Infection
- Renal failure or insufficiency

Reporting of Anticipated Events

All AEs will be recorded in the eCRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 10.4 (Appendix 4). Any anticipated event that meets serious criteria will be reported to the sponsor as described in Section 8.3.2. Each anticipated event will be assessed by the investigator at the individual case level and if considered to be drug-related will undergo expedited reporting (if appropriate) as per applicable clinical trial legislation to Health Authorities and IRB/ECs. If an anticipated event is considered disease-related or not related to study drug the event will be exempt from expedited reporting.

To meet US regulatory clinical trial legislation, the sponsor will perform aggregate review of anticipated events as outlined below, and if determined to be drug-related will implement expedited reporting of these events to Health Authorities and IRBs/ECs. If an interim analysis of trial results leads to an unblinded, aggregate review of safety data by the study team, the sponsor may terminate the review of pre-specified anticipated events outlined above.

Safety Assessment Committee (SAC)

A Safety Assessment Committee (SAC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The SAC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The SAC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study intervention based on a review of the aggregate data by arm.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan.

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Conference on (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated Clinical Trial Agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable

- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

FINANCIAL DISCLOSURE

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

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

INFORMED CONSENT PROCESS

Each subject (or a legally designated representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential subjects or their legally designated representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally designated representative is authorizing such access, which includes permission to obtain information about his or her survival status. It

also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed. The physician may also recontact the subject for the purpose of obtaining consent to collect information about his or her survival status.

The subject or legally designated representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's or his or her legally designated representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject. Where local regulations require, a separate ICF may be used for the required DNA component of the study.

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

If the subject or legally designated representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject or legally designated representative is obtained.

When prior consent of the subject is not possible, and the subject's legally designated representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or legally designated representative must be informed about the study as soon as possible and give consent to continue.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or his or her legally designated representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will

be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory PK and immunogenicity research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

STORAGE, USE, TRANSFER, AND RETENTION OF DATA AND SAMPLES

Study samples will be coded or anonymized at all times in accordance with the informed consent and will not be labeled with personal identifiers.

Investigator and study site will only store, use, transfer and retain data and study samples, including optional study samples, in accordance with the informed consent and applicable law, and in accordance with any separate written agreement with sponsor. Other than what is specified in a separate written agreement with sponsor, study site and investigator shall not conduct or facilitate any research by a third party not required by the protocol (i) on subjects if such research interferes with the conduct of the study or (ii) on samples collected from study subjects during the study, including optional samples, if the research relates to daratumumab or (iii) on data collected from study subjects during the study if the research relates to daratumumab.

Sponsor may store, use, transfer or retain the data and study samples, including optional study samples, for uses not specified by the protocol, including compatible research, in compliance with the informed consent and applicable law.

COMMITTEES STRUCTURE

Independent Data Monitoring Committee

An IDMC will be established according to regulatory agency guidelines (Section 9.8). This committee will consist of at least one medical expert in the relevant therapeutic area, 2 clinicians and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter.

USE OF INFORMATION AND PUBLICATION

All information, including but not limited to information regarding daratumumab supplied by the sponsor to the study site or investigator and not previously published, and any data analysis generated as a result of this study, are considered confidential and remain the sole property of the sponsor. Study site and investigator shall not use this information except in the performance of this study and shall not disclose this information to anyone except to persons involved in the study that need such information to assist in conducting the study, and then only on like terms of confidentiality and non-use.

Study site and investigator shall not publish study results except as required by law or as specified in a separate, written agreement between the sponsor and the study site or investigator.

The Sponsor will register the study and publish the study results in compliance with applicable law and may register the study or publish study results when not required.

Authorship of any peer-reviewed publications will be determined by mutual agreement in line with International Committee of Medical Journal Editors authorship guidelines.

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

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

The summary of the results from the primary MRD analysis, and the interim (approximately 98 events) and final (approximately 162 events) PFS analysis as described in Section 9.7, will be submitted to the EU database within one year after unblinding the data.

The disclosure of the study results will be performed after the end of study.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study site personnel before the start of the study. The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

ELECTRONIC CASE REPORT FORM COMPLETION

Electronic case report forms are prepared and provided by the sponsor for each subject in electronic format. All data relating to the study must be recorded in CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of the assessment by the investigator of all AEs and follow-up of AEs; concomitant medication; treatment receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the CRF and will be considered source data:

- Race
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination
- Myeloma Frailty Score

- ECOG, PRO questionnaires, health economic data

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system, but information collected through eSource may not be limited to that found in the CRF. Data in this system may be considered source documentation.

MONITORING

The sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

ON-SITE AUDITS

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. For trials performed under Regulation [EU] No. 536/2014, the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

STUDY AND SITE CLOSURE

Study Termination

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.4.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

Serious Adverse Event

A SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject 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)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Expected progression of disease should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For daratumumab, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure. Anticipated events will be recorded and reported as described in Appendix 2 (Section 10.2).

Adverse Event Associated with the Use of the Intervention

An AE is considered associated with the use of the intervention if the attribution is possible, probable, or very likely by the definitions listed below (see Attribution Definitions).

ATTRIBUTION DEFINITIONS

Not Related

An AE that is not related to the use of the drug.

Related

An AE that is related to the use of the drug.

SEVERITY CRITERIA

The severity assessment for an AE or SAE should be completed using the NCI-CTCAE Version 5. Any AE or SAE not listed in the NCI-CTCAE Version 5 will be graded according to investigator clinical judgment by using the standard grades.

SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study drug in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug. No MTD has been reached for daratumumab. However, if the dose exceeds the maximum tested dose of 2000 mg, then it will be considered as an overdose in this study
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug

- Medication error involving a sponsor product (with or without subject exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE page of the CRF.

PROCEDURES

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of any component of the treatment regimen. The only exception is for subjects who have withdrawn informed consent for study participation or for subjects who have received additional treatment with therapeutic intent for MM within 30 days after the last dose of any component of the treatment regimen. For subjects who have received additional treatment with therapeutic intent for MM during the AE reporting period, only AEs that are considered to be related to the study drug or any part of the backbone treatment regimen must be reported (unless the subject has been withdrawn from the study).

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

Death should not be recorded as an AE or SAE, but as the outcome of an AE. The event that resulted in the death should be reported as a SAE.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number

Serious Adverse Events

Serious adverse events, including those spontaneously reported to the investigator within 30 days after last dose of last study drug, and those that are considered related to study drug within the Follow-up Phase, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Appendix 2 (Section 10.2). (Note: Some countries require reporting of all AEs to the health authorities, eg, Japan will not identify anticipated events for the health authorities).

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study site personnel immediately, but no later than 24 hours after their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site and transmitted to the sponsor immediately, but no later than 24 hours after their knowledge of the event. The initial and follow-up reports of a SAE should be transmitted electronically or by facsimile (fax). The initial and follow-up reports of a SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a SAE, except hospitalizations for the following:

- If the subject has not experienced a significant medical event but is hospitalized overnight only for observation following injection of study drug, then the hospitalization should not be reported as a SAE.
- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).

- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new serious AE.
- For convenience the investigator may choose to hospitalize the subject for the duration of the intervention period.

Expected progression of disease should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements.

CONTACTING SPONSOR REGARDING SAFETY

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study site personnel within 24 hours after being made aware of the event.

If the defect is combined with a SAE, the study site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 8.4.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Subjects must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.4.4, Pregnancy and Appendix 4 (Section 10.4) Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

USER INDEPENDENT

Highly Effective Methods That Are User Independent *Failure rate of ≤1% per year when used consistently and correctly.*

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner

  (Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)

USER DEPENDENT

Highly Effective Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[b]
  - oral
  - injectable
- Sexual abstinence

  (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)

NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of >1% per year)

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
- Male or female condom with or without spermicide[c]
- Cap, diaphragm, or sponge with spermicide
- A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus-interruptus)
- Spermicides alone
- Lactational amenorrhea method (LAM)

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.
b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study drug.
c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.6. Appendix 6: IMWG Diagnostic Criteria

Multiple myeloma is defined as clonal bone marrow plasma cells ≥10% or biopsy proven bony or extramedullary plasmacytoma[a] and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the ULN or >2.75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min[b] or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L[g]
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT[c,d]
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage[a] ≥60%
  - Involved: uninvolved serum FLC ratio[e] ≥100
  - >1 focal lesions on MRI studies[f]

a. Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
b. Measured or estimated by validated equations.
c. If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.
d. PET-CT=^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography.
e. These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved FLC must be ≥100 mg/L.
f. Each focal lesion must be 5 mm or more in size.
g. Hemoglobin measurement performed as part of standard of care within 42 days before randomization is acceptable for screening for CRAB criteria; but must be performed within 21 days before randomization for other eligibility requirements.

Source: Rajkumar 2014[39]

10.7. Appendix 7: ECOG Performance Status Grade

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
Source: Oken 1982[34]	

10.8. Appendix 8: Calculated and Measured Creatinine Clearance

Cockcroft-Gault formula:

To calculate the subject's creatinine clearance (CrCl), use the following Cockcroft-Gault formula:

$$CrCl = \frac{(140 - \text{age [in years]}) \times \text{weight (kg)}}{(72 \times \text{serum creatinine [mg/dL]})} \quad (\times 0.85 \text{ for females})$$

If the serum creatinine is obtained using the International System of Units (SI) (ie, micromol/L), use the following formula to convert SI units to conventional (mg/dL) units (Manual of Laboratory and Diagnostic Tests, 2004):

- serum creatinine (micromol/L) divided by 88.4 = serum creatinine (mg/dL)

Formula to measure creatinine clearance:

$$CrCl = \frac{U_{Cr} \times U_{vol}}{P_{Cr} \times T_{min}}$$

$$\text{Corrected CrCl} = \text{CrCl} \times \frac{1.73}{\text{BSA}}$$

Notes: U_{Cr}, Urine creatinine concentration; U_{vol}, Urine volume from 24 hrs collection; P_{Cr}, plasma creatinine concentration; T_{min}, collection time in minutes (24 h x 60 min); BSA, body surface area.

If the BMI of a subject is >30kg/m^2, lenalidomide dosing should be based on the CrCl calculated with adjusted body weight.

Source: Cockcroft and Gault 1976[9]

10.9. Appendix 9: Modified Diet in Renal Disease Formula

For creatinine in **mg/dL**, the estimated glomerular filtration rate (e-GFR) for the modified diet in renal disease (MDRD) formula is:

e-GFR (MDRD) mL/min per $1.73m^2$= 175 × [serum creatinine (mg/dL)]$^{-1.154}$ × [age]$^{-0.203}$ × [1.212 if black] × [0.742 if female]

For creatinine in **µmol/L**, the estimated glomerular filtration rate (e-GFR) for the modified diet in renal disease (MDRD) formulas is:

e-GFR (MDRD) mL/min per $1.73m^2$= 175 x [serum creatinine (µmol/L)/88.4]$^{-1.154}$ × [age]$^{-0.203}$ × [1.212 if black] × [0.742 if female]

Source: Levey 2006[22]

10.10. Appendix 10: Serum Calcium Corrected for Albumin

If calcium is expressed in mg/dL and albumin is expressed in g/dL:
Corrected calcium (mg/dL) =
serum calcium (mg/dL) + 0.8 × (4 - serum albumin [g/dL])

If calcium is expressed in mmol/L and albumin is expressed in g/L:
Corrected calcium (mmol/L) =
serum calcium (mmol/L) + 0.02 × (40 - serum albumin [g/L])

Source: Burtis 1998[5]

10.11. Appendix 11: Asthma Guidelines

Components of Severity		Classification of Asthma Severity											
		Intermittent			Persistent								
					Mild			Moderate			Severe		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
Impairment Normal FEV_1/FVC : 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	Symptoms	≤ 2 days/week			≥ 2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤ 2x/month		1-2x/ month	3-4x/month		3-4x/ month	> 1x/week but not nightly		> 1x/ month	Often 7x/week	
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			≤ 2 days/week but not daily		>2 days/ week but not daily, and not more than 1x on any day	Daily			Several time per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
	Lung function FEV1 FEV1/FVC	N/A	Normal FEV1 between exacerbations >80% >85%	Normal FEV1 between exacerbations >80% Normal	N/A	>80% >80%	>80% Normal	N/A	60-80% 75-80%	60-80% Reduced 5%	N/A	<60% <75%	<60% Reduced 5%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1-year lasting >1 day and risk factors	≥2/year Relative annual risk may be related to FEV1.	≥2/year Relative annual risk may be related to FEV1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1-year lasting >1 day and risk factors	≥ 2/year Relative annual risk may be related to FEV1.	≥ 2/year Relative annual risk may be related to FEV1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/ 1-year lasting >1 day and	≥2/year Relative annual risk may be related to FEV1.	≥2/year Relative annual risk may be related to FEV1.

Components of Severity		Classification of Asthma Severity											
		Intermittent			Persistent								
					Mild			Moderate			Severe		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
					for persistent asthma			for persistent asthma			risk factors for persistent asthma		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for subjects in any severity category.											
Recommended Step for Initiating Treatment		Step 1			Step 2			Step 3 and consider short course of oral steroids	Step 3: medium dose ICS and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS OR Step 4 and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids
		In 2-6 weeks, evaluate level of asthma control that is achieved. 0-4 years: If no clear benefit is observed in 4-6 weeks, stop treatment and consider alternate diagnosis or adjusting therapy. 5-11 and 12+ years: adjust therapy accordingly.											

Components of Control		Classification of Asthma Control								
		Well Controlled			Not Well Controlled			Very Poorly Controlled		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
	Symptoms	≤ 2 days/week but not more than once on each day		≤ 2 days/ week	> 2 days/week or multiple times on ≤2 days/week		> 2 days/ week	Throughout the day		
Impairment	Nighttime awakenings	≤ 1x/month		≤ 2x/month	> 1x/month	≥ 2x/month	1-3x/week	> 1x/week	≥ 2x/week	≥ 4x/week
	Interference with normal activity	None			Some limitation			Extremely limited		
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			> 2 days/week			Several times per day		
	Lung function FEV1 or peak flow FEV1/FVC	N/A	> 80% > 80%	> 80%	N/A	60-80% 75-80%	60-80%	N/A	< 60% < 75%	< 60%
	Validated questionnaires ATAQ ACQ ACT			0 ≤ 0.75 ≥ 20			1-2 ≥ 1.5 16-19			3-4 N/A ≤ 15
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2/year					
		Consider severity and interval since last exacerbation								
	Reduction in lung growth/ Progressive loss of lung function	Evaluation requires long-term follow-up								
		• Maintain current step • Regular follow-up every 1-6 months			Step up 1 step	Step up at least 1 step	• Step up 1 step • Reevaluate	• Consider short course of oral steroids • Step up 1-2 steps		• Consider short course of oral steroids

Components of Control	Classification of Asthma Control								
	Well Controlled			Not Well Controlled			Very Poorly Controlled		
	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
Recommended Action for Treatment	• Consider step down if well controlled for at least 3 months			• **Before step up**: Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step. • **Reevaluate the level of asthma control in 2-6 weeks to achieve control**. 0-4 years: If no clear benefit is observed in 4-6 weeks, consider alternative diagnoses or adjusting therapy. 5-11 years: Adjust therapy accordingly. • **For side effects**, consider alternative treatment options.		in 2-6 weeks • For side effects, consider alternative treatment options	• **Before step up**: Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step. • **Reevaluate the level of asthma control in 2-6 weeks to achieve control**. 0-4 years: If no clear benefit is observed in 4-6 weeks, consider alternative diagnoses or adjusting therapy. 5-11 years: Adjust therapy accordingly. • **For side effects**, consider alternative treatment options.		• Step up 1-2 steps • Reevaluate in 2 weeks • For side effects, consider alternative treatment options

10.12. Appendix 12: Antihistamines That May Be Used Predose

The following antihistamines may be used predose, before Dara-SC injection (including, but not limited to):

- Diphenhydramine
- Cetirizine
- Fexofenadine
- Loratadine
- Clemastine
- Dexchlorpheniramine
- Promethazine*

* The IV use of promethazine should be avoided.

10.13. Appendix 13: Conversion Table for Glucocorticosteroid Dose

Glucocorticoid	Approximate Equivalent Dose (mg)	Half-life (Biologic) hours
Intermediate-Acting		
Methylprednisolone	4	18-36
Prednisolone	5	18-36
Prednisone	5	18-36
Triamcinolone	4	18-36
Long-Acting		
Betamethasone	0.6 – 0.75	36-54
Dexamethasone	0.75	36-54

10.14. Appendix 14: Body Surface Area Calculation

BSA should be calculated using the Mosteller Formula (shown below); however, the DuBois Formula can be used as an alternative.

$$\text{BSA} = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

or

$$\text{BSA} = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

10.15. Appendix 15: EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

10.16. Appendix 16: EORTC QLQ-MY20

EORTC QLQ – MY20

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		**Not at All**	**A Quite a Bit**	**Very Little**		**Much**
31.	Have you had bone aches or pain?	1	2	3	4	
32.	Have you had pain in your back?	1	2	3	4	
33.	Have you had pain in your hip?		1	2	3	4
34.	Have you had pain in your arm or shoulder?	1	2	3	4	
35.	Have you had pain in your chest?	1	2	3	4	
36.	If you had pain did it increase with activity?	1	2	3	4	
37.	Did you feel drowsy?	1	2	3	4	
38.	Did you feel thirsty?		1	2	3	4
39.	Have you felt ill?		1	2	3	4
40.	Have you had a dry mouth?		1	2	3	4
41.	Have you lost any hair?	1	2	3	4	
42.	Answer this question only if you lost any hair: Were you upset by the loss of your hair?		1	2	3	4
43.	Did you have tingling hands or feet?	1	2	3	4	
44.	Did you feel restless or agitated?	1	2	3	4	
45.	Have you had acid indigestion or heartburn?	1	2	3	4	
46.	Have you had burning or sore eyes?	1	2	3	4	

Please turn to next page

During the past week:		Not at All	A Little	Quite a Bit	Very Much
47.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48.	Have you been thinking about your illness?	1	2	3	4
49.	Have you been worried about dying?	1	2	3	4
50.	Have you worried about your health in the future?	1	2	3	4

10.17. Appendix 17: EQ-5D-5L

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

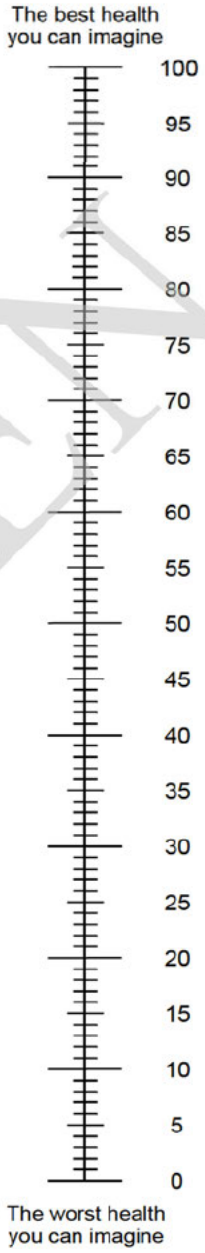
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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10.18. Appendix 18: New York Heart Association (NYHA) Functional Classification

NYHA Class Symptoms

Class I: Cardiac disease, but no symptoms and no limitation in ordinary physical activity (eg, shortness of breath when walking or climbing stairs).

Class II: Mild symptoms (mild shortness of breath or angina) and slight limitation during ordinary activity.

Class III: Marked limitation in activity due to symptoms, even during less-than-ordinary activity (eg, walking short distances [20–100 m]). Comfortable only at rest.

Class IV: Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

10.19. Appendix 19: Individual and Myeloma-related Risk factors

Risk assessment model for the management of venous thromboembolism in multiple myeloma patents treated with thalidomide or lenalidomide

	Actions
Individual risk factors	
Obesity[a]	If no risk factor or any one risk factor is present:
Previous venous thromboembolism	Aspirin 81–325 mg once daily
Central venous catheter or pacemaker	
Associated disease	If two or more risk factors are present:
Cardiac disease	LMWH (equivalent of enoxaparin
Chronic renal disease	40 mg once daily)
Diabetes	Full-dose warfarin (target INR 2–3)
Acute infection	
Immobilization	
Surgery	
General surgery	
Any anesthesia	
Trauma	
Medications	
Erythropoietin	
Blood clotting disorders	
Myeloma-related risk factors	
Diagnosis	
Hyperviscosity	
Myeloma therapy	
High-dose dexamethasone[b]	LMWH (equivalent of enoxaparin 40 mg once daily)
Doxorubicin	Full-dose warfarin (target INR 2–3)
Multiagent chemotherapy	

Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin.
[a]Obesity was defined as body mass index $\geqslant 30\,kgm^{-2}$.
[b]$\geqslant$480 mg per month.

Source: Palumbo 2008[38]

10.20. Appendix 20: Interpretation of The SEBIA Hydrashift 2/4 Daratumumab IFE Interference test

Background: Clinical response assessment in myeloma relies on serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE). As daratumumab is a monoclonal IgG kappa antibody, the SPEP and IFE can be positive for daratumumab at the serum levels anticipated during this protocol.

Implementation: To mitigate this interference, the sponsor will use the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test. During the period of central laboratory analysis, samples will be sent automatically to the central laboratory if daratumumab interference is suspected.

Interpretation of results: The results will be available to the investigator via the central laboratory interface and will be reported as follows:

DARA Hydra Impress1: result defined as "DARA detected", "DARA not detected", OR "DARA indeterminate"

DARA Hydra Impress2: result defined as "M-protein not detected" OR the specific protein detected (i.e. "IgG,k" or "IgA")

DARA Hydra Impress3: result defined as "M-protein not detected" OR the specific protein detected (i.e. "IgG,k" or "IgA")

- If Impress1 result is "DARA detected" and Impress2 and 3 results are "M-protein not detected", the patient may be in complete response (CR) if the other criteria for CR (including negative bone marrow aspirate/biopsy) are achieved.
- If Impress1 result is "DARA not detected" or "DARA indeterminate", the patient is still positive for underlying (endogenous) monoclonal protein and Impress2 and 3 can inform as to the type of endogenous protein still present. Therefore, this patient is not in a complete response (CR), because the CR response criteria requires a negative SPEP and serum IFE.
- If Impress1 result is "DARA detected" but there is also protein present and reported by Impress2 or 3, the patient is still positive for underlying (endogenous) monoclonal protein and Impress2 and 3 can inform as to the type of endogenous protein still present. Therefore, this patient is not in a complete response (CR), because the CR response criteria requires a negative SPEP and serum IFE.

10.21. Appendix 21: General Guidance on Study Conduct During the COVID-19 Pandemic

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by subjects and study-site personnel, travel restrictions/limited access to public places (including hospitals), and study site personnel being reassigned to critical tasks.

In alignment with health authority guidance, the sponsor is providing options for study related subject management in the event of disruption to the conduct of the study. This guidance does not supersede local or government requirements or the clinical judgment of the investigator to protect the health and well-being of subjects, his- or herself, and site staff. If, at any time, the investigator assesses that the risk of treatment may outweigh the benefit, study procedure or treatment will be interrupted, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, subjects will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Subjects will also be questioned regarding general health status to fulfill physical examination requirements. The PRO measures can be captured using site-assisted interview mode where the site will record the subjects' responses in the electronic tablet.

Every effort should be made to adhere to protocol-specified assessments for subjects in the study, including follow-up. Modifications to protocol-required assessments may be permitted after consultation between the subject and the investigator, and with agreement of the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Dosing delays, discontinuation of study treatments, and withdrawal from the study due to the coronavirus pandemic should be documented with the prefix "COVID-19-related" in the electronic case report form (eCRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

Subject Dosing Visits

- Evaluate the feasibility for each subject to return for scheduled dosing visits based on the local situation.
- Subjects who miss a scheduled dosing visit may be rescheduled to receive the missed dose at the next appropriate opportunity. Evaluate the subject's situation on a case by case basis. Every effort should be made to keep subjects on treatment if it is in their best interest, and to maintain phone contact with subjects who are unable to physically visit the hospital to monitor their safety and medication usage.

- The use of local laboratories for safety evaluations is permitted if access to the treating hospital is limited. All information should be collected regarding standard values for these laboratories.

Subject Disease Evaluation Visits

- Continue with central laboratory testing to the greatest extent possible. If central laboratory tests cannot be performed, the use of a local laboratory will be allowed for efficacy evaluations. Central laboratory testing should be resumed as soon as conditions permit, and can occur via home health care options or satellite central laboratory locations if available and approved by the sponsor.

Home Health Care and Tele-Health Visits

- In some circumstances, home health care (with approval from sponsor) and tele-health visits may be implemented per the clinical judgement of the investigator, where feasible and permissible by local policy and regulations.

- Subjects for whom there is no safety concern may have home health care and tele-health (conducted via phone or video conference) visits.

- See Section 8.3.1 for further details.

Exposure to COVID-19

- In the event a subject requires treatment for a coronavirus infection, refer to the protocol to determine any requirements for dose hold, dose modifications, or other prohibitions and considerations. Report the COVID-19 infection as an adverse event (AE) and any concomitant medications (CM) used to treat it to the sponsor following the usual CM and AE reporting requirements. Ensure any AEs of COVID-19 include the exact term "COVID-19" and any serious adverse events (SAE) document confirmed infection with coronavirus.

- It is important to follow local health authority guidance specific to your region of practice, such as social distancing, masking in public places, and vaccinations, including boosters.

- In the event a subject is diagnosed with a COVID-19 infection and requires treatment or is eligible for prophylactic treatment after contact with an individual infected with COVID-19, ensure that the subject receives all necessary treatments for COVID-19 that are approved (including those available under Emergency Use Authorization) in the country including, but not limited to antiviral drugs (eg. remdesivir, ritonavir, favipiravir, molnupiravir, paxlovid), monoclonal antibodies (casirivimab and imdevimab, bamlanivimab and etesevimab, sotrovimab), and dexamethasone.

On-site Monitoring Visits

- In the event on-site monitoring visits are not possible, as per institution policies, the sponsor's site managers may contact the investigator to arrange remote monitoring visits.

Additional on-site monitoring visits may be needed in the future to catch up on source data review and verification.

Study Drug Supply

- Since daratumumab must be administered in the clinic and closely monitored by well-trained health care providers, shipment of daratumumab to patients for at-home administration is not permitted.

- A direct-to-patient delivery of oral, self-administered medication will be allowed within countries where this is appropriate. This decision was made to allow study subjects access to oral study treatments in the event they miss scheduled dosing visits due to the pandemic. Therefore, if locally permitted, alternative solutions to arrange direct-to-patient provision of oral lenalidomide or dexamethasone that are part of the treatment regimen can be discussed with the Medical Monitor.

- A caregiver or family member may pick up oral study drug on behalf of the subject if first discussed with and agreed by the subject. The conversation with the subject must be documented in the subject's source records. The subject must name the individual who will pick up study drug on the subject's behalf. This is necessary for site staff to confirm the study drug is provided to the appropriate individual, ensure proper chain of custody of study drug, and to maintain subject privacy. Identification of who will pick up the study drug must be confirmed and documented in the subject's source record.

Protocol Deviations

- All deviations from the study protocol will be reported based on standard guidance. If related to the coronavirus pandemic situation, these deviations will be recorded as "COVID-19-related" prefix or category.

10.22. Appendix 22: Protocol Amendment History

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

Amendment 5 (24 March 2022)

Overall Rationale for the Amendment: To mitigate the impact of Coronavirus Disease 2019 (COVID-19) pandemic. Changes applied to the relevant sections of the protocol are summarized below.

Section Number and Name	Description of Change	Brief Rationale
6.8.2 Permitted Therapies	Text was updated to include COVID-19 vaccine permitted for study use. Verbiage clarified live, attenuated vaccines or those with suspected replication capabilities are not permitted.	To mitigate the impact of COVID-19 pandemic on study conduct/procedures.
8.1.1 Overview	The text in strikethrough has been deleted: 'During the treatment phase and prior to PD, the PRO measures will be completed using an electronic tablet (ePRO) ~~by the subject~~, unless the subject is unable to complete the visit in-person.'	Text has been removed to allow the site coordinator or proxy to use the electronic tablet to enter PRO responses on the subject's behalf.
10.21 Appendix 21: General Guidance on Study Conduct During the COVID-19 Pandemic	Amendment includes recommendation for vaccinations and therapies for COVID-19 infections.	To mitigate the impact of COVID-19 pandemic on study conduct/procedures.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 4 (1 October 2020)

Overall Rationale for the Amendment: To update the timeframes and landmark analyses for primary analysis of minimal residual disease (MRD) negativity rate. Primary endpoint of MRD negativity remains unchanged, but primary analysis will now occur at approximately 18 months in order to maximize MRD samples available for primary analysis, to ensure the maturity of MRD negativity at the primary analysis, and to mitigate the impact of Coronavirus Disease 2019 (COVID-19) pandemic on MRD sample collection.

Section number and Name	Description of Change	Brief Rationale
Synopsis: Statistical methods; 4.1. Overall Study Design; 4.2. Scientific Rationale for Study Design, Rationale for MRD as a Primary Endpoint	Text was updated to clarify that primary analysis of the overall MRD negativity rate will be performed at approximately 18 months after the last subject is administered his/her first dose of study treatment instead of 1 year.	To maximize MRD samples available for primary analysis due to COVID-19 pandemic. This will further ensure the maturity of the MRD negativity at the primary analysis, supported by the previous daratumumab studies (MMY3007 and MMY3008) in which accumulative MRD negativity rate plateaued at 18 months.
3.1.1. Objectives, Secondary objectives	Secondary objective "To evaluate patient-reported outcomes (PROs)" was included. This was previously indicated as an exploratory endpoint.	Moved from exploratory to secondary objective.
3.1.2. Endpoints, Secondary Endpoints	Other secondary endpoint "Mean change from baseline in the European Organization for Research and Treatment of Cancer	Moved from exploratory endpoint to secondary endpoint.

Section number and Name	Description of Change	Brief Rationale
	Quality of Life Questionnaire (EORTC QLQ) core 3-item (EORTC QLQ-C30) and the multiple myeloma 20-item (EORTC QLQ-MY20), and EuroQol Five Dimension Questionnaire (EQ-5D-5L) scales" was included. The endpoint was moved from exploratory to secondary objectives and further defined as the mean change from baseline.	
8.1.1. Overview	Text was updated to include that the PRO measures will be completed using an electronic tablet (ePRO) by the subject or with site-assisted telephone administration, per applicable interview-mode questionnaire.	To accommodate the site-assisted telephone option as part of the COVID-19 mitigation strategy.
8.2.1. Response Categories	Text was updated to clarify that the local laboratory results of blood and urine M-protein measurements may be used to determine disease response and progression.	Local laboratories may be used to determine response as well, in exceptional circumstances, as a part of the COVID-19 mitigation strategy.
8.2.4. Bone Marrow Examination	Text was updated to clarify that archived samples for MRD or cytogenetic evaluation may be requested to be sent to the central laboratory, if available, in cases in which there is difficulty in establishing baseline clonality for MRD or if screening baseline cytogenetics are not evaluable	To mitigate cases in which baseline samples were not evaluable for either cytogenetics or a baseline clone for MRD.
8.3.1. Home Health Care and Tele-Health Visits	A new section was included to describe home health care and tele-health visits with approval from the sponsor and per the clinical judgement of the investigator, where feasible and permissible by local policy and regulations.	To mitigate the impact of COVID-19 pandemic on study conduct/procedure.
8.3.6. Clinical Safety Laboratory Assessments	Urea was deleted from Serum Chemistry Panel during Cycles 1 through 8. Blood urea nitrogen (BUN) was added in Serum Chemistry Panel during Cycle 9 and beyond.	To delete duplicate urea sampling and to add BUN analysis in Cycles 1 through 8 and 9 and beyond by allowing either BUN or urea.
10.21. Appendix 21: General Guidance on Study Conduct During the COVID-19 Pandemic	New appendix was added.	To mitigate the impact of COVID-19 pandemic on study conduct/procedure.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 3 (19 November 2019)

Overall Rationale for the Amendment: The overall reason for the amendment is to expand the scope of efficacy review by Independent Data Monitoring Committee (IDMC) at different stages in the study. Additionally, to ensure that the subjects continue to receive treatment with other components of study treatment even if any one component is held, discontinued or reduced, to clarify that subsequent anti-myeloma therapies should not be administered until disease progression and in subjects who discontinue study treatment for reasons other than disease progression, should be monitored and subsequent treatment should not be started until documented disease progression. To provide clarifications regarding

the company which will conduct the Food and Drug Administration (FDA)-approved clonoSEQ minimal residual disease (MRD) assay and which version will be used.

Section number and Name	Description of Change	Brief Rationale
4.1. Overall Study Design; 4.2.1. Study-Specific Ethical Design Considerations; 9.8. Independent Data Monitoring Committee	Updated text regarding IDMC review to add efficacy review along with safety review after each interim review at the primary MRD analysis and the interim analysis of progression-free survival (PFS) in order to make recommendations regarding unblinding and continuation of the study.	To expand scope of IDMC review to include efficacy review at different stages in the study.
6.6.2.2. Daratumumab-Related Toxicity Management	Text was added to clarify that treatment with bortezomib, lenalidomide and dexamethasone may be continued if daratumumab is held or discontinued.	To ensure that the subjects continue to receive treatment with other components of study treatment even if any one component is held, discontinued or reduced.
6.6.3. Lenalidomide	Text was added to clarify that treatment with bortezomib, dexamethasone, and daratumumab (Arm B only) may be continued if lenalidomide is held or discontinued.	
6.6.4. Bortezomib	Text was added to clarify that treatment with lenalidomide, dexamethasone, and daratumumab (Arm B only) may be continued if bortezomib is held or discontinued.	
6.6.5. Dexamethasone	Text was added to clarify that treatment with bortezomib, lenalidomide, and daratumumab (Arm B only) may be continued if dexamethasone dose is reduced or interrupted.	
6.8.4. Subsequent Therapies	Text regarding non-permissibility of subsequent therapies until disease progression was further clarified.	To clarify that subsequent therapies should not be administered until disease progression is confirmed.
4.2. Scientific Rationale for Study Design	The name of the company who will conduct the FDA-approved clonoSEQ v2.0 MRD assay was changed from “Adaptive Biotechnology” to “Adaptive Biotechnologies”.	To specify that only FDA-approved clonoSEQ v2.0 will be used in this study for MRD analysis and correct the name of the company who will conduct this analysis.
8.8. Biomarkers	Text regarding use of any other alternative method for MRD assessment was deleted and text regarding use of only FDA-approved clonoSEQ v2.0 conducted at Adaptive Biotechnologies was added.	
9.4.4. Other Analyses	Text regarding use of the FDA-approved clonoSEQ v2.0 MRD assay was added.	
1.3. Schedule of Activities (SOA); 6.3. Bortezomib (Arms A and B)	Text was edited to specify that if a subject’s weight changes by more than 10% from baseline, the weight used for drug calculations should be adjusted and the dose of bortezomib will be re-calculated.	Bortezomib dose will be re-calculated if a subject’s weight changes by more than 10% from baseline.
1.3. Schedule of Activities (SOA)	Added a window of ±1 week for hepatitis B virus (HBV)-deoxyribonucleic acid (DNA) test which occurred every 6 weeks on Day 1, 8 and 15 for Cycles 1 to 8 with the exception of Cycle 1 Day 1. Added a window of ±1 month for HBV-DNA test which occurred every 12 weeks on Day 1, end of treatment (EOT) and prior to progressive disease (PD) for Cycles 9 and beyond, EOT, prior to PD and post PD.	To allow a window period for HBV-DNA testing.
2.1.5. Clinical Studies	Updated the list of indications for which daratumumab is approved in the United States (US).	To align with current approvals for daratumumab in the US.

Section number and Name	Description of Change	Brief Rationale
3.1.2. Endpoints	The definition of MRD negative status was revised to clarify that subjects who achieve MRD negativity after the switch to subsequent antimyeloma therapy will not be considered MRD negative. The reference to International Myeloma Working Group (IMWG) PD criteria was added and reference to IMWG diagnostic criteria was deleted.	To clarify definition of the primary endpoint and revise references.
4.2. Scientific Rationale for Study Design	The text regarding enzyme recombinant human hyaluronidase (rHuPH20) was modified.	To clarify the use of rHuPH20 in the daratumumab subcutaneous (SC) formulation.
5.1. Inclusion Criteria (Criterion 5)	Added text to clarify use of adjusted body weight if body mass index (BMI) is >30 kg/m^2 while calculating creatinine clearance using the Cockcroft-Gault formula.	To clarify use of adjusted body weight while calculating creatinine clearance during the Screening Phase.
5.2. Exclusion Criteria (Criterion 2)	The maximum limit of 4 days for prior therapy with dexamethasone was removed.	To allow longer courses of prior therapy with dexamethasone.
5.2. Exclusion Criteria (Criterion 5)	Patients with palliative focal radiotherapy for symptomatic pain management can participate in the study.	To allow a greater number of patients undergoing radiotherapy to participate in the study.
5.2. Exclusion Criteria (Criterion 10b)	Modified the definition of subjects seropositive for hepatitis B.	To ensure consistency with the Centers for Disease Control (CDC) terminology for hepatitis B.
5.3. Restrictions During Study Participation	Additional text regarding the pregnancy prevention plan for lenalidomide was added.	To further clarify the measures to mitigate the risk of embryo-fetotoxicity associated with lenalidomide.
1.3. Schedule of Activities (SOA) footnote e	Text regarding requirement of pregnancy test for women with regular and irregular menstrual cycles after last dose of lenalidomide was added.	
6.1.2. Daratumumab Administration	The text regarding major protocol deviation criteria for daratumumab administration was modified. The text was added to allow for option to administer lenalidomide at night.	To ensure consistency with the MPD criteria for daratumumab administration and add clarification to allow administration of lenalidomide at night, as it is the standard of care.
6.3. Bortezomib (Arms A and B); 6.6.4. Bortezomib	The text regarding minimum time period “must be at least 72 hours” between two doses of bortezomib was modified to “should be approximately 3 days”.	To allow flexibility in the time period between two doses of bortezomib.
6.6.1. Cycle delay	The text regarding cycle delay “from the planned start of new cycle” was deleted.	To allow flexibility in the counting the time period from the last cycle when none of the study medications are given.
6.6.3.1. Renal Impairment	Text was added to specify that lenalidomide doses can be re-escalated at the investigator’s discretion in the event of dose adjustment in subjects with changes in renal status during treatment.	To clarify lenalidomide dose re-escalation

Section number and Name	Description of Change	Brief Rationale
6.6.5. Dexamethasone (Table 8)	Text was added to clarify that dexamethasone will be skipped on days when daratumumab is not given on Arm B, or corresponding days for Arm A..	To clarify dexamethasone dose reduction guidelines.
6.6.6. Dose Modification Guidelines	A note was added regarding importance of physician's discretion and clinical judgement.	Physician's discretion and clinical judgement should prevail in dose modification decisions.
6.8.1.2. Bisphosphonate Therapy and Denosumab	Text was added to describe addition of denosumab as an alternative to bisphosphonate therapy.	To allow denosumab as an alternative to bisphosphonate therapy.
6.8.1.4. Prophylaxis for Bacterial Pneumonia and *Pneumocystis Carinii* Pneumonia	Text regarding bacterial pneumonia was added.	To include bacterial pneumonia in the list of diseases for which prophylaxis is recommended.
6.8.3. Prohibited Therapies	Prednisone was deleted and dexamethasone was added, and maximum dose of dexamethasone was further described.	To define prohibited corticosteroid, use to be consistent with doses that have an anti-myeloma effect.
7.2. Discontinuation of Study Treatment	The word 'one' was deleted.	To clarify the wording regarding discontinuation of any component of the study treatment.
8.1.2. Screening Phase	The wording "Cycle 1 Day 1" was deleted and "randomization" was added.	To clarify that timing of screening procedures will be performed within 28 days before randomization.
8.2.4. Bone Marrow Examination	The text regarding bone marrow examination was revised and details regarding which laboratories (central versus local laboratory) would perform bone marrow aspirate or bone marrow biopsy, or both were added.	To clarify the bone marrow assessment laboratory details.
8.2.6. Assessment of Lytic Disease	Text regarding IMWG diagnostic criteria (SLiM criteria [S=≥Sixty-percent (≥60%) clonal BM plasma cells; Li=serum free Light chain ratio involved: uninvolved ≥100; M=>1 focal lesion (≥5 mm each) detected by magnetic resonance imaging (MRI) studies]) and MRI lesion was added.	To align with IMWG diagnostic criteria (SLiM criteria) for assessment of lytic disease.
8.3.4. Electrocardiogram	The text was revised to recommend that procedures will be performed in the following order: electrocardiogram (ECG), vital signs, and blood draw.	To allow more flexibility in the order of performing the assessments.
8.3.5. Clinical Safety Laboratory Assessments	Serum urea test was added during Cycles 1 to 8.	To clarify the clinical safety laboratory assessments and allow flexibility of conducting the laboratory tests at the local laboratory.
8.3.5. Clinical Safety Laboratory Assessments	Text for assessment of calcium and albumin adjusted calcium test was revised to allow local laboratory assessments under exceptional circumstances if central laboratory is not evaluable.	
8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	The word 'procedure' was replaced with 'treatment'.	To clarify adverse event (AE) reporting period.

Section number and Name	Description of Change	Brief Rationale
3.1.1. Objectives	The patient-reported outcome (PRO) was moved from secondary to exploratory objective.	To clarify that the PRO endpoints will be for exploratory purpose.
3.1.2. Endpoints	The PRO endpoint was deleted from the list of secondary endpoints.	
9.6. Patient-reported Outcomes Analyses	The text regarding the PRO analyses was revised to indicate that these analyses are now exploratory.	
10.2. Appendix 2: Anticipated Events	Anemia, neutropenia, and thrombocytopenia were deleted from the anticipated events list. The review and reporting requirements for anticipated events were clarified. Revised "Anticipated Event Review Committee" (ARC) to "Safety Assessment Committee" (SAC).	Modified the list of anticipated events to remove any events that are known ADRs of daratumumab. Clarification that after unblinding of aggregate safety data by the sponsor's study team, there is no need for independent SAC review of anticipated events. Additional clarification of the reporting responsibilities for anticipated events to Health Authorities and Institutional Review Boards (IRB)/Independent Ethics Committees (IEC). Changed name of committee to be in alignment with company procedures.
10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations	The details regarding IDMC were added.	To describe further that the IDMC will be established according to regulatory guidelines.
10.4. Appendix 4: Adverse Events Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Removed definitions of severity criteria as they are specified in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 5.	Clarification to correct NCI-CTCAE version inconsistency.
Throughout the protocol	Minor grammatical, formatting, spelling or missed changes were made.	Minor errors were noted.

Amendment 2 (18 January 2019)

Overall Rationale for the Amendment: The overall reason for the amendment is in response to identification of a new important risk (hepatitis B virus [HBV] reactivation). Additionally, revisions and clarifications were made to considerations for lenalidomide use, sequence of secondary endpoints, as well as other measurement parameters throughout the Protocol.

Section number and Name	Description of Change	Brief Rationale
Table 1 Schedule of Activities	Added row for HBV serology, modified text for HBV DNA test, and identified the timepoints at	The text for identification of HBV reactivation, testing, and

Section number and Name	Description of Change	Brief Rationale
	which HBV serology and HBV DNA test would be conducted.	management of subjects with the potential for HBV reactivation was added or modified in response to identification of a new important risk (HBV reactivation).
5.2 Exclusion Criteria (Criterion 10)	Clarified language to exclude subjects who are seropositive for hepatitis B.	
6.8.1.7 Management of Hepatitis B Virus Reactivation	Added a new section providing information for the management of hepatitis B virus reactivation.	
8.1.1 Overview	Corrected the blood volume to be collected during Screening to approximately 50 mL, thus accounting for HBV serology.	
8.3.7 HBV Serology and DNA Tests	Added and revised information detailing the conduct of hepatitis B virus serology and DNA tests.	
References	Removed reference: Drafting Committee for Hepatitis Management Guidelines and the Japan Society of Hepatology (JSH). Guidelines for the Management of Hepatitis B Virus Infection. Hepatol Res. 2014;44 Suppl S1:1-58. Added reference: Tang DI, Geller NL. Closed testing procedures for group sequential clinical trials with multiple endpoints. Biometrics. 1999;55:1188-1192.	
5.1 Inclusion Criteria (Criterion 5)	Added "≥" sign for hemoglobin ≥7.5 g/dL, absolute neutrophil count (ANC) ≥1.0 x 10^9/L, and platelet count ≥70 x 10^9/L	Clarifications were made to the clinical laboratory value criteria during the Screening Phase.
5.3 Restrictions During Study Participation	Contraception must begin 4 weeks before initiating treatment with daratumumab **and lenalidomide**, and continue during the Treatment Phase, during dose interruptions and continuing for 4 weeks after the last dose of lenalidomide and 3 months following of the last dose of daratumumab.	Clarification was provided regarding the prohibition of treatment with lenalidomide during known pregnancy or potential for pregnancy.
7.2 Discontinuation of Study Treatment	Added clarification to discontinuation of study treatment if the subject becomes pregnant: unless the subject (or the subject's legally acceptable representative), investigator, and sponsor agree the benefits outweigh the risks to the fetus and continuation of study treatment, **except for lenalidomide,** is in the best interests of the subject.	
9.4.2 Efficacy Analyses	Text indicating the sequence of secondary endpoints was replaced: ~~A hierarchical testing approach will be used to control the family-wise Type I error rate at a 2-sided level of 0.05 for key secondary efficacy endpoints such as PFS, durable MRD negativity rate, and rate of CR or better. Details of the procedure will be specified in the SAP prior to any unblinded analysis.~~ **If the primary endpoint of overall MRD negativity rate is statistically significant, the key secondary endpoints (ie, CR or better rate, PFS,**	Clarification was made to the analysis of secondary endpoints.

Section number and Name	Description of Change	Brief Rationale
	and durable MRD negativity rate) will be sequentially tested, each with an overall two-sided alpha of 0.05, by utilizing a hierarchical testing approach as proposed by Tang and Geller (1999) that strongly controls family wise Type I error rate.	
10.20 Appendix 20: Interpretation of the SEBIA Hydrashift 2/4 Daratumumab IFE Interference Test	The following text was modified: Implementation: To mitigate this interference, the sponsor will use the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test. ~~to distinguish a positive SPEP/IFE due to the presence of daratumumab versus the presence of the underlying (endogenous) monoclonal protein. The SEBIA Hydrashift 2/4 Daratumumab IFE Interference test~~ **Samples** will be sent automatically to the central laboratory if **daratumumab interference is suspected**. ~~a subject with IgG kappa multiple myeloma has an SPEP at or below 0.2 g/dL on 2 or more consecutive cycles. In addition, the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test will be sent automatically to the central laboratory if a subject has an SPEP of zero, but persistently positive IFE for IgG kappa on 2 or more occasions.~~	Clarification was made to the implementation of the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test.
Table 1 Schedule of Activities 8.3.5 Clinical Safety Laboratory Assessments 10.6 Appendix 6: IMWG Diagnostic Criteria	Table 1 was updated to include instruction row for measurement of creatinine clearance. The notes for Bone marrow aspirate/biopsy were clarified: For screening ~~(collected within 42 days before randomization)~~ fresh aspirate required (archived samples will not be accepted). Modified creatinine measurement during Cycle 9 and beyond: creatinine **clearance (measured or calculated).** Footnote g was added for the event of anemia: **Hemoglobin measurement performed as part of standard of care within 42 days before randomization is acceptable for screening for CRAB criteria; but must be performed within 21 days before randomization for other eligibility requirements.**	Minor changes and clarifications were made throughout.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 1 (10 September 2018)

Overall Rationale for the Amendment: To add language describing hepatitis testing, which is now required across daratumumab studies for subjects who are positive for anti-HBc and/or anti-HBs.

Section number and Name	Description of Change	Brief Rationale
Table 1: Schedule of Activities - Treatment and Follow-Up Phases	Requirements for HBV-DNA monitoring at various timepoints during the study have	Language regarding hepatitis testing for subjects who are

Section number and Name	Description of Change	Brief Rationale
	been added to the Time and Events Schedule.	positive for anti-HBc and/or anti-HBs has been added.
Section 8.3.7: HBV-DNA Test	Clarification has been made to the requirements for HBV-DNA testing.	
Table 1: Schedule of Activities - Treatment and Follow-Up Phases	Text added to specify that for Arm A, vital signs are required only on Day 1 of every cycle.	Clarification to vital sign collection for subjects in Arm A versus Arm B has been made.
Section 8.3.3: Vital Signs	Details on the requirements for the collection of vital signs has been added.	
Table 2: Schedule of Activities - Pharmacokinetic/Immunogenicity Sample Collection Times – Arm B ONLY	Posttreatment Week 4 collections have been deleted.	Changes and clarifications made to the timepoints for collection of pharmacokinetic and immunogenicity samples.
Section 8.1.1: Overview	To coincide with the revisions made to the biomarker assessments and provide more granularity in the breakdown of the blood volumes for this study, the estimated total blood volumes have been updated.	To update biomarker assessments to require mandatory a fresh bone marrow aspirate for cytogenetics and to remove the option for archived sample for MRD at screening. Also, the description of the SEBIA Hydrashift Interference Test has been added to the protocol.
Section 8.2.1: Response Categories	Added text to indicate that for subjects with suspected daratumumab interference on SPEP and immunofixation, a reflex assay will be performed.	
New Appendix 20 (Section 10.20) Interpretation of The SEBIA Hydrashift 2/4 Daratumumab IFE Interference test Table 11 added	Included a description of the new SEBIA Hydrashift 2/4 Daratumumab IFE Interference test that will be used to distinguish a positive SPEP/IFE.	
Section 8.2.2: Myeloma Protein Measurements in Serum and Urine	Clarified the requirements for a fresh bone marrow aspirate at screening and the MRD assessment for cytogenetics evaluations.	
Section 8.2.4: Bone Marrow Examination Section 8.8: Biomarkers Section 9.4.4: Other Analyses - Biomarker Analyses Table 11 Bone Marrow Testing	Clarified the process for how the bone marrow aspirate will be portioned out for assessment. The title of the table was also revised.	
Appendix 4 (Section 10.4) Attribution Definitions	Revised the AE attribution definitions to limit to: Not Related: An adverse event that is not related to the use of the drug Related: An adverse event that might be due to the use of the drug	To coincide with the causality options presented on the revised SAE reporting form, the AE attribution definitions have been revised.
Appendix 4 (Section 10.4) Procedures	To align with the revision to the AE attribution definitions, revised text as follows: “For subjects who have received additional treatment with therapeutic intent for multiple myeloma during the AE reporting period, only AEs that are considered to be ~~possibly, probably, or definitely~~ related to the study drug or any part of the backbone treatment regimen	

Section number and Name	Description of Change	Brief Rationale
	must be reported (unless the subject has been withdrawn from the study)."	
Table 1: Schedule of Activities - Treatment and Follow-Up Phases Table 5 Dose Modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone Section 5.1 Inclusion Criteria Criterion #6g Section 5.2: Exclusion criterion #2 Exclusion criterion #11 Section 6.8.1.1 Prevention of Deep Vein Thrombosis and Pulmonary Embolism Section 8.2.3: Albumin and Serum Calcium Corrected for Albumin Appendix 9 (Section 10.9)	Clarifications regarding hematology, serum chemistry, and HBV-DNA collection have been made. Revised footnote f to specify that creatinine clearance is calculated by the Cockcroft-Gault formula and adjusted for body weight in ş ubjects with a body mass index >30 kg/m and that the eGFR (MDRD) or CKD-epi formulas can also be utilized to assess renal function. Exclusion criterion #2 has been revised. Exclusion criterion #11 has been revised. Linked to the correct appendix Revised text to specify that blood samples for calculating serum calcium corrected for albumin are to be analyzed by the central laboratory rather than by local laboratories. Modified Diet in Renal Disease Formula has been added	Miscellaneous edits/clarifications have been made to the protocol.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	14-Mar-2024 20:21:12 (GMT)	Document Approval