Clinical Protocol

A Phase 3 Study Comparing Daratumumab, VELCADE (bortezomib), Lenalidomide, and Dexamethasone (D-VRd) vs VELCADE, Lenalidomide, and Dexamethasone (VRd) in Subjects with Previously Untreated Multiple Myeloma who are Eligible for High-dose Therapy

Protocol EMN17/54767414MMY3014; Phase 3
JNJ-54767414 (daratumumab)
AMENDMENT 5

The term "sponsor" is used throughout the protocol. The sponsor is identified on the Contact Information page that accompanies the protocol.

EudraCT NUMBER: 2018-002992-16
EU TRIAL NUMBER: 2023-506125-10-00

Sponsor:
Stichting European Myeloma Network (EMN)
PPD

Sponsor representative: PPD

EMN

Status: Approved
Date: 28 February 2024
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-149334525, 9.0

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

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	09 July 2018
Amendment 1	04 September 2018
Amendment 2	09 April 2019
Amendment 3	20 March 2020
Amendment 4	27 June 2022
Amendment 5	28 February 2024

Amendment 5 (28 February 2024)

Overall Rationale for the Amendment: The key reasons for this protocol amendment are as follows:

- To redefine the timing of the overall survival (OS) analyses after PFS superiority was established at the first PFS interim analysis (clinical cutoff: 01 August 2023), including 1) forgoing the current first OS interim analysis (185 PFS events); 2) keeping the interim OS analysis at 285 PFS events (approximately 170 OS events; 55% of the total planned OS events) as the new first OS interim analysis; 3) adding another interim OS analysis at 75% of the total planned OS events (233 events); and 4) final OS analysis at 310 OS events.
- To change the disease evaluation schedule for subjects who stopped treatment before Cycle 7 Day 1 without confirmed PD to every 4 weeks (±7 days) for the first 2 years and then every 8 weeks (±14 days) relative to Cycle 1 Day 1 thereafter until confirmed PD, to align with standard of care.
- To provide protocol clarifications for better understanding.
- To align with EU CTR requirements.

The changes made to the clinical protocol EMN17/54767414MMY3014 as part of Protocol Amendment 5 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 18, Appendix 1: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
Title page	Updated EMN address.	To update address to new office location.
Title page; 1.1 Synopsis	Added EU TRIAL NUMBER.	To align with EU CTR requirements.
1.1 Synopsis	Added EudraCT NUMBER.	
Protocol Amendment Summary of Changes Table	Updated table header and moved previous amendments to new Section 18.1 (Appendix 1).	To align with current protocol template.
1.1 Synopsis	Within Table 1, added that vital signs and serum chemistry assessments are required when daratumumab is restarted after stopping due to sustained MRD negativity.	To clarify how often to monitor vital signs and laboratory assessments with daratumumab restart.
1.1 Synopsis	Within Table 1, clarified timing of patient-reported outcome (PRO) assessments post PD.	To align with Section 9.7.
1.1 Synopsis	To the Table 1 footnote describing disease evaluations for subjects who discontinue treatment prior to Cycle 7 Day 1 without confirmed PD, specified that these evaluations should be performed every 4 weeks (±7 days) for the first 2 years and then every 8 weeks (±14 days) relative to Cycle 1 Day 1 thereafter until confirmed PD.	To better align with standard of care.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis	To Table 2, added a footnote indicating that for subjects who meet criteria to stop daratumumab due to sustained MRD negativity, posttreatment daratumumab PK, daratumumab immunogenicity, and rHuPH20 immunogenicity will be collected 8 weeks after the last dose of daratumumab. If the subject restarts daratumumab, no further PK samples need to be drawn.	To clarify that the last dose PK should be done when daratumumab is stopped and not wait until end of treatment.
3.1 Overview of Study Design	To footnote for Figure 1 (study schematic), changed footnote to read "Restart therapy upon loss of CR or loss of MRD status" instead of "Restart therapy upon relapse from CR or loss of MRD status."	For consistency across protocol.
	Added text indicating that subjects who discontinued before disease progression must continue to have disease evaluations as specified in Table 1 and should not initiate any subsequent anticancer treatment until disease progression is confirmed per IMWG criteria and approved by medical monitor and documented in IWRS.	To clarify procedures for initiating subsequent anticancer treatment.
6 Dosage and Administration	Added table (Table 3) specifying the study medicinal products and their designations.	To align with EU CTR requirements.
6.1.2 Daratumumab Administration; 9.1.4 End-of-Treatment Visit	Clarified that subjects in Arm B who achieve MRD negativity and are continuing study assessments but are not receiving study drug should not complete an End-of-Treatment Visit.	For clarification.
6.1.2 Daratumumab Administration	Added that, following daratumumab restart, vital signs and hematology and serum chemistry laboratory assessments should be monitored prior to each daratumumab administration.	To clarify how often to monitor vital signs and laboratory assessments with daratumumab restart.
6.1.3.1 Daratumumab Predose Medication	Clarified that subjects who restart daratumumab after interruption due to sustained MRD negativity should be given dexamethasone 20 mg IV or PO for the first 2 doses and 10 mg for all subsequent doses.	To clarify dexamethasone administration following daratumumab restart.
6.2.2 Daratumumab Infusion-related Reactions	Added that if ocular symptoms (including choroidal effusion, acute myopia, and acute angle closure glaucoma) occur, daratumumab should be interrupted and immediate ophthalmologic evaluation should be sought prior to restarting daratumumab.	To align with updated safety data for daratumumab.
8.2 Permitted Therapies	Added that subjects may continue lenalidomide on the day of vaccine administration per institutional practice.	To clarify that there is no need to pause lenalidomide on the day of vaccine administration per institutional practice.
8.4 Subsequent Therapies	Clarified that it is not permissible to start other anti-myeloma therapy until disease progression is confirmed by IMWG criteria and approved by the medical monitor. Disease progression should be monitored and documented in the CRF, according to Table 1.	To clarify procedures for initiating subsequent anticancer treatment.
9.2.1 Response Categories	To the table describing criteria for loss of CR, added footnote stipulating that 2 consecutive assessments for reappearance of serum or urine M-protein are needed.	To clarify that confirmatory samples are needed before restarting daratumumab.

Section Number and Name	Description of Change	Brief Rationale
9.8 Safety Evaluations	For total bilirubin, removed that direct bilirubin is required if total bilirubin is abnormal.	To align with current practice.
10.2 Discontinuation of Study Treatment/Withdrawl From the Study	Removed the following text (shown in strikeout): 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.	For clarification.
11.2 Sample Size Determination	Removed the following text (shown in strikeout): Long-term follow-up for survival will continue until approximately 310 deaths have been observed ~~or 9 years have elapsed after the last subject is randomized, whichever occurs earlier~~.	To align with the updated timing of OS analyses.
11.12 Interim Analysis	Indicated that descriptive analysis of OS was performed at the time of the first PFS interim analysis and updated the timing for subsequent OS analyses.	To redefine the timing of the OS analyses after PFS superiority was established at the first PFS interim analysis (clinical cutoff: 01 August 2023).
11.13 Independent Data Monitoring Committee	Added that no further IDMC meetings will be scheduled after the primary endpoint was met, and safety data will continue to be reviewed by the sponsor. Clarified that the medical monitors will remain blinded regarding OS.	The primary endpoint was met at the first interim analysis of PFS, the study data were unblinded, and no new safety signals were observed; therefore, no further IDMC meetings will be scheduled.
16.2.4 Data Protection	Retitled section to “Data Protection” and made title of section (“Privacy of Personal Data”) a subheading.	To be consistent with EU CTR data protection requirements.
17.7 Record Retention	Added that 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.	To comply with EU CTR data requirements.
17.9.1 Study Completion/End of Study	Removed the following text (shown in strikeout): The study is considered completed when 310 deaths have been observed ~~or 9 years have elapsed after the last subject is randomized~~.	To align with the updated timing of OS analyses.
17.11 Use of Information and Publication	Clarified that the use of information applies to the study site as well as the investigator.	For clarification.
	Updated disclosure of results.	To align with Section 11.2.
18 Supporting Documentation and Operational Considerations	Added section for protocol amendment history and moved description of previous amendments to this section.	To align with current protocol template.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

SYNOPSIS

EudraCT NUMBER: 2018-002992-16
EU TRIAL NUMBER: 2023-506125-10-00

A Phase 3 Study Comparing Daratumumab, VELCADE (bortezomib), Lenalidomide, and Dexamethasone (D-VRd) vs VELCADE, Lenalidomide, and Dexamethasone (VRd) in Subjects with Previously Untreated Multiple Myeloma who are Eligible for High-dose Therapy

BENEFIT-RISK ASSESSMENT

Subjects in this study will be assigned in a randomized manner to receive either 1800 mg daratumumab SC in combination with VRd (D-VRd) as induction and consolidation therapy and in combination with lenalidomide maintenance therapy or VRd alone as induction and consolidation therapy and lenalidomide alone as maintenance therapy. The sequence of VRd induction/ASCT/VRd consolidation/lenalidomide maintenance is the global standard of care (SOC). While treatment with D-VRd has demonstrated a manageable safety profile consistent with the known safety profile of daratumumab SC and VRd alone, management guidelines for potential toxicities are detailed in the protocol. Overall, there is a positive benefit/risk profile for this patient population.

OBJECTIVES

The primary objective is to determine if the addition of daratumumab to bortezomib, lenalidomide, and dexamethasone (VRd) will prolong progression-free survival (PFS) defined as the time from the date of randomization to the date of disease progression (assessed by International Myeloma Working Group [IMWG] criteria) or death, compared with VRd alone.

Key secondary objectives include the following:

- To determine if the addition of daratumumab to VRd will improve clinical outcome as measured by:
  - Minimal residual disease (MRD) negativity rate post-consolidation and overall MRD negativity rate achieved at any time during the study
  - Overall response rate (ORR), rate of very good partial response (VGPR) or better, rate of complete response (CR) or better, rate of stringent CR (sCR) at post-induction, post-transplant, post-consolidation, and overall
  - Time to response
  - Duration of response
  - Progression-free survival on the next line of therapy (PFS2)
  - Overall survival (OS)
- To assess the safety profile of daratumumab+VRd (D-VRd)

OVERVIEW OF STUDY DESIGN

This is a randomized, open-label, multicenter study evaluating subjects with newly diagnosed multiple myeloma who are deemed eligible for high-dose therapy. Approximately 690 subjects will be stratified by International Staging System (ISS) Stage I, II, or III disease (β-2 microglobulin and albumin) and cytogenetics (standard risk or high risk as defined by presence of del17p, t[4;14] or t[14;16]), and then randomized in a 1:1 ratio. In Arm A, subjects will receive VRd for induction and consolidation, followed by lenalidomide (R) maintenance until disease progression. Subjects in Arm B will receive D-VRd for induction and consolidation followed by daratumumab and lenalidomide maintenance until disease progression. Subjects in Arm B who have a response of CR or better will stop therapy with daratumumab

after sustained MRD negativity (at or below the threshold of 10^{-5}) for 12 months and a minimum of 24 months of maintenance therapy. These subjects will continue lenalidomide maintenance therapy until disease progression. After stopping daratumumab therapy, subjects with sustained MRD negativity should restart therapy with daratumumab if there is a recurrence of MRD at 10^{-4} or higher or a confirmed loss of CR without disease progression, as evidenced by the reappearance of serum or urine monoclonal protein (M-protein) or increase to ≥5% plasma cells in bone marrow. After reinitiating daratumumab, the subject will continue daratumumab and lenalidomide therapy until disease progression.

DOSAGE AND ADMINISTRATION

Subjects will receive 6 cycles of treatment (4 cycles of treatment for induction and 2 cycles of treatment for consolidation) followed by maintenance (Cycle 7+).

Daratumumab will be given subcutaneously (SC) at 1800 mg to subjects in Arm B once every week for Cycles 1 to 2, then every 2 weeks for Cycles 3-6. For maintenance Cycles 7+, subjects will receive daratumumab (1800 mg) once every 4 weeks until documented disease progression or unacceptable toxicity.

Bortezomib will be given as a SC injection (1.3 mg/m^2) twice a week for 6 cycles.

Lenalidomide will be administered PO at 25 mg for 6 cycles. Subjects will start maintenance therapy (Cycle 7+), during which they will receive lenalidomide 10 mg daily PO on Days 1 to 28 (continuously) of each 28-day cycle until disease progression or unacceptable toxicity.

Dexamethasone will be administered PO at 40 mg on Days 1-4 and 9-12 during Cycles 1-6 as part of the VRd backbone regimen.

EFFICACY EVALUATIONS

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.

OTHER EVALUATIONS

Blood samples will be drawn from all subjects in Arm B to characterize the pharmacokinetics (PK) of daratumumab to the incidence of anti-daratumumab antibodies, and the prevalence and incidence of anti-rHuPH20 antibodies. Blood and bone marrow aspirate samples may be used to obtain information about potential markers of clinical response.

Data regarding subjects' health-related quality of life (HRQoL), symptoms, functioning, and general well-being will be captured using 3 patient-reported outcome (PRO) measures. Medical resource utilization (MRU) data will be collected.

SAFETY EVALUATIONS

Safety evaluations include adverse event (AE) monitoring, physical examinations, electrocardiograms (ECGs), echocardiogram (ECHO) or multigated acquisition (MUGA) scan (only required for subjects ≥65 years old), SC injection-site evaluations, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status.

STATISTICAL METHODS

Response to study treatment and progressive disease (PD) will be evaluated by a validated computer algorithm. The assumption is that the addition of daratumumab will decrease the risk of progression or death by 31% (hazard ratio [HR]=0.69).

Table 1: Time and Events Schedule

			Treatment Phase (28-day cycles)								Treatment Phase (28-day cycles)		Follow-up Phase	
	Notes	Screening Phase (within 28 days before random-ization)	Induction Treatment (Cycles 1 4)				Pre-ASCT (within 2 weeks of completing C4)	ASCT	Consolidation Treatment (Cycles 5-6)		Maintenance Treatment (Cycles 7+)	EOT	Prior to PD[a]	Post PD
			D1[b]	D8	D15	D22		(Refer to Section 9.1.3)	D1	D15	D1	Within 30 days after last dose		Every 4 months (±2 wks)
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, new malignancy, subsequent anticancer therapy, PRO assessments, and MRU.														
Informed consent	Subjects must sign the informed consent before any study related procedures performed[c]	X												
Demographics/ height/medical history		X												
Eligibility criteria		X												
Chest X ray or full dose chest CT scan	Acceptable for screening if performed as part of SOC within 42 days before randomization	X												
Spirometry test (ie, FEV1)	Required for all subjects ≥65 years old; if <65 years old, only required if known or suspected to have COPD. Acceptable for screening if performed as part of SOC within 42 days before randomization	X												
Diffusing Capacity of the Lung for Carbon Monoxide (DLCO)	Only required for subjects ≥65 years old	X												
ECOG performance status		X	C3D1 only				X		C5 only		C7D1 then every 12 weeks until PD (±7 days)		X	
12 lead ECG	Acceptable for screening if performed as part of SOC within 42 days before randomization	X		As clinically indicated								X		

			Treatment Phase (28-day cycles)								Treatment Phase (28-day cycles)		Follow-up Phase	
	Notes	Screening Phase (within 28 days before random-ization)	Induction Treatment (Cycles 1 4)				Pre-ASCT (within 2 weeks of completing C4)	ASCT	Consolidation Treatment (Cycles 5-6)		Maintenance Treatment (Cycles 7+)	EOT	Prior to PD[a]	Post PD
			D1[b]	D8	D15	D22		(Refer to Section 9.1.3)	D1	D15	D1	Within 30 days after last dose		Every 4 months (±2 wks)
Echocardiogram (ECHO)/ Multigated Acquisition (MUGA) Scan	Only required for subjects ≥65 years old	X												
Physical examination	Including neurological exam[d]	X		Symptom and disease directed exam as clinically indicated										
Vital signs[i]	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 daratumumab SC administration. For all other daratumumab SC administrations, including restart after stopping due to sustained MRD negativity, immediately prior to administration and immediately following completion of administration	X	X	X (Arm B C1 C2 only)	X (Arm B only)	X (Arm B C1 C2 only)			X	X (Arm B only)	X			
Weight[i]	On C1D1, immediately before daratumumab SC administration	X	X						X		X			
Laboratory Assessments														
Urine or serum Pregnancy test	For women of childbearing potential only. During screening, within 10 14 days prior to first dose and again within 24 hours prior to first dose. 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 and at the End of Treatment Visit. Please refer to Section 9.1.1 for details.													
Blood group and type and indirect antiglobulin test (IAT) results	ABO, Rh, and IAT to be assessed locally; once before the first daratumumab administration. Record on the subject's identification wallet card.		Arm B only; Pre-Dose C1D1											

			Treatment Phase (28-day cycles)								Treatment Phase (28-day cycles)		Follow-up Phase	
	Notes	Screening Phase (within 28 days before random-ization)	Induction Treatment (Cycles 1 4)				Pre-ASCT (within 2 weeks of completing C4)	ASCT	Consolidation Treatment (Cycles 5-6)		Maintenance Treatment (Cycles 7+)	EOT	Prior to PD[a]	Post PD
			D1[b]	D8	D15	D22		(Refer to Section 9.1.3)	D1	D15	D1	Within 30 days after last dose		Every 4 months (±2 wks)
Hematology[i]	At screening, acceptable to meet CRAB criteria if performed as part of SOC within 42 days before randomization. May be performed up to 3 days before study drug administration day. Results must be evaluated before each study drug administration, including every administration upon restart after stopping due to sustained MRD negativity.	X	X	X (C1 C2 only)	X	X (C1 C2 only)			X	X	X	X		
Serum chemistry[i]		X	X		X				X	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 9.8	X												
HBV DNA Monitoring	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 9.8	X	C3D1 only				X		C5D1 only		C7D1 then every 12 weeks during treatment	EOT and every 12 weeks for up to 6 months after the last dose of study treatment		
EMN Correlatives	Whole blood and bone marrow	X							X[h] (Post C6 only)					At PD
Whole blood MRD Evaluation	Whole blood	X		Whole blood will be collected at post consolidation[e] in subjects with VGPR or better. Additional samples will be collected at time of suspected CR/sCR. For subjects who achieve CR/sCR and remain on the study, additional samples will be collected every 3 months (±1 month of another collection) from 12 months to 36 months post C1D1 and yearly thereafter.										

			Treatment Phase (28-day cycles)								Treatment Phase (28-day cycles)		Follow-up Phase	
	Notes	Screening Phase (within 28 days before random-ization)	Induction Treatment (Cycles 1 4)				Pre-ASCT (within 2 weeks of completing C4)	ASCT	Consolidation Treatment (Cycles 5-6)		Maintenance Treatment (Cycles 7+)	EOT	Prior to PD[a]	Post PD
			D1[b]	D8	D15	D22		(Refer to Section 9.1.3)	D1	D15	D1	Within 30 days after last dose		Every 4 months (±2 wks)
Bone Marrow (BM) Aspirate MRD Evaluation	Bone Marrow[g]	X		Bone marrow aspirate samples will be collected at post consolidation[e] in subjects with VGPR or better. Additional BM aspirate samples are requested at the time of suspected CR/sCR to confirm CR/sCR and to evaluate MRD. For subjects who achieve CR/sCR, have not progressed, and remain on study, an additional BM aspirate will be obtained at 12, 18, 24, 30, and 36 months (±1 month) post C1D1 and yearly thereafter (±1 month). See Table 9 for details.										
Pharmacokinetic and Immunogenicity Evaluations described in Table 2.														
Disease Evaluations: Every effort should be made to conduct disease evaluations as per schedule (window ±7 days).														
Bone Marrow Exam Myeloma disease evaluation	Disease characterization (morphology and either immunohistochemistry, immunofluorescence, or flow cytometry) performed locally (within 42 days before randomization). Cytogenetics performed locally and centrally. Stratification based on central laboratory value.[f]	X		Bone marrow samples will be collected in subjects with VGPR or better at the time of suspected CR/sCR to confirm CR/sCR. See Table 9 for details.									See Table 9	
SPEP and SIFE, UPEP and UIFE	Central laboratory. SPEP/SIFE and UPEP/UIFE are to be performed within 14 days before C1D1. Repeat on C1D1 only if screening is done >14 days prior to C1D1. See Section 9.2.2 for details.	X[c]	X				X		X		Every 4 weeks for the first year of maintenance then every 8 weeks until PD		X	
Serum FLC	Central laboratory. For subjects with light chain myeloma, perform with every disease evaluation. Serum FLC required for all subjects to confirm CR/sCR.	X	X				X		X		Every 4 weeks for the first year of maintenance then every 8 weeks until PD		X	
Serum β2 microglobulin	Central laboratory	X												
Calcium, Albumin	Central laboratory	X	X				X		X		Every 4 weeks for the first year of maintenance then every 8 weeks until PD		X	

			Treatment Phase (28-day cycles)								Treatment Phase (28-day cycles)		Follow-up Phase	
	Notes	Screening Phase (within 28 days before random-ization)	Induction Treatment (Cycles 1 4)				Pre-ASCT (within 2 weeks of completing C4)	ASCT	Consolidation Treatment (Cycles 5-6)		Maintenance Treatment (Cycles 7+)	EOT	Prior to PD[a]	Post PD
			D1[b]	D8	D15	D22		(Refer to Section 9.1.3)	D1	D15	D1	Within 30 days after last dose		Every 4 months (±2 wks)
IgG, IgA, IgM, IgD, and IgE	Central laboratory	X												
Assessment of lytic lesion (skeletal survey, whole body low dose CT, PET/CT, or MRI)	Acceptable for screening if performed as part of SOC within 42 days before randomization. Refer to Section 9.2.7.	X		As clinically indicated									X	
Extramedullary plasmacytoma (MRI, PET/CT, full dose CT, or physical examination)	Subjects with history of plasmacytoma; acceptable for screening if performed as part of SOC within 42 days before randomization. Refer to Section 9.2.8.	X		If extramedullary plasmacytoma is present, repeat assessment is required every 4 weeks if baseline assessment was done by physical exam, or every 12 weeks if baseline assessment was done by radiologic exam.									X	
Patient reported outcome assessments (EORTC QLQ C30, EORTC QLQ MY20 & EQ 5D 5L)	It is recommended that PRO measures are completed before any other study procedures are performed on the day of the visit. It is advised that PRO measures are complete before any conversation on status with the health care provider.		C1D1 and C3D1				X		C5D1		C7D1 then every 12 weeks until PD	X	X	At the start of subse quent therapy, 4 weeks after start of subse quent therapy, then every 4 months until end of study (EQ 5D 5L only)
Medical resource utilization[i]	See Section 9.6 for details		X	X	X	C1 C2 only	X	X	X	X	X	X	X	
Ongoing Participant Review														
Concomitant therapy			Continuous from the time of signing of ICF until 30 days after last dose of the last component of study treatment											
Adverse events													Treatment related SAEs	

			Treatment Phase (28-day cycles)								Treatment Phase (28-day cycles)		Follow-up Phase	
	Notes	Screening Phase (within 28 days before random-ization)	Induction Treatment (Cycles 1 4)				Pre-ASCT (within 2 weeks of completing C4)	ASCT	Consolidation Treatment (Cycles 5-6)		Maintenance Treatment (Cycles 7+)	EOT	Prior to PD[a]	Post PD
			D1[b]	D8	D15	D22		(Refer to Section 9.1.3)	D1	D15	D1	Within 30 days after last dose		Every 4 months (±2 wks)
New malignancy monitoring, PFS2, and subsequent anticancer therapy and survival status			←					X				→	X	X
Study Drug Administration, Arm A and Arm B														
Dexamethasone 40 mg	Dispense on Day 1 for self administration			On Days 1 4, 9 12 of each cycle for Cycles 1 6 only (suspended for ASCT period)										
Bortezomib 1.3 mg/m^2	Administer by SC injection. Recalculate the dose if weight has changed ±10% from baseline.			On Days 1, 4, 8, 11 of each cycle for Cycles 1 6 only (suspended for ASCT period)										
Lenalidomide 25 mg in C1 C6, 10 mg in maintenance C7+	Dispense on Day 1 for self administration			On Days 1 21 of each cycle for Cycles 1 6 only (suspended for ASCT period)							Daily D1 D28 of each cycle for C7+			
Study Drug Administration, Arm B Only														
Daratumumab 1800 mg SC	Refer to IPPI for recommendations on daratumumab administration rate			On Days 1, 8, 15, 22 of each cycle for Cycles 1 and 2, then on Days 1 and 15 for Cycles 3 6							X			
Pre-administration Medications, Arm B only														
Dexamethasone 20 mg	Administer 1 3 hours before the daratumumab administration. Dexamethasone 20 mg IV or PO prior to the first 2 doses and 10 mg for all subsequent doses (must have absence of IRR adverse events for 2 doses prior to decreasing dose). On daratumumab administration days, backbone therapy substitutes for the premedication dexamethasone. Accordingly, 40 mg dexamethasone will be administered PO or IV prior to daratumumab in Cycles 1 6.		X	X	X	X			X	X	X			
Diphenhydra mine 25 50 mg (or equivalent)	Administer 1 3 hours before daratumumab SC administration		X	X	X	X			X	X	X			
Paracetamol 650 1000 mg			X	X	X	X			X	X	X			

			Treatment Phase (28-day cycles)								Treatment Phase (28-day cycles)		Follow-up Phase	
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			D1[b]	D8	D15	D22		(Refer to Section 9.1.3)	D1	D15	D1	Within 30 days after last dose		Every 4 months (±2 wks)
Montelukast 10 mg (recommended prior to daratumumab C1D1 and is optional before all other doses)			X											

a. For subjects who discontinue treatment prior to C7D1 without confirmed PD,
   - Disease Evaluations should be performed every 4 weeks (±7 days) for the first 2 years, then every 8 weeks (±14 days) relative to C1D1 until confirmed PD.
   - ECOG PS (including PRO and MRU) should be performed every 12 weeks (±14 days) relative to C1D1 until confirmed PD.

   For subjects who discontinue treatment after C7D1 without confirmed PD,
   - Disease Evaluations should be performed every 4 weeks (±7 days) for first year relative to C7D1 then every 8 weeks (±14 days) until confirmed PD.
   - ECOG PS (including PRO and MRU) should be performed every 12 weeks (±14 days) for first year relative to C7D1, then every 16 weeks (±14 days) relative to C7D1 thereafter, until confirmed PD.

   Subjects who decline any further follow up except survival status should be followed every 4 months.

b. Study treatment should be initiated within 3 days after randomization.

c. If the 24 hour 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 is sent to the central lab for analysis after the informed consent was obtained.

d. Subject's neurological examination should be performed during the Screening Phase by the treating physician (a neurologic specialist is not required).

e. For subjects with VGPR or better, obtain prior to C7D1 study drug administration.

f. For stratification purposes, if central cytogenetic results are not available (refer to Section 5).

g. 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. If baseline clonality is still not established, no further bone marrow samples should be collected for MRD assessments (Arm A). Subjects in Arm B with no baseline clonality or with non unique clone sequence may continue to have bone marrow samples collected for MRD for the purpose of daratumumab continuation determination.

h. If feasible, all subjects will have EMN correlative completed post consolidation and at disease progression.

i. After 24 months of maintenance therapy, vital signs, weight, hematology, serum chemistry, and MRU may be performed every 8 weeks for subjects who are not receiving daratumumab.

Abbreviations: Anti-HBc antibodies to hepatitis B core antigen; Anti-HBs antibodies to hepatitis B surface antigen; ASCT autologous stem cell transplant; BM bone marrow; C Cycle; COPD chronic obstructive pulmonary disease; CR complete response; CRAB calcium, renal, anemia, bone; CT computed tomography; d/D day(s); DLCO diffusing capacity of the lung for carbon monoxide; ECOG Eastern Cooperative Oncology Group; EORTC QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EMN European Myeloma Network; EQ-5D-5L EuroQol Five Dimension Questionnaire; ECG electrocardiogram; ECHO echocardiogram; EOT End-of-Treatment; FEV1 Forced Expiratory Volume (in 1 second); FLC free light chain; IAT indirect antiglobulin test; ICF informed consent form; Ig immunoglobulin; IP Investigational Product; IPPI Investigational Product Preparation Instructions; IRR infusion-related reaction; MRD minimal residual disease; MRI magnetic resonance imaging; MRU medical resource utilization; MUGA multigated acquisition; PCR polymerase chain reaction; PD progressive disease; PET positron emission tomography; PFS2 progression-free survival on next line of therapy; PRO patient-reported outcomes; Q4W every 4 weeks; Q8W every 8 weeks; Q12W every 12 weeks; SAE serious adverse event; SC subcutaneous; sCR stringent CR; SIFE serum immunofixation; SOC standard of care; SPEP serum M-protein quantitation by electrophoresis; UIFE urine immunofixation; UPEP urine M-protein quantitation by electrophoresis; VGPR very good partial response; wks weeks.

Table 2: Pharmacokinetic and Immunogenicity Evaluations (Arm B Only)

	Induction Treatment (Cycles 1-4)					**Consolidation Treatment (Cycles 5-6)**		**Maintenance Treatment (Cycles 7+)**			**Follow-up Phase**
	Cycle 1		**Cycle 3**		**Cycle 4**	**Cycle 5**		**Cycle 7**	**Cycle 9**	**Cycle 12**	
	D1[a]	D4[b]	D1[a]	D4[b]	D15	D1[a]	D4[b]	D1[a]	D1[a]	D1[a]	**Posttreatment Week 8 (±1 week)**
Daratumumab pharmacokinetics (serum)	X[a] predose	X	X[a] predose	X	X[a] predose	X[a] predose	X	X[a] predose	X[a] predose	X[a] predose	X[f]
Daratumumab immunogenicity[c,d]	X[a] predose				X[a] predose	X[a] predose		X[a,e] predose		X[a] predose	X[f]
rHuPH20 immunogenicity (plasma)[d]	X[a] predose				X[a] predose	X[a] predose		X[a,e] predose		X[a] predose	X[f]

a. Predose timepoints have a window of 0 days as they should always be predose on the day of dosing. On dosing days, sample collection may occur up to 2 hours before but not after the start of daratumumab administration. Samples collected on dosing days with visit windows should be collected on the actual day of daratumumab administration.
b. Day 4 timepoints have a window of ±1 day.
c. No additional sample needed; will be aliquoted from PK sample.
d. 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.
e. Daratumumab and rHuPH20 immunogenicity required only at C7D1 for subjects not receiving consolidation treatment (ie, C5 C6) after transplant.
f. For subjects who meet criteria to stop daratumumab due to sustained MRD negativity, posttreatment daratumumab PK, daratumumab immunogenicity, and rHuPH20 immunogenicity will be collected 8 weeks after the last dose of daratumumab. If the subject restarts daratumumab, no further PK samples need to be drawn.

Abbreviations: IRR injection related reaction; PK pharmacokinetic; rHuPH20 recombinant human hyaluronidase.

ABBREVIATIONS

AE	adverse event(s)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
Anti-HBc	antibodies to hepatitis B core antigen
Anti-HBs	antibodies to hepatitis B surface antigen
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
BSA	body surface area
BUN	blood urea nitrogen
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
COPD	chronic obstructive pulmonary disease
CR	complete response
CRAB	calcium, renal, anemia, bone
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography
C_{trough}	lowest drug concentration reached before the next dose is administered
Dara-IV	daratumumab for intravenous infusion
Dara-MD	daratumumab and recombinant human hyaluronidase for subcutaneous injection: mix and deliver
Dara-SC	daratumumab administered subcutaneously
DLCO	diffusing capacity of the lung for carbon monoxide
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
D-Rd	daratumumab in combination with lenalidomide and dexamethasone
D-Vd	daratumumab in combination with bortezomib and dexamethasone
DVMP	daratumumab in combination with bortezomib, melphalan, and prednisone
D-VRd	daratumumab in combination with bortezomib, lenalidomide, and dexamethasone
ECG	electrocardiograms
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC QLQ-MY20	European Organization for Research and Treatment of Cancer Multiple Myeloma Module
EOT	End-of-Treatment
EQ-5D-5L	EuroQol Group Five Dimensions Five Levels
ESM	External Safety Monitor
ESMO	European Society for Medical Oncology
FACS	fluorescence-activated cell sorting
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FLC	free light chain
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GHS	Global Health Status
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HR	hazard ratio
HRQoL	health-related quality of life
IAT	indirect antiglobulin test
ICF	informed consent form

ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFM	*Intergroupe Francophone du Myélome*
Ig	immunoglobulin
IMWG	International Myeloma Working Group
IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board
IRR	infusion-related reaction
ISS	International Staging System
IV	intravenous
IWRS	interactive web response system
MDRD	Modified Diet in Renal Disease
MoA	mechanism of action
M-protein	monoclonal protein
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRU	medical resource utilization
MUGA	multigated acquisition
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
PK	pharmacokinetic(s)
PO	orally
PQC	product quality complaint
PR	partial response
PRO	patient-reported outcome(s)
R	lenalidomide
RBC	red blood cell
Rd	lenalidomide-dexamethasone
rHuPH20	recombinant human hyaluronidase
SAE	serious adverse event
SC	subcutaneous
sCR	stringent complete response
SIFE	serum immunofixation
sIPPM	site Investigator Product Procedures Manual
SOC	standard of care
SPEP	serum M-protein quantitation by electrophoresis
SUSAR	suspected unexpected serious adverse reaction
SVR	sustained virologic response
TEAE	treatment-emergent adverse event
UIFE	urine immunofixation
ULN	upper limit of normal
UPEP	urine M-protein quantitation by electrophoresis
VCd	bortezomib, cyclophosphamide, and dexamethasone
Vd	bortezomib and dexamethasone
VGPR	very good partial response
VMP	bortezomib, melphalan, and prednisone
VRd	bortezomib, lenalidomide, and dexamethasone
VTd	bortezomib, thalidomide, and dexamethasone

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

1. INTRODUCTION

Daratumumab has multiple mechanism of actions (MoAs), including the direct targeting of tumor cells by selectively binding to CD38 molecules, immune mediated activity with antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity (CDC), 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.

Recombinant human hyaluronidase (rHuPH20) cleaves the repeating disaccharide subunits (N-acetyl-D-glucosamine and D-glucuronic acid) of hyaluronan, a polymeric, gel-like glycosaminoglycan (mucopolysaccharide) that are present in the subcutaneous (SC) tissue matrix. rHuPH20 acts locally and transiently within the SC space to increase the tissue dispersion and absorption of other injected drugs and fluids. A new presentation of daratumumab as a co-formulated product of daratumumab and rHuPH20 allows for the SC administration of daratumumab.

For the most comprehensive nonclinical and clinical information regarding daratumumab, refer to the latest version of the Investigator's Brochure 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.

1.1. Background

1.1.1. 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 in affected patients. Hypercalcemia, renal insufficiency or failure, and neurological complications are frequently reported signs and symptoms of the disease.

1.1.2. Treatment Options for Patients With Newly Diagnosed Multiple Myeloma

Over the past decade, the introduction of new classes of drugs, such as immunomodulatory drugs and proteasome inhibitors have changed the frontline treatment of patients with multiple myeloma (NCCN 2017, Durie 2017, Moreau 2013, Cavo 2011, Palumbo 2014). Multiple-drug combinations are superior to single- or double-agent combinations in treating multiple myeloma (Cavo 2012, van der Veer 2011). Bortezomib-based treatment regimens have demonstrated significant improvements in response, progression-free survival (PFS) and overall survival (OS) compared with non-bortezomib-based therapy, both in newly diagnosed transplant-ineligible patients and those suitable for induction and transplant (Sonneveld 2013, Dimopoulos 2009). Conventional means of assessing response are not sufficiently sensitive to measure low levels of residual bone

marrow disease so-called minimal residual disease (MRD). Therefore, currently, the goal of multiple myeloma treatment is achievement of MRD negativity per the most recent IMWG response criteria (Kumar 2016).

Patients with newly diagnosed multiple myeloma are classified as eligible for high-dose therapy or ineligible for high-dose therapy based on a patient's age, comorbidities, and functional status. The standard treatment approach for newly diagnosed patients who are considered eligible for high-dose therapy includes induction, high-dose chemotherapy and stem cell transplantation, and consolidation and maintenance.

Induction Therapy

Transplant-eligible patients are treated with an induction regimen to reduce the plasma cell disease burden and improve the depth of response. Response rates to induction therapy have been significantly increased using triple combination chemotherapy. Bortezomib-based induction regimens including bortezomib-lenalidomide-dexamethasone (VRd), bortezomib-cyclophosphamide-dexamethasone (VCd), and bortezomib-thalidomide-dexamethasone (VTd) improve response and prolong PFS/OS compared with the same regimens without bortezomib. The addition of bortezomib results in a higher rate of side effects, most notably peripheral neuropathy, but does not increase the risk of death during induction (Sonneveld 2013). For newly diagnosed patients who are eligible for autologous stem cell transplant (ASCT), VRd, VCd, and VTd are now considered standard induction regimens (Richardson 2010, Engelhardt 2014, Moreau 2013, NCCN 2017, Moreau 2017).

High-dose Chemotherapy and Stem Cell Transplantation

Autologous stem cell transplantation following high-dose therapy has now become the standard approach to improve and deepen response. After attaining at least a partial response (PR) on induction therapy, blood stem cells are mobilized in peripheral blood with the use of granulocyte colony-stimulating factor (G-CSF) with either cyclophosphamide, or in some cases, plerixafor (Mozobil) (Giralt 2009). ASCT in addition to combination chemotherapy has been shown to improve complete response (CR) rates and prolong median OS by approximately 12 months compared with chemotherapy without ASCT (Child 2003, Blade 2000).

Consolidation Therapy

Improved rates of CR and near CR (nCR), in the range between 10% and 30%, have been reported with post-ASCT use of bortezomib or lenalidomide as single agents (Mellqvist 2009, Attal 2009). Both VTd and VRd consolidation (2 cycles) following ASCT increased response and prolonged PFS (Leleu 2013, Sonneveld 2016).

Maintenance Therapy

Maintaining response after successful induction, high-dose chemotherapy with transplant and consolidation is an important goal in treating patients with multiple myeloma. Lenalidomide, given as maintenance therapy after ASCT, has been approved by the European Medicines Agency and Food and Drug Administration (FDA) based on 2 randomized Phase 3 studies. (McCarthy 2012, Attal 2012, Revlimid SmPC, Revlimid USPI). A meta-analysis including 3 studies evaluated

1208 subjects who received either lenalidomide or placebo post-ASCT as maintenance therapy and demonstrated improvement of both PFS and OS with lenalidomide maintenance therapy (McCarthy 2017).

1.1.3. VRd as Backbone Therapy Throughout Treatment

The VRd regimen initially was studied by Richardson and colleagues (Richardson 2010) in a Phase 1-2 study comparing VRd to lenalidomide and dexamethasone (Rd) for newly diagnosed patients with multiple myeloma, regardless of eligibility for high-dose therapy and ASCT. Sixty-six subjects were treated on this single-arm study. Overall response rate (ORR) was 100%, CR was 29%, and nCR was 11%. Twenty-eight subjects (42%) proceeded to undergo ASCT. Stem cell harvesting and engraftment were not affected adversely by the three-drug induction regimen. Thus, this study established VRd as a safe and effective induction regimen prior to ASCT.

The *Intergroupe Francophone du Myélome* (IFM*)* conducted a Phase 2 study of VRd in newly diagnosed patients with multiple myeloma who were eligible for ASCT (Roussel 2014). In this study, 31 subjects received 3 cycles of VRd followed by stem cell harvest and transplantation, followed by an additional 2 consolidation cycles of VRd, and one year of lenalidomide maintenance therapy. The ORR after 3 cycles of induction therapy was 94%, CR rate was 13%, and stringent CR (sCR) rate was 10%. Responses improved over the duration of the study with an overall CR rate of 10%, sCR rate of 48%, and 68% of subjects achieving MRD-negative status (at a sensitivity of 10^{-4}) by flow cytometry. Thus, this study demonstrated the improvement of response with the addition of VRd consolidation and lenalidomide maintenance therapy after ASCT.

The IFM cooperative group evaluated the VRd regimen in 700 newly diagnosed transplant-eligible subjects with multiple myeloma. Subjects were treated with 3 cycles of induction therapy with VRd; immediate ASCT; 2 cycles of consolidation with VRd; and 1 year of lenalidomide maintenance (n 350) or 8 cycles of VRd induction and 1 year of lenalidomide maintenance (salvage ASCT was to take place at the time of disease group) (n 350). Median PFS was significantly improved in the subjects with transplant as part of their initial therapy (50 months compared with 36 months, HR 0.65, 95% CI 0.53-0.8; p value <0.001). The CR rate was 59% in the VRd transplant arm compared with 48% in the VRd alone arm. The MRD negativity rate as measured by 7-color flow cytometry (between 10^{-4} and 10^{-5}) was 79% in the VRd transplant arm compared with 65% in the VRd alone arm (Attal 2017). Overall survival at 4 years did not differ between the 2 groups; 82% in VRd alone compared with 81% in the VRd transplant group. This study demonstrated the superiority of initial transplant with the VRd regimen with prolongation of PFS in addition to improvement of CR rate and MRD negativity rate.

The Spanish Myeloma Group (PETHEMA/GEM) evaluated the VRd regimen in a Phase 3 study with 458 patients enrolled and treated with 6 cycles of VRd followed by randomization to conditioning with Melphalan-200 mg vs Busulphan 9.6 mg/kg plus melphalan 140 mg prior to ASCT followed by 2 cycles of VRd after ASCT for both arms of the study (Rosinol 2019). Initial results showed an ORR of 85% at the end of induction therapy, with 39% of subjects achieving CR or better. Grade 3/4 neutropenia and thrombocytopenia were reported in 11% and 6% of

patients respectively. Grade 3 peripheral neuropathy was only 1% with no Grade 4 events. Dose reductions due to toxicity occurred in 31% of patients with 18% bortezomib reductions, 10% lenalidomide reductions, and 3% dexamethasone reductions. Sixty-one (61) patients (13%) discontinued the study prior to ASCT, 32 patients due to progressive disease (PD), 9 patients due to toxicity, 7 due to death, and 13 for other reasons. The median stem cell collection was 4.66×10^6. This study demonstrates the tolerability and deep responses with the VRd regimen.

1.2. Daratumumab

1.2.1. Intravenous Daratumumab Administration in Combination Therapy Studies

Two Phase 3 studies examined the safety and efficacy of daratumumab for intravenous infusion (Dara-IV) in combination with other therapies in the treatment of relapsed multiple myeloma:

- In Study MMY3003, subjects with multiple myeloma received intravenous (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 ORRs 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, and no new safety signals were identified.
- In Study MMY3004, subjects with multiple myeloma received IV daratumumab in combination with bortezomib and dexamethasone (DVd). At the time of the first interim analysis, treatment with DVd showed a 61% reduction in the risk for disease progression or death compared with bortezomib and 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, and no new safety signals were identified.

Three Phase 3 studies examined 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 IV daratumumab in combination with bortezomib, melphalan, and prednisone (DVMP). At the time of the primary analysis, treatment with DVMP resulted in a 50% reduction in the risk of disease progression or death compared with bortezomib, melphalan, and prednisone (VMP) alone. The median PFS was not reached in the daratumumab group; median PFS was 18.1 months in the VMP group. The ORRs were 91% for the DVMP group and 74% for the VMP group. The safety profile was consistent with the known safety profile of daratumumab and the backbone regimen, and no new safety signals were identified.
- In Study MMY3008, subjects with multiple myeloma received IV daratumumab in combination with lenalidomide and dexamethasone (DRd).
- In Study MMY3006, subjects with multiple myeloma received IV daratumumab in combination with bortezomib, thalidomide, and dexamethasone (D-VTd).

Collectively, the data from Studies 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.

One Phase 2 study is examining the safety and efficacy of Dara-IV in combination with VRd. In Study MMY2004 (NCT02874742), Dara-IV in combination with VRd, (D-VRd) is being compared to VRd alone in subjects with newly diagnosed multiple myeloma eligible for high-dose chemotherapy and ASCT. The primary endpoint of this study is 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.

The initial 16 subjects were enrolled in the safety run-in and data after all subjects completed 4 cycles of induction therapy is provided below (Voorhees 2017). During Cycle 1, 3 subjects experienced the following AEs that met the protocol-specified dose-limiting toxicity (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 DLT required treatment discontinuation. All 16 subjects experienced at least 1 treatment-emergent adverse event (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 AEs of febrile neutropenia. No subject died or discontinued treatment due to TEAEs. Daratumumab infusion-related reactions (all Grade ≤2) were reported in 31% of subjects during Cycles 1 to 4. All 16 subjects in the safety run-in had undergone stem cell mobilization with a median stem cell yield of 6.0×10^6 (range 3.5-10.6) CD34+ cells/kg.

The initial 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 continued to enroll approximately 200 subjects randomized 1:1 to D-VRd vs VRd. A prespecified interim analysis for safety after at least 50 patients completed 4 cycles of induction treatment and stem cell mobilization occurred on 4 April 2018, the Independent Data Monitoring Committee (IDMC) recommended that the study continue without modification.

1.3. Summary

VRd is now considered a standard of care (SOC) regimen for newly diagnosed patients with multiple myeloma (Moreau 2017, NCCN 2017). Daratumumab in combination with therapies

commonly used for the treatment of multiple myeloma has demonstrated improved efficacy with an acceptable safety profile in patients with previously treated and untreated multiple myeloma. The combination of D-VRd is being evaluated in Study MMY2004 and initial data from the safety run-in phase of the study shows that daratumumab can be combined safely with VRd.

1.4. Overall Rationale for the Study

Induction, high-dose therapy with stem cell rescue followed by consolidation and maintenance is a common treatment strategy in newly diagnosed patients with multiple myeloma who are deemed eligible to receive this therapy. The superiority of the VRd regimen has been established by the results of the Phase 3 study by Attal and colleagues (Attal 2017). That study also demonstrated greater depth of response, including a higher CR rate and MRD negativity rate as well as increased PFS in the VRd plus ASCT arm versus VRd alone.

While the treatment of newly diagnosed patients with multiple myeloma continues to improve, patients are still not cured. The most active combination to date is the VRd regimen previously described. The sponsor has observed preclinical synergism of daratumumab in combination with bortezomib and lenalidomide, which translated to compelling clinical data with daratumumab in combination with either bortezomib or lenalidomide in the relapsed/refractory setting, and bortezomib in the frontline setting. Thus, the combination of daratumumab with VRd is anticipated to further improve response rates in patients and may lead to improved long-term outcomes in newly diagnosed patients with multiple myeloma. Given this potential and based upon the initial safety and efficacy observed in the ongoing Phase 2 Study MMY2004, as well as continued positive results with daratumumab in various disease settings and combination regimens, this Phase 3 study is designed to demonstrate improved outcomes for patients treated with daratumumab+VRd. The Phase 3 study will utilize the SC formulation of daratumumab instead of the IV formulation utilized in the Phase 2 study, which may limit additional toxicity to patients treated with the quadruplet regimen.

1.5. Benefit-risk Assessment

Subjects in this study will be assigned in a randomized manner to receive either 1800 mg D-VRd as induction and consolidation therapy and in combination with lenalidomide maintenance therapy or VRd alone as induction and consolidation therapy and lenalidomide alone as maintenance therapy. The sequence of VRd induction/ASCT/VRd consolidation/lenalidomide maintenance is the global SOC. While treatment with D-VRd has demonstrated a manageable safety profile consistent with the known safety profile of daratumumab SC and VRd alone, management guidelines for potential toxicities are detailed in Section 6.2 and Section 6.4. Overall, there is a positive benefit/risk profile for this patient population.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

The primary objective is to determine if the addition of daratumumab to VRd will prolong PFS defined as the time from the date of randomization to the date of disease progression (assessed by International Myeloma Working Group [IMWG] criteria) or death, 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:
  - MRD negativity rate post-consolidation and overall MRD negativity rate achieved at any time during the study
  - ORR, rate of VGPR or better, rate of CR or better, rate of sCR at post-induction, post-transplant, post-consolidation, and overall
  - Time to response
  - Duration of response
  - Progression-free survival on the next line of therapy (PFS2)
  - OS
- To assess the safety profile of daratumumab+VRd (D-VRd)
- To evaluate pharmacokinetics (PK) of daratumumab
- To determine the immunogenicity of daratumumab and rHuPH20
- To evaluate patient-reported outcomes (PROs) and medical resource utilization (MRU)
- To evaluate stem cell yield after mobilization
- To evaluate time to engraftment post ASCT
- To evaluate the benefit/risk of stopping daratumumab upon sustained MRD negative status

Exploratory Objectives

The exploratory objectives are:

- To evaluate durability of MRD negativity.
- To evaluate whether the loss of MRD negative status through the monitoring of peripheral blood will be more sensitive than standard clinical evaluations to detect relapse of CR.
- To evaluate MRD negativity thresholds and durability of clinical response.

- To evaluate length of sustained MRD negative status and durability of clinical response.

2.1.2. Endpoints

Primary Endpoint

PFS is defined as the time from the date of randomization to the date of disease progression or death due to any cause, whichever occurs first.

Secondary Endpoints

The secondary efficacy endpoints are:

- Post-consolidation MRD negativity rate, defined as the proportion of subjects who achieve MRD negativity (at or below the threshold of 10^{-5}) at the end of consolidation.
- Overall MRD negativity rate, defined as the proportion of subjects who achieve MRD negativity (10^{-5}) at any time during the study.
- Overall ORR, rate of VGPR or better, rate of CR or better, and rate of sCR, defined as the proportions of subjects who achieved PR or better (or VGPR or better, or CR or better, or sCR) per the IMWG criteria at post-induction, post-transplant, post-consolidation, and overall.
- Progression-free survival on the next line of therapy (PFS2) is defined as the time from randomization to progression on the next line of treatment or death, whichever comes first.
- OS, measured from the date of from randomization to the date the subject's death.
- Time to response (PR or better), time to CR/sCR are defined as the time from randomization to date of initial response (or initial CR/sCR,).
- Duration of response (PR or better), duration of CR, duration of sCR, and duration of MRD negative status, are calculated from the date of the initial documentation of a response (PR or better), or CR or better, or sCR, or MRD negative status to the date of the first documented evidence of disease progression, as defined in the IMWG criteria, or death due to PD, whichever occurs first.
- Pharmacokinetic concentrations of daratumumab (further defined in Section 9.3).
- Immunogenicity of daratumumab and rHuPH20.
- Change in HRQoL, symptoms, and functioning using 2 European Organization for Research and Treatment of Cancer (EORTC) questionnaires and the EuroQol Group Five Dimensions Five Levels Questionnaires (EQ-5D-5L).
- Stem cell yield after mobilization (further defined in Section 9.1.3.2).
- Time to engraftment post ASCT defined as absolute neutrophil count (ANC) $\geq 0.5 \times 10^9$/L and platelet count $\geq 20 \times 10^9$/L.

Refer to Section 9, Study Evaluations for evaluations related to endpoints.

2.2. Hypothesis

The primary hypothesis is that the addition of daratumumab to VRd will prolong the PFS (assessed by the IMWG criteria) compared with VRd alone.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

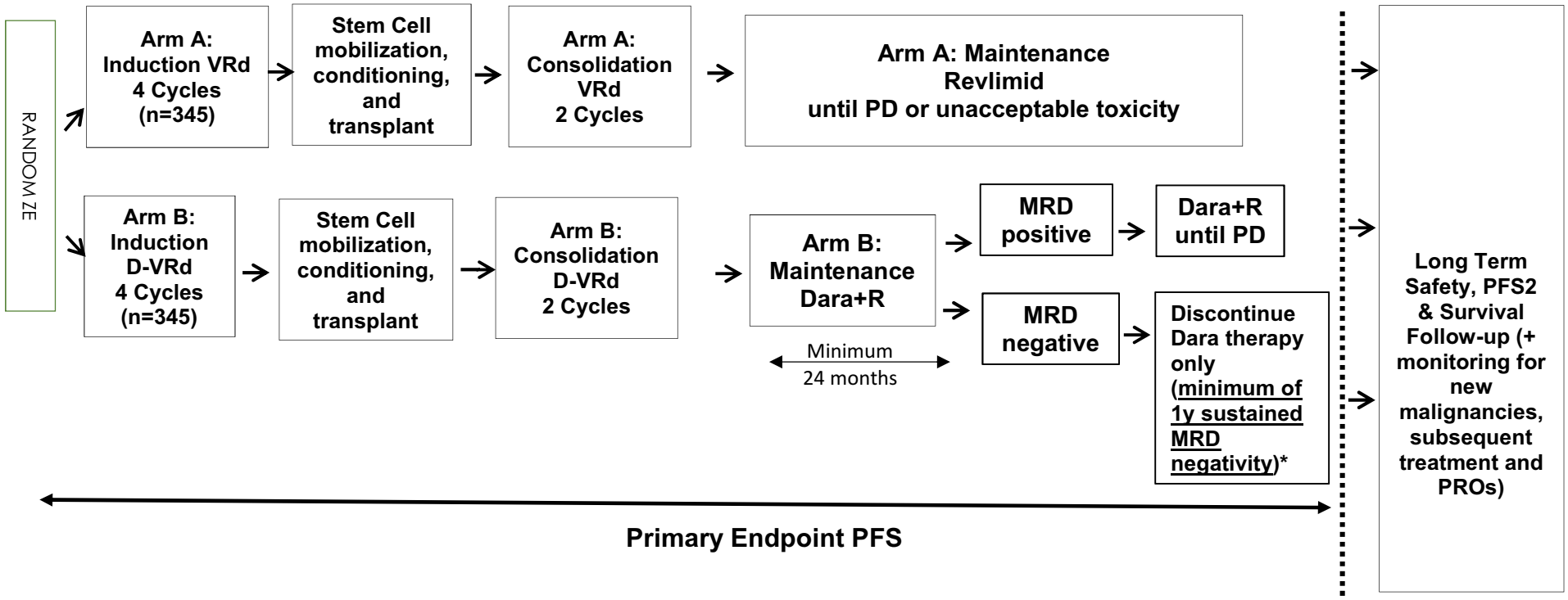
This is a randomized, open-label, multicenter study evaluating subjects with newly diagnosed multiple myeloma who are deemed eligible for high-dose therapy. Approximately 690 subjects will be stratified by International Staging System (ISS) Stage I, II, or III disease (β-2 microglobulin and albumin) and cytogenetics (standard risk or high risk as defined by presence of del17p, t[4;14] or t[14;16]) and then randomized in a 1:1 ratio.

The study will consist of 3 phases: a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will start up to 28 days before randomization. The Treatment Phase will extend from Cycle 1 Day 1 to discontinuation of all study treatment. The Treatment Phase will consist of six 28-day cycles, 4 cycles of induction, followed by ASCT, then 2 cycles of consolidation, followed by maintenance therapy until disease progression or unacceptable toxicity.

In Arm A, subjects will receive VRd for induction and consolidation, followed by lenalidomide (R) maintenance until disease progression or unacceptable toxicity. Subjects in Arm B will receive D-VRd for induction and consolidation followed by daratumumab and lenalidomide maintenance until disease progression or unacceptable toxicity. Subjects in Arm B who have a response of CR or better will stop therapy with daratumumab after sustained MRD negativity (at the threshold of 10^{-5}) for 12 months and after a minimum of 24 months of maintenance therapy. These subjects will continue lenalidomide maintenance therapy until disease progression or unacceptable toxicity. After stopping daratumumab therapy, subjects with sustained MRD negativity should restart therapy with daratumumab if there is a recurrence of MRD at 10^{-4} or higher or a confirmed loss of CR without IMWG-defined disease progression as evidenced by the reappearance of serum or urine monoclonal protein (M-protein) by immunofixation or electrophoresis by central laboratory or development of ≥5% plasma cells in bone marrow (refer to Table 7). After reinitiating daratumumab, the subject will continue daratumumab and lenalidomide therapy until disease progression or unacceptable toxicity.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



*Restart therapy upon loss of CR or loss of MRD status

Key: CR=complete response; Dara=daratumumab; D-VRd=daratumumab in combination with bortezomib, lenalidomide, and dexamethasone; MRD=minimal residual disease; PD=progressive disease; PFS2=progression-free survival on the next line of therapy; R=lenalidomide; VRd=bortezomib, lenalidomide, and dexamethasone.

Subjects will enter the Follow-up Phase once they experience documented disease progression or unacceptable toxicity leading to all study treatment discontinuation or if they have not achieved a response of PR or better by C7D1. In the Follow-up Phase, subjects who discontinued before disease progression must continue to have disease evaluations according to the Time and Events Schedule (Table 1) and should not initiate any subsequent anticancer treatment until disease progression is confirmed per IMWG criteria (Table 7). In addition, disease progression must be approved by the medical monitor and documented in interactive web response system (IWRS). After disease progression is documented, follow-up will be obtained at least every 4 months ±2 weeks. Subsequent anticancer treatment, disease progression data (per investigator assessment) on the first line of subsequent therapy, new malignancies, PRO assessments, and survival status will also be recorded.

3.2. Study Design Rationale

Rationale for Study Design

The VRd regimen in this study is based upon both the IFM 2009 Study that utilized 3 cycles of VRd induction followed by ASCT followed by 2 cycles of VRd consolidation therapy followed by 1 year of maintenance therapy with lenalidomide alone and the Gem2012Menos65 Study that utilized 6 cycles of VRd induction therapy followed by ASCT and 2 cycles of VRd consolidation therapy. The IFM 2009 Study utilized 21-day cycles vs the Gem2012Menos65 Study which utilized 28-day cycles. Current European Society for Medical Oncology (ESMO) guidelines recommend 4-6 cycles of induction therapy prior to ASCT, thus given the high response rates in both the IFM 2009 and the Gem2012Menos65 Studies, this study will utilize 4 cycles of induction therapy with a 28-day cycle to increase the lenalidomide dose intensity per cycle. This study will implement SC bortezomib (as in the Gem2012Menos65) as opposed to IV bortezomib, which was used in the IFM 2009 Study, as subcutaneous bortezomib decreases the rate and severity of neuropathy as compared to the intravenous formulation (Moreau 2011).

A meta-analysis of these 2 Phase 3 studies with 1,208 patients (605 patients in the lenalidomide maintenance group and 603 in the placebo or observation group) demonstrated superior PFS with lenalidomide maintenance compared to no maintenance. The median PFS was 52.8 months for the lenalidomide group and 23.5 months for the placebo or observation group (HR 0.48; 95% CI: 0.41, 0.55). At a median follow-up of 79.5 months for all surviving patients, the median OS had not been reached for the lenalidomide maintenance group and was 86.0 months for the placebo or observation group (HR 0.75; 95% CI: 0.63, 0.90; p .0001) (McCarthy 2017). Based on these data lenalidomide is approved as maintenance therapy post ASCT until disease progression (Revlimid SMPc). Thus, in the current protocol, lenalidomide maintenance therapy will continue until disease progression or unacceptable toxicity in both arms. In the experimental (Arm B) daratumumab is added to the standard lenalidomide maintenance. Daratumumab is planned to be discontinued during the maintenance phase in subjects who achieve sustained MRD negativity (10^{-5}) for at least 12 months and after receiving at least 24 months of maintenance treatment. The proposal for a daratumumab treatment-free interval will provide important data for patient management. After stopping daratumumab therapy, subjects with sustained MRD negativity

should restart therapy with daratumumab if there is a recurrence of MRD at 10^{-4} or higher or a confirmed loss of CR without disease progression (refer to Table 8).

Rationale for Subcutaneous Daratumumab

A new formulation of daratumumab for 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, a recombinant human hyaluronidase PH20 (rHuPH20) was used to facilitate the SC administration in order to decrease the volume required for 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, PK, 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 daratumumab administered subcutaneously (Dara-SC) in Study MMY1004 (San-Miguel 2018). The infusion-related reaction rate was 16% and consisted of Grade 1 or 2 chills, dyspnea, sneezing and allergic rhinitis, and 2 Grade 3 events of hypertension. None of the injection-related reaction (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 these clinical data and supported by the PK profile of Dara-SC (as described in the section below), 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.

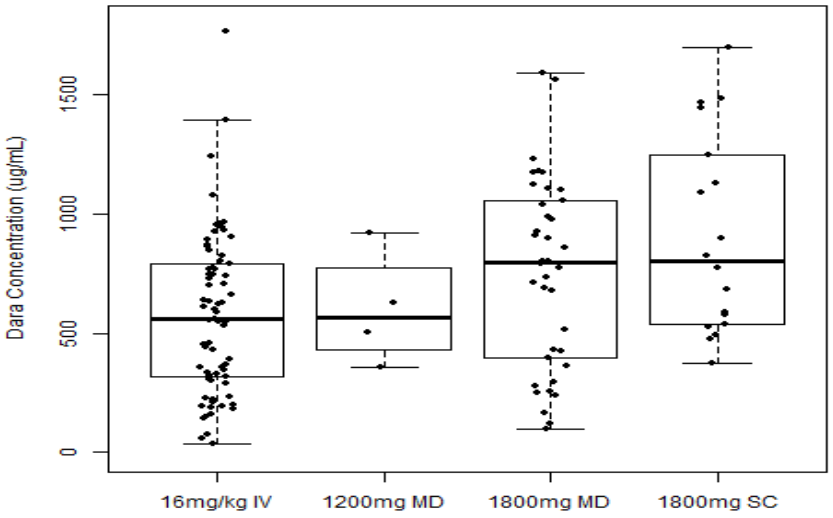
Rationale for Daratumumab Dose Regimen

Previous exposure-response analyses have demonstrated a strong correlation between ORR and the maximum trough concentration ($C_{trough,}$), which occurs at the end of weekly dosing (just prior to the C3D1 dose 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 of 03 Aug 2017, 18 subjects were evaluable for PK in Study MMY1004 Part 2. Analysis of the preliminary PK data indicated the 1800 mg Dara-SC (co-formulated) dose achieved maximum C_{trough} values comparable to, 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 754.62 µg/mL for the 1800 mg daratumumab and recombinant human hyaluronidase for subcutaneous injection: mix and deliver formulation (Dara-MD) cohorts (n 38), 617.17 µg/mL in Study GEN501 Part 2 (n 27), and 573.49 µg/mL in Study MMY2002 (n 73). The median value for maximum C_{trough} for Dara-SC (798.85 µg/mL) was similar to the value for 1800 mg Dara-MD (795.48 µg/mL) and slightly higher than the 16 mg/kg IV median values from Studies MMY2002

(559.62 µg/mL) and GEN501 (713.85 µg/mL). 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 % CV of 46 to 58% across the SC and IV doses (Figure 2).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 C3D1 (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.

Figure 2: Daratumumab Serum Concentration at C3D1 Ctrough Following Daratumumab Administered Subcutaneously (Study MMY1004) or Intravenously (Study MMY2002)



Footnotes:
Dots are individual observations; PK evaluable population is presented
1200 mg MD MMY1004 Part 1, 1200 mg mix & deliver cohort
1800 mg MD MMY1004 Part 1, 1800 mg mix & deliver cohorts
1800 mg SC MMY1004 Part 2, 1800 mg co formulant
16 mg/kg IV data are from Study MMY2002

Study MMY1004 Part 2 also showed that 1800 mg Dara-SC can be administered subcutaneously by injection with a median of 5 minutes (ranging from 2 to 11 minutes) and it is associated with a low incidence of IRRs, as noted above. The overall safety profile for the Dara-SC cohort is consistent with previously reported safety profiles for daratumumab IV administration and SC 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 daratumumab administered once every week for 2 cycles (28-day cycles) then every 2 weeks for 2 cycles to quickly achieve and maintain effective daratumumab concentrations. This is the same initial schedule studied with Dara-SC monotherapy in Studies MMY1004 and MMY3012. Following ASCT, consolidation will begin with

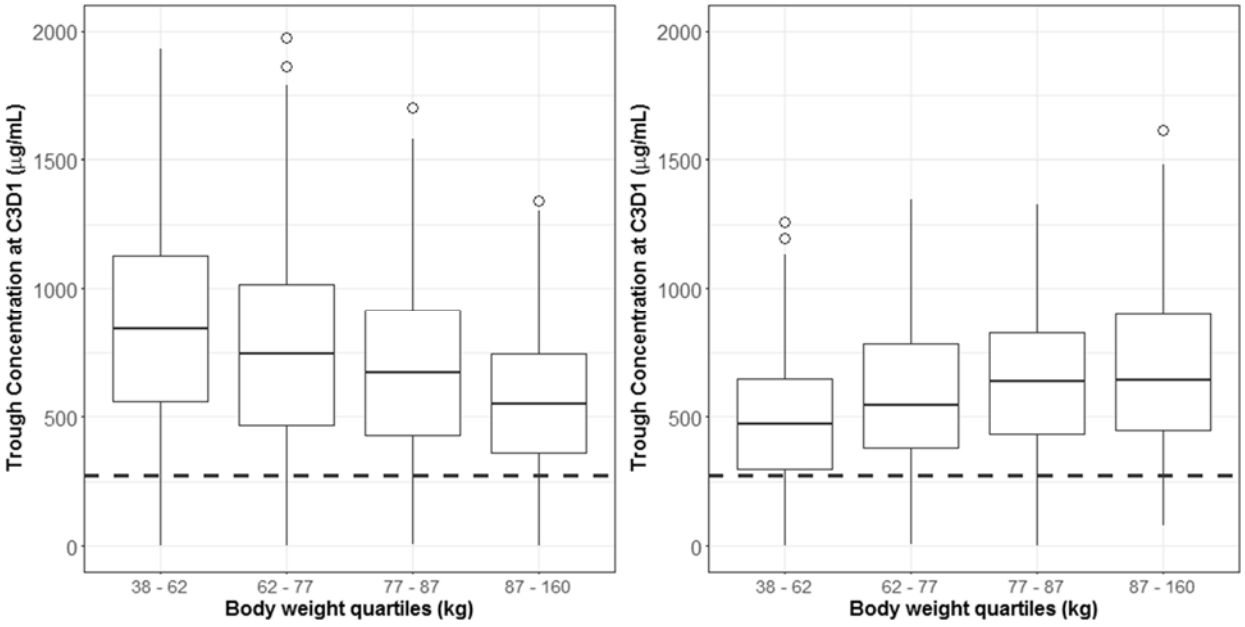
every-2-week dosing and then every-4-week dosing in maintenance; this progression to every-2-week and every-4-week dosing intervals is similar to other approved Dara-IV dosing regimens and Dara-SC. Subjects in Arm B who have delayed recovery post ASCT and exceed 12 weeks off daratumumab will skip the consolidation phase (Cycles 5-6) and proceed directly to maintenance therapy; these subjects will restart daratumumab dosing every 2 weeks for 4 doses (Cycles 7-8) to regain effective concentrations, and then continue every 4 weeks thereafter (for Cycles 9+). Subjects who achieve MRD negativity and go on to restart daratumumab after a daratumumab-free interval, will follow the same approved daratumumab schedule used for monotherapy (weekly for 8 weeks, every 2 weeks for 16 weeks, and every 4 weeks thereafter) to quickly achieve and maintain effective daratumumab concentrations.

Rationale for Fixed Dose

The body weight range in Part 1 of Study MMY1004 was 48 to 133 kg, which was similar to that in daratumumab IV studies (MMY2002 and GEN501, 38.4 to 160.2 kg). The preliminary maximum C_{trough} data for the Dara-MD 1800 mg dose were assessed across a range of simulated body weights and compared with the body weight based daratumumab IV dosing. Across the quartiles of weights for the simulated patients (n 1000), similar exposure was predicted for each dosing approach (either Dara-MD 1800 mg or daratumumab IV 16 mg/kg) (Figure 3). Furthermore, the variability in the exposure for Dara-MD 1800 mg in all weight quartiles was predicted to be similar compared with that for daratumumab IV 16 mg/kg. The fixed Dara-MD 1800 mg dose results in a median concentration that is close to the overall population median concentration, with a ratio of approximately 1 in each weight quartile (Figure 4). Based on these simulations and observations in the ongoing Study MMY1004, fixed dosing for SC administration is a feasible approach and will be used in this study. Dara-IV exhibits a wide therapeutic window and there is no apparent relationship between drug exposure in the therapeutic dose range and AEs of interest, which further supports the feasibility of utilizing a fixed dose approach in SC administration.

Figure 3: Predicted Maximal Trough Concentrations at Cycle 3 Day 1 for Dara-MD 1800 mg (Subcutaneous Administration) and Dara-IV 16 mg/kg (Intravenous Administration)

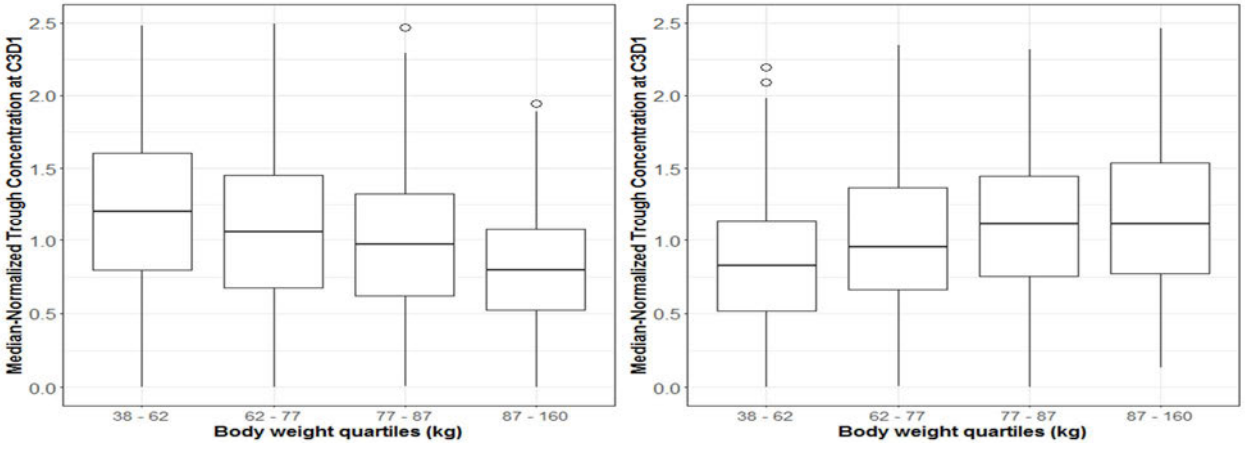
Dara-MD 1800 mg Dara-IV 16 mg/kg



Footnotes: Dashed line is the effective concentration of 274 µg/mL.
C3D1=Cycle 3 Day 1.

Figure 4: Predicted Median-normalized Maximal Trough Concentrations at Cycle 3 Day 1 (Ratio of Trough Concentrations and Median Trough Concentration for Overall Population at Each Dose) for Dara-MD 1800 mg (Subcutaneous Administration) and Dara-IV 16 mg/kg (Intravenous Administration)

Dara-MD 1800 mg Dara-IV 16 mg/kg



Footnotes: C3D1=Cycle 3 Day 1.
Ideal trough concentration is 1.0.

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 and other ongoing Phase 3 studies using Dara-SC. Products approved for commercial use, such as Herceptin SC (trastuzumab) and MabThera SC (rituximab), also contain 2000 U/mL of rHuPH20. A study in minipigs supports the use of this concentration of rHuPH20 for Dara-SC. The 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 Pharmacokinetic and Immunogenicity Evaluations

Data obtained from this study will provide information about the PK profile of Dara-SC in subjects with multiple myeloma who are eligible for ASCT. Therefore, samples will be obtained from all subjects receiving daratumumab 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.

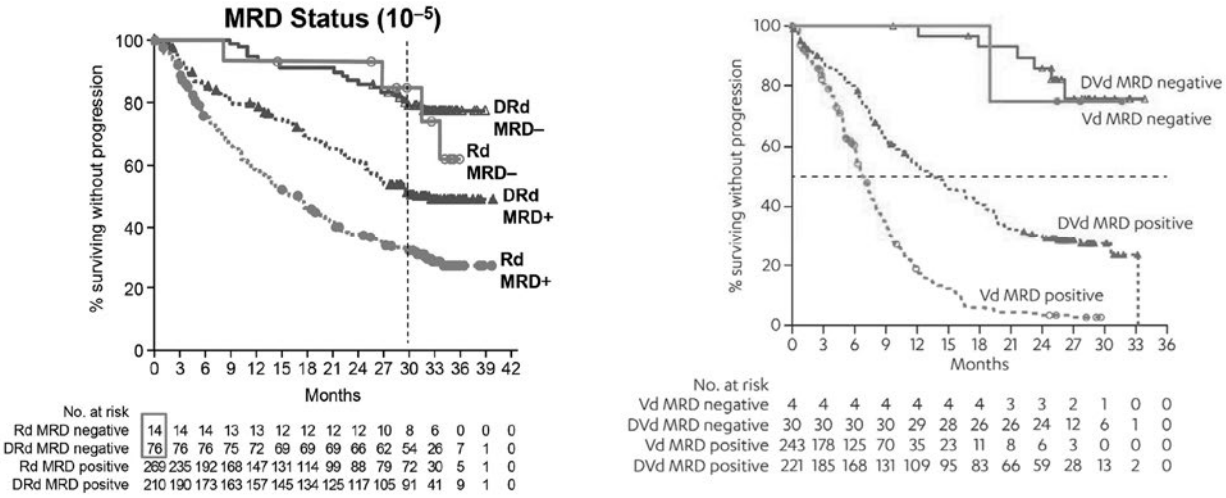
Immunogenicity to daratumumab and rHuPH20 is possible. Therefore, samples to determine the presence of anti-daratumumab antibodies and anti-rHuPH20 antibodies (immunogenicity) will be collected from all subjects receiving daratumumab. The information from these samples and data from other studies will be used to determine the immunogenicity of daratumumab and rHuP20.

Rationale for MRD as a Key Secondary Endpoint

Deepening the magnitude of response is an attainable goal with the advent of combination therapy with novel agents and ASCT. However, conventional means of assessing response are not sufficiently sensitive to measure low-levels of residual bone marrow disease, so-called MRD (Martinez-Lopez 2014). 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 (Landgren 2016, Lahuerta 2017, Munshi 2016).

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 improvement in both the number of subjects achieving MRD negativity as compared to the control arms as well as improvement in PFS for subjects who achieved MRD negative status (Avet-Loiseau 2016) (Figure 5). These studies utilized a NGS-based MRD assay to allow for the consistent evaluation in these global clinical studies. Data shown below reflect a sensitivity of 10^{5}.

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



Sensitive methodologies to detect MRD following a clinical response may define deeper levels of response that correlate with improved long-term outcome (Paiva 2015). The most commonly used sensitive methods to monitor MRD include NGS, allele-specific oligonucleotide polymerase chain reaction (PCR), and multiparametric flow cytometry (Rawstron 2008, Sarasquete 2005). Each method offers distinct advantages and disadvantages. Multiparametric flow cytometry has been widely applied in the diagnostic and prognostic evaluations of patients with myeloma and that it may have value in response assessment, particularly in the context of patients undergoing ASCT. (Owen 2005, Sarasquete 2005). The clonoSEQ MRD assay is an analytically validated NGS assay and is the most sensitive assay available that is seeking FDA approval with the ability to detect one malignant cell in the background of a million normal cells.

MRD will be initially 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 bone marrow aspirate samples will be obtained at specific landmarks 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.

Rationale for Biomarker Evaluations

Biomarkers collected in this study will provide information about daratumumab in multiple myeloma and will focus on 2 key objectives: the evaluation of MRD and the efficacy of daratumumab+VRd (compared to VRd alone) in high-risk molecular subgroups. Exploratory MRD assessment in whole blood may be evaluated as a more sensitive biomarker than standard clinical evaluations to detect loss of CR. In addition, exploratory studies may examine the effects of daratumumab+VRd on daratumumab's MoA following transplant by DNA/RNA sequencing. Samples may be used for immunophenotyping, which could include analysis of specific subsets of immune cells, such as cytotoxic T cells, regulatory T cells, and activated natural killer (NK) cells.

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 Outcomes Endpoints

PRO data complement data collected by clinicians and laboratory findings to describe the patient experience, directly reported by the subject. PRO data are supportive of the clinical endpoints and capture inputs required for cost-effectiveness modeling. In addition, the PRO data provide the patient perspective to communicate the value of treatment to patients, clinicians, regulators, and payers.

Summary of Anticipated Benefits and Risks

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 who are eligible for high-dose therapy, as proposed for investigation in Study MMY3014. This assessment is based upon the following:

- As presented in Section 1.1.2, there are several treatment options that exist for the treatment of patients with previously untreated multiple myeloma; however, strategies directed at improving and maintaining effective response for longer periods of time, as well as new treatment options directed at alternative MoAs are still needed to improve clinical outcomes for patients with the disease.
- The VRd backbone regimen to be used in this study is now considered a 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 1.1.3.
- 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 lenalidomide or bortezomib 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 the newly diagnosed transplant-ineligible setting, Study MMY3007 (studying the combination of daratumumab with VMP vs VMP) also showed a statistically significant improvement in PFS in the D-VMP arm of the study (see Section 1.2.1 for further details). Furthermore, data available from Study MMY2004 suggest that daratumumab can be combined safely with VRd (refer to Section 1.2.1). Preclinical synergism has also been observed with daratumumab in combination with bortezomib and lenalidomide.
- Given the potential advantages of SC administration, SC daratumumab will be used in this study. As presented earlier in this section and in the current daratumumab Investigator's Brochure, the safety and tolerability of SC daratumumab has been demonstrated in early phase studies.

- 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 (refer to Section 11.13).

In summary, there is a strong rationale for evaluating SC daratumumab in combination with VRd for the treatment of patients with previously untreated multiple myeloma who are eligible for high-dose therapy.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 28 days before randomization of the study drug. The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, 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 11.2, Sample Size Determination.

4.1. Inclusion Criteria

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

1. 18 to 70 years of age, inclusive.

2. 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 calcium, renal, anemia, bone (CRAB) criteria or biomarkers of malignancy criteria:

   CRAB criteria:

   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, CT, or PET-CT

   Biomarkers of Malignancy:

   a. Clonal bone marrow plasma cell percentage ≥60%
   b. Involved: uninvolved serum FLC ratio ≥100
   c. >1 focal lesion on magnetic resonance imaging (MRI) studies

3. Measurable disease as defined by any of the following:
   a. Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
   b. Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin FLC ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio
4. Newly diagnosed subjects for whom high-dose therapy and autologous stem cell transplantation is part of the intended treatment plan.
5. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 (see Attachment 1).
6. Clinical laboratory values meeting the following criteria during the Screening Phase (screening hematology and chemistry tests should be repeated if done more than 3 days before C1D1):

   Adequate bone marrow function:

   a. Hemoglobin ≥7.5 g/dL (≥4.65 mmol/L; prior red blood cell [RBC] transfusion or recombinant human erythropoietin use is permitted however transfusions are not permitted within 7 days of randomization to achieve this minimum hemoglobin count);
   b. Absolute neutrophil count (ANC) ≥1.0 x 10^9/L (G-CSF use is permitted);
   c. Platelet count ≥50 x 10^9/L if bone marrow is >50% involved in myeloma. Otherwise ≥75 x 10^9/L

   Adequate liver function:

   a. Aspartate aminotransferase (AST) ≤2.5 x ULN;
   b. Alanine aminotransferase (ALT) ≤2.5 x ULN;
   c. Total bilirubin ≤1.5 x ULN (except in subjects with congenital bilirubinemia, such as Gilbert syndrome, direct bilirubin ≤1.5 x ULN)

   Adequate renal function:

   a. Estimated creatinine clearance ≥30 mL/min. Creatinine clearance may be calculated using Cockcroft-Gault, eGFR (Modified Diet in Renal Disease [MDRD]; Attachment 2), or CKD-epi formula
   b. Corrected serum calcium ≤13.5 mg/dL (≤3.4 mmol/L); or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L) (see Attachment 3)

NOTE: For Criteria 7-11, 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.

7. Criterion modified per Amendment 2.

   7.1 Female subjects of reproductive childbearing potential (defined as post-menarche until post-menopause unless permanently sterilized) 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 and is consistent with the usual lifestyle of the subject. This birth control method must include one highly effective form of contraception (tubal ligation, intrauterine device [IUD], hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy with confirmation of procedure) 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.

8. 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 4.3.

9. 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.

10. 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).

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

12. Criterion modified per Amendment 2

    12.1 Signed an informed consent form (ICF) (or their legally acceptable 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. Subjects in emergency situations that do not allow for collection of informed consent are excluded.

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

4.2. Exclusion Criteria

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

1. Prior or current systemic therapy or SCT for any plasma cell dyscrasia, with the exception of emergency use of a short course (equivalent of dexamethasone 40 mg/day for a maximum 4 days) of corticosteroids before treatment.

2. 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.

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. Criterion modified per Amendment 2

   4.1 Radiation therapy for treatment of plasmacytoma within 14 days of randomization (palliative radiation for pain control secondary to lytic lesion is allowed within 14 days of randomization).

5. Plasmapheresis within 28 days of randomization.

6. Clinical signs of meningeal involvement of multiple myeloma.

7. Criterion modified per Amendment 2

   7.1 Pulmonary:

   a. Subjects <65 years old with chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) <50% of predicted normal

   b. Subjects ≥65 years old with a FEV1 <50% or diffusing capacity of the lungs for carbon monoxide [DLCO] <50%

8. Moderate or severe persistent asthma within the past 2 years (see Attachment 4), or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).

9. Criterion modified per Amendment 2

   9.1 Criterion modified per Amendment 4

   Any of the following:

   a. Known to be seropositive for human immunodeficiency virus (HIV). HIV antibody testing at screening should be performed per local health guidelines.

   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 hepatitis B core antigen [Anti-HBc] and/or antibodies to hepatitis B surface antigen [Anti-HBs]) must be screened using real-time 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, (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).

10. 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 the study procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this study.

11. Criterion modified per Amendment 2

    11.1 Any of the following:

    a. myocardial infarction within 6 months before randomization, or an unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV)

    b. uncontrolled cardiac arrhythmia

    c. screening 12-lead ECG showing a baseline QT interval >470 msec (exception: subjects with pacemaker)

    d. screening ECHO or MUGA scan for subjects aged ≥65-70: left ventricular ejection fraction (LVEF) <40%

12. Received a strong CYP3A4 inducer within 5 half-lives prior to randomization (Flockhart 2016: http://medicine.iupui.edu/flockhart/)

13. 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 or its excipients.

14. Criterion modified per Amendment 2

    14.1 Not able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder). Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. Subject is taking any prohibited medications as per Section 8.3. Subject is deprived of their freedom by a judicial or administrative decision, or subject is in psychiatric care. Subject is subjected to a legal protection measure or unable to provide their consent.

15. Pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of any component of the treatment regimen. Or, subject is a man who plans to father a child while enrolled in this study or within 3 months after the last dose of any component of the treatment regimen.

16. Major surgery within 2 weeks before randomization or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study. Kyphoplasty or Vertebroplasty is not considered major surgery.

17. Criterion modified per Amendment 2

    17.1 Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks or 5 half-lives of the respective drug/investigational medicinal product (IMP) (whichever is longer) before randomization or is currently enrolled in an interventional investigational study.

18. Contraindications to the use of any components of the backbone treatment regimens, per local prescribing information.

19. Gastrointestinal disease that may significantly alter the absorption of oral drugs

20. Vaccination with live attenuated vaccines within 4 weeks of first study agent administration.

21. Unable or unwilling to undergo antithrombotic prophylactic treatment.

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 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the study to be eligible for participation. For restrictions related to concomitant medications, please refer to Section 8.3.

1. 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 in the study, 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. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy. 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.

2. A man who has not had a vasectomy and who is sexually active with a woman of childbearing potential must agree to use a barrier method of birth control eg, condom with spermicidal foam/gel/film/cream/suppository, and all men must not donate sperm during the study, for 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.

3. All Investigators will comply with the respective Celgene country-specific Revlimid Risk Minimization Program (ie, pregnancy prevention program) as implemented in the post-marketing setting.

4. 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. Additional pregnancy tests may be required, as specified in the Celgene country-specific Revlimid Risk Minimization Program (ie, pregnancy prevention program).

5. Typically, IV contrast is not used in computed tomography (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.

6. Subjects must not donate blood during therapy and for at least 3 months following discontinuation of all study treatment.

5. TREATMENT ALLOCATION AND BLINDING

This is an open-label study. Subjects will be assigned in a randomized manner to receive either 1800 mg daratumumab SC in combination with VRd as induction and consolidation therapy and in combination with lenalidomide maintenance therapy or VRd alone as induction and consolidation therapy and lenalidomide alone as maintenance therapy.

Subjects will be stratified prior to randomization by ISS Stage I, II, or III (based upon central laboratory results for β-2 microglobulin and albumin) and by cytogenetics (standard risk or high risk as defined by presence of del17p, t[4;14] or t[14;16]), as centrally confirmed during screening. For stratification purposes, if cytogenetic results are not available (ie, due to technical reasons), local cytogenetic results may be used with the approval of the sponsor's medical monitor. If central and local cytogenetic results are not available, the subject will be assumed to be standard risk. The investigator will screen and if eligible randomize each subject using an IWRS. Each subject will be assigned a unique subject number.

6. DOSAGE AND ADMINISTRATION

Cycles 1-6 in induction and consolidation are 28 days (4 weeks) in duration, and treatment will be for a maximum of 4 induction cycles and 2 consolidation cycles. The cycles during the maintenance period Cycles 7+ are 28 days (4 weeks) in duration, and treatment will continue until disease progression or unacceptable toxicity.

On dosing days where the combination products are given with daratumumab, the study drug and chemotherapy should be administered in the following order:

- lenalidomide, dexamethasone, daratumumab, and bortezomib

The start of each cycle may occur ±3 days of the scheduled day to accommodate the schedule of the site or subject. Day 1 of subsequent cycles should be adjusted accordingly to maintain the intended cycle duration. All treatment cycles are 28 days.

In Cycles 1 and 2 with weekly daratumumab and Cycles 3-6 with bi-weekly daratumumab, administrations may be given within ±1 day of the scheduled day to accommodate the schedule of the site or subject. Additionally, twice weekly bortezomib or dexamethasone doses may be given within ±1 day of the scheduled day to accommodate the schedule of the site or subject. Changes to within-cycle dosing should not affect Day 1 of the next cycle. Subjects will be treated for the allowed maximal treatment period or until disease progression, unacceptable toxicity, or other reasons as listed in Section 10.2.

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

Table 3: Designations of Medicinal Products Used in the Study

Designation	Product
Investigational Medicinal Product	Daratumumab SC
AxMP/NIMP*	Bortezomib SC Lenalidomide PO Dexamethasone PO or IV

AxMP=auxiliary medicinal product; IV= intravenous; NIMP=noninvestigational medicinal product; PO=per os (oral); SC=subcutaneous
AxMP=EU CTR, NIMP=EU CTD
*The AxMP are authorized products in the European Economic Area.

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 to 5 minutes in the abdominal SC 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 Investigational Product Preparation Instructions (IPPI) for additional guidance on SC administration of Dara-SC. 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 an IRR with the first injection of study drug, subject condition on the day of dosing compared with prior dosing days. The dose of daratumumab will remain constant throughout the study.

Daratumumab will be given to subjects in Arm B once every week for Cycles 1 to 2, then every 2 weeks for Cycles 3-6. For maintenance Cycles 7+, subjects will receive daratumumab (1800 mg) once every 4 weeks until documented disease progression or unacceptable toxicity.

Subjects in Arm B who have a post ASCT recovery period that requires greater than 12 weeks off daratumumab and skip consolidation should restart therapy on the following schedule: daratumumab dosing every 2 weeks for 4 doses (Cycles 7-8 of maintenance therapy) then continue every 4 weeks, thereafter (for Cycles 9+).

In Arm B, subjects who achieve MRD negativity that is sustained for 12 months and have been treated on maintenance for at least 24 months will stop daratumumab treatment. MRD negative subjects are defined as those who achieve CR or better and achieve MRD negativity (at 10^{-5} threshold).

After stopping study daratumumab, subjects will continue lenalidomide maintenance therapy until disease progression or unacceptable toxicity. Subjects who previously stopped lenalidomide due to toxicity will stop daratumumab, continue study assessments as per the Treatment Phase even though the subject is not receiving active study treatment, and should not complete an End-of-Treatment Visit.

All subjects who stop daratumumab due to sustained MRD negativity will be monitored for loss of CR (Table 8) by urine and serum M-protein by central laboratories or development of ≥5% plasma cells in the bone marrow by local laboratories as outlined in the Time and Events Schedule (Table 1) and IMWG criteria as well as MRD status via bone marrow aspirate by central laboratories as per Table 1 and Table 9. Upon confirmed loss of CR or recurrence of MRD at 10^{-4} or higher, subjects must restart daratumumab until disease progression or unacceptable toxicity. Upon re-initiation of daratumumab treatment during maintenance, daratumumab will be given at a dose of 1800 mg SC:

- weekly for 8 weeks
- then every 2 weeks for 16 weeks
- then every 4 weeks until disease progression or unacceptable toxicity

All injections will be administered in an outpatient setting. As this is a restart of daratumumab, subjects will receive pre-administration medications and post-administration medications as outlined in Section 6.1.3 and Table 1 to prevent the reoccurrence of infusion-related reactions. Monitor vital signs, hematology, and serum chemistry prior to each daratumumab administration.

NOTE: Once treatment with lenalidomide is stopped due to toxicity, it cannot be restarted.

For subjects in Arm B whose MRD negativity at 10^{-5} threshold cannot be determined by NGS (due to lack of MRD index clone or non-unique clone sequence), MRD by next-generation flow (NGF) may be used to guide daratumumab stopping and restarting in agreement with the sponsor.

6.1.3. Guidelines for Prevention and Management of Injection Reactions

6.1.3.1. Daratumumab Predose 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 Attachment 5 for a list of antihistamines that may be used). Avoid IV promethazine.
- Dexamethasone 20 mg IV or PO prior to the first 2 doses and 10 mg for all subsequent doses (must have absence of IRR AEs for 2 doses prior to decreasing dose). Backbone therapy substitutes for the premedication dexamethasone. Accordingly, 40 mg dexamethasone will be administered PO or IV prior to daratumumab in Cycles 1-6. Substitutions for dexamethasone are allowed (refer to Attachment 6). For subjects who restarted daratumumab after interruption due to sustained MRD negativity, give dexamethasone 20 mg IV or PO for the first 2 doses and 10 mg for all subsequent doses.

- Predose administration of a leukotriene inhibitor (montelukast 10 mg PO) is recommended on Cycle 1 Day 1. The leukotriene inhibitor may be administered up to 24 hours before injection.

If necessary, due to timing constraints, all PO pre-administration medications may be administered outside of the clinic on the day of the injection, provided they are taken 1-3 hours before the injection.

6.1.3.2. Daratumumab Post-administration Medication

Consider administering low-dose oral methylprednisolone (≤20 mg) or equivalent on the day after the injection. However, if a VRd background regimen-specific corticosteroid (eg, dexamethasone) is administered on the day after the injection, additional post-injection corticosteroid is not required.

For 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), the following post-administration medications should be considered:

- Antihistamine (diphenhydramine or equivalent)
- Leukotriene inhibitor (montelukast or equivalent)
- 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 daratumumab administration. If subjects are hospitalized, then their FEV1 should be documented prior to 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-administration medications may be stopped.

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

6.2.1. Daratumumab 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. Daratumumab Infusion-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 (eg, 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. Please see the IPPI for further details. 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 administration 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 permanently discontinued.

6.2.2.1. Infusion-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.

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. Infusion-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 daratumumab administration may be restarted at the investigator's discretion. Please refer to the IPPI 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 must be permanently discontinued from daratumumab treatment.

6.2.2.3. Recurrent Infusion-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.

If daratumumab is interrupted for a longer period, for example during transplant period or in treatment-free period in maintenance, infusion-related reactions can re-occur.

6.3. Bortezomib, Lenalidomide, and Dexamethasone (VRd)

6.3.1. Bortezomib

6.3.1.1. Dose Calculation of Bortezomib

The amount (in mg) of bortezomib to be administered will be determined by body surface area (BSA), which will be calculated according to a standard nomogram (Attachment 7), there is no maximum dose. The calculated dose of bortezomib may be rounded to the nearest tenth of a mg (eg, a calculated dose of 2.34 mg may be rounded to 2.3 mg).

6.3.1.2. Bortezomib Administration

Subjects will receive 1.3 mg/m^2 bortezomib as a SC injection twice a week (Days 1, 4, 8, and 11) for Cycles 1-6; four 28-day induction cycles (Cycles 1 to 4), and two 28-day consolidation cycles (Cycles 5-6). Subjects will not receive bortezomib after Cycle 6. 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 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 must be at least 72 hours 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 sec bolus injection. Please refer to local prescribing information for further details on either SC or IV administration. On daratumumab administration days, bortezomib will be administered at the end of the daratumumab administration. No subjects will receive bortezomib after the first 6 cycles of treatment.

6.3.2. Lenalidomide Administration

Lenalidomide will be administered PO at 25 mg on Days 1 to 21 in Cycles 1-6; four 28-day induction cycles and two 28-day consolidation cycles. Subjects will start maintenance therapy at 10 mg daily PO on Days 1 to 28 (continuously) of each 28-day cycle until disease progression or unacceptable toxicity. After 3 cycles of maintenance therapy, if well tolerated, the lenalidomide dose may be increased to 15 mg daily, at the discretion of the investigator.

On daratumumab administration days, it is recommended that lenalidomide is administered either prior to or at the same time (preferred) as the pre-administration medications. 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. If the next dose is scheduled to be taken within 12 hours, the missed lenalidomide dose should be skipped.

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

6.3.3. Dexamethasone Administration

Dexamethasone will be administered on scheduled days as indicated in the Time and Events Schedule (Table 1) at 40 mg daily on Days 1-4 and Days 9-12 of each 28-day cycle during induction and consolidation (Cycles 1-6) as part of the VRd backbone regimen. On daratumumab administration days, dexamethasone backbone therapy substitutes for the premedication dexamethasone. Accordingly, 40 mg dexamethasone will be administered PO or IV 1-3 hours before the daratumumab administration. On days when daratumumab is not administered, dexamethasone is administered PO. Dexamethasone tablets are to be taken with or immediately after a meal or snack, preferably in the morning.

6.4. Dose Delays and Dose Modifications

Bortezomib, lenalidomide and dexamethasone doses may be reduced, or the treatment schedule may be modified for the management of the study drug-related toxicities. Subjects who need to discontinue treatment with any one component of study treatment (daratumumab, bortezomib, lenalidomide or dexamethasone) may continue to receive treatment with the other components of study treatment, as assigned. Investigators should refer to the bortezomib, lenalidomide and dexamethasone updated summary of product characteristics (SmPC) for further recommendations for dose delays and modifications.

6.4.1. 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 (see also Table 6). 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 should 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 Each Induction/Consolidation Cycle

Laboratory parameter	Requirements before each study agent administration
ANC	≥1.0 x 10^9/L
Platelet count	≥70 x 10^9/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 and a maximum of 28 days until recovery to the specified levels. Supportive care medications including transfusions should be administered at the investigator discretion.

Subjects should have adequate hematologic recovery (ANC≥1.0 x 10^9/L and platelets ≥75 x 10^9/L) following ASCT prior to initiating consolidation or maintenance therapy.

Should a subject be unable to tolerate therapy due to toxicity during the consolidation phase of therapy, the subject may proceed with the maintenance phase of the study (Cycle 7+) and skip the remaining consolidation cycles after discussion with the sponsor's medical monitor. 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 during induction or maintenance phases due to insufficient recovery from toxicity, subjects will discontinue taking the study treatment(s) permanently unless continuation approved by the sponsor's medical monitor. If subject permanently discontinues therapy procedures should be performed as outlined in Section 9.1.4.

6.4.2. Dose Modification Guidelines

Toxicities should be attributed, whenever possible, to a specific study drug. Reduction of all agents considered related to a toxicity should occur as per the guidelines below. When multiple toxicities are attributed to a study treatment, a dose adjustment should be made according to the guidelines for the most severe toxicity. Please refer to the tables below for dose reduction steps and dose modification guidelines. Once dose reduction for a medication has been implemented, unless otherwise stated specifically in the table below, dose re-escalation should not occur, unless in the judgment of the investigator, and in consultation with the sponsor's medical monitor, there is clinical benefit and a reasonable and acceptable risk profile.

6.4.2.1. Daratumumab

6.4.2.1.1. Daratumumab Dose Modification

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

6.4.2.1.2. 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

- 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 that was present at baseline or that lasts for <7 days after the last administration of daratumumab
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

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.

If daratumumab administration does not commence within the prespecified window (Table 5) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. A missed dose will not be made up.

Table 5: Daratumumab-related Toxicity Management

Cycles	Frequency	Dose Missed	Dosing Resumption
1 2	Weekly	>3 days	next planned weekly dosing date
3 6	Every 2 weeks	>7 days	next planned every 2 weeks dosing date
7+	Every 4 weeks	>14 days	next planned every four weeks dosing date

If a dose is delayed, then the dates of all subsequent doses must be adjusted. Any AE deemed to be related to daratumumab that requires a dose hold of more than 28 days will require consultation with the sponsor and the review of safety and efficacy to determine if daratumumab dosing may continue.

6.4.2.1.3. Daratumumab Interruption or Missed Doses

A daratumumab dose that is held for more than the permitted time (Table 5) from the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the sponsor at the earliest possible time. Subjects whose dose was delayed for more than 28 days, upon consultation with the sponsor and the review of safety and efficacy, may continue daratumumab dosing.

6.4.2.2. Lenalidomide

Lenalidomide dose adjustments are described in Section 6.4.2.2.1 and Section 6.4.2.2.2. See Table 6 for further dose modifications.

6.4.2.2.1. Dose Adjustments of Lenalidomide

Dose adjustments of lenalidomide will follow the approved labeling as follows:

Induction/consolidation (Cycles 1-6):

- Starting dose: 25 mg
- Dose level -1: 20 mg
- Dose level -2: 15 mg
- Dose level -3: 10 mg
- Dose level -4: 5 mg
- Dose level -5: Discontinue lenalidomide permanently

Maintenance (Cycles 7+)

	Starting dose (10 mg)	If dose increased (15 mg) [a]
Dose level 1	5 mg	10 mg
Dose level 2	5 mg (days 1 21 every 28 days)	5 mg
Dose level 3	Not applicable	5 mg (days 1 21 every 28 days)
	Do not dose below 5 mg (days 1 21 every 28 days)	

[a] After 3 cycles of lenalidomide maintenance, the dose can be increased to 15 mg orally once daily if tolerated, at the discretion of the investigator.

Dose adjustments should be based on the highest grade of toxicity that is ascribed to lenalidomide as noted in Table 6.

6.4.2.2.2. Renal Impairment

Adjustment 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 creatinine clearance (CrCl) <50 mL/min. The recommended doses for subjects with multiple myeloma and renal impairment are shown in Table 6. 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 6.

6.4.2.3. Bortezomib

6.4.2.3.1. Dose Adjustments of Bortezomib

Dose adjustments of bortezomib will follow the approved labeling as follows:

- Starting dose: 1.3 mg/m^2
- Dose level -1: 1.0 mg/m^2
- Dose level -2: 0.7 mg/m^2
- Dose level -3: discontinue bortezomib

Dose adjustments should be based on the highest grade of toxicity that is ascribed to bortezomib as noted in Table 6.

6.4.2.4. Dexamethasone

Dose adjustments should be based on the highest grade of toxicity that is ascribed to dexamethasone as noted in Table 6.

6.4.2.4.1. Dose Adjustments of Dexamethasone

- Starting dose: 40 mg
- Dose level -1: 20 mg
- Dose level -2: 10 mg
- Dose level -3: discontinue dexamethasone permanently (premedication for daratumumab may continue)

Dose modification guidelines for bortezomib, lenalidomide and, dexamethasone are provided in Table 6.

Table 6: 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.		
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.	Consider holding lenalidomide.	

Table 6: Dose Modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib	Lenalidomide	Dexamethasone
		Restart with lower concentration formulation. If recurrent consider IV bortezomib.		
	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.		

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

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib	Lenalidomide	Dexamethasone
Hematological	Neutropenia Grade 3 (without complications)	No dose reduction required of bortezomib. Consider treatment with G CSF.	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 ore recurrent episode reduce lenalidomide by 1 dose level.	
	Grade 3 neutropenia associated with fever (≥38.5°C) or Grade 4neutropenia	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 both 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.	
	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.

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

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib	Lenalidomide	Dexamethasone
Renal Impairment	Moderate renal impairment CrCl[f] 30 49 mL/min		Lenalidomide should be given at a dose of 10 mg daily[g] for Cycles 1 6 or 5 mg daily during maintenance Cycles 7+.	
	Severe renal impairment CrCl[f] <30 mL/min (not requiring dialysis)		Lenalidomide should be given at a dose of 15 mg **every 48 hrs**[g] for Cycles 1 6 or 5 mg daily on D1 D21 every 28 days during maintenance Cycles 7+.	
	End stage renal disease CrCl[f] <30 mL/min (requiring dialysis)		Lenalidomide should be given at a dose of 5 mg[g] daily for Cycles 1 6 or 5 mg daily on D1 D21 every 28 days during maintenance Cycles 7+. On dialysis days, 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.		

[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.
[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.
[g] Consider escalating dose to 15 mg daily after 2 cycles if well tolerated.

7. TREATMENT COMPLIANCE

Study drug (daratumumab) and the components of the backbone regimens will be administered or prescribed by qualified site staff, and the details of each administration will be recorded in the electronic case report form (eCRF). Additional details are provided in the Site Investigator Product Procedures Manual (sIPPM).

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 8.3. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

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 component of study treatment or until the start of subsequent anticancer treatment, if earlier. During the transplant period (defined as the period from the first day of hospitalization to the day before C5D1) only the concomitant treatments used to treat AEs specified in Section 9.1.3. should be recorded. Concomitant medications to manage AEs and SAEs will be recorded as per Section 12.3.1. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

8.1. Recommended Therapies

8.1.1. Prevention of Deep Venous Thrombosis

Lenalidomide has been associated with an increased risk of deep vein thrombosis and pulmonary embolism. Therefore, prophylaxis of venous thromboembolism (VTE) for all subjects is recommended according to IMWG guidelines (Palumbo 2008, Attachment 8). Both individual and myeloma-related risks of VTE should be considered in determining the type of thromboprophylaxis. In summary:

- Myeloma Risk factors:
  - All subjects during induction therapy Cycles 1-4 and for subsequent cycles in any subject for whom any myeloma therapy-related risk factor is present, low molecular weight heparin (LMWH) (equivalent of 40 mg enoxaparin once daily) or full-dose warfarin (target international normalized ratio [INR] 2-3) is recommended.
- Individual Risk factors:
  - If no risk factor, or any one risk factor is present, aspirin 81-325 mg once daily is recommended or dose per institutional standards.
  - If 2 or more risk factors are present, LMWH (equivalent of enoxaparin 40 mg once daily) or full-dose warfarin, INR 2-3, is recommended.

8.1.2. 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.

8.1.3. Prophylaxis Against Pneumocystis carinii Pneumonia

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

8.1.4. 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 PO 3 times a day, or 800 mg given PO 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 PO, twice a day or per institutional standards).

8.1.5. Prevention of Steroid Induced Gastritis

Dexamethasone and other corticosteroids may induce gastritis. Medications to prevent gastritis are permitted per institutional guidelines. For example, proton pump inhibitors (omeprazole or equivalent) or sucralfate, or H_2 blockers (ranitidine or equivalent) may be used.

8.1.6. Bisphosphonate Therapy

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 (Moreau 2013, NCCN 2017). 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 use the same route of bisphosphonate therapy for all subjects at their sites.

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

8.1.7. Management of Hepatitis B Virus Reactivation

Primary antiviral prophylaxis is permitted as per local SOC. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation. See Section 9.8.

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 SOC. Consult a liver disease specialist as clinically indicated.

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 (eg, 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.
- Vaccination is allowed per local guidelines (including annual influenza and inactivated SARS-CoV-2 vaccines, including mRNA-based vaccines), but vaccines should not be administered on the same day as study treatment administration; however, the subject may continue lenalidomide on the day of vaccine administration per institutional practice. Some types of vaccines (eg, live, attenuated or with suspected replication capabilities) are not permitted. Note that antibody responses to vaccines may be suboptimal during study treatment (Ariza-Heredia 2015; see Section 8.3 and Attachment 13).

Other symptoms may be managed according to institutional guidelines provided prohibited therapies are not administered (see Section 8.3).

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. Investigators should refer to the local bortezomib, lenalidomide and dexamethasone updated SmPC for drugs prohibited or to be used with precautions. 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, please refer to Flockhart 2016 (http://medicine.iupui.edu/flockhart/).

- Other agents that target CD38.
- Medications used for other indications that have antimyeloma properties (for example, interferon and clarithromycin) (Ghosh 2013, Rossi 2013, Niesvizky 2008).
- Approved or investigational treatments for multiple myeloma (including but not limited to conventional chemotherapies, immunomodulatory drugs [IMiDs], or proteasome inhibitors).
- 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 is prohibited. Non-steroidal anti-inflammatory agents should be avoided as they may exacerbate myeloma-related kidney disease.
- Administration of investigational, live attenuated, or replication-competent viral vector vaccines <4 weeks prior to the start of study treatment, during study treatment, or initiated <90 days after last dose of study treatment are prohibited.

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.

8.4. Subsequent Therapies

It is not permissible to start other antimyeloma therapy until disease progression is confirmed by IMWG criteria and approved by the medical monitor.

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

Administration of any other antimyeloma therapy to subjects who discontinue study drug for reasons other than disease progression should be monitored, and disease progression on such treatment should be monitored and documented in the CRF, according to the Time and Events Schedule (Table 1).

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedules (Table 1 and Table 2) 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.

PRO measures will be completed by the subject at the clinical site or by telephone, as an option, for assessments during the Follow-up Phase. 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 9.7 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 95 mL during screening, approximately 340 mL in the Induction/ASCT/Consolidation Phase (Cycles 1-6), approximately 370 mL in Year 1 of the Maintenance Phase, and approximately 280 mL annually in Year 2 and beyond of the Maintenance Phase. This includes laboratory assessments associated with safety, efficacy, and PK evaluations, as well as scientific research samples. At the End-of-Treatment Visit, approximately 15 mL of blood will be collected and approximately 10 mL will be collected for PK testing in the Follow-up Phase. Unscheduled samples may be taken for safety reasons (eg, IRR) or repeat samples may be taken in the event of technical issues with the samples taken.

9.1.2. 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, and a complete clinical evaluation will be performed as specified in the Time and Events Schedule (Table 1). 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, ECHO or MUGA (only required for subjects ≥65 years old), chest x-rays or full dose chest CT scans, spirometry, DLCO (only required for subjects ≥65 years old), or bone marrow aspirate/biopsy performed up to 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.

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 rescreening must sign a new ICF and then will be assigned a new screening number.

9.1.3. Treatment Phase

Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedules (Table 1 and Table 2). The Treatment Phase begins on Cycle 1 Day 1 and continues until disease progression, unacceptable toxicity, or for the other reasons outlined in Section 10.2. 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 study treatment, complete the End-of-Treatment Visit, and enter the Follow-up Phase.

9.1.3.1. Induction Treatment (Cycles 1-4)

Subjects will receive four 28-day cycles of VRd induction therapy (Cycles 1-4) as described in Section 6.2. Subjects in Arm B will receive daratumumab in addition to VRd as described in Section 6.1. Efficacy will be assessed at the start of each cycle.

9.1.3.2. Mobilization and Harvesting Stem Cells

Stem cell mobilization should be performed within 6 weeks after completion of Cycle 4 using local SOC. Sites should be prepared to utilize plerixafor in addition to standard agents such as cyclophosphamide and G-CSF to ensure adequate mobilization. Additional use of plerixafor is recommended if there is a suspicion of inadequate mobilization. The use of a second mobilization as per local SOC or alternatively a bone marrow harvest should occur to ensure adequate stem cell yield as per institutional practice, if the stem cell yield is deemed to be suboptimal per investigator discretion. An assessment of the efficiency of mobilization/harvesting will be recorded in the eCRF (please see Section 9.2).

9.1.3.3. Conditioning (Melphalan off Study as per Standard of Care)

Subjects should proceed to conditioning within 2 weeks after stem cell mobilization. Subjects will receive melphalan 200 mg/m^2 as conditioning therapy over a period of 24 to 48 hours prior to ASCT. Melphalan may be given at a lower dose of 140 mg/m^2, per institutional standards (ie, renal insufficiency).

9.1.3.4. Transplant (as per Standard of Care)

There should be no more than 12 weeks between end of induction and transplant. Subjects will have a single re-infusion of stem cells 24 to 48 hours after high-dose melphalan.

9.1.3.5. Engraftment/Recovery

Subjects will be monitored for successful engraftment by means of hematopoietic reconstitution (defined as ANC $\geq 0.5 \times 10^9$/L and platelet count $\geq 20 \times 10^9$/L). Supportive therapy will be administered according to institutional standards.

During the immediate post-transplant period (defined as the first day of high-dose melphalan administration to the day before Cycle 5 Day 1), neutropenia and thrombocytopenia resulting from bone marrow aplasia will not be recorded as AEs in the eCRF with the exception of failure to achieve adequate hematological values that are required to start consolidation. Only the following AEs, concomitant medications and procedures, and MRU associated with these AEs have to be recorded in the eCRF during this period:

- any evolution of an ongoing AE at the time of ASCT
- any new AE related, or that appears to be related, to daratumumab
- any new infection toxicity Grade 3 or higher
- any new oral mucositis toxicity Grade 3 or higher

9.1.3.6. Consolidation (Cycles 5-6)

Consolidation therapy should commence within 12 weeks of transplant when engraftment is complete (defined as ANC $\geq 0.5 \times 10^9$/L and platelet count $\geq 20 \times 10^9$/L) and when in the opinion of the investigator the subject is fit enough to tolerate subsequent systemic therapy (30-60 days post ASCT). In addition, subjects also need to meet the consolidation start criteria in Section 6.4.1. Subjects will receive two 28-day cycles of VRd as described in Section 6.3. Subjects assigned to Arm B will receive daratumumab as described in Section 6.1.2. For subjects who achieve hematopoietic reconstitution >12 weeks after ASCT, subjects should discuss continuation to consolidation versus maintenance therapy with the sponsor's medical monitor. Efficacy will be assessed at the start of each cycle.

9.1.3.7. Post-consolidation Efficacy Assessment

Subjects with a response of VGPR or better will be assessed for response and MRD once consolidation therapy is complete prior to Cycle 7 Day 1 study drug administration in subjects who are unable to complete consolidation due to toxicity or delayed engraftment consolidation.

9.1.3.8. Maintenance Treatment

Subjects will receive lenalidomide in 28-day cycles as described in Section 6.3.2. Subjects in Arm B will also receive daratumumab as described in Section 6.1.2. Efficacy will be assessed as per the Time and Events Schedule (Table 1).

9.1.4. 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. Subjects in Arm B who stop daratumumab due to

sustained MRD negativity and who have stopped lenalidomide due to toxicity should not complete an End-of-Treatment Visit but should continue assessments per Table 1 and Section 6.1.2.

Every effort should be made to conduct the End-of-Treatment Visit before the subject starts subsequent therapy. Posttreatment PK and immunogenicity samples should still be collected, even if a subsequent therapy has been initiated. 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 Section 12.

9.1.5. Posttreatment Phase (Follow-up)

The Follow-up Phase will begin once a subject permanently discontinues treatment with study medications. For all subjects who discontinue study drug without disease progression, disease evaluations by central laboratory should continue to be performed as specified in the Time and Events Schedule (Table 1) until documented disease progression. For subjects who discontinue study treatment without disease progression prior to transplant, disease evaluations at the central lab should continue to be performed as specified in the Time and Events Schedule (Table 1) until documented disease progression. Subsequent antimyeloma therapy must not start until after disease progression is confirmed per IMWG criteria (see Table 7) and approved in the IWRS system.

After documented disease progression, follow-up information will be obtained every 16 weeks (±14 days). The every 16-week follow-up contacts should be scheduled from the date of confirmed disease progression. Subsequent anticancer treatment and the associated response to treatment by local laboratories, including date of subsequent progression (PFS2) will be recorded. 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. (Rajkumar 2011).

Survival status will be obtained every 16 weeks. 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, the date and cause of death will be collected and documented in the eCRF.

NOTE: Subjects in Arm B who stop daratumumab due to sustained MRD negativity should continue study assessments as per the Time and Events Schedule (Table 1). These subjects remain on study as this period is not considered posttreatment follow-up.

9.2. Efficacy Evaluations

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.

9.2.1. Response Categories

Disease evaluations must be performed as outlined in the Time and Events Schedule (Table 1) on the scheduled assessment day (±7 days). Disease evaluations scheduled for treatment days should be carried out before study drug is administered. Testing of specimens use for disease evaluation will be performed by a central laboratory (unless otherwise specified).

This study will use the IMWG consensus recommendations for multiple myeloma treatment response criteria (Rajkumar 2011) presented in Table 7. For M-protein and immunofixation measurements in serum and 24-hour urine, and FLC measurements, the investigator will use results provided by the central laboratory. For subjects in Arm B, once the criteria for discontinuation of daratumumab has been met as per Section 6.1.2, subjects will be followed for loss of CR. If a subject meets the criteria for loss of CR without disease progression as noted in Table 8, the subject will then restart daratumumab as per Section 6.1.2. The criteria for loss of CR without disease progression is presented in Table 8 and only applies to subjects in Arm B who meet the above criteria. For subjects with suspected daratumumab interference on serum M-protein quantitation by electrophoresis (SPEP) and immunofixation (IFE), a reflex assay will be performed (Attachment 9). Subjects with confirmed daratumumab interference who meet all other clinical criteria for CR or sCR will be considered to have achieved CR/sCR.

Table 7: 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 percentage 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
CR complete response; FLC free light chain; IMWG International Myeloma Working Group; M protein monoclonal paraprotein; PC plasma cell; PD progressive disease; PR partial response; sCR stringent complete response; SD stable disease; VGPR very good partial response	
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 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: "25% increase" refers to M protein and FLC, 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

Table 8: Arm B Only (Section 6.1.2): Criteria for Loss of Complete Response Not Meeting Criteria for Disease Progression (Per Table 7)

Loss of CR	One or more of the following criteria: • Reappearance of serum M protein by immunofixation or electrophoresis (any value without confirmed PD)[a] • Reappearance of urine M protein by immunofixation or electrophoresis (any value without confirmed PD)[a] • Development of ≥5% plasma cells in the bone marrow

[a] Two consecutive assessments needed.

9.2.2. 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.

- IgG, IgA, IgM, IgD, and IgE at screening
- 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
- FLC assessment for subjects with light chain only myeloma AND for all subjects to confirm sCR

Blood and 24-hour urine samples will be collected as specified in the Time and Events Schedule (Table 1) 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 performed at least one day later. Disease evaluations will continue beyond loss of CR until disease progression 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 IFE (McCudden 2010). For subjects in Arm B with daratumumab interference on serum IFE, the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test (Attachment 9) 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 reflex assay will be implemented as part of response criteria. 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.

9.2.3. 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, as specified in the Time and Events Schedule (Table 1) 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 7). 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 Attachment 3.

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.

9.2.4. 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.

9.2.5. Bone Marrow Examination

Bone marrow aspirate or biopsy will be performed at screening for clinical staging (morphology, central 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 may 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. A fresh bone marrow aspirate at screening is required (archived samples will not be accepted). 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. Bone marrow aspirates performed for assessment of MRD or confirmation of CR should be repeated if the collection was inadequate.

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. If baseline clonality is still not established, no further bone marrow samples should be collected for MRD assessments.

Table 9: 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 for cytogenetic analysis by conventional FISH while a second portion of the bone marrow aspirate will be used for MRD index clone identification (calibration). If the MRD index clone is not identified, then an archived sample might be requested in order to repeat the clone identification assay. A third portion of the bone marrow may be used for additional biomarker assessments.
During Treatment/Follow-Up	**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.)*	**MRD Assessments: Bone marrow aspirates will be collected as follows:** -During post-consolidation[b] in subjects with VGPR or better. -At time of suspected CR/sCR. -For subjects who achieve CR/sCR, have not progressed and remain on the study, additional bone marrow aspirate will be obtained at 12, 18, 24, 30, and 36 months post Cycle 1 Day 1 (±1 month) and yearly thereafter (±1 month).[c] **EMN correlative studies: Bone marrow aspirates will be collected:** -If feasible, for all subjects during post-consolidation and at disease progression.

CR=complete response; FISH=fluorescence in situ hybridization; IF=immunofluorescence; IHC=immunohistochemistry; MRD=minimal residual disease; sCR=stringent complete response; VGPR=very good partial 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] Obtain prior to C7D1 study drug administration.
[c] If one of these time points for MRD sampling 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.

9.2.6. Minimal Residual Disease Assessment

In this study, bone marrow and whole blood samples will be collected for MRD assessment when a bone marrow aspirate is performed at screening and at the subsequent timepoints outlined in Table 9 and the Time and Events Schedule (Table 1). Bone marrow aspirates performed for assessment of MRD should be repeated if the collection was inadequate. Note: for subjects who achieve CR/sCR, whole blood samples are collected every 3 months (±1 month) from 12 to 36 months post C1D1, and yearly thereafter; bone marrow samples are collected at Month 12, 18, 24, 30, and 36 months post C1D1, and yearly thereafter (±1 month).

9.2.7. 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. Please 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. MRI or low-dose CT scan are acceptable methods for evaluation of bone disease and may be included at the discretion of the investigator (see the disease response criteria in Table 7). If a radionucleotide 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 radionucleotide 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 these cases, disease progression may be documented 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 x-rays are necessary. In instances when changes are subtler, a repeat x-ray should be performed in 1 to 3 weeks.

9.2.8. Documentation 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. CT scan evaluations are an acceptable alternative if there is no contraindication to the use of intravenous contrast. PET 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 disappearance of the plasmacytoma or confirmed disease progression. If assessment can only be performed using imaging, then evaluation of extramedullary plasmacytomas should be done every 12 weeks starting from Cycle 1 Day 1 until disappearance of the plasmacytoma or confirmed disease progression. 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%, from the smallest measurable size during the study and new plasmacytomas must not have developed (see the disease response criteria in Table 7). 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.

9.3. Pharmacokinetics and Immunogenicity

Serum samples will be used to evaluate the PK of daratumumab, as well as anti-daratumumab antibodies. Plasma samples will be used to evaluate anti-rHuPH20 antibodies. Serum samples collected for PK and immunogenicity analyses 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 samples. Subject confidentiality will be maintained.

9.3.1. Evaluations

Samples to assess both the serum concentration (PK) of daratumumab and the generation of anti-daratumumab antibodies (immunogenicity) will be drawn from all subjects in Arm B according to the Time and Events Schedule (Table 2). 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 PK 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 anti-rHuPH20 antibodies according to the Time and Events Schedule (Table 2). 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.

9.3.2. Analytical Procedures

Serum samples will be analyzed to determine concentrations of anti-daratumumab antibodies using validated immunoassay methods.

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.

9.3.3. Pharmacokinetic Parameters

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

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

The parameters, C_{min}, and $C_{max,}$ will be determined based on the assigned collection timepoints. If there are sufficient data, population PK 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 PK analysis plan and results of the analysis will be presented in a separate report.

9.3.4. 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 Time and Events Schedule. Daratumumab concentrations 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 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, serum and plasma samples should be obtained, if possible, for determination of anti-daratumumab antibodies and anti-rHuPH20 antibodies. 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 disease progression 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.

9.4. Pharmacokinetic/Pharmacodynamic Evaluations

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. Biomarkers/EMN Correlatives

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 Time and Events Schedule (Table 1) 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 cytogenetics evaluations 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 Ig heavy and light chains as specified in Table 9. If this methodology is unavailable, or determined to be scientifically inferior, then alternative methods for MRD assessment may be utilized.

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. If baseline clonality is not established or for subjects with non-unique clone sequence, no further bone marrow samples should be collected for MRD assessments for subjects in the VRd arm, however subjects in the D-VRd arm without baseline clonality or with non-unique clone sequence may have MRD assessment by NGF for the purpose of determining daratumumab continuation.

Whole blood samples will be collected from subjects, as specified in the Time and Events Schedule, for processing to plasma and peripheral blood mononuclear cells and for peripheral MRD evaluation. Exploratory evaluation of MRD using whole blood may also be performed to determine the utility as a more sensitive biomarker than standard clinical evaluations to detect loss of CR. To explore the impact of the VRd regimen on daratumumab's mechanisms of action, the whole blood samples may be used to evaluate daratumumab's immunomodulatory MoA, where specific subsets of immune cells such as cytotoxic T cells, regulatory T cells, and activated NK cells may be evaluated by fluorescence-activated cell sorting (FACS) or cytometry/time-of-flight mass spectrometry and T-cell receptor sequencing. Proteomic analysis may also be used to evaluate changes in proteins in circulation to evaluate potential markers of clinical response.

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.

9.6. Medical Resource Utilization

MRU data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study. These data will be analyzed to assess MRU across treatment arms and may be used for modeling purposes. 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)

Please see eCRF completion guidelines.

9.7. Patient-reported Outcomes

Subjects health-related quality of life (HRQoL), symptoms, functioning, and general well-being will be captured using 3 PRO measures: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (Attachment 10), European Organization for Research and Treatment of Cancer Multiple Myeloma Module (EORTC QLQ-MY20) (Attachment 11), and the EQ-5D-5L (Attachment 12). These measures will be administered according to the Time and Events Schedule (Table 1) to understand how subjects self-reported health state changes over time and the difference between-treatment arms during induction, consolidation, maintenance, and post-progression. The hypothesis that treatment with daratumumab maintains a subject's HRQoL when added to a triplet regimen will be tested using established meaningful change thresholds and statistical significance between groups.

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. The PRO measures should be completed before any conversation on status with the health care provider. 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.

EORTC QLQ-C30 version 3 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 Item") and responses are reported

using a verbal rating scale. The 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 patients with multiple myeloma. Reliability, validity, and clinically meaningful change have been demonstrated (Wisloff 1996, Wisloff 1997). 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 (Cocks 2007). 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 less than 30 minutes. Key PRO endpoints include the GHS, physical functioning, fatigue, and pain scales from the EORTC QLQ-C30 and the Disease Symptoms scale from the EORTC QLQ-MY20.

The EQ-5D-5L is a generic measure of health status. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, selfcare, 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) (Herdman 2011). 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 4 months, 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 eCRF. If the subject is unable to complete the EQ-5D-5L, the reason for not completing the questionnaire will be documented (ie, too ill, subject refused). This can be done by interview as part of the telephone contact documented in the eCRF.

9.8. Safety Evaluations

Safety evaluations will include AE monitoring, physical examinations, ECG monitoring, ECHO or MUGA (only required for subjects ≥65 years old), 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 that occur during the study must be recorded in the Adverse Event eCRF page. 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.

Based on previous experience with daratumumab in humans, in vitro studies, and animal toxicological findings, IRRs/allergic reactions, haemolysis, 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.

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 acceptable 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. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting. For AE reporting during the transplant period, please see Section 9.1.3.5.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event eCRF page. The laboratory reports must be filed with the source documents.

The following tests will be performed by the local laboratory, unless otherwise specified:

- Hematology Panel

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

- Serum Chemistry Panel

During screening and induction and consolidation Cycles 1-6:

-blood urea nitrogen (BUN) or urea
-creatinine
-sodium
-glucose
-AST
-ALT
-alkaline phosphatase
-lactic acid dehydrogenase (LDH)
-potassium
-uric acid
-total bilirubin (direct bilirubin if total bilirubin is abnormal)
-total protein

During maintenance treatment Cycles 7+:

-AST
-ALT
-total bilirubin
-BUN or urea
-creatinine

- Other Laboratory Tests

HBV Serology:

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.

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 SOC within 3 months prior to first dose.

HBV DNA Tests:

Subjects who are positive for Anti-HBc 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 Time and Events Schedule (Table 1). Where required by local law, the results of HBV testing may be reported to the local health authorities.

Serum Pregnancy Test: Women of childbearing potential only. Urine pregnancy test allowed if results from a serum pregnancy test will not be promptly available. Lenalidomide is contraindicated for use during pregnancy, as even a single dose can induce a high frequency of severe and life-threatening birth defects. Guidelines presented in the Celgene lenalidomide pregnancy prevention program as per local lenalidomide labeling must be followed. If pregnancy or a positive pregnancy test does occur, then lenalidomide study treatment must be discontinued immediately, and the subject should be referred to an obstetrician experienced in reproductive toxicity for further evaluation and counselling.

Calcium and Albumin Adjusted Calcium: These parameters will be part of the efficacy evaluations as specified in Section 9.2.3). Albumin will be analyzed by the central and local laboratories. 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.

Indirect Antiglobulin Test (IAT):

Blood type, Rh, and 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 or phenotyping) determined before the first injection of daratumumab along with information on the IAT interference for healthcare 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 interference with IAT by treating reagent RBCs with dithiothreitol (DTT) (Chapuy 2015, Chapuy 2016).

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

a) Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units

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

Uncrossmatched, 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 Investigator's Brochure.

Stem Cell Harvest: For subjects who receive ASCT, record number of CD34+ cells collected and transplanted, agents used for mobilization, and hematopoietic engraftment information.

Pulmonary Function Test: All subjects with known or suspected COPD must have a FEV1 test during Screening. Additionally, all subjects ≥65 years old must have FEV1 and DLCO assessment at Screening for confirmation of eligibility. Refer to Section 6.1.3.2 for details on subjects with higher risk of respiratory complications.

Electrocardiogram (ECG): 12-lead ECGs will be performed as specified in the Time and Events Schedule (Table 1). Whenever 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, then the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Echocardiogram (ECHO)/ Multigated Acquisition (MUGA) scan: All subjects ≥65 years old will have an ECHO or MUGA scan performed to assess LVEF for confirmation of eligibility in Screening.

Physical Examination and Vital Signs: 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 Time and Events Schedule (Table 1). Thereafter, only a symptom and disease directed physical examination is required. Abnormalities will be recorded in the appropriate sections of the eCRF.

Vital signs (heart rate, temperature, blood pressure) will be performed as specified in the Time and Events Schedule (Table 1). 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). Only vital signs taken at screening or associated with an AE will be recorded in the eCRF; all measurements will be recorded in the source documents.

Eastern Cooperative Oncology Group (ECOG) Performance Status: Eastern Cooperative Oncology Group 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.

9.9. Sample Collection and Handling

The actual dates and times of sample collection must be recorded on the laboratory requisition form. Refer to the Time and Events Schedule 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.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. 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.

10.2. Discontinuation of Study Treatment/Withdrawal From the Study

Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the study if he or she must discontinue study treatment; 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 Time and Events Schedule (Table 1).

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment.

- 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 is in the best interests of the subject (at a minimum, lenalidomide must be permanently discontinued if a subject becomes pregnant or has a positive pregnancy test). Discontinuation of all study treatment is also acceptable if mandated by local regulations.
- The subject (or the subject's legally acceptable representative) withdraws consent for administration of study drug.
- The subject experiences unacceptable toxicity, including IRRs described in Section 6.2, Management of Injection-site and Injection-related Reactions.
- The subject experiences disease progression (please see below); loss of CR is not considered as disease progression.
- The subject experiences a new malignancy that cannot be treated by surgery alone (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). Subjects who require radiation therapy for treatment of new malignancy must have study treatment discontinued unless, upon consultation with the sponsor's medical monitor and review of data, continuation is agreed upon. Subjects who require systemic treatment of a new malignancy must end study treatment but should continue to be followed for PFS2 and OS.

The primary reason for discontinuation of study treatment will 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 9.2.1, 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.

Withdrawal From the Study

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
- Sponsor terminates the study

If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a subject withdraws consent before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study treatment assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. 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.

10.3. Withdrawal From the Use of Research Samples

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

11. STATISTICAL METHODS

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.

11.1. Subject Information

The primary analysis population will be the intent-to-treat population, which will include all randomized subjects. Safety will be evaluated for the population of all treated subjects.

Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median 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.

11.2. Sample Size Determination

It is assumed that median PFS is 63 months for the VRd group, and the addition of daratumumab will decrease the risk of progression or death by 31% (HR 0.69; estimated median PFS of 91 months for D-VRd group). To achieve 85% power with a 2-sided alpha of 0.05, 285 PFS events are needed. Assuming a 12-month accrual and 64-month of additional follow-up, approximately 690 subjects (345/arm) will be needed.

Long-term follow-up for survival will continue until approximately 310 deaths have been observed. This will provide approximately 70% power to detect a 25% reduction in the risk of death (HR 0.75) with a log-rank test at a 2-sided alpha of 0.05.

11.3. Efficacy Analyses

Response to study treatment and PD will be evaluated by a validated computer algorithm.

Primary Endpoint

For PFS, the primary analysis will consist of a stratified log-rank test for the comparison of the PFS distribution between the 2 treatment groups. The Kaplan-Meier method will be used to estimate the distribution of overall PFS for each treatment. The treatment effect (HR) and its 2-sided 95% confidence intervals are to be estimated using a stratified Cox regression model with treatment as the sole explanatory variable. In addition, sensitivity analyses, utilizing landmark PFS approach or time-dependent Cox regression method, may also be performed to further characterize the treatment effect.

Secondary Endpoints

Secondary time-to-event efficacy endpoints, including PFS2 and OS, will be analyzed using the same method as for PFS. For OS, the final analysis will occur after approximately 310 deaths have been observed. Earlier analyses, in which OS is analyzed, will be considered as interim analyses. Even if the significance of PFS has already been established, testing of OS will continue as planned until a definitive conclusion on OS is reached. The details about testing of OS over time are specified in Section 11.12.

Comparison between the 2 treatment groups of response-related endpoints at different timepoints and other binary endpoints will be conducted using the stratified Cochran Mantel-Haenszel test. The Mantel-Haenszel odds ratio will be provided along with its 2-sided 95% confidence interval and will be provided as the measure of treatment effect. Time to and duration of response (PR or better), CR/sCR, and MRD negative status will be summarized descriptively without formal statistical comparison.

A hierarchical testing will be used for the secondary efficacy endpoints to achieve strong control of the overall familywise Type I error rate at a 2-sided significance level of 0.05. The details of the testing procedure will be prespecified in a Statistical Analysis Plan that will be finalized prior to the first interim analysis for the primary endpoint.

11.4. Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed on the PK-evaluable population, defined as subjects assigned to Arm B who have received at least 1 dose of daratumumab and have at least one PK 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. All subjects and samples excluded from the analysis will be clearly documented.

Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point and PK parameters of daratumumab: C_{min}, and C_{max}.

If sufficient data are available, then population PK analysis of serum concentration-time data of daratumumab may be performed and may include data from other studies. If the population PK

analysis is conducted, details will be given in a population PK analysis plan and the results of the analysis will be presented in a separate report.

11.5. Immunogenicity Analyses

The incidence of anti-daratumumab antibodies will be summarized for all subjects who receive at least 1 dose of daratumumab and have appropriate samples for detection of anti-daratumumab antibodies (ie, subjects with at least 1 sample obtained after their first dose of daratumumab). The incidence of anti-rHuPH20 antibodies will be summarized for all subjects who receive a dose of daratumumab and have appropriate samples for detection of anti-rHuPH20 antibodies. A listing of subjects who are positive for anti-daratumumab antibodies or anti-rHuPH20 antibodies will be provided.

11.6. Biomarker Analyses

Baseline bone marrow aspirate samples will be evaluated by a NGS 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 (Ladetto 2014) and for cytogenetics evaluations. Several studies have demonstrated that MRD status is correlated with PFS and OS (Martinez-Lopez 2014). In this study, bone marrow and whole blood samples will be collected when a bone marrow aspirate is performed at screening and at the subsequent timepoints outlined in Table 9 and Time and Events Schedule (Table 1). Whole blood sample will be collected from subjects as outlined in the Time and Events Schedule and processed to plasma and peripheral blood mononuclear cells and may be used to evaluate daratumumab's immunomodulatory MoA. Evaluation of MRD in whole blood may be performed to determine the utility in monitoring loss of CR.

11.7. 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.

11.8. Medical Resource Utilization Analyses

MRU 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.

11.9. 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. Full details on meaningful change thresholds and statistical analyses will be provided in the Statistical Analysis Plan.

11.10. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) dictionary. In general, AEs that occurred during the induction/consolidation and maintenance stages will be summarized separately. Treatment-emergent adverse events for each stage will be defined as events that occur or worsen after administration of the first dose of during that stage and through 30 days after the last dose of study drug in that stage and before the next phase of treatment begins. Adverse events will be summarized by system organ class and preferred terms, NCI toxicity grade, and by action taken with study treatment.

Summaries, listings, datasets, or subject narratives will be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe or a SAE event. These will be provided using the same formats as those used for AEs.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point.

Worst toxicity grade during treatment will be presented, per NCI-CTCAE Version 5. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Vital Signs

Descriptive statistics of pulse, temperature, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

11.11. Benefit-risk Analyses

Benefit-risk assessment of daratumumab, bortezomib, lenalidomide, and dexamethasone (D-VRd) vs bortezomib, lenalidomide, and dexamethasone (VRd) will be conducted by comparing between-treatment differences of key efficacy and safety endpoints. Efficacy endpoints may include PFS, PFS2, MRD negativity rate overall and post-consolidation, OS, duration of response and improvement in PRO measures. Safety endpoints may include serious infections (eg, pneumonia, lower respiratory tract infection), atrial fibrillation, diarrhea, injection 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 not in this list, but that show a clinically meaningful between-treatment difference may be included.

For benefit-risk 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 on the benefit-risk assessment will be provided in a separate benefit-risk Statistical Analysis Plan.

11.12. Interim Analysis

Two interim analyses for PFS are planned for this study. The first interim analysis will be performed when approximately 143 PFS events have occurred (corresponds to 50% of the total planned PFS events). The second interim analysis for PFS will be performed when approximately 185 PFS events have occurred (corresponds to 65% of the total planned PFS events). The significance level for superiority and futility (non-binding) at the interim analyses for PFS will be determined based on the observed number of PFS events at each interim analysis, using the Hwang-Shih-DeCani alpha/beta spending function with gamma parameter -2.5. The 2-sided alpha to be spent at the first interim, second interim and final PFS analyses are 0.0112, 0.0126, and 0.0414, respectively.

Descriptive analysis of OS was performed at the time of the first PFS interim analysis. After the superiority of PFS has been established at the first PFS analysis, 2 formal interim OS analyses will be conducted. The first interim OS analysis will be performed when approximately 285 PFS events (approximately 170 OS events; 55% of the total planned OS events) have occurred. The second interim OS analysis will be performed when approximately 233 OS events have occurred (75% of the total planned OS events). The final OS analysis will be at the end of the study or after approximately 310 deaths have been observed. A Pocock alpha spending function will be used to determine the OS stopping boundary at each interim analysis based on the observed number of deaths at that time.

11.13. Independent Data Monitoring Committee

An IDMC, consisting of 2 clinicians and 1 statistician who are independent experts not otherwise participating in the study, will be established to review safety results after approximately 100 subjects have completed the induction phase (ie, Cycle 1 through Cycle 4) plus stem cell mobilization and again after approximately 100 subjects have completed the consolidation phase (ie, Cycle 5 and Cycle 6). In addition, the IDMC will review cumulative safety data on a regular basis before the primary PFS analysis. After each of these reviews, the IDMC will make recommendations regarding the continuation of the study. The details will be provided in a separate IDMC charter. At the first interim analysis of PFS, the primary endpoint was met, and the study data were unblinded. No new safety signals were observed. No further IDMC meetings will be scheduled after the primary endpoint was met. Safety data will continue to be reviewed by the sponsor. The medical monitors will remain blinded regarding OS.

12. ADVERSE EVENT REPORTING

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.

12.1. Definitions

12.1.1. 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 treatment. 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 International Conference on Harmonisation [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 Section 12.3.1, All Adverse Events, 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).

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

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.

12.1.3. 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 will be graded according to investigator clinical judgment by using the standard grading as outlined in the CTCAE version 5.

12.2. Special Reporting Situations

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

- Overdose of a sponsor study drug. No maximum tolerated dose 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/patient 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 eCRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the serious adverse event page of the eCRF.

12.3. Procedures

12.3.1. 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 final dose of study treatment with the exception of the transplant period (see Section 9.1.3.5 for specific AEs to be reported). 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 multiple myeloma within 30 days after the final dose of any component of the treatment regimen. 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 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).

SAEs, including those spontaneously reported to the investigator within 30 days after the last dose of 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.

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.

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

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. 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 eCRF 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.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). 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.

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

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a SAE should be transmitted electronically or 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 eCRF). 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 SAE.

- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment 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 (see Section 12).

12.3.3. 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 or experiences a positive pregnancy test during the study must discontinue lenalidomide study treatment. Discontinuation of all study treatment is also acceptable if mandated by local regulations. Because the effect of the study treatment on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above. Investigators should follow the local label for guidance on subject education and ensure that all subjects adhere to the lenalidomide Global Pregnancy Prevention Plan. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. 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.

13. 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.

13.1. 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 12.3.2 Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contact Information 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.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug

The daratumumab supplied for this study is a colorless to yellow liquid and sterile concentrate of 120 mg/mL in a vial. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

14.2. Packaging

Daratumumab is supplied in glass vials containing daratumumab at a concentration of 120 mg/mL.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. Each vial will contain a study-specific label with a unique identification number.

14.4. Preparation, Handling, and Storage

All study drug vials must be stored in the original carton in a refrigerator ranging from 2°C to 8°C and must not be utilized after the expiry date printed on the label. The product must be protected from light and must not be frozen. Daratumumab does not contain preservatives; therefore, any unused portion remaining in the vial must be discarded.

Refer to the IPPI and Pharmacy Manual for details regarding dose preparation, storage, and handling of diluted solutions.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the subject must be documented on the drug accountability form. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return to the sponsor of unused study drug

will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Study Protocol
- Investigator's Brochure
- Site Investigator Product Procedures Manual (sIPPM)
- Investigational Product Preparation Instructions (IPPI)
- Laboratory manual and laboratory kits
- Electronic data capture (eDC) Manual
- Sample ICF Trial Center File, and corresponding site-specific documentation
- Subject study tools, emergency ID card etc, (as applicable per country)
- Investigator study tools and quick reference cards, as required
- NCI-CTCAE Version 5
- PRO questionnaires and user manuals: PRO questionnaires will include the EORTC QLQ-C30, EORTC QLQ-MY20, and the EQ-5D-5L. Sample questionnaires are provided in Attachment 10, Attachment 11, and Attachment 12, but should not be used for collection of subject data
- IWRS Manual

16. ETHICAL ASPECTS

16.1. Study-specific Design Considerations

Despite significant progress in the treatment of patients with multiple myeloma, it still remains uncured, indicating the need for new therapeutic strategies for these patients. Daratumumab has already shown marked activity as a monotherapy in heavily pre-treated patients. Its approval by the FDA in 2016, when used in combination with lenalidomide and dexamethasone, or bortezomib

and dexamethasone, highlights the potential clinical benefit of daratumumab as a backbone therapy for the treatment of patients with multiple myeloma who have received at least 1 prior therapy. Further, the approval by the FDA in 2018 of daratumumab in combination with bortezomib, melphalan, and dexamethasone for the treatment of patients with newly diagnosed multiple myeloma, highlights the potential benefit of daratumumab in combination with backbone therapy for the treatment of newly diagnosed patients. The combination of daratumumab with bortezomib, lenalidomide, and dexamethasone, is also likely to provide clinical benefits to patients with newly diagnosed multiple myeloma.

Several other protein therapeutics are approved for SC administration in combination with rHuPH20. Dara-SC is given as an injection over approximately 3 to 5 minutes as compared with the 4 to 7-hour IV infusion time for Dara-IV. Further, Dara-SC is given in a volume of 15 mL vs 500-1000 mL infusion volume for Dara-IV. Study MMY1004 provided preliminary safety and efficacy data which suggest that, in patients with multiple myeloma, SC administration of daratumumab may enable similar or better response rates compared with Dara-IV. Furthermore, to date, the rate of IRRs with Dara-SC administration has been substantially lower than the rate reported with Dara-IV administration. Dara-SC, which will be used in Study MMY3014, will offer several tangible benefits for both patients and health care providers, as described above.

An IDMC will be established to review safety data on a regular basis throughout the duration of the study as well as at 2 planned PFS interim analyses. Based on the data presented in Section 1.2, 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 Section 16.2.3, a legally acceptable representative may provide consent on behalf of the subject.

Blood volumes drawn for all phases of the study are provided in Section 9.1.1. The total blood volume to be collected is considered to be acceptable for subjects participating in a cancer clinical study and reasonable over the time frame of the study.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

GCP 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.

16.2.2. 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).

16.2.3. Informed Consent

Each subject (or a legally acceptable 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 acceptable 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 or 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 acceptable 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 acceptable 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 acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject or legally acceptable 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 acceptable representative is obtained.

When prior consent of the subject is not possible and the subject's legally acceptable 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 acceptable representative must be informed about the study as soon as possible and give consent to continue.

16.2.4. 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 acceptable representative) includes information about, and where required per applicable regulations, 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, or make requests concerning his or her personal data in accordance with applicable data protection law. 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.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

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.

16.2.5. Long-term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand daratumumab, to understand multiple myeloma, to understand differential drug responders, and to develop tests/assays related to daratumumab and multiple myeloma. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Use of Samples in Future Research).

16.2.6. 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 16.1, Study-specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. 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) involves 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 eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. 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.

17.2.2. 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

17.3. 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 enrolled into the study, the date seen and age at initial informed consent will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

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 all AEs and follow-up of AEs; concomitant medication; drug 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 minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- 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 electronic source 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 are electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All eCRF 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 eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, 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 eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into the eCRF in English. The eCRF 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 subjective 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 an eCRF are needed after the initial entry into the eCRF, 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.

17.6. 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 eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review the eCRF 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.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF 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.

17.8. 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 the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF 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.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed when 310 deaths have been observed or when the sponsor decides to stop the study (whichever occurs earlier). The sponsor will ensure that subjects benefiting from treatment with daratumumab will be able to continue receiving treatment after the end of the study. 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.

17.9.2. 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

17.10. 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.

17.11. Use of Information and Publication

All information, including but not limited to information regarding daratumumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The study site and investigator agree to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The study site and investigator understand that the information developed in the study will be used by the sponsor in connection with the continued development of daratumumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study

site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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 PFS interim analysis 1, as described in Section 11.12, may be submitted to the EU database within 1 year of the intermediate data analysis date.

The summary of the results from the OS interim analyses 1 and 2, as described in Section 11.12, may be submitted to the EU database within 1 year of the intermediate data analysis date.

The disclosure of the study results will be performed after the end of study per local regulatory requirements.

18. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

18.1. Appendix 1: Protocol Amendment History

Amendment 4 (27 June 2022)

The overall reason for the amendment: The key reasons for this protocol amendment are to align study visits with disease evaluation visits for both study arms, to include protocol text with respect to COVID-19 vaccines and guidance during the COVID-19 pandemic or another natural disaster, to update protocol text to align with EU CTR requirements including merging country-specific amendments into this Protocol Amendment 4, and to allow next-generation flow (NGF) in the Maintenance phase for determination of minimal residual disease (MRD) status to guide stopping/restarting of daratumumab. Other changes include minor corrections, additional clarifications, and consistency updates.

Applicable Section(s)	Description of Change(s)
Rationale: To align study and disease evaluations visits and for clarification purposes.	
Table 1 (Time and Events Schedule)	Added *italicized* text; removed strikethrough text for footnote "a": For subjects who discontinue treatment prior to C7D1 without confirmed PD, • Disease Evaluations *should be performed* every 4 weeks (±7 days) *relative to C1D1 until confirmed PD*. • ~~and~~ ECOG PS (including PRO and Medical Resource Utilization) *should be performed* every 12 weeks (±14 days) relative to *C1D1* until confirmed PD; For subjects who discontinue treatment after C7D1 without confirmed PD, • Disease Evaluations *should be performed* every 4 weeks (±7 days) for first year relative to C7D1 then every 8 weeks (±~~7~~ *14* days) *until confirmed PD*. • ~~and~~ ECOG PS (including PRO and Medical Resource Utilization) *should be performed* every 12 weeks (±14 days) for first year relative to C7D1, then every 16 weeks (±14 days) relative to C7D1 thereafter, until confirmed PD. Footnote "i" (new) added to Vital Signs, Weight, Hematology, Serum Chemistry, and Medical Resource Utilization: After 24 months of maintenance therapy, vital signs, weight, hematology, serum chemistry, and medical resource utilization may be performed every 8 weeks for subjects who are not receiving daratumumab.
Rationale: To incorporate the previously issued COVID-19 appendix. Text within the COVID-19 appendix and within the body of the protocol was updated to mitigate the impact of the COVID-19 pandemic and natural disasters on study conduct/procedures and to provide guidance on COVID-19 vaccinations.	
8.2.Permitted Therapies	Text updated to include COVID-19 vaccines permitted for study use. Updated text clarifies live, attenuated vaccines or those with suspected replication capabilities are not permitted. Also added text to clarify that COVID-19 vaccinations should not be administered on the same day as study treatment administration.
8.3.Prohibited Therapies	Italicized text added; strikethrough text removed: Administration of *investigational*, live attenuated*, or replication competent viral vector* vaccines *<4 weeks prior to the start of* ~~during~~ study treatment, *during study treatment,* or *initiated* ~~within~~ <90 days after last dose of study treatment *are prohibited*.
Attachment 13: COVID-19 and Natural Disaster Guidance on Study Conduct and COVID-19 Vaccine Timing	Attachment 13 (new) – incorporated the previously issued COVID-19 appendix and added guidance on study conduct during the COVID-19 pandemic or another natural disaster. This new attachment also includes guidance on COVID-19 testing, COVID-19 vaccine timing, COVID-19 prevention and treatment, and COVID-19 resources.

References	Added Ariza-Heredia literature reference.
Rationale: To align with EU CTR requirements.	
Synopsis; 1.5.Benefit-risk Assessment (new)	Added text for benefit/risk
16.2.4.Privacy of Personal Data	Updated text to align with latest departmental template.
Rationale: Merge country-specific changes into global amendment; health authority request.	
4.2.Exclusion Criteria	Added text clarifying that HIV antibody testing at screening should be performed per local health guidelines.
10.2.Discontinuation of Study Treatment/ Withdrawal From the Study; 12.3.3.Pregnancy	Added text clarifying that discontinuation of all study treatment in case of pregnancy is acceptable if mandated by local regulations.
Rationale: To allow NGF for determination of MRD status in subjects who cannot use NGS	
6.1.2.Daratumumab Administration	Moved text related to definition of MRD-negative subjects. Also removed reference to NGS for MRD-negativity threshold. Added *italicized* text: *For subjects in Arm B whose MRD negativity at 10^{-5} threshold cannot be determined by NGS (due to lack of MRD index clone or non unique clone sequence), MRD by next generation flow (NGF) may be used to guide daratumumab stopping and restarting in agreement with the sponsor.*
9.5.Biomarkers/EMN Correlatives	Added *italicized* text; removed strikethrough text: If baseline clonality is ~~still~~ not established *or for subjects with non unique clone sequence*, no further bone marrow samples should be collected for MRD assessments *for* ~~patients~~ *subjects in the VRd arm, however subjects in the D VRd arm without baseline clonality or with non unique clone sequence may have MRD assessment by NGF for the purpose of determining daratumumab continuation.*
Rationale: To provide additional clarification and/or improve readability and/or align with protocol text.	
Synopsis; 3.1.Overview of Study Design	Added/modified text to clarify that subjects with a response of CR or better (in Arm B) will stop daratumumab after sustained MRD negativity for 12 months and a minimum of 24 months of maintenance therapy.
3.1.Overview of Study Design	Added text regarding evidence of IMWG-defined disease progression
3.1.Overview of Study Design	Added PRO assessments to list of data collected/recorded.
3.2.Study Design Rationale	Added *italicized* text; removed strikethrough text: Daratumumab is planned to be discontinued during the maintenance phase in subjects who achieve sustained MRD negativity (10^{-5}) for at least ~~1 year~~ *12 months and* after receiving at least ~~2 years~~ *24 months* of maintenance treatment. Updated text with respect to recurrence of MRD and restarting daratumumab.
Figure 1 (Schematic Overview of the Study)	Added text regarding monitoring for new malignancies, subsequent treatment and PROs; spelled out 24 months (*from 24 mos*)

6.1.2.Daratumumab Administration	Added *italicized* text; removed strikethrough text: *All subjects who stop daratumumab due to sustained* MRD-negativ*ity* ~~subjects are defined as those who achieve CR or better and achieve MRD negativity (based on the NGS 10^{-5}). These subjects~~ will be monitored for loss of CR (Table 7) by urine and serum *M protein by central laboratories* or development of ≥5% plasma cells in the bone marrow *by local laboratories* as outlined in the Time and Events Schedule (Table 1) and IMWG criteria as well as MRD status via bone marrow aspirate *by central laboratories* as per Table 1 and Table 8. Upon *confirmed* loss of CR or ~~loss~~ *recurrence* of MRD ~~negative status (~~at 10^{-4}~~)~~ or higher, subjects must restart daratumumab ~~with the following treatment regimen~~ until disease progression or unacceptable toxicity. Added text regarding stopping of lenalidomide due to toxicity, subjects will stop daratumumab and continue study assessments per treatment phase requirements. Added *italicized* text: *As this is a restart of daratumumab,* subjects will receive pre-administration medications and post-administration medications as outlined in Section 6.1.3 *to prevent the reoccurrence of infusion related reactions.* *NOTE: Once treatment with lenalidomide is stopped due to toxicity, it cannot be restarted.* Added bullets to text regarding re-initiation of daratumumab treatment.
8.3.Prohibited Therapies	Added *italicized* text; removed strikethrough text: Systemic corticosteroids (>10 mg ~~prednisone~~ *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 *is prohibited*.
8.4.Subsequent Therapies	Added text to clarify that local laboratory can be used for additional testing following confirmation of disease progression.
9.1.5.Posttreatment Phase (Follow-up)	Added *italicized* text; removed strikethrough text: For subjects who discontinue study treatment without disease progression prior to transplant, disease evaluations at the central lab should continue to be performed as specified in the Time and Events Schedule (Table 1) until documented disease progression~~, even if subject initiates subsequent anti-cancer therapy~~. *Subsequent antimyeloma therapy must not start until after disease progression is confirmed per IMWG criteria (see Table 6) and approved in the IWRS system (see Table 6) and approved in the IWRS system.* Subsequent anticancer treatment and *the associated* response to treatment *by local laboratories*, including date of subsequent progression (PFS2) will be recorded ~~and survival status will be obtained.~~ Added text indicating survival status will be obtained every 16 weeks. Added note indicating subjects who stop daratumumab due to sustained MRD-negativity should continue study assessments/stay on study (Arm B).

	Added *italicized* text; removed strikethrough text: For all subjects ~~who complete~~ or discontinue study drug without disease progression, disease evaluations *by central laboratory* should continue to be performed as specified in the Time and Events Schedule (Table 1) until documented disease progression.
9.2.2.Myeloma Protein Measurements in Serum and Urine	Added clarification that daratumumab interference on serum IFE is applicable to subjects *in Arm B*.
Rationale: To align protocol text with recent label updates.	
4.3.Prohibitions and Restrictions	Added *italicized* text; removed strikethrough text: Subjects must not donate blood during therapy and for at least ~~4 weeks~~ *3 months* following discontinuation of ~~lenalidomide~~ *all study treatment*.
Rationale: To consolidate bone marrow assessments and assessments to confirm sCR; clarification.	
Table 1 (Time and Events Schedule)	Added *italicized* text: *Bone marrow samples will be collected in subjects with VGPR or better at the time of suspected CR/sCR to confirm CR/sCR*. See Table 8 *for details.*
Rationale: To provide additional clarification with respect to the collection of bone marrow samples.	
Table 1 (Time and Events Schedule)	Added text to footnote "g" to clarify that when baseline clonality is not established, no further bone marrow is to be collected for Arm A. Also, added text to clarify that when there is no baseline clonality or there is a non-unique clone sequence, subjects in Arm B can continue to have bone marrow collected for MRD for the determination of daratumumab continuation.
Rationale: To correct protocol text.	
Table 1 (Time and Events Schedule); 3.1.Overview of Study Design; 10.2.Discontinuation of Study Treatment/ Withdrawal From the Study	Changed "second primary malignancy" to "new malignancy"
Table 6 (IMWG Consensus Recommendations for Multiple Myeloma Treatment Response Criteria)	Removed text regarding bone marrow plasma cell percentage under Progressive Disease Response category
1.1.3.VRd as Backbone Therapy Throughout Treatment; References	Literature reference updated: Rosinol 2017 updated to Rosinol 2019.
Rationale: General updates.	
Title page	Updated confidentiality statement.
All pages	Added FOIA Exemption footer.
Rationale: Minor grammatical, formatting, or spelling changes were made.	

Throughout the protocol	Synopsis – added italicized text: After stopping daratumumab therapy, subjects with sustained MRD negativity should restart therapy with daratumumab if there is a recurrence of MRD at 10^{-4} or higher or a confirmed loss of CR without disease progression, as evidenced by *the* reappearance of serum or urine monoclonal protein (M-protein) or increase to ≥5% plasma cells in bone marrow. Table 1 – added italicized text; removed strikethrough text: Every 4 months (EQ-5D-5L only), *at s*~~S~~tart of subsequent therapy and 4 weeks after start of subsequent therapy Synopsis (abbreviations updated)

Amendment 3 (20 March 2020)

The overall reason for the amendment: to remove language related to anticipated adverse events and align text with the daratumumab program standard language.

Applicable Section(s)	Description of Change(s)
Rationale: To provide clarity on sampling requirements for MRD evaluations.	
Table 1	Separate line items were created/text was updated to distinguish unique MRD sampling requirements for whole blood and bone marrow aspirates.
Rationale: Language related to anticipated adverse events is being removed from the protocol since this refers to a Janssen procedure which is not being utilized in this study. EMN, as the sponsor of the study, has been and will continue to determine the regulatory reporting of SAEs per health authority regulatory guidance as per their standard process.	
12.1.1.Adverse Event Definitions and Classifications; 12.3.1.All Adverse Events; Attachment 13 (Anticipated Events)	Removed text and attachment related to anticipated adverse events.
Rationale: To eliminate the possibility of inconsistency between the NCI-CTCAE version number referenced in the protocol and the standard AE grade description included in the protocol.	
12.1.3.Severity Criteria	Removed definitions of severity criteria as they are specific in NCI-CTCAE v5.
Rationale: To ensure extramedullary plasmacytoma assessment occurs per protocol. Text was also modified for additional clarity.	
Table 1	Additional clarification was added for extramedullary plasmacytoma assessment requirements when performed by physical exam or by radiologic exam.
9.2.8.Documentation of Extramedullary Plasmacytomas	Text was added to further clarify that extramedullary plasmacytoma assessments are required every 12 weeks starting from Cycle 1 Day 1 until disappearance of the plasmacytoma or confirmed disease progression. Also, text was modified to better clarify sampling requirements following the disappearance of plasmacytoma.
Rationale: To allow for archival samples to be submitted for subjects whose baseline clone was not established and when calibration continues to fail, no further bone marrow samples should be collected for MRD assessments.	
9.2.5.Bone Marrow Examination; 9.5.Biomarkers/EMN Correlatives; Table 1	Text was added to specify that archived samples will not be accepted for MRD or cytogenetic evaluation at screening and may be requested to be sent to the central laboratory, if available, in cases in which there is difficulty establishing baseline clonality for MRD. If baseline clonality is still not established, no further bone marrow samples should be collected for MRD assessments.
Rationale: Text was updated to align with the daratumumab program standard protocol text, where applicable.	
6.1.2.Daratumumab Administration; 16.1.Study-specific Design Considerations	Bolded text was added: Daratumumab (1800 mg) will be administered by SC injection by manual push over **approximately** 3 to 5 minutes in the abdominal SC tissues in left/right locations, alternating between individual doses.
9.8.Safety Evaluations; 10.2.Discontinuation of Study Treatment/ Withdrawal From the Study; 12.3.3.Pregnancy	Modified text to align with daratumumab program standard protocol text related to pregnancy.

Applicable Section(s)	Description of Change(s)
10.2.Discontinuation of Study Treatment/ Withdrawal From the Study	Bolded text was added: The subject experiences a second primary malignancy that cannot be treated by surgery alone (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). **Subjects who require radiation therapy for treatment of second primary malignancy must have study treatment discontinued unless, upon consultation with the sponsor's medical monitor and review of data, continuation is agreed upon. Subjects who require systemic treatment of a new malignancy must end study treatment but should continue to be followed for PFS2 and OS.**
Rationale: Text was modified throughout for alignment with other protocol sections and/or for improved readability/clarity.	
Synopsis	Bolded text was added; strikethrough text was removed: Subjects will ~~then~~ start maintenance therapy (Cycle 7+), during which they will receive lenalidomide 10 mg daily PO on Days 1 to 28 (continuously) of each 28 day cycle until disease progression or unacceptable toxicity.Dexamethasone will be administered PO at 40 mg on Days 1-4 and 9-12 during Cycles 1-6 **as part of the VRd backbone regimen**.
Table 1; 9.1.3.7.Post-consolidation Efficacy Assessment	Clarification of subjects with a response of VGPR or better was added to Section 9.1.3.7.
Table 1	Text was updated for whole blood MRD evaluations: bolded text was added; strikethrough text was removed: For subjects who achieve CR/**sCR** and ~~are still~~ **remain** on the study, additional samples will be collected every 3 months (±1 month of another collection) from 12 months to 36 months post-C1D1 and ~~then~~ yearly thereafter. Also, bolded text was added; strikethrough text was removed: **It is recommended that** PRO measures ~~should be~~**are** completed before any other study procedures are performed on the day of the visit. **It is advised that PRO measures are completed before any conversation on status with the health care provider.** Text was added advising sites to recalculate the bortezomib dose when a subject's weight has changed ±10% from baseline. Footnote a was updated to include assessment windows and text was added which clarifies follow-up requirements for subjects who decline any further follow-up except survival status. An assessment window was added to the ECOG performance status maintenance phase Day 1. Footnote e was modified to clarify sampling to occur prior to C7D1 study drug administration. Footnote g was added which provides clarification on the use of archived samples for establishing baseline clonality for MRD. Footnote h was added which provides clarification that all subjects will have EMN correlative completed post-consolidation and at disease progression.
Table 2	Text in footnote a – "study drug" was changed to "daratumumab".
1.2.1.Intravenous Daratumumab Administration in Combination Therapy Studies	Non-applicable text was removed "results of this study are not yet available". Also, text was corrected to include bortezomib for summary of Study MMY3006. Also, the abbreviation of "VTd" was correct to "D-VTd".
2.1.2.Endpoints	The definition of duration of response was updated to include text clarifying the calculation should also include the timepoint until death due to PD.

Applicable Section(s)	Description of Change(s)
6.Dosage and Administration	Text was added to clarify treatment cycles are 28 days. Also, dexamethasone was added to the dosing window previously described for bortezomib only.
6.1.2.Daratumumab Administration	Table cross-references were added. Text was added to clarify that daratumumab doses will remain constant throughout the study. Also bolded text was added; strikethrough text was removed: These subjects will be monitored for loss of CR **(Table 7)** by urine and serum **or development of ≥5% plasma cells in the bone marrow** as outlined in the Time and Events Schedule (Table 1) and **IMWG criteria as well as** MRD status via bone marrow aspirate as per **Table 1 and** Table 8. Bolded text was added: Subjects in Arm B who have a post-ASCT recovery period that requires greater than 12 weeks off daratumumab **and skip consolidation** should restart therapy on the following schedule: daratumumab dosing every 2 weeks for 4 doses (Cycles 7-8 of maintenance therapy) then continue every 4 weeks, thereafter (for Cycles 9+). Strikethrough text was removed since details are summarized in other sections in the protocol: ~~Every effort should be made to keep subjects on the planned dosing schedule. However, doses given within 3 days of the scheduled Day 1 dose are permitted. All treatment cycles are 28 days.~~
6.1.3.2.Daratumumab Post-administration Medication	The text “VRd” was added.
6.2.2.3.Recurrent Infusion-related Reactions	Text was added to clarify that long daratumumab dose interruptions could result in reoccurrence of infusion-related reactions.
6.3.2.Lenalidomide Administration	Text was updated: bolded text was added; strikethrough text was removed: Lenalidomide will be administered PO at 25 mg on Days 1 to 21 in Cycles 1-6; four 28-day induction cycles and two 28-day consolidation cycles. ~~Following consolidation, s~~Subjects will ~~then~~ start maintenance therapy~~, during which they will receive lenalidomide~~**at** 10 mg daily PO on Days 1 to 28 (continuously) of each 28-day cycle until disease progression or unacceptable toxicity.
6.3.3.Dexamethasone Administration	The text “as part of the VRd backbone regimen” was added.
6.4.1.Cycle Delay	Strikethrough text was removed: ~~During the cycle delay, daratumumab, bortezomib, dexamethasone and lenalidomide, (all applicable) must be held.~~
6.4.2.1.2.Daratumumab-related Toxicity Management	Text was updated to reflect daratumumab dose holds exceeding 28 days will require consultation with the sponsor to determine continuation of dosing (changed from requiring permanent discontinuation of daratumumab).
8.4.Subsequent Therapies	Text was updated to include additional data collection requirements for subsequent therapy for multiple myeloma treatment.

Applicable Section(s)	Description of Change(s)
9.1.3.2.Mobilization and Harvesting Stem Cells	Bolded text was added: Stem cell mobilization should be performed **within 6 weeks** after completion of Cycle 4 using local standard of care. Also, additional guidance was added regarding plerixafor treatment for suspected inadequate mobilization. Also, bolded text was added; strikethrough text was removed: The use of a second mobilization as per local standard of care or alternatively a bone marrow harvest ~~is permitted~~ **should occur to ensure adequate stem cell yield as** per institutional practice, if the stem cell yield is deemed to be sub-optimal per investigator discretion.
9.1.3.3.Conditioning (Melphalan off Study as per Standard of Care)	Bolded text was added; strikethrough text was removed: Subjects **should proceed to conditioning within 2 weeks after stem cell mobilization. Subjects** will receive melphalan 200 mg/m^2 as conditioning therapy over a period of 24 to 48 hours prior to ASCT. Melphalan may be given at a lower dose of 140mg/m^2, per institutional standards~~, if the subject has~~ **(ie,** renal insufficiency**)**.
9.1.3.4.Transplant (as per Standard of Care)	Bolded text was added; strikethrough text was removed: ~~Autologous stem cell transplant should be completed within approximately 6 weeks after stem cell mobilization/harvest.~~ There should be ~~approximately~~ **no more than** 12 weeks between end of induction and transplant.
9.1.3.5.Engraftment/ Recovery	Bolded text was added; strikethrough text was removed: Subjects will be monitored for successful engraftment **by means of hematopoietic reconstitution** (~~ie,~~**defined as** ANC ≥0.5 x 10^9/L and platelet count ≥20 x 10^9/L). Also, text was updated to include additional data collection requirements and to updated text from "at the start of consolidation" to "during this period".
9.1.3.6.Consolidation (Cycles 5-6)	Bolded text was added; strikethrough text was removed: Consolidation therapy ~~may~~**should** commence **within 12 weeks of transplant** when engraftment is complete **(defined as ANC ≥0.5 x 10^9/L** and **platelet count ≥20 x 10^9/L)** and when in the opinion of the investigator the subject is fit enough to tolerate subsequent systemic therapy **(30-60 days post ASCT). In addition, subjects also need to** ~~and~~ meet~~s~~ the consolidation start criteria in Section 6.4.1. Subjects will receive two 28-day cycles of VRd as described in Section 6.3. Subjects assigned to Arm B will receive daratumumab as described in Section 6.1.2. For subjects who ~~are unable to initiate consolidation therapy due to delayed~~achieve ~~immune~~**hematopoietic** reconstitution (~~ie, ANC ≥0.5 x 10^9/L and platelet count ≥20 x 10^9/L) exceeding~~>12 weeks after ASCT, **should discuss**~~, subjects may proceed to maintenance therapy upon discussion~~ **continuation to consolidation versus maintenance therapy** with the **sponsor's** medical monitor. Efficacy will be assessed at the start of each cycle.
9.1.5.Posttreatment Phase (Follow-up)	Bolded text was added; strikethrough text was removed: **After documented disease progression, follow-up information will be obtained every 16 weeks (±14 days). The every 16-week follow-up contacts should be scheduled from the date of confirmed disease progression.** ~~Thereafter s~~**S**ubsequent anticancer treatment and response to treatment including date of subsequent progression (PFS2) will be recorded and survival status will be obtained.
9.2.1.Response Categories	Text was added which clarifies that subjects who meet criteria for discontinuation of daratumumab in Arm B will be followed for loss of CR; subjects who meet criteria for loss of CR without disease progression will restart daratumumab as per protocol. Also, text was added to specify that the criteria for loss of CR without disease progression only applies to subjects in Arm B who meet the criteria as per protocol.

Applicable Section(s)	Description of Change(s)
Table 6	Text was updated to remove MR response and footnote updated to align with IMWG criteria used for this protocol. Also, normal ranges for FLC ratio were removed since testing is performed by a central laboratory.
Table 7	Table title was updated to specify applicability to Arm B. Also, bolded text was added: Reappearance of serum M-protein by immunofixation or electrophoresis **(any value without confirmed PD)**; Reappearance of urine M-protein by immunofixation or electrophoresis **(any value without confirmed PD)**.
Table 8	For clarity, text was restructured/text was bulleted/bolded and text for bone marrow testing during treatment was updated to include applicability during follow-up. Also, bolded text was added; strikethrough text was removed: • **During** post-consolidation[b] in subjects with VGPR or better. • A~~dditional bone marrow aspirates will be collected a~~t the time of suspect CR/sCR~~ and~~ • For subjects who achieve CR/**sCR**, have not progressed~~,~~ and remain on the study, additional bone marrow aspirate will be obtained at 12, 18, 24, 30, and 36 months post Cycle 1 Day 1 (±1 month) and yearly thereafter (±1 month).[c] • ~~A portion of the bone marrow may be used for additional biomarker assessments~~ **EMN correlative studies: Bone marrow aspirates will be collected:** -If feasible, for all subjects during post-consolidation and at disease progression. Also, text was added to clarify that archived samples may be requested/used when the MRD index clone is not identified at screening. Footnote c was updated to clarify applicability for MRD sampling.
9.2.6.Minimal Residual Disease Assessment; 11.6.Biomarker Analyses	Text was updated to clarify both bone marrow and whole blood samples are collected for MRD assessments. Also, a note was added to Section 9.2.6 to clarify bone marrow and whole blood sampling requirements for subjects who achieve CR/sCR.
9.7. Patient-reported Outcomes	The following sentence was added: PRO measures should be completed before any conversation on status with the health care provider.
9.8.Safety Evaluations	Bolded text was added: For subjects who receive ASCT, record number of CD34+ cells collected **and transplanted**, agents used for mobilization, and hematopoietic engraftment information.
10.2.Discontinuation of Study Treatment/ Withdrawal From the Study	The following text was removed to align with other sections of the protocol: 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 unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.
12.3.1.All Adverse Events	Bolded text was added; strikethrough text was removed: 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 final dose of study ~~drug~~ **treatment with the exception of the transplant period (see Section 9.1.3.5 for specific AEs to be reported).**
Rationale: Throughout the protocol, minor edits were applied.	
Table 1	Abbreviation added (BM=bone marrow) and bolded text was added to ECOG performance status at maintenance phase (Day 1): C7D1 then every 12 **weeks**.

Applicable Section(s)	Description of Change(s)
5.Treatment Allocation and Blinding; 6.4.1.Cycle Delay; 6.4.2.Dose Modification Guidelines; 9.1.3.6.Consolidation (Cycles 5-6)	For consistency, the word “sponsor’s” was added prior to “medical monitor”
6.1.3.1.Daratumumab Predose Medication; 6.1.3.2.Daratumumab Post-administration Medication; 6.2.1.Daratumumab Local Injection-Site Reactions; 6.2.2.Daratumumab Infusion-related Reactions	Title headings were updated to include “Daratumumab”
6.3.2.Lenalidomide Administration	The text “should be” was changed to “is”.
6.4.1.Cycle Delay	In 2 instances, “must” was changed to “should”. Also, a cross reference to Table 5 was added.
6.4.2.1.1.Daratumumab Dose Modification	Strikethrough text was removed: Individual dose modification of daratumumab is not permitted, ~~but~~ dose delay is recommended as the primary method for managing daratumumab-related toxicities.
9.5.Biomarkers/EMN Correlatives	FACs was updated to FAC**S**
Attachment 6	Strikethrough text was removed: ~~I~~Intermediate-Acting

Amendment 2 (09 April 2019)

The overall reason 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, secondary endpoints, dosing, as well as other measurement parameters throughout the Protocol. Revisions noted below are representative of the changes; new text is displayed in bold font, and deleted text is noted with strikethrough.

Applicable Section(s)	Description of Change(s)
Rationale: The text for identification of HBV reactivation, testing, and management of subjects with the potential for HBV reactivation was added or modified in response to identification of a new important risk (HBV reactivation).	
Table 1 Time and Events Schedule	Added row for HBV serology, modified text for HBV DNA test, and identified the timepoints at which HBV serology and HBV DNA test would be conducted.
4.2 Exclusion Criteria (Criterion 9)	Clarified language to exclude subjects who are seropositive for hepatitis B and hepatitis C.
8.1.7 Management of Hepatitis B Virus Reactivation	Added a new section providing information for the management of hepatitis B virus (HBV) reactivation.
9.8 Safety Evaluations	Added and revised information detailing the conduct of hepatitis B virus serology and DNA tests.
9.1.1 Overview	Modified the total blood volume collected for the study to 95 mL.
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.
Rationale: Modification was made to the Secondary Endpoints.	
2.1.2 Endpoints	Post-consolidation secondary endpoints were removed to eliminate duplication with previous endpoint: ~~Post-consolidation ORR, rate of VGPR or better rate of CR or better, and rate of sCR, defined as the proportions of subjects who achieved PR or better (or VGPR or better, or CR or better, or sCR) by the end of consolidation per the IMWG criteria.~~
Rationale: Clarification was provided regarding contraception and the prohibition of treatment with lenalidomide during known pregnancy or potential for pregnancy.	
Table 1 Time and Events Schedule	Table 1 (Urine or serum pregnancy test) was updated to include pregnancy testing at the End-of-Treatment Visit, for consistency with Section 4.3.
4.1 Inclusion Criteria (Criterion 7)	The text of the Criterion was modified for clarity and readability.

Applicable Section(s)	Description of Change(s)
4.3 Prohibitions and Restrictions	Modification to Restriction 1: Contraception must begin 4 weeks before initiating treatment **in the study** ~~with daratumumab~~, 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. Modification to Restriction 3: **All Investigators will comply with the respective Celgene country-specific Revlimid Risk Minimization Program (ie, pregnancy prevention program) as implemented in the post-marketing setting.** ~~All subjects must adhere to the local lenalidomide Risk Evaluation and Mitigation Strategy (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).~~ Modification to Restriction 4: Additional pregnancy tests may be required, as specified in the **Celgene country-specific Revlimid Risk Minimization Program (ie, pregnancy prevention program).** ~~local lenalidomide 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).~~
9.8 Safety Evaluations	Modified language for Serum Pregnancy Test: If pregnancy does occur, then **lenalidomide** study treatment ~~should~~ **must** be discontinued immediately
12.3.3 Pregnancy	Modified sentence for clarity: Any subject who becomes pregnant during the study must ~~be promptly withdrawn from the study and discontinue further~~ **discontinue lenalidomide** study treatment.
Rationale: Modifications, clarifications, and corrections were made to screening, laboratory, and disease assessments.	
Table 1 Time and Events Schedule	Revised timing for ECOG performance status (Maintenance): C7D1 then **every 12 weeks** ~~Q4W for the first year of maintenance and Q8W thereafter~~ until PD
Table 1 Time and Events Schedule; 9.8 Safety Evaluations	Revised notes for Spirometry test: **Required for all subjects ≥65 years old; if < 65 years old, only required if** ~~Subjects with~~ known or suspected **to have** COPD ~~only~~. Revised instructions for Pulmonary Function Test: **All** subjects with known or suspected COPD ~~or asthma~~ must have a FEV1 test during Screening. **Additionally, all subjects ≥65 years old must have FEV1 and DLCO assessment at Screening for confirmation of eligibility**.
Synopsis; Table 1 Time and Events Schedule; 9.1.2 Screening Phase; 9.8 Safety Evaluations	Added assessment and associated notes: Echocardiogram (ECHO)/Multigated Acquisition (MUGA) Scan (only required for subjects ≥65 years old). Added to Safety Evaluations: Echocardiogram (ECHO)/ Multigated Acquisition (MUGA) scan: All subjects ≥65 years old will have an ECHO or MUGA scan performed to assess left ventricular ejection fraction (LVEF) for confirmation of eligibility in Screening.
Table 1 Time and Events Schedule; 9.1.2 Screening Phase	Added assessment and associated notes: Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) (only required for subjects ≥65 years old).
Table 1 Time and Events Schedule	Revised timing for EMN Correlatives (Post PD) to indicate At PD.

Applicable Section(s)	Description of Change(s)
Table 1 Time and Events Schedule	Added note to Disease Evaluations heading: **Every effort should be made to conduct disease evaluations as per schedule (window ±7 days).** Revised notes for SPEP and SIFE, UPEP and UIFE to indicate repeat measurement on C1D1 only if screening is done >14 days prior to C1D1. For Assessment of lytic lesion and Extramedullary plasmacytoma, added clarifications to indicate specific tests to be performed, and cross-references to applicable sections. Revised timing of Patient reported outcome assessments (Maintenance treatment): C7D1 then every ~~third cycle~~ **12 weeks** until PD Text was modified to replace the terms Q4W and Q8W with every 4 weeks and every 8 weeks, respectively. The text of footnote a of Table 1 (for Follow-up Phase, Prior to PD) was revised for clarity and timing.
9.1.5 Posttreatment Phase (Follow-up)	Added clarification: **For subjects who discontinue study treatment without disease progression prior to transplant, disease evaluations at the central lab should continue to be performed as specified in the Time and Events Schedule (Table 1) until documented disease progression, even if subject initiates subsequent anti-cancer therapy.**
Rationale: Clarifications were made to dosing of the components of study treatment.	
Table 1 Time and Events Schedule	Clarification was added for dexamethasone administration: **Administer 1-3 hours before the daratumumab administration. Dexamethasone 20 mg IV or PO prior to the first 2 doses and 10 mg for all subsequent doses (must have absence of IRR adverse events for 2 doses prior to decreasing dose).** **On daratumumab administration days, backbone therapy substitutes for the pre-medication dexamethasone. Accordingly, 40 mg dexamethasone will be administered PO or IV prior to daratumumab in Cycles 1-6.** ~~On daratumumab dosing days in C1-C6, dexamethasone should only be given once as pre-administration medication 1-3 hours before the daratumumab SC administration.~~
6.1.3.1 Predose Medication	Clarification was added for dexamethasone administration: **Backbone therapy substitutes for the pre-medication dexamethasone. Accordingly, 40 mg dexamethasone will be administered PO or IV prior to daratumumab in Cycles 1-6.**
6.3.3 Dexamethasone Administration	Text was revised for clarity: On daratumumab administration days, ~~during induction/consolidation, dexamethasone may~~ **dexamethasone backbone therapy substitutes for the pre-medication dexamethasone. Accordingly, 40 mg dexamethasone will** be administered **PO or IV** ~~intravenously~~ 1**-3** hour**s** before the daratumumab administration.
6.4 Dose Delays and Dose Modifications	Added instructions that subjects who discontinue a component of study treatment may continue to receive the other components according to individual drug SmPC recommendations.
6.4.2.2.1 Dose Adjustments of Lenalidomide; Table 5	Instructions for dose adjustments of lenalidomide were revised to align with dose reduction steps outlined in the lenalidomide SmPC (Nov 2018) for lenalidomide maintenance in subjects who have undergone ASCT.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification was made to prohibited therapies.	
8.3 Prohibited Therapies	Instructions were clarified: The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. **Investigators should refer to the local bortezomib, lenalidomide and dexamethasone updated summary of product characteristics (SmPC) for drugs prohibited or to be used with precautions.** Use of the treatments listed below is prohibited during the study Clarification for live attenuated vaccines was added: **Administration of live attenuated vaccine during study treatment or within 90 days after last dose of study treatment.**
Rationale: Clarifications were made to instructions for transplant therapy.	
9.1.3.2 Mobilization and Harvesting Stem Cells	Text was modified to clarify timing and methods for stem cell mobilization according to standard of care.
9.1.3.4 Transplant (as per Standard of Care)	Text was added for clarity: **Autologous stem cell transplant should be completed within approximately 6 weeks after stem cell mobilization/harvest. There should be approximately 12 weeks between end of induction and transplant.**
9.1.3.5 Engraftment/ Recovery	Text was modified for clarity: Only the following AEs **and only concomitant medications associated with these AEs** have to be recorded in the eCRF at the start of consolidation (Cycle 5 Day 1):
Rationale: Minor changes and clarifications were made throughout.	
4.1 Inclusion Criteria	Criterion 12 was modified: Signed an informed consent form (ICF) (or their legally acceptable 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. **Subjects in emergency situations that do not allow for collection of informed consent are excluded.**
4.2 Exclusion Criteria	Criterion 4 was modified for clarity: Radiation therapy **for treatment of plasmacytoma** within 14 days of randomization **(palliative radiation for pain control secondary to lytic lesion is allowed within 14 days of randomization)**. Criterion 7 was re-worded for clarity. Criterion 11b was modified for clarity: uncontrolled cardiac arrhythmia ~~or clinically significant electrocardiogram (ECG) abnormalities~~ Criterion 11c was modified for consistency: screening 12-lead ECG showing a baseline QT interval >470 msec **(exception: subjects with pacemaker)** Criterion 11d was re-worded for clarity. Criterion 13 was updated to include lenalidomide **or its excipients**. Criterion 14 was modified to encompass additional situations: **Subject is taking any prohibited medications as per Section 8.3. Subject is deprived of their freedom by a judicial or administrative decision, or subject is in psychiatric care. Subject is subjected to a legal protection measure or unable to provide their consent.** Criterion 17 was modified to provide further clarity regarding the time since the use of a prior investigational drug or invasive investigational medical device.

Applicable Section(s)	Description of Change(s)
6 Dosage and Administration	Text was re-worded for clarity: In Cycles 1 and 2 **with** weekly daratumumab **and Cycles 3-6 with bi-weekly daratumumab**, administrations may be given within ±1 day of the scheduled day to accommodate the schedule of the site or subject.
6.1.2 Daratumumab Administration	Correction was made to MRD-negative status (revised to 10^{-4})
6.2 Management of Injection-site and Infusion-related Reactions	Modified section title and sub-section titles to indicate ~~Injection-~~**Infusion**-related Reactions.
9.1.2 Screening Phase	Modified text for consistency with Table 1: Screening procedures will be performed within 28 days before **randomization** ~~Cycle 1 Day 1~~;
9.1.3.6 Consolidation (Cycles 5-6)	Correction made: For subjects who are unable to ~~tolerate~~ **initiate** consolidation therapy due to delayed immune reconstitution
9.8 Safety Evaluations	Added "ECHO or MUGA (only required for subjects ≧65 years old)" Added "SC injection-site evaluations" for consistency Modified elements in the Serum Chemistry Panel from "urea" to "**BUN or** urea", added clarification to measurement of bilirubin, and indicated the timing to be during **Screening** and induction and consolidation.
Table 1 Time and Events Schedule; 9.2.2 Myeloma Protein Measurements in Serum and Urine	Added measurement of IgD.
9.5 Biomarkers/ EMN Correlatives	Section name updated to Biomarkers/EMN Correlatives.
Attachment 13 Anticipated Events	Reporting of Anticipated Events was revised with specific instructions on reporting to US FDA.
Abbreviations	Added and corrected abbreviated terms.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (04 Sept 2018)

The overall reason for the amendment: To add language describing hepatitis testing, which is now required across daratumumab studies for subjects who are positive for anti-HBc or anti-HBs.

Applicable Section(s)	Description of Change(s)
Rationale: Language regarding hepatitis testing for subjects who are positive for anti-HBc or anti-HBs has been added.	
Table 1: Time and Events Schedule;	Requirements for HBV DNA monitoring at various timepoints during the study have been added to the Time and Events Schedule.
9.8 Safety Evaluations	Clarification has been made to the requirements for HBV DNA testing.
Rationale: Clarification to vital sign collection for subjects in Arm A versus Arm B has been made.	
Table 1: Time and Events Schedule;	Text added to specify that for Arm A, vital signs are required only on Day 1 of every cycle.
9.8 Safety Evaluations	Details on the requirements for the collection of vital signs have been added.
Rationale: Changes and clarifications were made to the timepoints for collection of pharmacokinetic and immunogenicity samples.	
Table 2: Pharmacokinetic and Immunogenicity Evaluations (Arm B Only)	Posttreatment Week 4 collections have been deleted. Clarification has been made to specify that daratumumab and rHuPH20 immunogenicity are required only at Cycle 7 Day 1 for subjects not receiving consolidation treatment (ie, Cycles 5-6) after transplant.
Rationale: To update biomarker assessments to require a mandatory 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.	
Table 1: Time and Events Schedule	Revised the line entry title for "Biomarkers" to "EMN Correlatives" and updated timepoints for collection. Updated the MRD Evaluation row for clarity.
9.1.1 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.
9.2.1 Response Categories; New Attachment 9: Interpretation of The SEBIA Hydrashift 2/4 Daratumumab IFE Interference Test; 9.2.2 Myeloma Protein Measurements in Serum and Urine	Added text to indicate that for subjects with suspected daratumumab interference on SPEP and immunofixation, a reflex assay will be performed. Included a description of the new SEBIA Hydrashift 2/4 Daratumumab IFE Interference test that will be used to distinguish a positive SPEP/IFE.
9.2.5 Bone Marrow Examination; 9.5 Biomarkers; 11.6 Biomarker Analyses	Clarified the requirements for a fresh bone marrow aspirate at screening and the MRD assessment for cytogenetics evaluations.
Table 8: Bone Marrow Testing	Clarified the process for how the bone marrow aspirate will be portioned out for assessment.

Applicable Section(s)	Description of Change(s)
Rationale: To align with the causality options presented on the revised SAE reporting form, the AE attribution definitions have been revised.	
12.1.2 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
12.3.1 All Adverse Events	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 must be reported (unless the subject has been withdrawn from the study)."
Rationale: Miscellaneous edits/clarifications have been made to the protocol.	
Title page	EudraCT number has been added: 2018-002992-16.
Table 1: Time and Events Schedule	Clarified that hematology collection is required on Day 8 and Day 22 during Cycles 1 and 2 only. Added timepoints for body weight measurements. To align with the study treatment visits, clarified that MRU is to be assessed on D22 of Cycle 1 and Cycle 2 only and that MRU is not to be assessed in Follow-up Post-PD.
Table 5: Dose Modification Guidelines for Bortezomib, Lenalidomide, and Dexamethasone	Revised footnote f to specify that creatinine clearance is calculated by the Cockcroft-Gault formula and adjusted for body weight in subjects with a body mass index >30 kg/m^2 and that the eGFR (MDRD) or CKD-epi formulas can also be utilized to assess renal function.
9.2.3 Albumin and Serum Calcium Corrected for Albumin	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.
11.12 Interim Analysis	Clarified the wording relating to the interim OS analyses.
Deleted Section 12.4 Reporting, Monitoring, and Review of Safety Events for the Subjects Enrolled at Sites in Japan; Deleted (old) Attachment 12: Reporting, Monitoring, and Evaluating Safety Events for the Subjects Enrolled at Sites in Japan	The section and attachment that described the procedures specific to reporting adverse events in Japan have been removed as now no sites in Japan are planned to participate in the study.
New Attachment 2: Modified Diet in Renal Disease Formula; References	A new attachment with the MDRD formula has been added, and a cross-reference to it has been added to Inclusion Criterion #6. A new citation for Levey 2006 has been added.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

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Attachment 1: ECOG Performance Status Score Scale

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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Reference: Oken 1982

Attachment 2: Modified Diet in Renal Disease Formula

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

eGFR (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 (eGFR) for the MDRD formula is:

eGFR (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

Attachment 3: 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 mM/L and albumin is expressed in g/L:

Corrected calcium (mM/L) =

serum calcium (mM/L) + 0.02•(40 - serum albumin [g/L])

Source: Burtis 1998

Attachment 4: 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	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		
Normal FEV_1/FVC : 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	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 for persistent asthma	≥2/year Relative annual risk may be related to FEV_1.	≥2/year Relative annual risk may be related to FEV_1.	≥2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥2/year Relative annual risk may be related to FEV_1.	≥2/year Relative annual risk may be related to FEV_1.	≥2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥2/year Relative annual risk may be related to FEV_1.	≥2/year Relative annual risk may be related to FEV_1.
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients 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 CS 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

Attachment 5: 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.

Attachment 6: 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

Attachment 7: 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

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

Attachment 8: Individual and Myeloma-related Risk Factors

	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.

Attachment 9: 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 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 will be sent automatically to the central laboratory if 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.

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

DARAHydra Impress1: result defined as “DARA detected”, “DARA not detected”, OR “DARA indeterminate”

DARAHydra Impress2: result defined as “M-protein not detected” OR the specific protein detected (i.e. “IgG,k” or “IgA”)

DARAHydra 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 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 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 CR, because the CR response criteria requires a negative SPEP and serum IFE.

Attachment 10: EORTC QLQ-C30

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

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

Attachment 11: 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 Little	Quite a Bit	Very 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	

Attachment 12: 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 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

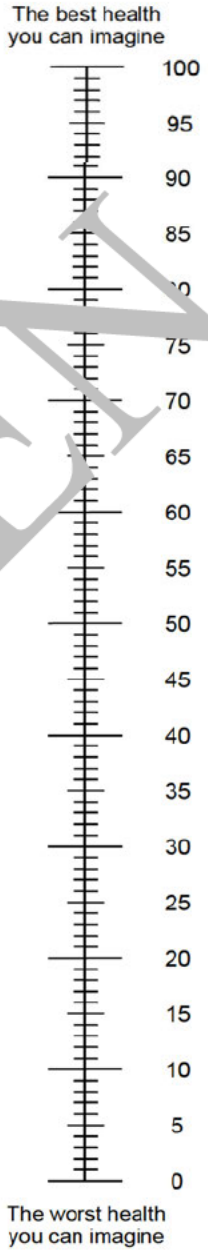
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 = ☐



Attachment 13: COVID-19 and Natural Disaster Guidance on Study Conduct and COVID-19 Vaccine Timing

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic or another natural disaster 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 recent 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 any 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 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 any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for subjects on 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. Discontinuations 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), or "natural disaster-related", when applicable.

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. If a subject has tested positive for COVID-19, the investigator should contact the European Myeloma Network (EMN) Medical Monitor to discuss plans for study treatment and follow-up. Modifications made to the study conduct as a result of the coronavirus pandemic should be summarized in the Clinical Study Report.

For COVID-19: Testing for COVID-19 should be performed according to local guidance. If a subject has tested positive for COVID-19, the following should be reported in the eCRF:

- all cases of COVID-19, regardless of severity or causality (including asymptomatic COVID-19).
- all medications given to prevent (including vaccines) or treatments COVID-19.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

These emergency provisions are meant to ensure subject safety on study while site capabilities are compromised by COVID-19-related or other natural disaster-related restrictions. As restrictions are lifted, sites should revert to study conduct as outlined in the current protocol as soon as feasible.

Subject Dosing Visits

- Evaluate the feasibility for each subject to return for scheduled dosing visits based on the local situation. For subjects who are unable to come to the site for scheduled visits and/or if site capabilities are compromised by COVID-19-related or other natural disaster-related restrictions, contact (eg, telephone, videoconference, or other channels) with the subject should be made in advance, to collect information on the subject's current health status and any new or ongoing adverse events and concomitant medications. Normal study procedures should be followed for the applicable visits as closely as possible even if lab assessments and physical exams are performed locally. Where local laboratories are used, it is important to ensure appropriate documentation of laboratory reference ranges. The remote contact with the subject (as allowable per local regulations), should be documented in the subject source record.
- Continue with mobilization and ASCT after Cycle 4 as outlined in the protocol, if feasible based on local requirements. Consider mobilization of stem cells with granuloctye colony-stimulating factor/Plerixafor without high-dose cyclophosphamide.
- Should ASCT require postponement due to local requirements (ie, closure of hospital to transplant procedures) due to the coronavirus pandemic, ensure to collect stem cells after completion of Cycle 4 as per protocol. Then proceed with Cycles 5 and 6 first as extensional induction treatment and perform the transplant procedure immediately following Cycle 6. The pre-ASCT visit should occur within 2 weeks after completion of Cycle 6. Following recovery from ASCT, proceed directly with maintenance therapy (ie, consolidation will be skipped as the cycles of bortezomib, lenalidomide, and dexamethasone (VRd) or daratumumab in combination with bortezomib, lenalidomide, and dexamethasone (D-VRd) were given prior to transplant and only 6 total cycles of VRd or D-VRd will be given to any subject in the study). The post-consolidation bone marrow analysis for MRD should occur prior to initiation of maintenance therapy.
- 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 and contact the EMN Medical Monitor. 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.
- As subject safety and benefit is the priority, investigators may make the decision to provide other available therapy to subjects on the study. This should be discussed with the EMN Medical Monitor and recorded in source documents and the eCRF with the reason for administration.
- 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 during the coronavirus pandemic. Central laboratory testing should be resumed as soon as conditions permit.

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 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 term "COVID-19" and any serious adverse events (SAE) document confirmed infection with coronavirus.

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 (a list of countries will be provided). This decision was made to allow study subjects access to oral trial 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 EMN 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.
- If locally permitted, alternative solutions to arrange bortezomib dosing on Cycle Day 1, 4, 8, or 11 can be discussed with the EMN Medical Monitor.

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 with a as "COVID-19-related" prefix or category.

Guidance on COVID-19 Vaccine Timing and COVID-19 Prevention and Treatment

It is recommended that subjects receive prophylactic COVID-19 vaccination and boosters when locally available, at the discretion of investigator judgment or institutional practice, and in compliance with the study protocol and local labels for the vaccine. Below is general guidance for consideration.

Many vaccines against COVID-19 are being developed with different technologies and platforms and may have safety and efficacy profiles that are not fully characterized even after preliminary health authority approval. However, the benefit-risk ratio of receiving a COVID-19 vaccine among patients with multiple myeloma is considered to be positive and should be considered for administration while in compliance with the study protocol and when not otherwise contraindicated for use in the vaccine label.

Per protocol, live attenuated vaccines must be completed within 4 weeks of first study agent administration (see Section 4.2) or >90 days after last dose of study treatment (see Section 8.2 and Section 8.3). There are no specific timing restrictions for inactivated vaccines, such as vaccines which use alternative technology like mRNA or replication-incompetent viral vectors, per protocol (mRNA vaccines are recommended). Enrollment into an interventional clinical trial for an experimental vaccine is prohibited during study. Any vaccination, including COVID-19 vaccinations, must be recorded on the Concomitant Medication page of the eCRF.

No data are currently available to suggest that COVID-19 vaccines pose specific or additional safety risk beyond other vaccines for patients with multiple myeloma undergoing treatment. Theoretically, a diminished immune response may occur in immunocompromised patients, and therefore these patients may have reduced vaccine effectiveness.

Several organizations and journals have published recommendations for COVID-19 vaccine administration in cancer patients, including:

- Garassino, M. C. et al. The ESMO call to action on COVID-19 vaccinations and patients with cancer: Vaccinate. Monitor. Educate. Ann. Oncol.
  - https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic
- Nature Reviews Clinical Oncology: COVID-19 vaccine guidance for patients with cancer participating in oncology clinical trials Desai A, Gainor JF, Hegde A, et al. (March 15, 2021) DOI: 10.1038/s41571-021-00487-z.
  - https://www.nature.com/articles/s41571-021-00487-z
- European Society for Blood and Marrow Transplantation
  - https://www.ebmt.org/covid-19-and-bmt
- American Society for Transplantation and Cellular Therapy (ASTCT): https://www.hematology.org/covid-19/ash-astct-covid-19-vaccination-for-hct-and-car-t-cell-recipients Centers for Disease Control and Prevention (CDC)
  - https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html

- National Comprehensive Cancer Network (NCCN)
  - https://www.nccn.org/docs/default-source/covid-19/2021 covid-19_vaccination_guidance_v5-0.pdf?sfvrsn b483da2b_116

Based on guidance from the organizations listed above, the following measures should be implemented to minimize subjects' risk of severe COVID-19 infection:

- Subjects should be reminded that the ongoing pandemic is still putting them at risk of contracting COVID-19. Investigators should ask subject to continue to limit their risk of exposure to infected individuals as much as possible and strictly adhere to prevention measures such as proper masking, hand hygiene, social distancing, and avoiding travel and public transportation to the extent possible.
- Investigators should discuss with subjects the importance of COVID-19 vaccines in the prevention of severe illness, hospitalization, and death from COVID-19. Subjects should assume that any vaccination administered prior to receiving study treatment no longer provides protection. For this reason, it is strongly recommended that all subjects receive a full COVID-19 vaccination series (eg, a primary vaccine and boosters for mRNA vaccines) (Note: mRNA vaccines are recommended). In addition, if not already vaccinated, caregivers, family, and household contacts should be advised to receive COVID-19 vaccination as well.
- Investigators should consider prophylaxis (eg, Evusheld, if available in the region) to reduce subjects' risk of severe/fatal COVID. It is critical that subjects understand that multiple myeloma patients may not seroconvert until after the 3rd COVID-19 vaccine dose and as a result they may remain at a very high risk of severe COVID-19 for at least 2 to 3 months after starting vaccination.
- Investigators should instruct subjects to notify them or study-site staff immediately if they are diagnosed with COVID-19, even if asymptomatic, so that appropriate treatment measures can be determined.

If available in the region, antivirals (eg, Paxlovid or other available agents) should be considered early after COVID-19 diagnosis. Antiviral treatment with Paxlovid is highly recommended *as soon as possible,* typically within the first 5 days after a COVID-19 diagnosis. Refer to the Paxlovid prescribing information for any drug-drug interactions and contraindications. Subjects may remain asymptomatic or have minimal symptoms for a period of time prior to deteriorating. Investigators should make subjects aware that these drugs may potentially significantly lower their risk of severe COVID-19.

INVESTIGATOR AGREEMENT

JNJ-54767414 (daratumumab)
Clinical Protocol EMN17/54767414MMY3014 Amendment 5

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: PPD European Myeloma Network (EMN)

Signature: PPD Date: 29 February 2024
(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.

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 158
Status: Approved, 28 February 2024

Signature

User	Date	Reason
PPD	04-Mar-2024 09:08:26 (GMT)	Document Approval