Janssen Research & Development *

Clinical Protocol

A Phase 2 Study of Daratumumab Subcutaneous (Dara-SC) Administration in Combination with Carfilzomib and Dexamethasone (DKd) Compared with Carfilzomib and Dexamethasone (Kd) in Participants with Multiple Myeloma who have been Previously Treated with Daratumumab to Evaluate Daratumumab Retreatment

Protocol 54767414MMY2065; Phase 2

AMENDMENT 2

JNJ-54767414 (daratumumab)

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US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

EudraCT NUMBER*:* 2018-004185-34

Status: Approved
Date 3 June 2021
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-171113763, 4.0

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	03-Jun-2021
Amendment 1	14-Oct-2019
Original Protocol	29-Jan-2019

Amendment 2 (03 June 2021)

Overall Rationale for the Amendment: The overall rationale for the amendment is to expand eligibility. This amendment expands eligibility to participants who received prior daratumumab subcutaneous, participants who received up to 3 prior lines of therapy, and participants who are seropositive for human immunodeficiency virus (HIV) and meet specified criteria for managing the disease.

Section Number and Name	Description of Change	Brief Rationale
Protocol Title 1.1. Synopsis: Objectives and Endpoints, Hypothesis, Overall Design; 2.3. Benefit/Risk Assessment; 3. Objectives and Endpoints; 4.1. Overall Design; 5.1. Inclusion Criteria (Criteria 3 and 5); 5.2. Exclusion Criteria (Criterion 4); 9.1. Statistical Hypothesis	'Daratumumab intravenous (Dara-IV)' was modified to 'daratumumab'.	To expand eligibility to include participants who received prior subcutaneous (SC) daratumumab.
5.2. Exclusion Criteria (Criterion 1)	Deleted Criterion 1 'Previous treatment with Dara-SC'.	
1.1. Synopsis: Hypothesis, Overall Design; 3. Objectives and Endpoints; 4.1. Overall Design; 4.2. Scientific Rationale for Study Design; 5.1. Inclusion Criteria (Criterion 5); 9.1. Statistical Hypothesis	Eligibility criteria of '1 or 2 prior lines of therapy' was modified to '1 to 3 prior lines of therapy'.	To expand eligibility to include participants who received up to 3 prior lines of therapy.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (Table 1): TTE or MUGA	Added text 'with the same methodology as used at screening'.	To maintain consistency in methodology used for trans-esophageal echocardiogram (TTE) and multiple-gated acquisition (MUGA).
1.3. Schedule of Activities (Table 1): Vital signs and Diary review	Added 'Cycles 1 and 2, only' to Vital signs in Arm B at Day 22. Added 'Cycles 1 and 2, only' to Diary review at Day 22.	To clarify that timing of indicated assessments will be recorded at Day 22 only at Cycles 1 and 2.
1.3. Schedule of Activities (Table 1): HBV DNA testing	Added '±4 weeks' to hepatitis B virus (HBV) DNA testing during treatment phase.	To add window period.
5.1. Inclusion Criteria (Criterion 2)	Deleted 'Multiple myeloma diagnosis according to the International Myeloma Working Group (IMWG) diagnostic criteria'.	This study evaluates daratumumab retreatment and therefore does not apply the IMWG criteria.
5.2. Exclusion Criteria (Criterion 18)	The exclusion criterion has been modified to exclude only those participants who have tested seropositive for HIV with 1 or more of the following: • Not receiving highly active antiretroviral therapy (ART) • Had a change in ART within 6 months of the start of screening • Receiving ART that may interfere with study treatment (consult Sponsor for review of medication prior to enrollment) • CD4 count <350 at screening • Acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within 6 months of start of screening • Not agreeing to start ART and be on ART >4 weeks plus having HIV viral load <400 copies/mL at end of 4-week period (to ensure ART is tolerated and HIV controlled)	To include participants who are seropositive for HIV and meet specified criteria for managing the disease.
6.1.1.4. Dose Modification	Text was revised. Text in ~~strikethrough~~ has been deleted, text in **bold** has been added. ~~The study intervention must be held if any of the following criteria are met, to allow for recovery from toxicity, regardless of relationship to study intervention~~ **If any of the following criteria are met and the toxicity is more than expected for the backbone therapy (carfilzomib, 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**	To clarify that daratumumab should be held only if events are not attributed to carfilzomib or dexamethasone (Kd).

Section Number and Name	Description of Change	Brief Rationale
	from toxicity as noted below	
6.5.2.2. Prevention of Steroid Induced Gastritis	The information related to prevention of steroid induced gastritis was moved from '6.5.1. Required Therapies' to '6.5.2. Recommended Therapies'. Subsequent section numbers were renumbered as shown below- 6.5.2.3. Therapy for Tumor Lysis Syndrome; 6.5.2.4. Therapy for Pneumocystis carinii/jirovecii; 6.5.2.5. Management of Hepatitis B Virus Reactivation	To indicate that prevention of steroid induced gastritis is a recommended rather than required therapy so that it is not mandatory.
6.5.3. Permitted Therapies 6.5.4. Prohibited Therapies	Text was added indicating vaccinations are allowed per local guidelines with a reference to 6.5.4. Prohibited Therapies. Text was added clarifying the restriction of live-attenuated and replication-competent viral vector vaccines.	To clarify permitted/prohibited vaccinations.
6.5.4. Prohibited Therapies	Systemic corticosteroids, described as '>10 mg prednisone' was changed to '>10 mg dexamethasone'.	To be consistent with daratumumab protocol standard language.
Table 8	Carfizomib dosing guidelines for tumor lysis syndrome, neuropathy, hypertension, dyspnea, pulmonary toxicity, and progressive multifocal leukoencephalopathy were added to the table. Carfizomib dosing guidelines for micro-angiopathy were updated. Elevation in liver function tests were categorized as 'Hepatic dysfunction and related investigations'. Updated table abbreviations based on the added text.	To update information about the existing and new carfilzomib risks.
Table 10	Progressive disease was revised to Text in ~~strikethrough~~ has been deleted, text in **bold** has been added. 'Only in participants without measurable serum and urine M-protein levels and without measurable disease by free light chain levels, bone marrow plasma cell percentage **irrespective of baseline status; the** ~~(~~absolute percentage must be ≥10%~~)~~ ~~Bone marrow plasma cell percentage: the absolute percentage must be >10%~~	To clarify that the absolute percentage of bone marrow plasma cell percentage is irrespective of baseline status and to remove redundant text.
9.4.2. Safety Analysis	Deleted text 'Change from baseline to the worst adverse event (AE) grade experienced by the participant during the study will be provided as shift tables'. The term 'intervention-emergent AEs" was replaced by 'treatment-emergent AEs'.	To remove duplicate text. The text was also mentioned in 'Clinical Laboratory Tests' in the same section. To maintain consistency within the text.

Section Number and Name	Description of Change	Brief Rationale
10.16. Appendix 16: Hepatitis B Virus Testing	Added Appendix 16 including the information about Hepatitis B Virus Testing. Subsequent section number was renumbered as 10.17. Appendix 17: Protocol Amendment History. Appendix 16 was cross-referred in 1.3. Schedule of Activities (Table 1) and 5.2. Exclusion Criteria (Criterion 18).	To include the information about the HBV screening guide to be used to determine participant eligibility for the study.
Title Page	The confidentiality statement in title page was updated as per latest template.	To align with latest protocol template.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. The term 'subject' was replaced by 'participant'. The footer was updated as per latest template.	Minor errors were noted. To maintain consistency within the text. To align with latest protocol template.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 2 Study of Daratumumab Subcutaneous (Dara-SC) Administration in Combination with Carfilzomib and Dexamethasone (DKd) Compared with Carfilzomib and Dexamethasone (Kd) in Participants with Multiple Myeloma who have been Previously Treated with Daratumumab to Evaluate Daratumumab Retreatment

OBJECTIVES AND ENDPOINTS

Objectives

Primary Objective

The primary objective is to compare the efficacy (rate of very good partial response [VGPR] or better as best response as defined by the International Myeloma Working Group [IMWG] criteria) of Dara-SC in combination with Kd with the efficacy of Kd in participants with relapsed refractory multiple myeloma who were previously exposed to daratumumab to evaluate daratumumab retreatment.

Secondary Objectives

The secondary objectives are:

To further characterize the efficacy (progression-free survival [PFS], overall survival [OS], overall response rate [ORR], rate of complete response [CR]/stringent complete response [sCR]) of Dara-SC in combination with Kd

- To evaluate the minimal residual disease (MRD) negativity rate and durability of MRD negativity status
- To characterize the safety of Dara-SC in combination with Kd
- To determine time to next treatment
- To evaluate the pharmacokinetics (PK) of Dara-SC
- To determine the immunogenicity of daratumumab and recombinant human hyaluronidase PH20 (rHuPH20)

Endpoints

Primary Endpoint

The primary endpoint of this study is the rate of VGPR or better as defined by the IMWG criteria.

Secondary Endpoints

The secondary endpoints are:

- ORR (rate of partial response [PR], VGPR, CR, sCR)
- Rate of CR/sCR
- PFS
- OS
- MRD negativity rate
- Time to next treatment

- Serum daratumumab concentrations
- Prevalence and incidence of anti-daratumumab antibodies and anti-rHuPH20 antibodies

Hypothesis

Daratumumab SC in combination with Kd will have a higher VGPR or better rate than Kd in participants who have previously received 1 to 3 prior lines of therapy including a line containing daratumumab.

OVERALL DESIGN

This is a Phase 2, open-label, randomized, multicenter study to determine the efficacy of DKd in adult participants with relapsed refractory multiple myeloma who had 1 to 3 prior line(s) of treatment including a line containing daratumumab to evaluate daratumumab retreatment. Participants must have completed daratumumab at least 3 months prior to randomization. The study will be conducted in 3 phases: Screening, Treatment, and Follow-Up. During the Treatment Phase, participants will be randomized to receive Kd or DKd. Participants will be stratified by prior proteasome inhibitor exposure and daratumumab-free interval (3-6 months, >6 months). Participants in both arms will receive study intervention until confirmed progressive disease (PD), death, intolerable toxicity, start of a new treatment for multiple myeloma, withdrawal of consent, or end of the study, whichever occurs first. Follow up of participants for disease progression and survival will continue during the Follow-up Phase.

NUMBER OF PARTICIPANTS

Approximately 230 participants will be randomized 1:1 in 2 treatment arms.

INTERVENTION GROUPS AND DURATION

Participants will be treated with Kd alone (Arm A) or Dara SC in combination with Kd (Arm B) in 28-day cycles.

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, extramedullary plasmacytomas, and serum calcium corrected for albumin.

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Samples will be collected from all participants to assess both the serum concentration (pharmacokinetics) of daratumumab and the presence and generation of anti-daratumumab antibodies (ADAs; immunogenicity) according to the Schedule of Activities. Samples will also be collected from all participants in Arm B to evaluate the immunogenicity of rHuPH20 according to the Schedule of Activities.

BIOMARKER EVALUATIONS

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

SAFETY EVALUATIONS

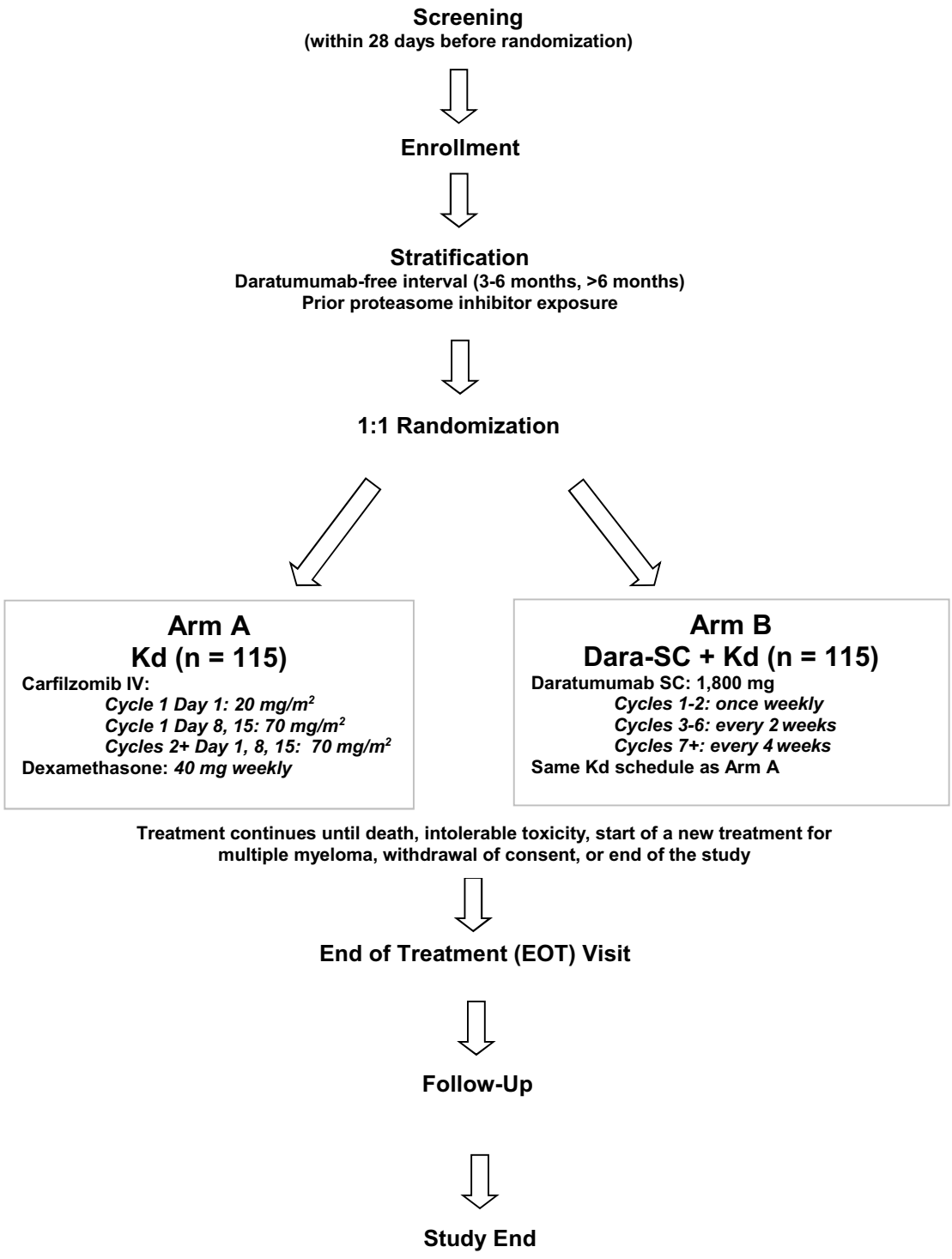
Safety evaluations will include a review of adverse events, clinical laboratory test results, vital sign measurements, electrocardiograms (or multiple-gated acquisition [MUGA] scans), physical examination findings, and assessment of Eastern Cooperative Oncology Group (ECOG) performance status grade.

STATISTICAL METHODS

The primary endpoint of this study is the rate of VGPR or better as defined by the IMWG criteria. The sample size is based on the assumption that the VGPR or better rate is 60% for DKd and 45% for Kd. In the current study, 230 participants (assigned 1:1) are needed in order to detect an absolute 15% increase in VGPR or better rate with 70% power using a 2-sided chi-squared test at the 10% significance level. The rate of VGPR or better will be compared between the 2 treatment arms using the stratified Cochran-Mantel-Haenszel test. The primary analysis will be conducted approximately 6 months after the last participant receives the initial dose of study intervention. An interim futility analysis will occur when 40% of participants are enrolled and treated for 6 months.

1.2. Schema

Figure 1: Schematic Overview of the Study



1.3. Schedule of Activities

Table 1: Schedule of Activities

Assessments		Screening Phase	Treatment Phase (28-day cycles) Treatment (C1+)				EOT	Follow-up Phase Follow-up[a]	Follow-up Phase Survival[a]
		Days -28 to -1	Day 1	Day 8	Day 15	Day 22	Post-treatment Week 4	Post-treatment Week 8	Every 16 weeks after PD
Visit window			±3 days (Except Cycle 1)	±1 day	±1 day	±1 day	+7 days	±7 days	±14 days
Study Procedures									
Study intervention is to be initiated within 3 days after randomization. Subsequent to Cycle 1, the start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or participant. After EOT, and prior to PD, participants in both treatment arms will continue to return for disease evaluations.									
Informed consent	Must sign before any study-related procedures	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)	Participants with known or suspected COPD only; acceptable for screening if performed as part of SOC within 42 days before randomization	X							
ECOG performance status	Prior to any other study procedures planned for the same day	X	C3, C5, C7, then Q8W thereafter until PD					X	

Table 1: Schedule of Activities

Assessments		Screening Phase	Treatment Phase (28-day cycles)				EOT	Follow-up Phase	
			Treatment (C1+)					Follow-up[a]	Survival[a]
		Days -28 to -1	Day 1	Day 8	Day 15	Day 22	Post-treatment Week 4	Post-treatment Week 8	Every 16 weeks after PD
Visit window			±3 days (Except Cycle 1)	±1 day	±1 day	±1 day	+7 days	±7 days	±14 days
12-lead ECG	Acceptable for screening if performed as part of SOC within 42 days before randomization	X	As clinically indicated				X		
TTE or MUGA[b]		X	Every 6 months (±2 weeks) after C1D1, until end of treatment, or if clinically indicated, with the same methodology as used at screening						
Physical examination	Including neurological examination[c]	X	A physical examination is to be performed at each treatment visit. Physical examinations should be symptom- and disease-directed, as clinically indicated						
Vital signs (temperature, pulse/heart rate, respiratory rate, blood pressure)	Arm A	X	X (measure prior to carfilzomib dosing)						
	Arm B, on C1D1, required immediately before, at end of, and at 0.5 and 1 hour after end of Dara-SC administration. For other Dara-SC administrations, immediately prior to and immediately after end of administration. On carfilzomib-only dosing days, performed prior to carfilzomib dosing.	X	X	X	X	X Cycles 1 and 2, only			
Weight			X						

Table 1: Schedule of Activities									
Assessments		**Screening Phase**	**Treatment Phase (28-day cycles)**				**EOT**	**Follow-up Phase**	
			Treatment (C1+)					**Follow-up[a]**	**Survival[a]**
		Days -28 to -1	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Post-treatment Week 4**	**Post-treatment Week 8**	**Every 16 weeks after PD**
Visit window			**±3 days (Except Cycle 1)**	**±1 day**	**±1 day**	**±1 day**	**+7 days**	**±7 days**	**±14 days**
Laboratory Assessments									
Urine or serum Pregnancy test	For women of childbearing potential only. During screening, on C1D1, and at EOT visit (with additional pregnancy tests if required by local health authorities).[d]								
Blood group and type and IAT results	ABO, Rh, and IAT assessed once locally before the first Dara-SC administration. Record on the participant's identification wallet card.		Arm B only; predose C1D1						
Hematology	May be performed up to 3 days before study intervention administration day. Results must be evaluated before each study intervention administration. At C1D1, tests do not need to be repeated if they were performed within the previous 7 days.	X	X	X	X	X Cycles 1 and 2, only	X		
Serum chemistry		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 8.2.7.	X							

Table 1: Schedule of Activities

Assessments		Screening Phase	Treatment Phase (28-day cycles)				EOT	Follow-up Phase	
			Treatment (C1+)					Follow-up[a]	Survival[a]
		Days -28 to -1	Day 1	Day 8	Day 15	Day 22	Post-treatment Week 4	Post-treatment Week 8	Every 16 weeks after PD
Visit window			±3 days (Except Cycle 1)	±1 day	±1 day	±1 day	+7 days	±7 days	±14 days
HBV DNA testing	For participants with serologic evidence of resolved HBV infection (i.e., positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. Refer to Section 8.2.8 and Appendix 16	X	Q12W during treatment (±4 weeks)				X	Q12W for up to 6 months after the last dose of study treatment	
Whole Blood Biomarkers	-Flow/Immunophenotyping -CyTOF		Predose C1D1, C4D1						
Plasma Based Biomarkers	Plasma		Predose C1D1, C4D1						
MRD Evaluation	Bone marrow See Table 3	X	See Table 3						
Pharmacokinetic and Immunogenicity Evaluations are described in Table 2.									

Table 1: Schedule of Activities

Assessments		Screening Phase	Treatment Phase (28-day cycles)				EOT	Follow-up Phase	
			Treatment (C1+)					Follow-up[a]	Survival[a]
		Days -28 to -1	Day 1	Day 8	Day 15	Day 22	Post-treatment Week 4	Post-treatment Week 8	Every 16 weeks after PD
Visit window			±3 days (Except Cycle 1)	±1 day	±1 day	±1 day	+7 days	±7 days	±14 days
Disease Evaluations (See Section 8.1 for additional details)									
During study treatment, disease evaluations must be performed every 28 days (±7 days) until disease progression. If participant discontinues study treatment for reasons other than disease progression, disease evaluations should be conducted every 8 weeks (±7 days) until disease progression is confirmed or start of subsequent therapy.									
Bone marrow examination, myeloma disease evaluation	Disease characterization (morphology and either immunohistochemistry, immunofluorescence, or flow cytometry) and cytogenetics performed locally (within 42 days before randomization).[e]	X	See Table 3						
SPEP and SIFE, 24-hour UPEP and UIFE[f]	Central laboratory. SPEP/SIFE and UPEP/UIFE within 28 days before C1D1	X[g]	X					X (Prior to PD: Q8W (±7 days) until PD)	
Serum FLC	Central laboratory. For participants with light chain myeloma, perform with every disease evaluation. Required to confirm CR/sCR	X	X					X (Prior to PD: Q8W (±7 days) until PD)	
Serum β2-microglobulin	Central laboratory	X							
Calcium, albumin	Central laboratory	X	X					X (Prior to PD: Q8W (±7 days) until PD)	

Table 1: Schedule of Activities

Assessments		Screening Phase	Treatment Phase (28-day cycles) Treatment (C1+)				EOT	Follow-up Phase Follow-up[a]	Follow-up Phase Survival[a]
		Days -28 to -1	Day 1	Day 8	Day 15	Day 22	Post-treatment Week 4	Post-treatment Week 8	Every 16 weeks after PD
Visit window			±3 days (Except Cycle 1)	±1 day	±1 day	±1 day	+7 days	±7 days	±14 days
IgG, IgA, IgM, IgD, and IgE	Central laboratory	X	Every 3 months (±1 month) during treatment. Testing for IgD and IgE will only be performed for participants with IgD and IgE-type myeloma.						
Assessment of lytic lesion	Acceptable for screening if performed as part of SOC within 42 days before randomization	X	As clinically indicated, using the same methodology as used at screening					X (Prior to PD: as clinically indicated until PD)	
Extramedullary plasmacytoma	Participants with history of plasmacytoma; acceptable for screening if performed as part of SOC within 42 days before randomization.	X	If applicable, using the same methodology as used at screening: by physical exam Q4W (±7 days), by radiologic exam Q12W. If assessed by physical exam, repeat assessment on C1D1 if not done within 14 days prior to randomization					X (Prior to PD: continue as during treatment until PD)	
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 intervention							
Adverse events								Treatment-related SAEs	
Medical resource utilization			X	X	X	X	X	X	X
SPM monitoring			X	X	X	X	X	X	X
PFS2, subsequent anticancer therapy and survival status							X	X	X
Study Treatment Arm A and Arm B									
Dexamethasone 40 mg[h,i]	Administrations can be IV or PO.[h]		X[h]	X	X	X (Cycles 1-9 only for Arm A and Arm B)			

Table 1: Schedule of Activities									
Assessments		**Screening Phase**	**Treatment Phase (28-day cycles)**				**EOT**	**Follow-up Phase**	
			Treatment (C1+)					**Follow-up[a]**	**Survival[a]**
		Days -28 to -1	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Post-treatment Week 4**	**Post-treatment Week 8**	**Every 16 weeks after PD**
Visit window			**±3 days (Except Cycle 1)**	**±1 day**	**±1 day**	**±1 day**	**+7 days**	**±7 days**	**±14 days**
Prehydration for Carfilzomib[j]	Adequate hydration is required prior to dosing in Cycle 1, especially in patients at high risk of tumor lysis syndrome or renal toxicity. Prehydration is required for C1. Continue in subsequent cycles if participant's condition or risk factors require it.		X	X	X				
Carfilzomib 20 mg/m^2 on C1D1, then 70 mg/m^2 subsequent doses	30 minute (±5 minutes) IV infusion		X	X	X				
Diary review	Accountability/exposure check for dexamethasone PO		X Except Cycle 1	X	X	X Cycles 1 and 2, only	X		
Pre-administration Medications, Arm B									
Diphenhydramine 25-50 mg (or equivalent)			Administer 1-3 hours before Dara-SC administration only[k]						
Paracetamol 650-1000 mg									

Table 1: Schedule of Activities

Assessments		Screening Phase	Treatment Phase (28-day cycles)				EOT	Follow-up Phase	
			Treatment (C1+)					Follow-up[a]	Survival[a]
		Days -28 to -1	Day 1	Day 8	Day 15	Day 22	Post-treatment Week 4	Post-treatment Week 8	Every 16 weeks after PD
Visit window			±3 days (Except Cycle 1)	±1 day	±1 day	±1 day	+7 days	±7 days	±14 days
Montelukast 10 mg	Recommended prior to Dara-SC C1D1 and optional before all other Dara-SC doses								
Study intervention Administration, Arm B Only									
Daratumumab 1800 mg SC[i]	Refer to IPPI for recommendations on Dara-SC administration rate		On Days 1, 8, 15, 22 for Cycles 1 and 2; Days 1 and 15 for Cycles 3-6; Day 1 for Cycles 7+						

a. For participants who discontinue study intervention before PD, disease evaluations should continue to be performed at the frequency specified in Table 3 until confirmed PD, death, intolerable toxicity, start of a new treatment for multiple myeloma, withdrawal of consent, or end of the study, whichever occurs first.
b. All participants will have a baseline transthoracic ECHO (TTE) or multiple-gated acquisition (MUGA) scan during screening, including assessments of systolic and diastolic left ventricular function and right ventricular function. Routine TTE or MUGA scan (every 6 months) should not be assessed within 4 days after Dara-SC injection. However, TTE or MUGA scan should be performed within 72 hours of cardiac failure event initiation, regardless of the timing in relation to injection. A trans-esophageal echocardiogram (TEE) will be an acceptable alternative to TTE or MUGA if performed as part of standard of care.
c. The participant's neurological examination should be performed during the screening phase by the treating physician (a neurologic specialist is not required).
d. The screening pregnancy test must be within 14 days of randomization. Serum or urine pregnancy tests are acceptable at every timepoint.
e. Cytogenetics include t(4;14); t(14;16) and del (17p) and optionally 1q. If local FISH testing is unavailable, this may be performed centrally upon approval of the sponsor.
f. Blood samples for SPEP and SIFE must be collected on the same day that 24-hour urine samples for UPEP and UIFE starts or stops.
g. 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.
h. See Sections 6.1.2 and 6.1.2.1 for detailed dexamethasone administration information. Dexamethasone 40 mg weekly must be administered as 20 mg by IV infusion or PO on Cycle 1 Day 1, then 20 mg by IV infusion or PO on Cycle 1 Day 2. Dexamethasone 40 mg doses subsequent to Cycle 1 Day 2 may be administered by IV infusion or PO weekly.
i. For participants on Arm B, on days when more than 1 investigational product is administered, the required order of administration is as follows: dexamethasone, pre-administration medications for Dara-SC, Dara-SC, then carfilzomib.
j. See Section 6.1.3.1 for information regarding prehydration required prior to dosing in Cycle 1.

k. See Section 6.1.1.1 for detailed administration information.

Abbreviations: C=Cycle; COPD=chronic obstructive pulmonary disease; CR=complete response; CT=computed tomography; CyTOF=mass cytometry; Dara-SC=daratumumab administered subcutaneously; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; EOT=End-of-Treatment; FEV1=Forced Expiratory Volume (in 1 second); FLC=free light chain; HBV=hepatitis B virus; IAT=indirect antiglobulin test; ICF=informed consent form; Ig=immunoglobulin; IPPI=Investigational Product Preparation Instructions; IV=intravenous; MRD=minimal residual disease; MUGA=multiple-gated acquisition; PD=progressive disease; PFS2=progression-free survival on next line of therapy; PO=oral; 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; SPM=second primary malignancy; TEE= trans-esophageal echocardiogram; TTE=transthoracic echocardiogram; UIFE= urine immunofixation; UPEP=urine M-protein quantitation by electrophoresis; VGPR=very good partial response.

Table 2: Pharmacokinetic and Immunogenicity Evaluations

	Treatment Phase			Follow-up Phase
	Cycle 1	**Cycle 3**	**Cycle 7**	**Post-treatment Week 8 (±1 week)**
	Day 1[a]	**Day 1[a]**	**Day 1[a]**	
ARM A				
Daratumumab pharmacokinetics (serum)	X	X		
Daratumumab immunogenicity[b]	X			
ARM B				
Daratumumab pharmacokinetics (serum)	X[a] predose	X[a] predose	X[a] predose	X
Daratumumab immunogenicity[b,c]	X[a] predose		X[a] predose	X
rHuPH20 immunogenicity (plasma)[c]	X[a] predose		X[a] predose	X

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 drug administration. Samples collected on dosing days with visit windows should be collected on the actual day of study drug administration.
b. No additional sample needed; will be aliquoted from PK sample.
c. 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.

Abbreviations: IRR=infusion-related reaction; PK=pharmacokinetic; rHuPH20=recombinant human hyaluronidase.

Table 3: 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 for cytogenetic analysis[a] by conventional FISH performed locally.	A portion of fresh bone marrow aspirate collected will be used for MRD index clone identification (calibration) performed centrally.
During Treatment	At time of suspected CR/sCR: Evaluate Plasma cell percentage in the bone marrow to confirm CR Evaluate clonality of plasma cells (by flow cytometry, IHC or IF[b]) 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 at time of suspected CR/sCR and for participants who achieve CR, have not progressed, and remain on the study, additional bone marrow aspirate will be obtained at 12, 18, and 24 months post Cycle 1 Day 1 (±1 month).[c]

a. Cytogenetics include t(4;14); t(14;16) and del (17p) and optionally Amplification 1q. If local FISH testing is unavailable, this may be performed centrally upon approval of the sponsor.
b. 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.
c. If one of these time points occurs within 1 month of suspected CR/sCR, a repeat bone marrow will not be requested.

Abbreviations: 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

2. INTRODUCTION

For the most comprehensive nonclinical and clinical information regarding daratumumab, refer to the latest version of the Investigator's Brochure (IB) for daratumumab. The term “study intervention” used throughout the protocol, refers to daratumumab subcutaneous (Dara-SC) administration in combination with carfilzomib and dexamethasone (DKd) or carfilzomib and dexamethasone (Kd). The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

2.1. Background

2.1.1. Multiple Myeloma

For relapsed or refractory multiple myeloma, the treatment is determined on an individual basis where the patient’s age, prior therapy, bone marrow function, co-morbidities, patient preference and time to relapse are considered. Common standard of care regimens use either a proteasome inhibitor (PI) or an immunomodulatory agent (IMiD) in combination with dexamethasone with or without a monoclonal antibody (mAb) such as daratumumab. With each successive relapse, the depth and duration of response typically decreases. After relapse from PIs or IMiDs, patients are often retreated with drugs that have the same mechanism of action to which they have been sensitive. Ultimately, the disease becomes refractory and all effective treatment options are exhausted and patients who are heavily pretreated or refractory to both a PI and an IMiD have a dismal prognosis, are difficult to get back into a durable remission, and have a median overall survival (OS) of only 8 to 9 months.[10,23,24] For patients who are refractory to at least 3 of the common PIs (bortezomib or carfilzomib) and IMiDs (lenalidomide or pomalidomide), the median OS decreases to only 5 months.[23] As such, multiple myeloma remains incurable.

2.1.2. Daratumumab

Daratumumab is a human $IgG1_{\kappa}$ mAb that binds with high affinity to a unique epitope on cluster of differentiation 38 (CD38). It is a targeted immunotherapy that attacks tumor cells that overexpress CD38, a transmembrane glycoprotein, in a variety of hematological malignancies including multiple myeloma. Daratumumab induces lysis of CD38-expressing tumor cells, including multiple myeloma tumor cells that were freshly isolated from patients, by a number of mechanisms, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis, through activation of complement proteins, natural killer (NK) cells, and macrophages, respectively.[6,20]

2.1.3. Daratumumab IV

In the European Union (EU), daratumumab is approved for the following indications:

- As monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a PI and an IMiD and who have demonstrated disease progression on the last therapy.

- In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- In combination with bortezomib, melphalan, and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

In the United States (US), daratumumab is approved for the following indications:

- As monotherapy, for the treatment of adult patients with multiple myeloma who have received at least 3 prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.
- In combination with lenalidomide and dexamethasone in newly diagnosed adult patients who are ineligible for autologous stem cell transplant and in adult patients with relapsed or refractory multiple myeloma who have received at least 1 prior therapy.
- In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy.
- In combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and a PI.
- In combination with bortezomib, melphalan, and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
- In combination with bortezomib, thalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.

2.1.4. Daratumumab SC

A new formulation of daratumumab for subcutaneous (SC) administration has been developed to avoid the long infusion time that frequently requires hospitalization with intravenous (IV) administration of daratumumab and to lessen the rate and severity of infusion-related reactions (IRRs) observed with IV daratumumab. A recombinant human hyaluronidase PH20 (rHuPH20) was used to facilitate the SC administration of daratumumab to decrease the volume required for SC administration.

This SC formulation of daratumumab has been evaluated in Study MMY1004, an open-label, multicenter, dose escalation Phase 1b study. Study MMY1004 was designed to assess the safety, pharmacokinetics (PK), and efficacy of Dara-SC plus rHuPH20 in participants with relapsed or refractory multiple myeloma. The fixed SC dose of 1800 mg was selected from Part 1 of the study based on cumulative review of PK and safety data and confirmed with Dara-SC in Part 2. Similar or greater maximum trough concentrations (C_{trough}) were observed following

administration of 1800 mg Dara-SC compared to 16 mg/kg daratumumab IV (Dara-IV). After a median treatment duration of 5.6 months, 25 participants received at least 1 dose of 1800 mg Dara-SC in Study MMY1004.[22] The IRR rate was 16%; events were mostly Grade 1 or 2 and included chills, dyspnea, sneezing and allergic rhinitis, and two Grade 3 events of hypertension. None of the IRRs led to treatment discontinuation. Injection-site reactions (ISRs) included erythema in 24% of participants, and induration at injection site was experienced by 1 participant (4%). The overall response rate (ORR) was 52%, with 28% very good partial responses (VGPRs). Median time to response was 1 month. Median progression free survival (PFS) has not been reached.

The efficacy and AE profile of Dara-SC is consistent with that of Dara-IV with a lower rate of IRRs (12% with Dara-SC versus 48% in Dara-IV monotherapy and combination studies), which mainly occur with the first injection. Based on these clinical data and supported by the PK profile of Dara-SC, the safety and efficacy profile of Dara-SC appears similar to the profile Dara-IV. The profile of Dara-SC may be better with regard to IRR. The SC formulation is currently being tested in Study MMY3012, a Phase 3 study of Dara-IV versus Dara-SC in participants with relapsed or refractory multiple myeloma.

2.2. Study Rationale

Daratumumab responders who relapse have been reported to become re-sensitized (responded again) following an adequate treatment break or by switching to a different daratumumab-containing combination regimen.[1,2] Two patients with triple refractory (IMiDs, PIs, and cytostatics) multiple myeloma were retreated with Dara-IV with a partial response after relapsing from a prior line of therapy containing daratumumab.[2] A retrospective study of 41 patients at Emory University Hospital, using daratumumab in combination with pomalidomide and dexamethasone, showed that patients with prior daratumumab exposure may be effectively retreated with daratumumab in a re-intensified dosing schedule.[1] These data suggest that retreatment with daratumumab may result in a multiple myeloma disease response. However, the clinical benefit of daratumumab retreatment has not been systematically evaluated. As daratumumab moves into frontline treatment, evidence to support retreatment with daratumumab among patients with disease progression is needed.

The dosing schedule of carfilzomib in combination with dexamethasone (Kd) to be used in this study has been approved by the Food and Drug Administration (FDA) for patients with relapsed or refractory multiple myeloma who had 1 to 3 prior line(s) of therapy. The Phase 3 ENDEAVOR study, in which 929 patients were enrolled compared the efficacy of Kd with bortezomib-dexamethasone (Vd) in patients who progressed on 1 to 3 prior regimen(s).[7] Participants (n 464) received twice weekly carfilzomib at 20 mg/m^2 on Days 1-2 of Cycle 1, and subsequent doses of 56 mg/m^2 thereafter as a 30 minute IV infusion. All patients received 20 mg dexamethasone (IV or oral [PO]) on Days 1, 2, 8, 9, 15, 16, 22, and 23 of every cycle. The Kd group had an ORR of 77% compared with 63% in the Vd arm; median PFS of 18.7 months compared with 9.4 months in the Vd arm; and median OS of 47.6 months compared with 40 months in the Vd arm. On-study deaths due to adverse events (AEs) occurred in 4% of

participants. Forty eight percent (48%) of participants had serious adverse events (SAEs). The most frequent Grade 3 or higher AEs were anemia (14%), hypertension (9%), thrombocytopenia (8%) and pneumonia (7%).

To evaluate a more convenient carfilzomib dosing schedule, the Phase 3 ARROW study compared once weekly (70 mg/m^2) with twice weekly (27 mg/m^2) carfilzomib dosing in 478 participants with relapsed or refractory multiple myeloma.[15] The once weekly group received carfilzomib (30 min IV infusion) on Days 1, 8, and 15 of all cycles (20 mg/m² Day 1 during Cycle 1; 70 mg/m² thereafter). The twice weekly group received carfilzomib (10-min IV infusion) on Days 1, 2, 8, 9, 15, and 16 (20 mg/m² Days 1 and 2 during Cycle 1; 27 mg/m² thereafter). All patients received dexamethasone (40 mg on Days 1, 8, 15 [all cycles] and 22 [Cycles 1 9 only]). The once weekly group had a higher median PFS compared to the twice weekly group, 11 months compared with 8 months, respectively. The ORR in the once-weekly group was 62.9% (95% confidence interval [CI], 56.5-69.0) compared with 40.8% (95% CI, 35.5-47.3) in the twice-weekly group (P <.0001); 7% of patients and 2% of patients, respectively, achieved a complete response (CR) or stringent complete response (sCR). The incidence of Grade 3 AEs was higher in the once weekly group (68%) compared with the twice weekly group (62%). The most common events in the once weekly group were anemia (18%), pneumonia (10%), and thrombocytopenia (7%). The once weekly group had 2% treatment-related deaths and 58 total deaths, and the twice weekly group had 1% treatment-related deaths and 68 total deaths. This study resulted in the recent FDA approval of the carfilzomib once weekly (70 mg/m^2) dose.

Study MMY1001 is a Phase 1b study evaluating the safety and efficacy of Dara-IV with Kd. Participants received once weekly carfilzomib (30 min IV infusion) on Days 1, 8, and 15 of all cycles (20 mg/m² Day 1 during Cycle 1; 70 mg/m² thereafter). Participants with 1-4 prior line(s) of therapy (n 85) had a VGPR or better rate of 68% and an 81% ORR. In a subgroup analysis of participants with 1-2 prior line(s) of therapy (n 60), the VGPR or better rate was 73% and the ORR was 87%. Grade 3 or 4 treatment-emergent adverse events (TEAEs) were reported in 73% of participants receiving DKd. The most frequently reported Grade 3 or 4 TEAEs (≥10%) in the DKd cohort were thrombocytopenia (31%), anemia (21%), lymphopenia (22%), neutropenia (21%), hypertension (14%), and asthenia (12%). For further details and the most up-to-date information about Study MMY1001, refer to the most current IB.

Given the growing use of lenalidomide in newly diagnosed multiple myeloma (especially in the maintenance setting), as well as safety and efficacy data of using carfilzomib in patients with relapsed and refractory multiple myeloma, evaluation of the safety and efficacy of the addition of Dara-SC to this regimen is proposed.

2.3. Benefit/Risk Assessment

The combination of Kd with Dara-SC is hypothesized to have a positive benefit-risk profile when used for the treatment of patients with relapsed/refractory multiple myeloma who were previously exposed to daratumumab. This hypothesis is based on the following:

Daratumumab responders who relapse may respond following a treatment break or by switching to a new daratumumab-containing combination regimen, as detailed in Section 2.2.

The Kd regimen to be used in this study has been approved for patients with relapsed or refractory multiple myeloma who had 1 to 3 prior line(s) of therapy (see Section 2.1.1).

The addition of daratumumab to the Kd regimen may improve initial disease control and long-term outcomes, based on data from an ongoing Phase 1b study (Study MMY1001) of the safety and efficacy of Dara-IV with Kd (see Section 2.2).

Given the potential advantages of SC administration, Dara-SC will be used in this study. As presented in Section 2.1.4 and the current daratumumab IB, the safety and tolerability of Dara-SC has been demonstrated. Previous exposure-response analyses have demonstrated a strong correlation between ORR and the maximum daratumumab C_{trough}. Analysis of the preliminary PK data indicated the 1800 mg Dara-SC dose achieved maximum C_{trough} values comparable with, or higher than, those observed for Dara-IV 16 mg/kg as detailed in Section 4.2.

Considering the above, there is a strong rationale for evaluating Dara-SC in combination with Kd for the treatment of relapsed refractory multiple myeloma patients previously exposed to daratumumab. More detailed information about the known and expected benefits and risks of daratumumab are provided in the IB.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES

Primary Objective

The primary objective is to compare the efficacy (rate of VGPR or better as best response as defined by the International Myeloma Working Group [IMWG] criteria) of Dara-SC in combination with Kd with the efficacy of Kd in participants with relapsed refractory multiple myeloma who were previously exposed to daratumumab to evaluate daratumumab retreatment.

Secondary Objectives

The secondary objectives are:

- To further characterize the efficacy (PFS, OS, ORR, rate of CR/sCR) of Dara-SC in combination with Kd
- To evaluate the minimal residual disease (MRD) negativity rate and durability of MRD negativity status
- To characterize the safety of Dara-SC in combination with Kd
- To determine time to next treatment
- To evaluate the PK of daratumumab
- To determine the immunogenicity of daratumumab rHuPH20

ENDPOINTS

Primary Endpoint(s)

The primary endpoint of this study is the rate of VGPR or better as defined by the IMWG criteria.

Secondary Endpoint(s)

The secondary endpoints are:

- ORR (rate of partial response, VGPR, CR, sCR)
- Rate of CR/sCR
- PFS
- OS
- MRD negativity rate
- Time to next treatment
- Serum daratumumab concentrations
- Prevalence and incidence of anti-daratumumab antibodies and anti-rHuPH20 antibodies

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

Daratumumab SC in combination with Kd will have a higher VGPR or better rate than Kd in participants who have previously received 1 to 3 prior lines of therapy including a line containing daratumumab.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, open-label, randomized, multicenter study to determine the efficacy of DKd in adult participants with relapsed refractory multiple myeloma who had 1 to 3 prior line(s) of treatment including a line containing daratumumab to evaluate daratumumab retreatment. Participants must have completed daratumumab at least 3 months prior to randomization. A target of 230 participants will be randomized in 2 treatment arms of 115 each. A diagram of the study design is provided in Section 1.2 Schema.

The study will be conducted in 3 phases: Screening, Treatment, and Follow-Up. Screening begins at the time the participant provides written consent for study participation. During the Screening Phase, participants will be screened for study eligibility within 28 days prior to study randomization. All eligibility criteria must be met prior to starting study intervention.

During the Treatment Phase, participants will be stratified by prior PI exposure and daratumumab-free interval (3-6 months, >6 months) and then assigned randomly to receive Kd or DKd. Participants in both arms will receive study intervention until confirmed progressive disease (PD), death, intolerable toxicity, start of a new treatment for multiple myeloma, withdrawal of consent, or end of the study, whichever occurs first. Participants should start study intervention within 3 days after randomization. Participants will be closely monitored for AEs, laboratory abnormalities, and clinical response. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. If disease progression is confirmed, then the participant will discontinue study intervention, complete the End-of-Treatment Visit, and enter the Follow-up Phase.

Follow-up will continue until the end of study, no later than 2 years after the last participant has received their initial dose of study intervention or when the sponsor decides to stop the study. The sponsor will ensure that participants benefiting from treatment with Dara-SC or carfilzomib continue to receive treatment after the end of the study.

All study evaluations will be conducted according to the Schedule of Activities (Table 1 to Table 3). Myeloma protein measurements in serum and urine for disease evaluations will be performed by a central laboratory (unless otherwise specified). Bone marrow testing will be performed by both local and central laboratories. This study will use the IMWG consensus recommendations for multiple myeloma treatment response criteria[9,21] presented in Table 10. Response will be determined using a validated computer algorithm.

Safety evaluations will include a review of AEs, laboratory test results, vital sign measurements, physical examination findings, and assessment of Eastern Cooperative Oncology Group (ECOG) performance status grade. Follow up of participants for disease progression and survival will continue during the Follow-up Phase.

An interim futility analysis will be conducted after 40% of participants are enrolled and treated for at least 6 months (approximately 1 year after first participant randomized). The primary analysis will be conducted approximately 6 months after the last participant receives the initial dose of study intervention. At this time, the clinical study report (CSR) will be written, or the CSR will be written at the time of interim futility analysis if the results lead to stopping the study. A final analysis will occur at study completion/end of the study to update PFS2, OS, second primary malignancy, and safety. Study completion/end of the study will be no later than 2 years after the last participant has received the initial dose of study intervention.

4.2. Scientific Rationale for Study Design

This study will test the hypothesis that daratumumab retreatment in combination with Kd, following at least a 3-month daratumumab-free interval, would result in an improved clinical benefit over Kd alone, in relapsed and refractory multiple myeloma. The study population includes patients who have had 1 to 3 prior line(s) of therapy and have demonstrated at least a partial response for 4 months to daratumumab. Given the setting of retreatment with

daratumumab, a clinically meaningful primary endpoint would be VGPR rate or better as it represents a 90% or more reduction in detectable abnormal paraproteins.

The patients will be stratified based on daratumumab-free interval and prior PI exposure. It is unknown whether the degree to which CD38 re-expression or the additional immune modulating responses secondary to daratumumab may correlate to retreatment clinical benefit. The inclusion of this stratification criterion is to guard against potential influence on patient response. Post hoc analyses will examine the need for, and optimal length of a daratumumab-free interval prior to retreatment with daratumumab. CD38 expression starts to slowly increase when daratumumab is gradually cleared. By the end of a 3-month daratumumab-free interval, daratumumab remaining levels are very low, and CD38 expression starts to increase again. It can take up to 5 months for CD38 expression to reach its initial levels.[18] However, in previous studies CD38 expression levels did not correlate with response to daratumumab treatment either in a monotherapy or in combination setting. Stratification by 3-6 months and >6 months serves to address this point. CD38-expressing immune cell populations are mostly depleted immediately after first daratumumab infusion and remain like this as long as daratumumab is present.

Daratumumab has a mean linear half-life associated with linear elimination of 18 to 23 days following monotherapy and combination treatment. A 3-month daratumumab-free-interval is 4 to 5 half-lives, which allows time for washout of most of the daratumumab from serum prior to initiation of study treatment. Hence, a minimum of 3-month daratumumab-free-interval is necessary to determine the effect, if any at all, of daratumumab in retreatment.

Blinding, Control, Study Phase/Periods, Intervention Groups

This study is not blinded. An active control will be used to determine the sensitivity of the clinical endpoints in this study. Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups.

Rationale for Subcutaneous Daratumumab

Subcutaneous administration of daratumumab has been chosen for this study to avoid the long infusion time that frequently requires hospitalization with Dara-IV and to lessen the rate and severity of IRRs observed with Dara-IV.

Biomarker Collection

This study provides an opportunity to evaluate whether daratumumab retreatment results in significant and deep responses in participants who responded to initial treatment with daratumumab. Having as a goal to achieve deep and sustained responses, the measurement of MRD is important as a key differentiator. Daratumumab's mechanisms of action are a combination of direct on-tumor as well as immunomodulatory actions. In this study, by means of immune profiling, the aim is to identify alterations in immune cell subgroups which might result

in a secondary response to daratumumab. Being able to better understand the disease's biology in association with the clinical data might guide a rationale for combination therapies.

Pharmacokinetics and Immunogenicity Assessments

Data obtained from this study will provide information about the PK profile of DKd in participants with multiple myeloma and previous daratumumab exposure. Data will also be used to assess the residual daratumumab serum concentration at the start of treatment in the Kd arm following at least 3-month daratumumab-free interval. Therefore, samples will be obtained from all participants 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-participant variability in this population.

Immunogenicity to daratumumab or rHuPH20 is possible. The prevalence and incidence of daratumumab immunogenicity may be different in this population that has previously been exposed to daratumumab, therefore, the presence of anti-daratumumab antibodies and anti-rHuPH20 antibodies will be determined from samples collected from all participants.

Medical Resource Utilization Data Collection

Treatment of multiple myeloma with daratumumab SC administration in combination with Kd versus Kd alone may result in lower utilization of:

- Duration of hospitalization (total length of stay, including duration by each hospital unit)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters (including physician, nurse practitioner or emergency room visits, tests and procedures)

Therefore, comparison will be done across intervention groups.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants 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 participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The primary ethical concerns based on the mode of action of daratumumab are infection and hematological disturbances. Therefore, the protocol requires the review of past medical history of infections and hematological laboratory results prior to study intervention administration. CD38 is distributed in erythrocytes and platelets. A significant reduction of platelets was reported in an animal study. Across daratumumab trials, thrombocytopenia was also reported. However, safety laboratory monitoring did not show a clinically meaningful reduction of platelets. Anemia was also reported in daratumumab trials. Free hemoglobin was mildly elevated, but other parameters

did not support hemolysis. No bleeding events were observed. Routine safety laboratory measurement of red blood cells (RBCs) and platelets will be closely monitored in this study.

In a previous study with SC administration of daratumumab (Study MMY1004), a lower incidence of IRRs was observed compared to the IRR rate reported from studies with IV administration of daratumumab. However, IRRs may still occur and may develop at a later timepoint than previously observed with IV administration due to the more gradual absorption. Participants will therefore be observed for at least 6 hours on their first day of Dara-SC administration. Apart from IRRs, a similar toxicity profile has been shown for SC versus IV administration for anemia, thrombocytopenia, and other toxicities. During this study local tolerability at the SC injection site will be closely monitored as well.

The addition of Dara-IV in combination with Kd in a subgroup analysis of Study MMY1001 demonstrated a 73% VGPR rate or better in patients with relapsed or refractory multiple myeloma previously treated with 1 to 2 prior lines of therapy. Carfilzomib weekly in combination with dexamethasone in patients with relapsed or refractory multiple myeloma demonstrate VGPR or better rate of 34% in ARROW study, and 44% in CHAMPION-1 study in patients previously treated with 1 to 3 prior lines of therapy. The safety profile of weekly Kd and the addition of daratumumab is comparable. For further details and the most up-to-date information about single-agent studies, please refer to the Investigator's Brochure. The efficacy of daratumumab retreatment in combination with Kd in patients who are carfilzomib naive is unknown. In this study, participants randomized to Arm A or Arm B will be closely monitored for both safety and efficacy.

Blood volumes drawn are provided in Section 8. The total blood volume to be collected is considered to be acceptable for participants with multiple myeloma participating in a clinical study and reasonable over the timeframe of the study.

4.3. Justification for Dose

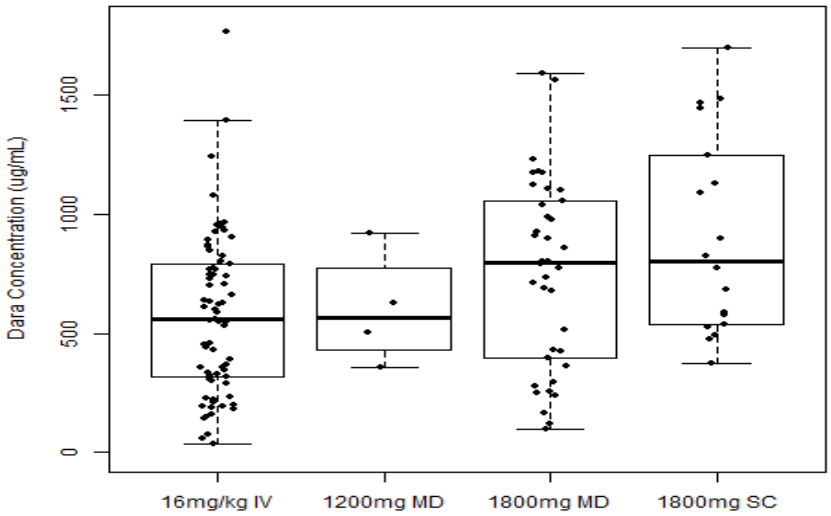
4.3.1. Rationale for Daratumumab SC Dose Regimen

Previous exposure-response analyses have demonstrated a strong correlation between ORR and the C_{trough}, of daratumumab, which occurs at the end of weekly dosing (just prior to the Cycle 3 Day 1 dose in the 16 mg/kg 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.

Eighteen participants were evaluable for PK analyses 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 SC 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 % coefficient of variation 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 Cycle 3 Day 1 (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 Cycle 3 Day 1 C_{trough} 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 SC 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 safety profile for the Dara-SC cohort is consistent with previously reported safety profiles for Dara-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, as well as this Phase 2 study.

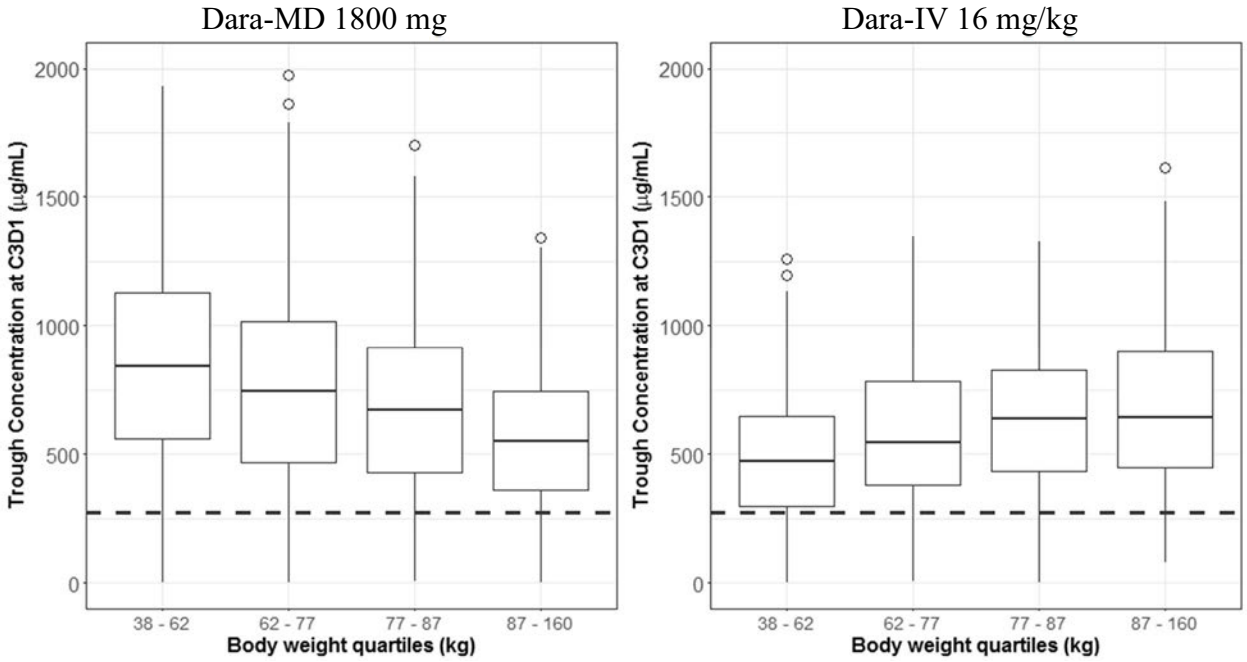
The daratumumab schedule utilized for this study is the same as has been used in the DKd cohort of Study MMY1001 with Dara-IV and as monotherapy in Studies MMY1004 and MMY3012

with Dara-SC. The dose regimen is 1800 mg Dara-SC weekly for 2 cycles, every 2 weeks for 4 cycles, and every 4 weeks thereafter (cycles are 4 weeks); this schedule is intended to quickly achieve and maintain effective daratumumab concentrations.

4.3.2. Rationale for Daratumumab Fixed Dose

The body weight range in Part 1 of Study MMY1004 was 48 to 133 kg, which was similar to that in Dara-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 Dara-IV dosing. Across the quartiles of weights for the simulated participants (n 1000), similar exposure was predicted for each dosing approach (either Dara-MD 1800 mg or Dara-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 Dara-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.

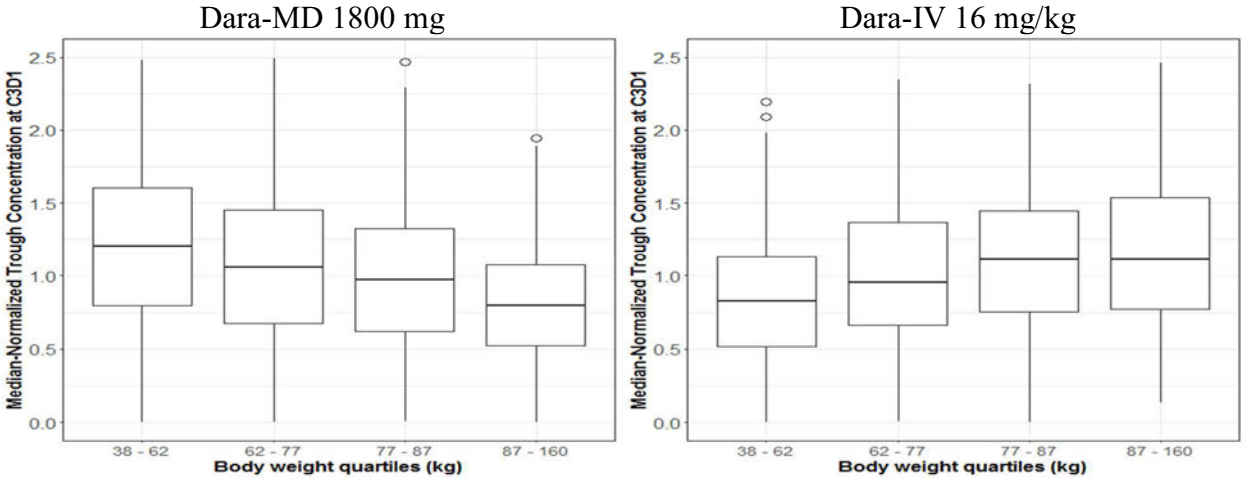
Figure 3: Predicted Maximal Trough Concentrations at Cycle 3 Day 1 for Dara-MD 1800 mg (Subcutaneous Administration) and Dara-IV 16 mg/kg (Intravenous Administration)



Footnotes: Dashed line is the effective concentration of 274 µg/mL.

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)



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

4.3.3. Rationale for Carfilzomib Dose Selection

The carfilzomib weekly dosing was chosen based on the Phase 3 ARROW study that compared once weekly carfilzomib (70 mg/m^2) with twice weekly carfilzomib (27 mg/m^2) in combination with dexamethasone.[15] The once weekly carfilzomib regimen had a 3.6 month longer PFS and a higher proportion of participants achieving response. No additional or new toxic effects were identified in the once weekly dosing regimen and the safety profile was consistent with the known safety profile of carfilzomib. Hence, this study will use the carfilzomib once weekly (70 mg/m^2) dosing regimen in combination with dexamethasone to reduce the dosing and administration burden on participants.

Participants will receive 20 mg/m^2 carfilzomib as a 30-minute IV infusion on Cycle 1 Day 1. The second dose of carfilzomib will be escalated to 70 mg/m^2, as a 30-minute IV infusion on Cycle 1 Days 8 and 15.

4.4. End of Study Definition

The end of study is no later than 2 years after the last participant has received their initial dose of study intervention or when the sponsor decides to stop the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days before randomization. Refer to Section 5.4, Screen Failures, for conditions under which the repeat of any screening procedures is allowed. Screening begins at the time the participant provides written consent for study participation.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

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

1. At least 18 years of age.

2. Criterion modified per Amendment 2

   2.1. Documented multiple myeloma as defined by the criteria below:

   Measurable disease at screening as defined by any of the following:

   Serum M-protein level ≥1.0 g/dL in participants with immunoglobulin G (IgG) type, or serum M-protein level ≥0.5 g/dL in participants with non- IgG type, or urine M-protein level ≥200 mg/24 hours; or

   Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin free light chain (FLC) ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio.

3. Criterion modified per Amendment 2

   3.1. Evidence of a response (partial response or better based on investigator's determination of response by IMWG criteria) to daratumumab-containing therapy with response duration of at least 4 months.

4. Criterion modified per Amendment 1

   4.1. Participants must have progressed from or be refractory to their last line of treatment. Relapsed or refractory disease as defined below:

   Relapsed disease is defined as an initial response to previous treatment, followed by confirmed PD by IMWG criteria >60 days after cessation of treatment.

   Refractory disease is defined as <25% reduction in M-protein or confirmed PD by

IMWG criteria during previous treatment or ≤60 days after cessation of treatment.

5. Criterion modified per Amendment 2

5.1. Received 1 to 3 prior line(s) of treatment of which one contained daratumumab and completed daratumumab at least 3 months prior to randomization. A single line of therapy may consist of 1 or more agents, and may include induction, hematopoietic stem cell transplantation, and maintenance therapy. Radiotherapy, bisphosphonate, or a single short course of corticosteroids (no more than the equivalent of dexamethasone 40 mg/day for 4 days) would not be considered prior lines of therapy.

6. ECOG Performance Status score of 0, 1, or 2 (Appendix 7).

7. Pretreatment clinical laboratory values meeting the following criteria during the Screening Phase:

   a) hemoglobin ≥8 g/dL (≥5 mmol/L) (without prior RBC transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted);

   b) absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L (prior growth factor support is permitted but must be without support within the 7 days prior to the laboratory test);

   c) platelet count $\geq 75 \times 10^9$/L for participants in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count of $\geq 50 \times 10^9$/L. Transfusions are not permitted within 7 days of testing to achieve this minimum platelet count.

   d) aspartate aminotransferase (AST) ≤2.5 × upper limit of normal (ULN);

   e) alanine aminotransferase (ALT) ≤2.5 × ULN;

   f) total bilirubin ≤1.5 × ULN; except in participants with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 × ULN is required);

   g) estimated creatinine clearance (CrCl) ≥20 mL/min per 1.73 m^2. CrCl to be calculated using estimated glomerular filtration rate Modification of Diet in Renal Disease (MDRD) formula (Appendix 8).

   h) albumin-corrected serum calcium ≤14 mg/dL (≤3.5 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L) (Appendix 9)

8. Criterion modified per Amendment 1

8.1. Women of childbearing potential must commit to either abstain continuously from

heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously. This includes one highly effective form of contraception (tubal ligation, intrauterine device, hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). A reduction in the effectiveness of oral contraceptives during carfilzomib treatment cannot be excluded. In addition, because of the increased risk of venous thromboembolic events associated with carfilzomib, women should avoid the use of hormonal contraceptives that are associated with a risk of thrombosis during treatment with carfilzomib. Women of childbearing potential who are using oral contraceptives or a hormonal method of contraception that is associated with a risk of thrombosis should switch to an alternative method of highly effective contraception. Contraception must begin with study treatment initiation and continue for 3 months after discontinuing study treatment. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy.

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 study treatment.

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

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

9. Women of childbearing potential must have a negative urine or serum pregnancy test at screening within 14 days prior to randomization.

10. Criterion modified per Amendment 1

10.1. Each participant must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study. Participants must be willing and able to adhere to the prohibitions and restrictions specified in this protocol, as referenced in the ICF.

5.2. Exclusion Criteria

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

1. Criterion deleted per Amendment 2

2. Previous treatment with carfilzomib.

3. Previous treatment with daratumumab within the last 3 months prior to randomization.

4. Criterion modified per Amendment 2

   4.1. Discontinuation of daratumumab due to a daratumumab-related AE.

5. History of malignancy (other than multiple myeloma) unless all treatment of that malignancy was completed at least 2 years before consent and the patient has no evidence of disease. Further exceptions are squamous and basal cell carcinomas of the skin and 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.

6. Allergies, hypersensitivity, or intolerance to daratumumab, hyaluronidase, mAbs, human proteins, or their excipients (refer to the IB), or known sensitivity to mammalian-derived products. Known history of allergy to Captisol (a cyclodextrin derivative used to solubilize carfilzomib).

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

8. Criterion modified per Amendment 1

   8.1. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before randomization (except for investigational anti-myeloma treatments, which cannot be taken within 2 weeks or 5 PK half-lives of the treatment from the date of randomization, whichever is longer).

9. Pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study intervention.

10. Plans to father a child while enrolled in this study or within 3 months after the last dose of study intervention.

11. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

12. Criterion modified per Amendment 1

    12.1. Received anti-myeloma treatment within 2 weeks or 5 PK half-lives of the treatment from the date of randomization, whichever is longer. The only exception is

emergency use of a short course of corticosteroids (equivalent of dexamethasone 40 mg/day for a maximum of 4 days; see Appendix 10) up to 21 days before treatment. A list of anti-myeloma treatments with the corresponding PK half-lives is provided in the Site Investigational Product Procedures Manual.

13. Received autologous stem cell transplant within 12 weeks before the date of randomization, or the participant has previously received allogeneic stem cell transplant (regardless of timing).

14. Plans to undergo a stem cell transplant prior to progression of disease on this study.

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

16. Clinical signs of meningeal involvement of multiple myeloma.

17. Either of the following:

    a) Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) is <50% of predicted normal. Note that FEV1 testing also is required for participants suspected of having COPD and participants must be excluded if FEV1 is <50% of predicted normal.

    b) Known moderate or severe persistent asthma, or a history of asthma within the last 2 years, or currently has uncontrolled asthma of any classification (Appendix 11). (Participants who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.)

18. Criterion modified per Amendment 2

    18.1. Participant is:

    a) known to be seropositive for human immunodeficiency virus (HIV), with 1 or more of the following:

        i. Not receiving highly active antiretroviral therapy (ART)
        ii. Had a change in ART within 6 months of the start of screening
        iii. Receiving ART that may interfere with study treatment (consult Sponsor for review of medication prior to enrollment)
        iv. CD4 count <350 at screening
        v. Acquired immunodeficiency syndrome (AIDS)-defining

opportunistic infection within 6 months of start of screening

vi. Not agreeing to start ART and be on ART >4 weeks plus having HIV viral load <400 copies/mL at end of 4-week period (to ensure ART is tolerated and HIV controlled)

b) seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Participants with resolved infection (ie, participants 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 polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Participants 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 (See Appendix 16).

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).

19. Concurrent medical or psychiatric condition or disease (eg, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease, pulmonary hypertension) that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study.

20. Uncontrolled hypertension, defined as an average systolic blood pressure >159 mmHg or diastolic >99 mmHg despite optimal treatment (measured following European Society of Hypertension/European Society of Cardiology 2013 guidelines).

21. Clinically significant cardiac disease, including:

Myocardial infarction within 6 months before date of randomization, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV; Appendix 12).

Uncontrolled cardiac arrhythmia (Grade 2 or higher by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version 4.03) or clinically significant electrocardiogram (ECG) abnormalities.

Transthoracic echocardiogram or MUGA scan showing left ventricular ejection fraction <40%.

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

23. Myelodysplastic syndrome, plasma cell leukemia (>2.0 × 10^9/L circulating plasma cells by standard differential) or Waldenström's macroglobulinemia or POEMS syndrome

(polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) or amyloidosis.

24. Not able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder) or the participant has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise their well-being) or that could prevent, limit, or confound the protocol-specified assessments.

25. Major surgery within 2 weeks before randomization, or has not fully recovered from an earlier surgery, or has major surgery planned during the time the participant is expected to participate in the study or within 2 weeks after the last dose of study intervention administration. Kyphoplasty or vertebroplasty are not considered major surgery. Note: participants with planned surgical procedures to be conducted under local anesthesia may participate. If there is a question whether a procedure is considered a major surgery, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study.

26. Plasmapheresis within 28 days before randomization. Pleural effusions requiring thoracentesis within 14 days prior to randomization. Ascites requiring paracentesis within 14 days prior to randomization. Grade 3 or worse neuropathy within 14 days prior to randomization.

27. Cirrhosis of the liver.

28. Intolerance to hydration due to preexisting pulmonary or cardiac impairment.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 4.

5.3. Restrictions During Study Participation

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.5, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

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

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

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

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not enrolled into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once their condition changes. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Participants who are determined to be eligible for the study after rescreening must sign a new ICF and will be assigned a new participant number.

6. STUDY INTERVENTION

6.1. Study Interventions Administered

Participants will be treated with Kd alone (Arm A) or Dara-SC in combination with Kd (Arm B) in 28-day cycles as detailed in Table 4.

Table 4: Study Interventions Administered

Study Intervention Dose	Study Intervention Schedule
Daratumumab 1800 mg SC (Arm B only)	On Days 1, 8, 15, 22 for Cycles 1 and 2, Days 1 and 15 for Cycles 3-6, Day 1 for Cycles 7+
Dexamethasone 40 mg (Arms A and B)	On Days 1,8, 15, 22 for Cycles 1-9[a], then on Days 1, 8, 15 for Cycles 10+
Carfilzomib 20 mg/m^2 on Cycle 1 Day 1, then 70 mg/m^2 thereafter (Arms A and B)	On Days 1, 8, and 15 of each cycle

a For Cycle 1 only, dexamethasone dose will be 20 mg on Cycle 1 Day 1, a second dose of 20 mg will be given on Cycle 1 Day 2. From Cycle 1 Day 8 onward, dexamethasone will be given as a single 40 mg dose as described.

Dara-SC and carfilzomib will be administered by qualified site staff, and the details of each administration will be recorded in the electronic case report form (eCRF). Participants will be provided with a treatment diary which will be used to assess compliance with dexamethasone treatment. Additional details are provided in the Site Investigational Product Procedures Manual (SIPPM) or equivalent document.

Guidelines regarding the discontinuation of study intervention and participant discontinuation/withdrawal are provided in Section 7.

6.1.1. Daratumumab (Arm B Only)

Dara-SC will be administered by SC injection at a fixed dose of 1800 mg. The dose of Dara-SC will remain constant throughout the study, and dose modification of Dara-SC (increase or decrease) is not permitted. On days when more than one investigational product is administered, the required order of administration is as follows: dexamethasone (see Section 6.1.2), pre-administration medications for Dara-SC (see Sections 6.1.1.1), Dara-SC, then carfilzomib (see Section 6.1.3). Dose delay is the primary method for managing daratumumab-related toxicities as summarized in Section 6.1.1.4.

Doses will be administered by manual push over 3-5 minutes in the abdominal SC tissue in left/right locations, alternating between individual doses. The volume of the SC solution for injection 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. Participants will receive pre-administration medications and post-administration medications as outlined in Sections 6.1.1.1 and 6.1.1.2, respectively. All participants in Arm B 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 Dara-SC injections may include but are not limited to the following: participants with a higher risk of respiratory complications (eg, participants with mild asthma or participants with COPD who have an FEV1 <80% at screening or developed FEV1 <80% during the study without any medical history), participants with IRR with first injection of Dara-SC, or participants with a decreased condition on day of dosing compared to prior dosing day.

If an IRR develops, then the injection should be temporarily interrupted or slowed down (see Section 6.1.1.3.2). In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or anaphylactic reaction, Dara-SC should be discontinued and no additional Dara-SC should be administered to the participant. See Section 6.1.1.3.1 for instructions on the management of local ISRs.

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

Dara-SC will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients. For a definition of study intervention overdose, refer to Section 8.4, Treatment of Overdose.

6.1.1.1. Pre-administration Medication

On days when more than 1 investigational product is administered, the required order of administration is as follows: dexamethasone (see Section 6.1.2), pre-administration medications for Dara-SC, Dara-SC, then carfilzomib.

To decrease the risk of IRRs, all participants on Arm B will receive the following medications 1-3 hours prior to each Dara-SC administration:

- An antihistamine: diphenhydramine 25-50 mg IV or PO, or equivalent (see Appendix 13 for list of antihistamines that may be used). Avoid IV promethazine.
- Paracetamol (acetaminophen) 650-1000 mg IV or PO.
- Montelukast 10 mg is recommended on Cycle 1 Day 1 only up to 3 hours prior to the Dara-SC injection and is optional before all other doses.

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

6.1.1.2. Post-administration Medication

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

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

In addition, participants at-risk for respiratory complications may be hospitalized for monitoring for up to 2 nights after an injection after Dara-SC administration. If participants are hospitalized, then their FEV1 should be measured before discharge. If these participants are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after all injections. If the participant 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 participant is released from the hospital/clinic. If, after 4 full doses, an at-risk participant experiences no major IRR, then these post-injection medications may be stopped.

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

6.1.1.3.1. Local Injection-site Reactions

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

6.1.1.3.2. Infusion-related Reactions

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

If an IRR develops, then Dara-SC administration should be temporarily interrupted. Participants who experience AEs during Dara-SC administration must be treated for their symptoms. Participants should be treated with paracetamol (acetaminophen), antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, participants may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, participants may require vasopressors. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or an anaphylactic reaction, Dara-SC should be discontinued.

Infusion-related Reactions of Grade 1 or Grade 2

If the investigator assesses a Grade 1-2 IRR to be related to administration of study intervention, then the Dara-SC administration should be interrupted. When the participant's condition is stable, Dara-SC administration may be restarted at the investigator's discretion. Refer to the SIPPM for further details regarding continuation of Dara-SC administration.

If the participant 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 participant must be permanently discontinued from Dara-SC treatment.

Infusion-related Reactions of Grade 3 or Higher

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

If the intensity of the AE returns to Grade 3 after restart of the Dara-SC administration, then the participant must be permanently discontinued from Dara-SC treatment.

For IRR AEs that are Grade 4, the Dara-SC administration must be stopped, and the participant permanently discontinued from Dara-SC treatment.

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 Dara-SC administration, the participant must be permanently discontinued from Dara-SC treatment.

6.1.1.4. Dose Modification

Dose modification of 1800 mg Dara-SC (increase or decrease) is not permitted. Dose delay is the primary method for managing daratumumab-related toxicities. On the first day of each new treatment cycle and before each dose of study intervention, the participant 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 4.03. Cycle delays will be based on the toxicity experienced during the previous cycle of therapy or newly encountered on Day 1 of a cycle.

If any of the following criteria are met and the toxicity is more than expected for the backbone therapy (carfilzomib, 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:

- Grade 4 hematologic toxicity, except for Grade 4 lymphopenia
- Grade 3 or higher thrombocytopenia with bleeding
- Febrile neutropenia of any grade
- Neutropenia with infection, of any grade
- Grade 3 or higher nonhematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of Dara-SC
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of Dara-SC
  - Grade 3 pain associated with symptoms of multiple myeloma (bone/joint pain)

Study intervention should be resumed when the toxicity has resolved to ≤Grade 2. If study intervention administration does not commence within the prespecified window of the scheduled administration date (Table 5), 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 Administration Schedule for Dose Delays

Cycles	Frequency	Dose Held	Dosing Restart
1 and 2	Weekly (q1wk)	>3 days	Next planned weekly dosing date
3 to 6	Every 2 weeks (q2wks)	>7 days	Next planned every 2 weeks dosing date
7+	Every 4 weeks (q4wks)	>14 days	Next planned every 4 weeks dosing date

Any dose hold of more than 28 days due to toxicity will result in permanent discontinuation of Dara-SC. Dose holds of more than 28 days for other reasons should be discussed with the sponsor. If a dose delay occurs, then PK and pharmacodynamic assessments should be performed on the actual day of study intervention administration, not on the original scheduled administration day.

Delay of Day 1 drug dosing in any given cycle should not result in a skipped dose but should lead to a delay of the entire cycle instead. A minimum of 4 days between Dara-SC doses must be observed.

A study intervention dose held for more than 3 days 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. Participants missing ≥3 consecutive planned doses of study intervention for reasons other than toxicity should be withdrawn from study intervention, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

6.1.2. Dexamethasone (Arms A and B)

Dexamethasone 40 mg weekly must be administered as 20 mg by IV infusion or PO on Cycle 1 Day 1, then 20 mg by IV infusion or PO on Cycle 1 Day 2. Dexamethasone 40 mg doses subsequent to Cycle 1 Day 2 may be administered by IV infusion or PO weekly. For days when dexamethasone is given in the absence of carfilzomib and in the absence of Dara-SC, it may be given within ±2 days for each scheduled dose.

On days when more than 1 investigational product is administered, the required order of administration is as follows: dexamethasone, pre-administration medications for Dara-SC, Dara-SC, then carfilzomib.

For Arm A, dexamethasone will be administered between 30 minutes to 4 hours prior to carfilzomib followed by carfilzomib dosing.

For Arm B, during weeks when dexamethasone, Dara-SC and carfilzomib will be administered, dexamethasone will be administered within 1 to 3 hours prior to the Dara-SC, followed by Dara-SC dosing and then carfilzomib dosing (dexamethasone must be administered no more than 4 hours prior to carfilzomib dosing). During weeks when dexamethasone and Dara-SC will be administered; dexamethasone will be administered within 1 to 3 hours prior to the Dara-SC, followed by Dara-SC dosing. During weeks when dexamethasone and carfilzomib will be administered, dexamethasone will be administered between 30 minutes to 4 hours prior to carfilzomib followed by carfilzomib dosing.

6.1.2.1. Dexamethasone: Dosage Adjustments, Dosage Discontinuation

All dexamethasone administrations must be within 2 days of the scheduled administration. However, it must be given on days carfilzomib or Dara-SC will be administered.

For participants 75 years of age or older, initial starting dexamethasone dose of 20 mg weekly IV/PO is permitted. Dexamethasone 20 mg weekly must be administered as 20 mg by IV infusion or PO on Cycle 1 Day 1 and subsequently administered by IV infusion or PO weekly. If participant is intolerant to dexamethasone 20 mg weekly IV/PO, dose reduction to 12 mg weekly IV/PO is permitted and may be administered as a split dose over 2 days; 8 mg on the first day and 4 mg on the second day. If participant is intolerant to dexamethasone 12 mg weekly IV/PO, dose reduction to 8 mg weekly IV/PO is permitted and must be administered as a single dose.

For participants younger than 75 years of age, or underweight (body mass index [BMI]<18.5), or who are intolerant to dexamethasone 40 mg once weekly IV/PO, subsequent dexamethasone may be administered at a split dose of 20 mg twice weekly IV/PO. If a participant is intolerant of a split dose of 20 mg twice weekly IV/PO, then dexamethasone dose reduction to 20 mg weekly IV/PO is permitted and may be administered at a split dose of 10 mg twice weekly IV/PO. If participant is intolerant to dexamethasone 20 mg weekly IV/PO, dose reduction to 12 mg weekly IV/PO is permitted and may be administered as a split dose over 2 days; 8 mg on the first day and 4 mg on the second day.

Dexamethasone will be permanently discontinued after 2 dose reductions in the event of additional dexamethasone-related toxicities. At the investigator's discretion, dexamethasone may be tapered prior to complete discontinuation according to institutional practice. The participant may continue on treatment with the other protocol specified drug(s). Guidelines for dexamethasone-related toxicities are summarized in Table 6.

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

Table 6: Treatment Guidelines for Dexamethasone-related Toxicity

Symptom	Findings	Recommended Action
Cardiovascular	Edema >Grade 3 (anasarca or limiting function and unresponsive to therapy)	• Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose by another dose decrement. • Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Gastrointestinal Toxicity	Dyspepsia, gastric or duodenal ulcer, or gastritis Grade 1 or 2 (requiring medical management)	• Continue dexamethasone at same dose and treat with therapeutic doses of histamine 2 (H2) blockers, or proton pump inhibitor. • Consider adding sucralfate or other antiulcer treatment as clinically indicated. • If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
	Dyspepsia, gastric or duodenal ulcer, or gastritis ≥Grade 3 (requiring hospitalization or surgery)	• Hold dexamethasone until symptoms return to baseline. • Restart dexamethasone at 1 dose decrement along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. • If symptoms persist despite above measures, discontinue dexamethasone permanently.
	Acute pancreatitis	• Discontinue dexamethasone permanently.
General Disorders	Limb edema >Grade 3 (>30% limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self-care activities of daily living)	• Hold dexamethasone until symptoms return to baseline. • Diuretics as needed, and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose by another dose decrement. • Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Psychiatric Disorders	Confusion or mood alteration ≥Grade 2 (interfering with function ± interfering with activities of daily living)	• Hold dexamethasone until symptoms return to baseline. • Restart dexamethasone at 1 dose decrement. • If symptoms persist despite above measures, reduce by another dose decrement.
Musculoskeletal	Muscle weakness ≥Grade 2 (symptomatic and interfering with function ± interfering with activities of daily living)	• Decrease dexamethasone by 1 dose decrement. • If weakness persists, decrease dose by another dose decrement. • Discontinue dexamethasone permanently if symptoms persist.
Metabolism and Nutrition Disorders	Hyperglycemia ≥Grade 3 (fasting glucose >250 mg/dL)	• Withhold dexamethasone, treat with insulin or other hypoglycemic agents as needed until glucose is ≤Grade 2 (<250 mg/dL) then resume dexamethasone. • If uncontrolled despite above measures, decrease dose by 1 dose decrement until ≤Grade 2 (<250 mg/dL).
All Other	Other toxicity ≥Grade 3 felt related to dexamethasone	• Hold dexamethasone dose. Resume at 1 dose decrement when toxicity has resolved to ≤Grade 2. • If toxicity recurs, hold dexamethasone dose until toxicity has resolved to ≤Grade 2 and resume dexamethasone dose by another dose decrement. • If toxicity recurs despite 2 dose decrements, discontinue dexamethasone permanently.

6.1.3. Carfilzomib (Arms A and B)

Carfilzomib will be administered in 28-day cycles. All cycles will start 28 days (±3) after the start of the prior cycle. Once-weekly carfilzomib must never be administered within the 5 days following a previous carfilzomib infusion. Carfilzomib IV will be administered at a dose of 20 mg/m^2 on Cycle 1 Day 1, then 70 mg/m^2 thereafter over 30 minutes (±5 minutes). On days when more than 1 investigational product is administered, the required order of administration is as follows: dexamethasone, pre-administration medications for Dara-SC, Dara-SC, then carfilzomib.

The amount (in mg) of carfilzomib to be administered will be determined by body surface area (BSA), which will be calculated according to a standard nomogram (Appendix 14). The calculated dose of carfilzomib may be rounded to the nearest milligram (eg, a calculated dose of 152.5 mg may be rounded to 153 mg). Additionally, participants with BSA >2.2 m^2 should be given a dose based on a BSA of 2.2 m^2. Dose adjustments must be made for weight gains/losses of ≥20% of baseline body weight.

6.1.3.1. Prehydration (for Arm A and Arm B)

Adequate hydration is required prior to dosing in Cycle 1, especially in patients at high risk of tumor lysis syndrome or renal toxicity. The recommended hydration includes both oral fluids (30 mL per kg at least 48 hours before Cycle 1 Day 1) and intravenous fluids (250 mL to 500 mL of normal saline or other appropriate IV fluid prior to each dose in Cycle 1). If needed, administer an additional 250 mL to 500 mL of intravenous fluids following carfilzomib administration. Continue oral or intravenous hydration as needed in subsequent cycles, if the participant's condition or risk factors require it. Monitor patients for evidence of volume overload and adjust hydration to the participant's needs, especially in patients with or at risk for cardiac failure. The total volume of prehydration and the reason for prehydration after Cycle 1 will be recorded.

6.1.3.2. Carfilzomib: Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Carfilzomib may be discontinued, temporarily delayed, or dosage temporarily reduced, in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants the discontinuation, temporary delay or dose reduction, as indicated in Table 7 and Table 8. The participant will be considered on protocol treatment while receiving either carfilzomib or Dara-SC (ie, if either carfilzomib or Dara-SC are discontinued or interrupted, the participant is still considered on treatment if still taking the other investigational product).

If Day 1 of a cycle is delayed, all subsequent doses within the cycle and day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. However, if a within-cycle dose is delayed, then the dates of the subsequent within-cycle doses should not be adjusted. For within-cycle doses, if administration does not commence within the allowable window 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. Administration may be within ±2 days for each scheduled dose.

If a participant requires an interruption of carfilzomib of more than 4 weeks, the participant should be removed from study treatment. Exceptions to this must be discussed with the study medical monitor.

Table 7: Carfilzomib Dosing Guidelines for Treatment-emergent Hematologic Toxicity

Hematologic Toxicity	Recommended Action[a]	
Thrombocytopenia		
When platelets fall to ≤30 × 10^9/L	If platelets 10–30 × 10^9/L without evidence of bleeding	Continue at same dose
	If evidence of bleeding or platelets <10 × 10^9/L	Withhold dose until platelets return to ≥10 × 10^9/L and/or bleeding is controlled, then resume at same dose.
For each subsequent drop to ≤30 × 10^9/L	If platelets 10–30 × 10^9/L without evidence of bleeding	Continue at same dose
	If evidence of bleeding or platelets <10 × 10^9/L	Withhold dose until platelets return to ≥10 × 10^9/L and/or bleeding is controlled, then resume at 1 dose decrement.
Neutropenia		
When ANC falls to ≤0.75 × 10^9/L	If ANC 0.5–0.75 × 10^9/L	Continue at same dose.
	If ANC <0.5 × 10^9/L	Withhold dose until ANC returns to ≥0.5 × 10^9/L, then resume at same dose.
For each subsequent drop to ≤0.75 × 10^9/L	If ANC 0.5–0.75 × 10^9/L	Continue at same dose.
	If ANC <0.5 × 10^9/L	Withhold dose until ANC returns to ≥0.5 × 10^9/L, then resume at 1 dose decrement.
Neutropenic fever	If <1000/mm^3 and single temperature >38.3°C OR temperature >38.0°C for more than 1 hour	Withhold dose until ANC returns to baseline grade, then resume at same dose.

a. The maximum allowed dose interruption is 28 days.
Abbreviations: ANC = absolute neutrophil count.

Table 8: Carfilzomib Dosing Guidelines for Treatment-emergent Nonhematologic Toxicities

Nonhematologic Toxicity	Recommended Action[a]
Renal Dysfunction	
Serum creatinine equal to or greater than 2 × baseline, or CrCl <15 mL/min (or CrCl decreases to ≤50% of baseline), or need for dialysis	• Withhold dose and continue monitoring renal function (serum creatinine or creatinine clearance). • If attributable to carfilzomib, resume when renal function has recovered to within 25% of baseline; start at 1 dose level reduction. • If not attributable to carfilzomib, dosing may be resumed at the discretion of the physician. • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. For patients on dialysis receiving carfilzomib, the dose is to be administered after the dialysis procedure.
Hepatic Dysfunction and Related Investigations	
≥Grade 3 elevation in liver function tests (AST, ALT, or total bilirubin)[b]	• Withhold dose. Resume at 1 dose decrement when toxicity has resolved to baseline.[c]

Table 8: Carfilzomib Dosing Guidelines for Treatment-emergent Nonhematologic Toxicities	
Nonhematologic Toxicity	**Recommended Action[a]**
Grade 3 Infection	• Withhold carfilzomib until infection resolves. Resume carfilzomib at same dose.
Congestive heart failure	• Any participant with symptoms of congestive heart failure, whether or not drug related, must have the dose held until resolution or return to baseline, after which treatment may continue at a reduced dose, or the participant may be permanently discontinued. • If no resolution after 4 weeks, the participant will be withdrawn from all study treatment.
LVEF Reductions	
For resting LVEF <40% or reduction of LVEF to <55% if the drop is greater than 20% from baseline	• Withhold until LVEF returns to >40% or, if held due to a drop to <55%, to within 15% of baseline. Resume at 1 dose decrement.[c]
Micro-Angiopathy	
Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)	• If suspected TTP/HUS, withhold carfilzomib. • Manage symptoms per standard of care including plasma exchange as clinically indicated. • If the diagnosis of TTP/HUS is excluded, carfilzomib administration may resume if clinically appropriate. • If TTP/HUS is confirmed, permanently discontinue carfilzomib.
Tumor Lysis Syndrome	
3 or more of the following: • Increase in creatinine of ≥50% from baseline • Increase in uric acid of ≥50% from baseline • Increase in phosphate of ≥50% from baseline • Increase in potassium of ≥30% from baseline • Decrease in calcium from baseline OR • Increase in LDH of ≥2-fold from baseline	• Hold carfilzomib until all abnormalities in serum chemistries have resolved; resume at full dose.
Neuropathy	
Grade 2 with emergent pain or Grade 3 Grade 4	• Hold carfilzomib until resolved to ≤Grade 2 without pain; then resume at 1 dose decrement. • Permanently discontinue carfilzomib.
Hypertension (SBP ≥140 and/or DBP ≥90)	
<Grade 3 ≥Grade 3	• Continue at the same dose if initiation of appropriate treatment controls hypertension • Hold carfilzomib until resolution to normal or baseline. Initiate appropriate anti-hypertensive therapy prior to resuming carfilzomib at 1 dose decrement.
Dyspnea (≥Grade 2)	• Hold carfilzomib until resolution to Grade 1 or baseline, then resume at 1 dose decrement. Investigate cause and record findings. If caused by another adverse event listed in this table, follow recommendations for that adverse event.

Table 8: Carfilzomib Dosing Guidelines for Treatment-emergent Nonhematologic Toxicities	
Nonhematologic Toxicity	**Recommended Action[a]**
Pulmonary toxicity: non-infectious interstitial lung disease, acute respiratory failure, ARDS (≥Grade 3)	• Hold carfilzomib until resolution to Grade 1 or baseline and restart at 1 dose decrement.
Progressive Multifocal Leukoencephalopathy (PML)	• Participants should be monitored for any new or worsening neurologic, cognitive, or behavioral signs or symptoms that may be suggestive of PML as part of the differential diagnosis of CNS disorders. • If PML is suspected, withhold administration of carfilzomib; participants should be promptly referred to a specialist and appropriate diagnostic testing should be initiated. • Discontinue carfilzomib if PML diagnosis is confirmed. If the diagnosis is excluded, carfilzomib can be restarted at the same dose.
Any Other Drug-Related Nonhematologic Toxicity ≥Grade 3	• For carfilzomib attribution, withhold dose. • Resume at 1 dose decrement when toxicity has resolved to Grade 2 or less or to baseline grade. • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. • Additional dose modification guidance for adverse drug reactions are per the carfilzomib IB.
Pulmonary Hypertension	• Withhold until resolved or returned to baseline • Restart at the dose used prior to the event or reduce dose by 1 dose level (ie, 27 mg/m^2 to 20 mg/m^2 for the twice weekly schedule or 70 mg/m^2 to 56 mg/m^2 for the once weekly schedule), at the discretion of the physician. • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician.
Posterior reversible encephalopathy syndrome (PRES; with symptoms including headaches, altered mental status, seizures, visual loss, and hypertension)	• If suspected PRES, withhold carfilzomib. • Consider evaluation with neuroradiological imaging for onset of visual or neurological symptoms suggestive of PRES. • If the diagnosis of PRES is excluded, carfilzomib administration may resume if clinically appropriate.

Note: Carfilzomib dose schedule does not need to be adjusted for baseline renal dysfunction.
a. The maximum allowed dose interruption is 28 days.
b. If AST or ALT is ≥3 × ULN, the "evaluation of treatment-emergent liver abnormalities" eCRF should be completed.
c. Dose reduction should be attempted first to manage treatment-emergent toxicities.
Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; ARDS = Acute respiratory distress syndrome; AST = aspartate aminotransferase; CNS = central nervous system; CrCl = creatinine clearance; DBP = diastolic blood pressure; eCRF = electronic Case Report Form; HUS=hemolytic uremic syndrome; IB = Investigator's Brochure; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; mL = milliliter(s); PRES=posterior reversible encephalopathy syndrome; SBP = systolic blood pressure; ULN = upper limit of normal; TTP=thrombotic thrombocytopenic purpura.

6.1.3.3. Carfilzomib: Dose Reduction Levels

Dose reduction levels of carfilzomib for toxicity management of individual participants are provided in Table 9. Participants that require a dose level reduction and tolerate the reduced dose for 1 full cycle, may at the discretion of the treating physician increase the dose to a prior dose starting with the next cycle except when the dose reduction is due to: pulmonary

hypertension, pulmonary toxicity, Grade 3 or worse cardiac failure, and drug-induced hepatotoxicity.

Table 9: Dose Decrements for Carfilzomib

Dose[a, b] (mg/m^2)	First Dose Reduction Dose -1 (mg/m^2)	Second Dose Reduction Dose -2 (mg/m^2)	Third Dose Reduction Dose -3 (mg/m^2)
70	56	45	36

a. If dose reduction of carfilzomib is required on Cycle 1 Day 1, the investigator should contact the medical monitor to discuss the situation, before any additional doses of carfilzomib are administered.
b. For patients with baseline chronic hepatic impairment (mild, moderate), reduce the starting and subsequent doses of carfilzomib by 25% (ie, 15 mg/m^2 Cycle 1 Day 1 and 52.5 mg/m^2 Cycle 1 Day 8 and thereafter).

Abbreviations: CxDx = Cycle X Day X

6.1.3.4. Carfilzomib: Guidelines for Hematologic Toxicity

Guidelines for carfilzomib dose modification in the event of thrombocytopenia and neutropenia are summarized in Table 7.

6.1.3.5. Carfilzomib: Guidelines of Nonhematologic Toxicity

Guidelines for dose modification in the event of nonhematologic toxicities are summarized in Table 8.

6.1.4. Conditions Not Requiring Dose Reduction

Carfilzomib, Dara-SC, and dexamethasone do not need to be held in the following cases:

- Grade 3 nausea, vomiting, or diarrhea (that responds within 7 days to adequate treatment of antiemetics and/or antidiarrheal agents)
- Grade 3 dexamethasone-related hyperglycemia
- Isolated Grade 3 g-glutamyl transferase elevation
- Grade 3 fatigue (unless persisting for >7 days)
- Alopecia

6.2. Preparation/Handling/Storage/Accountability

Detailed instructions for preparation, handling, and storage of study interventions will be supplied in the SIPPM, IPPI, or equivalent document.

Refer to the SIPPM for additional guidance on study intervention preparation, handling, and storage.

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. All study intervention will be stored and

disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

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

Study intervention 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 intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by prior protease inhibitor exposure and daratumumab-free interval (3-6 months, >6 months). The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

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

6.4. Study Intervention Compliance

Study intervention will be administered by qualified site staff, and the details of each administration will be recorded in the eCRF. Additional details are provided in the SIPPM or equivalent document.

6.5. Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.5.4. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

All prestudy antineoplastic and multiple myeloma therapies must be recorded at screening. Other prestudy therapies administered from the signing of the ICF must be recorded at screening. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

Routine systemic use of clinically significant 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 intervention or until the start of subsequent anticancer treatment, if earlier.

Concomitant medications to manage AEs and SAEs will be recorded. Concomitant therapies should also be recorded beyond 30 days only in conjunction with SAEs that meet the criteria outlined in SAEs in Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information.

Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication.

6.5.1. Required Therapies

6.5.1.1. Prophylaxis for Herpes Zoster Reactivation

The initiation of antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting study intervention and continuing for 3 months following study intervention is required. 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 PO, twice a day or per institutional standards), or valacyclovir (eg, 500 mg given PO, twice a day or per institutional standards), initiated within 1 week after the start of study intervention.

6.5.2. Recommended Therapies

6.5.2.1. Bisphosphonate Therapy

Bisphosphonate therapy is strongly recommended for all participants with evidence of lytic destruction of bone or with osteopenia. Bisphosphonate therapy is recommended to be continued per treatment guidelines.[16,17] Commercially available IV bisphosphonates (pamidronate and zoledronic acid) are preferred when available, and should be used according to the manufacturer's recommendations, as described in the prescribing information, for participants 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 participants at their sites.

Participants who are currently using bisphosphonate therapy when they enter the study should continue the same treatment.

6.5.2.2. Prevention of Steroid Induced Gastritis

Dexamethasone and other steroids may induce gastritis. Medications to prevent gastritis are strongly recommended. Acceptable therapies include proton pump inhibitors (omeprazole or equivalent), sucralfate, or H2 blockers (ranitidine or equivalent) initiated within 1 week after the start of study intervention.

6.5.2.3. Therapy for Tumor Lysis Syndrome

Participants should be monitored for symptoms of tumor lysis syndrome. Management of tumor lysis syndrome, including hydration for abnormal laboratory test results such as hyperkalemia, hyperuricemia, and hypocalcemia, is highly recommended. High-risk participants (ie, those with a high tumor burden) should be treated prophylactically in accordance with local standards (eg, vigorous hydration, diuretics, allopurinol 300 mg daily, and medication to increase urate excretion).

6.5.2.4. Therapy for Pneumocystis carinii/jirovecii

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

6.5.2.5. Management of Hepatitis B Virus Reactivation

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for participants at risk for HBV reactivation see Section 8.2.8.

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

6.5.3. Permitted Therapies

Participants 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:

- Antivirals
- Colony stimulating factors, erythropoietin, and transfusion of platelets and red cells are allowed.
- Laxatives or stool softeners
- Adequate hydration is recommended for prevention of myeloma-related kidney disease.

- Vaccination is allowed per local guidelines (see Section 6.5.4 for Prohibited Therapies).

Other symptoms may be managed according to institutional guidelines provided prohibited therapies are not administered (see Section 6.5.4, Prohibited Therapies).

6.5.4. Prohibited Therapies

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

- Concomitant administration of any other antineoplastic therapy for the intention of treating multiple myeloma is prohibited, including medications that target CD38, as well as medications used for other indications that have anti-myeloma properties (eg, interferon and clarithromycin). Continuation of study intervention (during or after emergency orthopedic surgery or radiotherapy because of participant benefit) may only occur in the absence of disease progression and after consultation with and approval by the sponsor.
- Concomitant administration of investigational agents and of commercially available agents with activity against or under investigation for multiple myeloma are prohibited.
- Systemic corticosteroids (>10 mg dexamethasone per day or equivalent) other than those given as backbone therapy and for IRRs should be avoided.
- Nonsteroidal anti-inflammatory agents should be avoided to prevent myeloma-related kidney disease.
- 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 participant for whom delay of systemic therapy is not appropriate, but radiotherapy field must not include a measurable extramedullary plasmacytoma. Radiotherapy must occur within the first 2 cycles of study intervention and only if disease progression has not occurred. Before radiotherapy, the sponsor will review the participant data and confirm that disease progression has not occurred.
- Administration of live-attenuated and replication-competent viral vector vaccines are prohibited.

6.6. Intervention After the End of the Study

The sponsor will ensure that participants benefiting from study treatment will be able to continue receiving Dara-SC and carfilzomib after the end of the study until these agents are commercially available or available from another source. Subsequent therapy is left to the investigator's discretion. Subsequent therapy should be documented in the CRF.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Completion

A participant 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, died, and has not withdrawn consent for study participation before the end of the study.

7.2. Discontinuation of Study Intervention

A participant will not be automatically withdrawn from the study if he or she has to discontinue intervention. The End-of-Treatment Visit and Follow-up visit assessments should continue as specified in Schedule of Activities (Table 1).

A participant's study intervention must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue all study interventions. End of treatment is defined as discontinuation of all study interventions. Participants who discontinue one of the 3 study interventions may continue the other study interventions.
- The participant becomes pregnant unless the participant, investigator, and sponsor agree the benefits outweigh the risks to the fetus and continuation of study intervention is in the best interests of the participant. Refer to Appendix 6.
- The participant withdraws consent for administration of additional study intervention
- The participant starts concurrent (non-protocol) treatment for multiple myeloma
- The participant experiences intolerable toxicity, including IRRs (see Section 6.1.1.3)
- The participant experiences disease progression as defined by IMWG criteria (see Table 10). Neither relapse from CR nor clinical relapse are considered as disease progression.
- The participant experiences a second primary malignancy that cannot be treated by surgery alone. However, a participant who develops a malignancy that can be cured surgically may continue to receive the assigned study treatment and should continue to be followed for subsequent progression of multiple myeloma.
- The participant initiates treatment with a prohibited medication.

If a participant discontinues study intervention for any reason before the end of the Treatment Phase, disease assessments should be obtained and scheduled assessments should be continued until disease progression is confirmed. The participant will complete the End-of-Treatment Visit and enter the Follow up Phase. Follow-up will continue until the end of study. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed. The primary reason for discontinuation of study treatment is to be recorded in the CRF.

7.3. Participant Discontinuation/Withdrawal from the Study

A participant will not be automatically withdrawn from the study if they have to discontinue study intervention before the end of the intervention regimen.

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

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

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study intervention assigned to the withdrawn participant may not be assigned to another participant. Additional participants will not be entered. If a participant discontinues study intervention and withdraws from the study before the end of the Treatment Phase, End-of-Treatment and Follow-up assessments should be obtained. If the reason for withdrawal from the study is withdrawal of consent to study intervention and all procedures and follow-up, then no additional assessments are allowed.

7.4. Lost to Follow-up

If a participant is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the participant and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented. Refer to Section 7.3, Participant Discontinuation/Withdrawal from the Study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (Table 1 to Table 3) summarizes the frequency and timing of efficacy, PK, immunogenicity, biomarker, medical resource utilization, and safety.

Urine and blood collections for PK assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

Medical resource utilization data will be collected. Refer to Section 8.7, Medical Resource Utilization for details.

The total blood volume (based on a median of 16 cycles) is 766 mL. This includes screening, cycles inclusive of safety, blood typing, daratumumab PK and immunogenicity and rHuPH20 immunogenicity, biomarkers, disease evaluations and pregnancy testing and EOT and follow up. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Sample Collection and Handling

Refer to the Schedule of Activities (Table 1 to Table 3) for the timing and frequency of all sample collections. The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, US Pharmacopeia (or equivalent) sodium heparin of 10 U/mL and charged with a volume equal to the dead space volume of the lock. If a mandarin (obturator) is used, blood loss due to discard is not expected.

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.

Study-Specific Materials

The investigator will be provided with the following supplies:

- IBs for daratumumab and carfilzomib
- Investigational Product Preparation Instructions
- Site Investigational Product Procedures Manual
- Laboratory manual
- IWRS Manual
- eCRF completion guidelines
- ICF
- Participant identification wallet card, including space for blood type and indirect antiglobulin test (IAT) result
- Participant treatment diary
- Other manuals and guidance documents as needed

8.1. Efficacy Assessments

8.1.1. Response Categories

During study treatment, disease evaluations must be performed every 28 days (±7 days) until disease progression. If a participant discontinues study treatment for reasons other than disease progression, disease evaluations should be conducted every 8 weeks (±7 days) until confirmed disease progression, death, start of a new treatment for multiple myeloma, withdrawal of consent, or the end of the study, whichever occurs first. Disease evaluations will be performed by a central laboratory (unless otherwise specified). This study will use the IMWG consensus recommendations for multiple myeloma treatment response criteria[8,11,21] presented in Table 10. All serum and urine disease evaluations will be performed by a central laboratory according to Section 1.3. For quantitative immunoglobulin, M-protein, and immunofixation measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory. For participants with light chain multiple myeloma, only serum FLC assay will be performed routinely. Otherwise, serum FLC assay test results will be analyzed by the central laboratory only for the assessment of sCR. For participants with suspected daratumumab interference on serum M-protein quantitation by electrophoresis (SPEP) and immunofixation, a reflex assay will be performed (Appendix 15). Participants with confirmed daratumumab interference who meet all other clinical criteria for CR or sCR will be considered CR/sCR.

Table 10: International Uniform Response Criteria Consensus Recommendations

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.
Minimal response (MR)	• ≥25% but ≤49% reduction of serum M-protein, *and* • Reduction in 24-h urine M-protein by 50–89% • In addition to the above criteria, if present at baseline, a 25% to 49% reduction in the size of soft tissue plasmacytomas also is required
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR, MR, or PD

Table 10: International Uniform Response Criteria Consensus Recommendations

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 participants 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 participants without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage irrespective of baseline status; the 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; MR minimal response; 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 participants in whom the only measurable disease is by serum FLC levels: CR in such participants indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such participants requires a >90% decrease in the difference between involved and uninvolved FLC levels.

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

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

Clinical Relapse

Clinical relapse is defined using the definition of clinical relapse in IMWG criteria.[9,11,21] In IMWG criteria, clinical relapse is defined as requiring one or more of the following direct indicators of increasing disease or end organ dysfunction that are considered related to the underlying plasma cell proliferative disorder:

1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, magnetic resonance imaging, or other imaging
2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross diameters of the measurable lesion
3. Hypercalcemia (>11.5 mg/dL; >2.875mM/L)
4. Decrease in hemoglobin of more than 2 g/dL (1.25 mM) or to less than 10 g/dL
5. Rise in serum creatinine by more than or equal to 2 mg/dL (≥177 mM/L)
6. Hyperviscosity

In some participants, bone pain may be the initial symptom of relapse in the absence of any of the above features. However, bone pain without imaging confirmation is not adequate to meet these criteria in studies.

Disease progression must be consistently documented across clinical study sites using the criteria in Table 10. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed. It is important that instances of disease progression be reported to the sponsor as soon as possible. Diagnosis and documentation of disease progression will be reported to the sponsor within 24 hours of suspected disease progression. The medical monitor will review the information to confirm that the IMWG criteria for disease progression have been met. If the medical monitor agrees that disease progression has occurred, then a confirmation will be returned to the investigator, and the participant will be withdrawn from study intervention. If the medical monitor considers that the IMWG criteria for disease progression have not been met, then the medical monitor will contact the investigator to discuss the participant.

For continuation of study intervention, the IMWG response will be determined on an ongoing basis by the investigator. For data analysis and reporting, however, the sponsor will use a validated computer algorithm that has been shown to provide consistent review of the data necessary to determine disease progression and response according to IMWG criteria.

For participants who discontinue study intervention before disease progression, disease evaluations should continue to be performed as described in the Schedule of Activities (Table 1 to Table 3), until confirmed disease progression, death, start of a new treatment for multiple myeloma, withdrawal of consent, or the end of the study, whichever occurs first. Blood and urine for disease evaluations scheduled for treatment days should be collected before study intervention is administered.

8.1.2. Myeloma Protein Measurements in Serum and Urine

Blood and 24-hour urine samples will be collected as specified in the Schedule of Activities (Table 1 to Table 3) until the development of confirmed disease progression. Samples for M-protein measurements will be sent to and analyzed by a central laboratory. Only one serum and one 24-hour urine sample per time point are required by the central laboratory to perform the following tests:

- Serum Quantitative Immunoglobulins: All participants will be evaluated for IgG, immunoglobin A (IgA), immunoglobin M (IgM), immunoglobin D (IgD), and immunoglobin E (IgE) at screening. During the study, participants with IgD or IgE disease will be evaluated for IgG, IgA, IgM, IgE, and IgD and participants with IgG, IgA, or IgM disease will be evaluated for IgG, IgA, and IgM.
- Serum M-Protein quantification by electrophoresis (SPEP)
- Serum immunofixation at screening and thereafter when a CR is suspected. If daratumumab interference is suspected based on SPEP and immunofixation electrophoresis (IFE) results, additional reflex IFE testing may be performed.
- Serum FLC assay
- 24-hour urine M-protein quantitation by electrophoresis (UPEP)
- Urine immunofixation at screening and thereafter when a CR is suspected

Disease progression based on one of the laboratory tests alone must be confirmed by at least one repeat investigation.

Participants with a urine M-protein on UPEP ≥100 mg/24h at screening will provide samples for UPEP assessment on the same schedule as SPEP throughout the study according to the Schedule of Activities (Table 1). Blood samples for SPEP and SIFE must be collected on the same day that 24-hour urine samples for UPEP and UIFE starts or stops. Participants may stop collecting samples for UPEP assessments after Cycle 1 Day 1 only if 1) they have urine M-protein <100 mg/24h at screening, or 2) they have measurable urine M-protein ≥100 mg/24h at screening but then urine M-protein <100 mg/24h at 2 consecutive post-baseline measurements. A urine sample for UPEP assessment should be obtained to document VGPR, CR, and sCR and at suspected disease progression for all participants with measurable disease by SPEP or UPEP (non-FLC), regardless of UPEP collection exemptions as described above.

Serum and urine immunofixation tests and serum FLC assay will be performed at screening, Day 1 of each cycle, and thereafter when a CR is suspected (when serum or 24-hour urine M-protein electrophoresis [by SPEP or UPEP] are 0 or nonquantifiable). For participants with suspected daratumumab interference on serum immunofixation, another reflex assay using the anti-idiotype mAb will be used to confirm daratumumab migration on immunofixation. Participants that meet all other IMWG criteria for CR, and whose positive immunofixation is confirmed to be daratumumab, will be considered complete responders. However, for participants with light chain multiple myeloma, serum FLC assay will be performed routinely. Serum immunofixation assay samples will be split into 2 aliquots, with 1 reserved for potential follow-on testing if daratumumab interference with immunofixation is suspected. As daratumumab is a monoclonal IgG antibody, additional serum samples may be utilized to monitor for potential daratumumab interference with immunofixation.

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

8.1.3. Serum Calcium Corrected for Albumin

Blood samples for calculating serum calcium corrected for albumin will be collected as specified in the Schedule of Activities (Table 1) and analyzed centrally until the development of confirmed disease progression. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L) can indicate disease progression or relapse if it is not attributable to any other cause (see disease response criteria in Table 10). Calcium binds to albumin and only the unbound (free) calcium is biologically active; therefore, the serum calcium level must be adjusted for abnormal albumin levels ("corrected serum calcium"). The formula for adjustment is presented in Appendix 9.

When blood is analyzed at a local laboratory, measurement of free ionized calcium is an acceptable alternative to corrected serum calcium to determine hypercalcemia. Free ionized calcium levels greater than the ULN (local laboratory reference ranges) are considered to be hypercalcemic for this study.

8.1.4. 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 and used for the assessment of International Staging System staging at study entry. The central laboratory will also measure albumin at any time during the study that a serum calcium sample is taken.

8.1.5. Bone Marrow Examination

Bone marrow assessments to be performed locally and centrally are summarized in Table 3. MRD evaluation will be performed centrally, while the cytogenetic analysis will be performed locally. If cytogenetic analysis is not available locally, this may be done centrally with agreement of the sponsor. The following FISH probes should be used for cytogenetic analysis:

- Required: t(4;14); t(14;16), del (17p)
- Optional: Amplification 1q

8.2. Safety Assessments

AEs will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Appendix 5. Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF. Any 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 condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities (Table 1).

8.2.1. Physical Examination

A complete physical examination (including neurological examination) should be performed during screening. Thereafter, a physical examination that is symptom- and disease-directed as clinically indicated is to be performed at each treatment visit. Abnormalities will be recorded in the appropriate section of the eCRF.

8.2.2. Vital Signs

Temperature, pulse/heart rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse/heart rate measurements will be assessed sitting with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

8.2.3. Electrocardiogram

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants 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, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Appendix 3. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

8.2.5. Pulmonary Function Test

Participants with known or suspected COPD must have a spirometry FEV1 test during screening.

8.2.6. Indirect Antiglobulin Test

Blood group and type, Rh, and IAT should be done before the first dose of Dara-SC. Participant RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first study intervention administration.

Daratumumab interferes with the IAT, which is a routine pre-transfusion test performed to identify a participant's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/rhesus D antigen (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. Participants will receive a participant identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first study intervention administration, along with information on the IAT interference for healthcare providers/blood banks. Participants are to carry this card throughout the Treatment Phase and for at least 6 months after study intervention ends. Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol.[4,5]

Possible methods for blood banks to provide safe RBCs for transfusion to participants 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 dithiothreitol-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 IB

8.2.7. HBV Serology

All participants 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 unless this was performed as part of standard of care within 3 months prior to first dose.

8.2.8. HBV-DNA Test

Participants who are positive for Anti-HBc or Anti-HBs will undergo testing for hepatitis B DNA by PCR. Participants 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, participants who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the Schedule of Activities (Table 1). Where required by local law, the results of HBV testing may be reported to the local health authorities.

8.2.9. Eastern Cooperative Oncology Group Performance Status

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

8.2.10. Transthoracic Echocardiogram or Multiple-Gated Acquisition Scan

Participants must have a transthoracic echocardiogram (TTE) or Multiple-Gated acquisition (MUGA) scan according to the Schedule of Activities (Table 1) showing left ventricular ejection fraction $\geq$40%. A trans-esophageal echocardiogram (TEE) will be an acceptable alternative to TTE or MUGA if performed as part of standard of care.

8.3. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, 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.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver or surrogate) for the duration of the study. Anticipated events will be recorded and reported as described in Appendix 2.

For further details on AEs and SAEs (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Appendix 5.

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

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study intervention; during the follow-up phase, only treatment-related SAEs will be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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 eCRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. In the event that the Serious Adverse Event eCRF cannot be completed, information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted electronically or by facsimile (fax).

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

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 5.

8.3.3. Regulatory Reporting Requirements for Serious Adverse Events

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). For anticipated events reported as individual SAEs, the sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the intervention caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the

institute where required). The sponsor assumes responsibility for appropriate reporting of anticipated events to the regulatory authorities according to requirements of the countries in which the studies are conducted. The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

8.3.4. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants 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 participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study intervention unless the participant, investigator, and sponsor agree the benefits outweigh the risks to the fetus and continuation of study intervention is in the best interests of the participant. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.5. Disease-Related Events and Disease-Related Outcomes That Do Not Need to be Reported as Adverse Events or Serious Adverse Events

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.

8.4. Treatment of Overdose

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.

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

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

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

8.5. Pharmacokinetics

Serum samples will be used to evaluate the PK of daratumumab. Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

8.5.1. Evaluations

Venous blood samples will be collected for measurement of serum concentrations of daratumumab and anti-daratumumab antibodies according to the Schedule of Activities (Table 1 and Table 2).

Samples will also be collected from all participants in Arm B to evaluate the immunogenicity of rHuPH20 according to Table 2.

Venous blood samples will be collected, and each serum sample will be divided into 3 aliquots (1 each for PK, anti-daratumumab antibodies, and a back-up). Samples collected for analyses of daratumumab serum concentration and antibody to daratumumab may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

8.5.2. Analytical Procedures

Pharmacokinetics

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

Immunogenicity

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

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

8.5.3. Pharmacokinetic Parameters and Evaluations

Parameters

The trough concentrations will be reported by visit and treatment. Data from this study may be pooled with other studies to conduct a population PK analysis of serum concentration-time data

of daratumumab. If performed, details will be provided in a population PK analysis plan and results of the analysis will be presented in a separate report.

Pharmacokinetic/Pharmacodynamic Evaluations

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

8.5.4. Immunogenicity Assessments

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

When an IRR occurs associated with daratumumab administration, 2 blood samples should be obtained, if possible, for determination of antibodies to daratumumab and antibodies to rHuPH20. Daratumumab serum concentration will also be determined from the daratumumab IRR sample for interpreting immunogenicity data. If the infusion reaction results in treatment discontinuation, then participants 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.

Participants who discontinue study intervention or withdraw from the study before confirmation of PD should have samples collected at the time of early discontinuation. Participants who discontinue study intervention will also be asked to return for immunogenicity evaluation during the Follow-up Phase.

8.6. Biomarkers

Bone marrow aspirate samples collected at screening will be subjected to DNA sequencing to establish a multiple myeloma clone for MRD monitoring (calibration). MRD assessment by via the FDA cleared clonoSEQ V2.0 next generation sequencing (NGS) for the assessment of MRD for patients with multiple myeloma and several studies have demonstrated that MRD status is correlated with PFS and OS.[12,14] In this study, bone marrow samples will be collected when a bone marrow aspirate is performed at screening and at the subsequent points outlined in the Schedule of Activities (Table 1 and Table 3). Bone marrow aspirates will be utilized for assessment of MRD by NGS of immunoglobulin heavy and light chains as specified. If this

methodology is unavailable, or determined to be scientifically inferior, then alternative methods for MRD assessment may be utilized.

Whole blood samples will be collected from participants as outlined in the Schedule of Activities (Table 1) and processed to isolate plasma and peripheral blood mononuclear cell (PBMCs). Changes in immune subpopulations; including T cells (cytotoxic, regulatory memory), B cells, NK cells and myeloid derived suppressor cells, as a result to treatment with daratumumab, could be contributing factors to its duration of response. Therefore, subsequent PD might come as a result of alterations in the daratumumab-induced equilibrium. The data will be analyzed using mass cytometry (CyTOF) and fluorescence-activated cell sorting and in association with clinical data may be examined to identify specific signatures associated with response and resistance.

8.7. Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit)
- Number and character of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications)

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

Dara-SC in combination with Kd will have a higher VGPR or better rate as the best response than Kd in participants who have previously received 1 to 3 prior line(s) of therapy including daratumumab.

9.2. Sample Size Determination

Based on Study MMY1001 study data, the rate of VGPR or better as the best response was 68% for DKd participants not previously treated with daratumumab. If VGPR or better rate is assumed to be 60% for DKd and 45% for Kd in the current study, 230 participants (assigned 1:1) are needed in order to detect an absolute 15% increase in VGPR or better rate with 70% power using a 2-sided chi-squared test at the 10% significance level.

9.3. Populations for Analyses

Analysis of the primary and secondary efficacy endpoints will be based on the intent-to-treat (ITT) analysis set, which will include all randomized participants. All safety analyses are to be performed on data from the all treated analysis set, which will include all participants who received at least 1 dose of study intervention. Pharmacokinetic analyses will be performed on the PK-evaluable population, defined as participants who have at least one PK sample concentration value.

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

The primary endpoint of VGPR rate or better is defined as the proportion of participants who achieve VGPR, CR, or sCR as the best response according to the IMWG criteria, after initial dose of study intervention and before disease progression or start of subsequent anti-myeloma treatment. The rate of VGPR or better will be compared between the treatment arms using the stratified Cochran-Mantel-Haenszel test. The stratification factors are prior PI exposure and daratumumab-free interval (3-6 months, >6 months) at randomization.

Categorical secondary endpoints including ORR, rate of CR/sCR, and MRD negativity rate, will be analyzed similarly as the primary endpoint. The time-to-event efficacy endpoints, such as PFS, OS, and time to next treatment, will be analyzed using the Kaplan-Meier method.

The primary analysis will be carried out with a 2-sided alpha level of 0.10. The secondary efficacy analyses will be carried out using 2-sided alpha level of 0.10 without multiplicity adjustment.

The primary analysis will be conducted approximately 6 months after the last participant receives the initial dose of study intervention. An interim futility analysis will occur when 40% of participants are enrolled and treated for 6 months. A final analysis will occur at study completion/end of the study to update PFS, survival, second primary malignancy and safety.

9.4.2. Safety Analyses

The baseline value for safety assessment is defined as the value collected at the time closest to, but prior to, the start of study intervention administration. The safety parameters to be evaluated are the incidence, severity, and type of AEs, clinically significant changes in the participant's physical examination findings, vital signs measurements, and clinical laboratory results. Exposure to investigational product and reasons for discontinuation of study intervention will be tabulated.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs are AEs with onset during the intervention phase or that are a consequence of a pre-existing condition that has

worsened since baseline. All reported AEs will be included in the analysis. Adverse events will be summarized by system organ class, preferred term, worst grade experienced by the participant, and by dose level. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or a SAE.

Parameters with predefined NCI-CTCAE toxicity grades will be summarized.

Clinical Laboratory Tests

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

Electrocardiogram

Electrocardiogram data will be summarized on categories of normal, abnormal, either clinically significant or not clinically significant.

Vital Sign

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

Physical Examination

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

9.4.3. Other Analyses

Pharmacokinetic Analyses

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

Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point.

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

Biomarkers Analyses

Baseline bone marrow aspirate samples will be evaluated by a NGS assay to establish the myeloma clone (calibration) and for MRD monitoring. In this study, bone marrow samples will be collected when a bone marrow aspirate is performed at screening and at the subsequent timepoints outlined in the Schedule of Activities (Table 1 and Table 3). Whole blood sample will be collected from participants as outlined in the Schedule of Activities (Table 1 to Table 3) and processed to plasma and PBMCs.

Any biomarker measurements will be listed, tabulated, and where appropriate, plotted. Statistical analyses will be done to aid in the understanding of the results. Results of biomarker may be presented in a separate report.

Immunogenicity Analyses

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

Pharmacokinetic/Pharmacodynamic Analyses

PK/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.

Medical Resource Utilization Analyses

Medical resource utilization will be descriptively summarized by intervention group.

9.5. Interim Analysis

An interim futility analysis will be conducted after 40% of participants are enrolled and treated for 6 months. The rate of VGPR or better will be the primary endpoint for the futility analysis. If the observed rate of VGPR or better in the DKd group is no higher than the rate in the Kd group, then the null hypothesis (no treatment difference in rate of VGPR or better) will be accepted, and the study will be terminated. This criterion only serves as a statistical guidance. Assuming the rate of VGPR or better in the Kd group is 45%, the probability of early termination is at least

53% if in fact the rate in the DKd group is no higher than 45%, and the probability of termination is no greater than 8% if in fact the rate of VGPR or better in the DKd group is at least 60%.

9.5.1. Data Review Committee

An internal Data Review Committee (DRC) will be established as noted in Committees Structure in Appendix 4. The scheduled DRC meetings will take place when the first 60 participants complete 1 cycle of the study treatment, and every 6 months thereafter. In addition, there will be a scheduled meeting to review the results of the interim futility analysis.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ADA	anti-daratumumab antibodies
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
antiHBC	antibodies to hepatitis B core antigen
antiHBS	antibodies to hepatitis B surface antigen
ART	antiretroviral therapy
AST	aspartate aminotransferase
BMI	body mass index
BSA	body surface area
C_{max}	maximum observed concentration
C_{min}	mean minimum observed concentration
CD38	cluster of differentiation 38
COPD	chronic obstructive pulmonary disease
CR	complete response
CrCl	creatinine clearance
CSR	clinical study report
CT	computed tomography
C_{trough}	maximum trough concentration
CyTOF	mass cytometry
Dara-IV	daratumumab administered intravenously
Dara-MD	daratumumab and recombinant human hyaluronidase for SC injection: mix and deliver formulation
Dara-SC	daratumumab subcutaneous
DKd	daratumumab SC in combination with carfilzomib and dexamethasone
DRC	Data Review Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
e-GFR	estimated glomerular filtration rate
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FISH	fluorescence in situ hybridization
FLC	free light chain
FVC	forced vital capacity
GCP	Good Clinical Practice
H2	histamine 2
HBV	hepatitis B virus
HCV	hepatitis C virus
HRT	hormonal replacement therapy
IAT	indirect antiglobulin test
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IF	immunofluorescence

IFE	immunofixation electrophoresis
IgA	immunoglobin A
IgD	immunoglobin D
IgE	immunoglobin E
IgG	immunoglobin G
IgM	immunoglobin M
IHC	immunohistochemistry
IMiD	immunomodulatory agents
IMWG	International Myeloma Working Group
IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board
IRR	infusion-related reaction
ISR	injection-site reaction
ITT	intent-to-treat
IV	intravenous(ly)
IWRS	interactive web response system
Kd	carfilzomib and dexamethasone
LDH	lactic acid dehydrogenase
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MDRD	Modified Diet in Renal Disease
MRD	minimal residual disease
MUGA	multiple-gated acquisition
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
NK	natural killer
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression free survival
PFS2	progression-free survival on next line of therapy
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PO	oral
PQC	product quality complaint
PRES	posterior reversible encephalopathy syndrome
RBC	red blood cell
RhD	rhesus D antigen
rHuPH20	recombinant human hyaluronidase PH20
SAC	Safety Assessment Committee
SAE	serious adverse event
SC	subcutaneous(ly)
sCR	stringent complete response
SIFE	serum immunofixation
SIPPM	Site Investigational Product Procedures Manual
SOC	standard of care
SPEP	serum M-protein quantitation by electrophoresis
SPM	second primary malignancy
SUSAR	suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TEE	trans-esophageal echocardiogram
TTE	transthoracic echocardiogram
TTP/HUS	thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
UIFE	urine immunofixation

ULN	upper limit of normal
UPEP	urine M-protein quantitation by electrophoresis
Vd	bortezomib-dexamethasone
VGPR	very good partial response

10.2. Appendix 2: Anticipated Events

Anticipated Event

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

For the purposes of this study the following events will be considered anticipated events:
Bleeding
Bone diseases
Hypercalcemia
Hyperuricemia
Hyperviscosity syndrome
Infection
Renal failure or insufficiency

Reporting of Anticipated Events

All AEs will be recorded in the eCRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described under All AEs in Appendix 5. Any anticipated event that meets SAE criteria will be reported to the sponsor as described in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information. Each anticipated event will be assessed by the investigator at the individual case level and if considered to be drug-related will undergo expedited reporting (if appropriate) as per applicable clinical trial legislation to Health Authorities and IRBs/IECs. If an anticipated event is considered disease-related or not related to study drug the event will be exempt from expedited reporting.

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

Safety Assessment Committee (SAC)

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

Statistical Analysis

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

10.3. Appendix 3: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities (Table 1) by the local laboratory:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Hemoglobin Platelet count	White Blood Cell (WBC) count Absolute neutrophil count Absolute lymphocyte count
Serum Chemistry	Sodium Potassium Creatinine Glucose (fasting or non-fasting) Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT) Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)	Total bilirubin Alkaline phosphatase Lactic acid dehydrogenase (LDH) Uric acid Calcium and albumin-adjusted calcium[a]
Other Screening Tests	Serum or urine pregnancy testing for women of childbearing potential only	
	HBV DNA (For participants with serologic evidence of resolved HBV infection (i.e., positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally)	
	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])	

[a] These parameters will be part of the efficacy evaluations as specified in Section 8.1.3

10.4. Appendix 4: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

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

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

Protocol Amendments

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

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

Regulatory Approval/Notification

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

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention 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, participant 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 Food and Drug Administration [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 participant:

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

Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants 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 participants
- 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 participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant 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 participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB 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 intervention

- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants 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 participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

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

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

Country Selection

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

Other Ethical Considerations

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

FINANCIAL DISCLOSURE

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

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

INFORMED CONSENT PROCESS

Each participant 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 participant 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 participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants 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 participant will receive for the treatment of his or her disease. Participants 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 participant 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 participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant 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 the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF

Where local regulations require, a separate ICF may be used for the required DNA component of the study.

If the participant 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 participant is obtained.

When prior consent of the participant is not possible, 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 participant and to ensure compliance with applicable regulatory requirements. The participant must be informed about the study as soon as possible and give consent to continue.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from participants 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 participants confidential.

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

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory PK and immunogenicity research is not conducted under standards appropriate for the return of data to participants. 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 participants 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.

DATA REVIEW COMMITTEE (DRC) STRUCTURE

A DRC will be established to ensure the continuing safety of the participants enrolled in this study and to review safety results at the planned interim analyses. Committee membership responsibilities, authorities, and procedures will be documented in its charter.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

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 investigator agrees 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 investigator understands 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 CSR 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 CSR has been issued will be reported in a separate report and will not require a revision of the CSR.

Study participant 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 (ICMJE) 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 the 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 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.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, 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 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.

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in eCRF. 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 participant's source documents. Data must be entered

into eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the electronic data capture (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.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant 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; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

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

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

The following data will be recorded directly into the eCRF and will be considered source data (ie, must be recorded in patient medical records):

Race

Blood pressure and pulse/heart rate

Height and weight

Details of physical examination

ECOG, medical resource utilization data

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

- Referral letter from treating physician 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 participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

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

MONITORING

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

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

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. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

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

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, 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.

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

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

STUDY AND SITE CLOSURE

Study Termination

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

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

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

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

10.5. Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per 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 All AEs under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

An SAE event 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 participant 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 participant 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 intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For daratumumab, the expectedness of an AE will be determined by whether or not it is listed in the IB. For Kd, the expectedness of an AE will be determined by whether or not it is listed in the package insert/summary of product characteristics.

Adverse Event Associated With the Use of the Intervention

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

ATTRIBUTION DEFINITIONS

Not Related

An AE that is not related to the use of the study intervention.

The following attributions are considered "Not Related":

Not Related

An adverse event that is not related to the use of the intervention.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Related

An AE that is related to the use of the study intervention.

The following attributions are considered "Related":

Possible

An adverse event that might be due to the use of the intervention. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the intervention. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

SEVERITY CRITERIA

The severity assessment for an AE or SAE should be completed using the NCI CTCAE Version 4.03.

SPECIAL REPORTING SITUATIONS

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

Overdose of a sponsor study intervention

Suspected abuse/misuse of a sponsor study intervention

Accidental or occupational exposure to a sponsor study intervention

Medication error involving a sponsor product (with or without participant/patient exposure to the sponsor study intervention, eg, name confusion)

Exposure to a sponsor study intervention from breastfeeding

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

PROCEDURES

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, 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.

For all studies with an outpatient phase, including open-label studies, the participant 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 participant 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

Participant number

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant'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 intervention or to factors unrelated to study conduct

It becomes unlikely that any additional information can be obtained (participant 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 an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as an SAE, except hospitalizations for the following:

If the participant has not experienced a significant medical event but is hospitalized overnight only for observation following injection of study intervention, 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 participant for the duration of the intervention period.

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the SAE definition (refer to Adverse Event Definitions and Classifications in Appendix 5).

CONTACTING SPONSOR REGARDING SAFETY

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

PRODUCT QUALITY COMPLAINT HANDLING

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

Procedures

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

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

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

10.6. Appendix 6: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.4 and Appendix 5.

Female participants:

Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously. This includes one highly effective form of contraception (tubal ligation, intrauterine device, hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). A reduction in the effectiveness of oral contraceptives during carfilzomib treatment cannot be excluded. In addition, because of the increased risk of venous thromboembolic events associated with carfilzomib, women should avoid the use of hormonal contraceptives that are associated with a risk of thrombosis during treatment with carfilzomib. Women of childbearing potential who are using oral contraceptives or a hormonal method of contraception that is associated with a risk of thrombosis should switch to an alternative method of highly effective contraception. Contraception must begin with study treatment initiation and continue for 3 months after discontinuing study treatment. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy.

Male participants:

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

Definitions

Woman of Childbearing Potential

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

Woman Not of Childbearing Potential

premenarchal
A premenarchal state is one in which menarche has not yet occurred.

postmenopausal
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.

If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.

permanently sterile
Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

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

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

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT
Highly Effective Methods That Are User Independent *Failure rate of ≤1% per year when used consistently and correctly.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
Intrauterine device
Intrauterine hormone-releasing system
Bilateral tubal occlusion
Vasectomized partner

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

USER DEPENDENT
Highly Effective Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]

- oral
- intravaginal
- transdermal
- injectable

Progestogen-only hormone contraception associated with inhibition of ovulation[b]

- oral
- injectable

Sexual abstinence

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

NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of >1% per year)
Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
Male or female condom with or without spermicide[c]
Cap, diaphragm, or sponge with spermicide
A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
Periodic abstinence (calendar, symptothermal, post-ovulation methods)
Withdrawal (coitus-interruptus)
Spermicides alone
Lactational amenorrhea method

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

10.7. Appendix 7: Eastern Cooperative Oncology Group Performance Status Score

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

Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair (Oken 1982[19]).

10.8. Appendix 8: Modified Diet in Renal Disease Formula

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

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

For creatinine in **µmol/L**, the e-GFR for the MDRD formulas is:

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

Source: Levey 2006[13]

10.9. Appendix 9: Serum Calcium Corrected for Albumin

If calcium is expressed in mg/dL and albumin is expressed in g/dL:
Corrected calcium (mg/dL)

serum calcium (mg/dL) + 0.8 × (4 - serum albumin [g/dL])

If calcium is expressed in mmol/L and albumin is expressed in g/L:
Corrected calcium (mmol/L)

serum calcium (mmol/L) + 0.02 × (40 - serum albumin [g/L])

(Burtis 1998[3])

10.10. Appendix 10: Conversion Table for Glucocorticosteroid Dose

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

10.11. Appendix 11: Asthma Guidelines

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

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
Recommended Step for Initiating Treatment	Step 1			Step 2			Step 3 and consider short course of oral steroids	Step 3: medium dose ICS and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS OR Step 4 and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids
	In 2 6 weeks, evaluate level of asthma control that is achieved. 0 4 years: If no clear benefit is observed in 4 6 weeks, stop treatment and consider alternate diagnosis or adjusting therapy. 5 11 and 12+ years: adjust therapy accordingly.											

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

10.12. Appendix 12: New York Heart Association Functional Classification

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity (eg, shortness of breath when walking or climbing stairs).
II	Mild symptoms (mild shortness of breath or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity (eg, walking short distances [20–100 m]). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

10.13. Appendix 13: Antihistamines That May Be Used Predose

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

Cetirizine

Fexofenadine

Loratadine

Clemastine

Dexchlorpheniramine

Promethazine*

* The IV use of promethazine should be avoided.

10.14. Appendix 14: Body Surface Area Calculation

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

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

or

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

10.15. Appendix 15: Interpretation of the SEBIA Hydrashift 2/4 Daratumumab Immunofixation Electrophoresis 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. Samples will be sent automatically to the central laboratory if daratumumab interference is suspected.

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

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 (ie, "IgG,k" or "IgA")

DARAHydra Impress3: result defined as "M-protein not detected" OR the specific protein detected (ie, "IgG,k" or "IgA")

If Impress1 result is "DARA detected" and Impress2 and 3 results are "M-protein not detected", the patient may be in complete response (CR) if the other criteria for CR (including negative bone marrow aspirate/biopsy) are achieved.

If Impress1 result is "DARA not detected" or "DARA indeterminate", the patient is still positive for underlying (endogenous) monoclonal protein and Impress2 and 3 can inform as to the type of endogenous protein still present. Therefore, this patient is not in a complete response (CR), because the CR response criteria requires a negative SPEP and serum IFE.

If Impress1 result is "DARA detected" but there is also protein present and reported by Impress2 or 3, the patient is still positive for underlying (endogenous) monoclonal protein and Impress2 and 3 can inform as to the type of endogenous protein still present. Therefore, this patient is not in a complete response (CR), because the CR response criteria requires a negative SPEP and serum IFE.

10.16. Appendix 16: Hepatitis B Virus Testing

HBV serology is not required at screening if this was performed as part of standard of care within 3 months prior to the start of administration of study intervention. The HBV screening guide below will be used to determine participant eligibility for the study.

Eligibility Related to Hepatitis B Test Results

Action	Hepatitis B Test Result			
	HBsAg	anti-HBs	anti-HBc	HBV-DNA[a]
Exclude	Participants who are HBsAg positive or HBV-DNA positive are excluded from the study regardless of the status of anti-HBs and anti-HBc.			
Include	Negative	Negative	Negative	Not required
	Negative	Positive	Positive	Negative
	Negative	Negative	Positive	Negative
	Negative	Positive	Negative	Negative[b]

anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; PCR=polymerase chain reaction

[a] In participants with negative HBsAg test, an HBV-DNA quantification test is required in the following participants to determine eligibility:

i. Participants who are anti-HBs positive and without history of vaccination
ii. Participants with positive anti-HBc and either positive or negative anti-HBs.
iii. Upon enrollment, participants requiring HBV-DNA PCR testing at screening will require ongoing screening for HBV-DNA by PCR every 12 weeks up to 6 months after last dose of study treatment.

[b] Participants with serologic findings suggestive of HBV vaccination (ie, 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.

10.17. Appendix 17: Protocol Amendment History

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

Amendment 1 (14 October 2019)

Overall Rationale for the Amendment: The overall rationale for the amendment is to include the language clarifying the need for contraception for all participants to continue for 3 months after the end of study treatment as well as the caution for women who are at high risk for thrombosis to use other means of birth control other than hormonal birth control which carries the highest risk of thrombosis.

Section number and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria (Criterion 8); 10.6. Appendix 6, Contraceptive and Barrier Guidance and Collection of Pregnancy Information	Changed language to eliminate requirement for 4 weeks of contraception prior to starting study treatment. Added requirement to continue contraception until 3 months after end of treatment for men and women.	Revisions made to align with a daratumumab-wide program change in language to other protocols. Added this requirement to align with current labelling of daratumumab.
5.1. Inclusion Criteria (Criterion 8); 10.6. Appendix 6, Contraceptive and Barrier Guidance and Collection of Pregnancy Information	Added recommendation for women with an increased risk of thrombosis to avoid hormonal contraception as carfilzomib also increases risk of venous thromboembolic events.	Added this recommendation to align with current labelling of carfilzomib.
1.3. Schedule of Activities (Table 1), Physical examination row; 8.2.1. Physical Examination	Text was modified to clarify timing and description of physical examination requirements.	Physical examination is required at each treatment visit.
1.3. Schedule of Activities (Table 1), Urine or serum Pregnancy test row	Decreased frequency of pregnancy testing to Screening and Cycle 1 Day 1 during the study. Added requirement for a pregnancy test at End-of-Treatment (EOT) visit.	High frequency of pregnancy testing is not necessary as none of the drugs in this study are known to be teratogenic. Given drug half-lives a pregnancy test will be required to confirm that women of childbearing potential are not pregnant 4 weeks post therapy.
8. Study Assessments and Procedures	Decreased the total blood volume collected during the study.	The decrease in the number of pregnancy tests has resulted in less blood being collected.

Section number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (Table 1) 1.3. Schedule of Activities (Table 3) 8.1.5. Bone Marrow Examination	Additional language was added to Footnote e: "If local FISH testing is unavailable, this may be performed centrally upon approval of the sponsor." Same text was added for Footnote a. Additional language was added: "If cytogenetic analysis is not available locally, this may be done centrally with agreement of the sponsor. The following FISH probes should be used for cytogenetic analysis:"	Certain sites could not perform local fluorescence in situ hybridization (FISH) testing, so a provision was made for central testing with approval of the sponsor.
1.3. Schedule of Activities (Table 1), SPEP and SIFE, 24-hour UPEP and UIFE row 8.1.2. Myeloma Protein Measurements in Serum and Urine	Footnote f was added: "Blood samples for SPEP and SIFE must be collected on the same day that 24-hour urine samples for UPEP and UIFE starts or stops." Subsequent footnotes were re-lettered. Same text was added for blood samples to this section.	Clarification was needed to ensure accurate timing for specimen collections.
Section 1.3. Schedule of Activities (Table 1) 8.2.10. Transthoracic Echocardiogram or Multiple-Gated Acquisition Scan 10.1. Appendix 1, Abbreviations	Footnote b had new text added: "A trans-esophageal echocardiogram (TEE) will be an acceptable alternative to TTE or MUGA if performed as part of standard of care." which was included as a possible modality to evaluate cardiac function. Abbreviation for TEE added to Schedule of Activities abbreviation table. Same text was added for TEEs to this section. Abbreviation for TEE added to abbreviation table.	Allowing TEEs already performed as part of standard of care will reduce unnecessary procedures.
2.1.3. Daratumumab IV	Updated the list of current approved daratumumab indications in the United States (US).	The indication list for daratumumab IV use in adult multiple myeloma patients was updated to be current with the date of this amendment.
2.2. Study Rationale	Wording was clarified to indicate that the Kd schedule proposed in this study is Food and Drug Administration (FDA) approved.	Clarification was requested to avoid the potential implication that this regimen is approved in Europe.

Section number and Name	Description of Change	Brief Rationale
4.1. Overall Design 6.6. Intervention After the End of the Study	Revised language to indicate that participants benefiting from study treatment will be able to continue receiving Dara-SC and carfilzomib after the end of the study. Revised language to indicate that participants benefiting from study treatment will be able to continue receiving both study drugs and indicated the source of the study drugs after the study ends.	Clarification that participants will be able to receive both study drugs after the study ends. Clarification that participants will be able to receive both study drugs and indicated the source of the study drugs after the study ends.
5. Study Population	Wording was changed to indicate that screening for eligible participants will be performed within 28 days before randomization.	Timeframe for screening period being based on randomization date was made to maintain consistency within the protocol.
5.1. Inclusion Criteria (Criterion 4)	Added sentence "Participants must have progressed from or be refractory to their last line of treatment."	Added sentence to clarify relapse/refractory disease requirement (participants must be relapse/refractory to *last* line of treatment.
5.1. Inclusion Criteria (Criterion 10); 7.2. Discontinuation of Study Intervention; 8.3. Adverse Events and Serious Adverse Events; 8.3.4. Pregnancy; 10.4. Appendix 4, Regulatory, Ethical, and Study Oversight Considerations	Removed references to a participant's legally acceptable representative. In Section 10.4. changes occur in Informed Consent Process, Data Protection Section.	The study does not provide for a legally acceptable representative to provide consent for participants to join this study.
5.2. Exclusion Criteria (Criterion 8, Criterion 12)	Clarified that investigational treatment washout period is measured by date of randomization for this study.	Previously references were made to randomization date and date of first dose of daratumumab; clarification was needed to specify the date of reference is the date of randomization.
6.1. Study Interventions Administered (Table 4)	Footnote a was added to the table. Table was clarified to indicate that Cycle 1 Day 1 dose of dexamethasone is given as a split dose on Cycle 1 Day 1 and Cycle 1 Day 2.	Table text was updated to align with protocol text.
6.1.2.1. Dexamethasone: Dosage Adjustments, Dosage Discontinuation	Added information that "*Note that the dose modifications above are suggested, but physician discretion and clinical judgment should prevail*."	Information added to align with other daratumumab protocols to allow for the clinical judgement of investigators regarding steroid dose reductions and modifications.
6.5. Concomitant Therapy	Revised timeframe to begin from the signing of the ICF for recording of prestudy therapies at screening.	Clarification of the timing of prestudy medications to be recorded.

Section number and Name	Description of Change	Brief Rationale
6.5.1.2. Prevention of Steroid Induced Gastritis	Revised language to indicate that medications to prevent gastritis are strongly recommended.	Clarification to allow for clinical judgement in the administration of medications for treatment to prevent gastritis.
6.5.2.1. Bisphosphonate Therapy	Revised language to indicate that it is preferred that investigators use the same route of bisphosphonate therapy for all participants at their sites.	To avoid protocol deviations, it is preferred and not required that investigators follow the same procedure for administration of bisphosphonate therapy at their sites.
6.5.4. Prohibited Therapies	Revised language to indicate that systemic corticosteroids other than those given as backbone therapy and for infusion-related reactions (IRRs) should be avoided.	Clarification to allow for clinical judgement in the administration of steroids for treatment of potential adverse events.
6.5.4. Prohibited Therapies	Information was added to explain that when providing emergency radiotherapy, the "radiotherapy field must not include a measurable extramedullary plasmacytoma".	Clarification to avoid radiation of measurable disease that could be used as part of response criteria.
8. Study Assessments and Procedures	In Study-Specific Materials, added IB for carfilzomib to list of items provided to the study sites.	Added IB for carfilzomib for completeness of items provided to the study site.
9.5. Interim Analysis	Added information on the futility analysis plan.	Added information to provide statistical guidance on futility analysis.
9.5.1. Data Review Committee	Added details on the meeting schedule of the Data Review Committee (DRC).	Details of the meeting schedule for the DRC were requested in the protocol by the Bioresearch Quality & Compliance (BRQC) Department at Janssen.
10.2. Appendix 2, Anticipated Events	Deleted the terms anemia, neutropenia, and thrombocytopenia from the anticipated events list.	These hematological laboratory adverse events are already listed as Adverse Drug Reactions (ADRs) for daratumumab. Therefore, they should not be included on this list.
10.2. Appendix 2, Anticipated Events	Revised language for expedited reporting of drug-related anticipated events to Health Authorities and IRBs/IECs.	Revisions made to align with a daratumumab-wide program change in language to clarify reporting responsibilities for anticipated events to Health Authorities and IRBs/IECs.
10.2. Appendix 2, Anticipated Events	Added details specifying when the Safety Assessment Committee (SAC) reviews of pre-specified anticipated events may be terminated.	Revisions made to align with a daratumumab-wide program change in language to other protocols. Following unblinding of aggregate safety data by the sponsor's study team, there is no need for independent SAC review of anticipated events.
10.1. Appendix 1, Abbreviations; 10.2. Appendix 2, Anticipated Events	Changed name of "Anticipated Event Review Committee" to "Safety Assessment Committee"	Changed name of committee to be in alignment with Janssen SOP (21Dec2018) for "Identification, Analysis, Assessment, and Reporting of Anticipated Events".

Section number and Name	Description of Change	Brief Rationale
10.4. Appendix 4, Regulatory, Ethical, and Study Oversight Considerations	Data Review Committee Structure Section: Changed name of "Data Monitoring Committee" to "Data Review Committee"	Changed name of committee for alignment with other references in the protocol as well as other documents (eg, DRC Charter)
10.5. Appendix 5, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Attribution Definitions Section: Added definitions of attributions not related, doubtful, possible, probable, very likely.	Added definitions which were missing from the original protocol.
10.5. Appendix 5, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Severity Criteria Section: Eliminated definitions of severity criteria; retained only reference to NCI CTCAE Version 4.03 as source of definitions.	Revisions made to align with a daratumumab-wide program change in language to other protocols.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. Text in ~~strikethrough~~ has been deleted, text in **bold** has been added:	Minor errors were noted
Title Page	Added "**Janssen Biopharma Inc**." to the sponsorship statement	Added an additional Janssen operating company to the list of legal entities to comply with protocol template updates.
6.1.3.3. Carfilzomib: Dose Reduction Levels (Table 9)	In footnote "a" deleted text for "on Cycle 1 Day 1 ~~or Cycle 1 Day 2~~, the investigator" In footnote "b" deleted text for "(ie, 15 mg/m^2 Cycle 1 Day 1 ~~and 2~~ and 52.5 mg/m^2 Cycle 1 Day 8 and thereafter)	Correction for a content error (wrong day included for dose reduction of carfilzomib).
9.4.2. Safety Analyses	In Clinical Laboratory Tests, edited sentence "Descriptive statistics will be calculated for **selected** ~~each~~ laboratory analytes at baseline…"	Wording changed to comply with protocol template updates.
10.1. Appendix 1, Abbreviations	Deleted ~~and Trademarks~~ from the title of this section.	Wording changed to comply with protocol template updates.
10.1. Appendix 1, Abbreviations	Added **Data Review Committee (DRC)**	Made corrections to protocol for consistency throughout the document.
Appendix 3, Clinical Laboratory Tests	White Blood Cell count – changed "~~C~~BC" to "**W**BC"	Made corrections to protocol for consistency throughout the document.

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INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

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

(Day Month Year)

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

Signature

User	Date	Reason
PPD	03-Jun-2021 14:52:32 (GMT)	Document Approval