Janssen Research & Development *

Clinical Protocol

A Multicenter Phase 2 Study to Evaluate Subcutaneous Daratumumab in Combination with Standard Multiple Myeloma Treatment Regimens

Protocol 54767414MMY2040; Phase 2
AMENDMENT 5

JNJ-54767414 (daratumumab)

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

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	20 December 2017
Amendment 1	06 June 2018
Amendment 2	12 October 2018
Amendment 3	31 January 2019
Amendment 4	28 January 2020
Amendment 5	30 September 2020

Amendments below are listed beginning with the most recent amendment.

Amendment 5 (30 September 2020)

The overall reason for the amendment: The overall reason for the amendment is to define when the clinical cutoff for the final analysis will occur which marks the end of data collection, to define the end of study, and to clarify access to study drugs for subjects who continue to receive study treatment after data collection has ended.

Applicable Sections	Description of Changes
Rationale: To clarify when the clinical cutoff for the final analysis will occur at which time the data collection will end.	
Synopsis: Dosage and Administration; 3.1 Overview of Study Design; 9.1.5 Final Analysis to End of Study; 17.9.1 End of Data Collection and End of Study	The data cutoff for the final analysis and the end of data collection will occur approximately 10 months after the last subject is enrolled in the D-Kd cohort. Subsequently, the clinical database will be locked for the final analysis.
3.1 Overview of Study Design	Text was updated to clarify that the data from the end of the data collection through the end of study will be reported in a Clinical Study Report (CSR) addendum.
9.1.4 Post-treatment Phase (Follow-Up)	Information regarding end of study was moved to Section 9.1.5 (a new section as of this amendment).
17.5 Case Report Form Completion; 17.9.1 End of Data Collection and End of Study	Text updated to clarify that data collection in the electronic case report form (eCRF) will not be performed after the database is closed for the final analysis.
Rationale: To define the end of study.	
9.1.5 Final Analysis to End of Study (new section)	End of study was defined.
9.6 Safety Evaluations	Text was added to indicate that after the data collection has ended, only serious adverse events will be collected.
12.3.3 Pregnancy	It was clarified that pregnancy reporting will continue until the end of study.
17.9.1 End of Data Collection and End of Study	Section heading was updated to “End of Data Collection and End of Study”. End of study was defined.

Rationale: To clarify the access to study drugs and to describe the study procedures for subjects who continue to receive study drugs after the data collection has ended.	
Synopsis: Dosage and Administration; 3.1 Overview of Study Design; 9.1.1 Overview; 17.9.1 End of Data Collection and End of Study	Text added to indicate that subjects who are benefiting from study treatment can continue receiving the study drugs after the end of the data collection until the study drugs are commercially available, available from another source, or until study completion.
Time and Events Schedules Table 1, Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9; 3.1 Overview of Study Design; 9.1.1 Overview; 9.1.5 Final Analysis to End of Study; 9.6 Safety Evaluations; 10.2 Discontinuation of Study Treatment/Withdrawal from the Study; 12.3.2 Serious Adverse Events; 12.3.3 Pregnancy; 17.5 Case Report Form Completion; 17.9.1 End of Data Collection and End of Study	Reference to Attachment 15 was added to provide a description of respective study procedures for subjects who continue to receive study drugs after the data collection has ended.
9.1.4 Post-treatment Phase (Follow-Up)	Information regarding access to study drugs for subjects who continue to receive study treatment was moved to Section 9.1.5 (a new section as of this amendment).
9.1.5 Final Analysis to End of Study (new section)	New section was added to include information that subjects benefiting from study treatment can continue receiving the study drugs after the end of data collection until the study drugs are commercially available, available from another source (eg, via a dedicated long-term extension study), or until study completion.
10.1 Completion	Text was updated to indicate that subjects can transition into receiving study drugs (including, but not limited to, daratumumab SC) which are commercially available or available from another source.
Attachment 15: Continuation of Treatment After Clinical Cutoff for the Final Analysis (End of the Data Collection)	Attachment 15 (new): provides the study procedures for the subjects who will continue receiving study drugs after the data collection ends.
Rationale: Data for the experience survey will no longer be collected.	
3.1 Overview of Study Design	The text regarding experience survey was deleted because data collection will not be occurring.
Rationale: Text in the protocol was clarified.	

10.2 Discontinuation of Study Treatment/Withdrawal from the Study	Clarified that documentation of progressive disease (PD) status in interactive web response system (IWRS) is not required after end of data collection.
12.1.1 Adverse Event Definitions and Classifications	Text was added to clarify the definition of medically important events. The following text was added: Examples of such medical events include second primary malignancy.
Rationale: Text was added to describe daratumumab approvals in the United States (US) and European Union (EU).	
1. Introduction	Text was added to clarify the most updated approval status of daratumumab IV and SC for all indications. Text reflecting the old approval status was deleted.
References	References for recent Summary of Product Characteristics (SmPC) and United States Package Insert (USPI) were added.
Rationale: Template-related changes were made.	
Confidentiality Statement; Running Footer	Updated the confidentiality statement and running footer based on the current template.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. List of abbreviations was updated.

Amendment 4 (28 January 2020)

The overall reason for the amendment: The overall reason for the amendment is to clarify the timing of the primary analysis for the daratumumab subcutaneous (SC), carfilzomib and dexamethasone (D-Kd) cohort and the end of study. In addition, this amendment includes updated text to align with the daratumumab program standard language for anticipated events and pregnancy/contraception.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify the timing of the primary analysis for the D-Kd cohort and the end of study.	
3.1. Overview of Study Design; 11.3. Efficacy Analyses	The following text was added: 'The cutoff for the primary analysis for the D-Kd cohort will occur at least 6 months after approximately the 60th subject is enrolled in the D-Kd cohort.'
3.1. Overview of Study Design; 9.1.4. Post-treatment Phase (Follow-Up)	Clarification was added that the study will end approximately 18 months after the last subject is enrolled in the D-Kd cohort.
Rationale: To clarify contraception requirements and pregnancies in partners of male subjects, which align with daratumumab program standard language, and to include lenalidomide- and carfilzomib-specific contraception guidance.	
4.1. Inclusion Criteria	Criterion #8: Modified to describe the timeline for use of contraception for women and insist on use of one highly effective form of contraception along with one additional effective contraceptive method. Also edited text regarding male contraception requirement. Criterion #8: Added cross-reference to Attachment 13. Criterion #9: Deleted text '~~men must agree not to donate sperm for the purposes of~~

Applicable Section(s)	Description of Change(s)
	~~assisted reproduction'~~ and added text 'male subjects of reproductive potential must not donate semen or sperm during the study, during dose interruptions, or for 3 months after the last dose of any study drug.
4.3. Prohibitions and Restrictions; 9.6. Safety Evaluations; 12.3.3. Pregnancy; Attachment 13: Contraceptive (and Barrier) Guidance and Collection of Pregnancy Information	Added cross-reference to Attachment 14.
Attachment 13: Contraceptive (and Barrier) Guidance and Collection of Pregnancy Information	Attachment 13 (new): added to provide clarification of definitions and contraceptive guidance and collection of pregnancy information in studies which use daratumumab and are specific for lenalidomide and carfilzomib.
Attachment 14: Lenalidomide Global Pregnancy Prevention Plan	Attachment 14 (new): added to include the lenalidomide global pregnancy prevention plan.
9.6. Safety Evaluations; 12.3.3. Pregnancy	Additional text regarding the pregnancy reporting requirements and pregnancy prevention plan for lenalidomide, and pregnancies in partners of male subjects was added.
10.2. Discontinuation of Study Treatment/Withdrawal from the Study	Text was added to specify that if a positive pregnancy test occurred in a subject enrolled in lenalidomide containing cohort, lenalidomide was to be discontinued immediately or if it occurred in the partner of a male subject enrolled in lenalidomide containing cohort investigator was to be informed immediately.
Rationale: To clarify the timing of dexamethasone administration in relation to carfilzomib administration.	
6.1.4. D-Kd Cohort; 6.4.1.1 Pre-administration Medication	Added text 'When carfilzomib is given first'.
6.1.4. D-Kd Cohort	Deleted '~~will~~' and added 'should' for administration of carfilzomib followed by daratumumab SC when both are given on the same day.
Table 13 Treatment Schedule and Dosing (D-Kd Cohort); 6.1.4. D-Kd Cohort	Deleted '~~will~~' and added 'should' for administration of half dose of dexamethasone before and after administration of daratumumab.
Rationale: Modified the list of anticipated events to remove any events that are known adverse drug reactions of daratumumab. Clarification that after unblinding of aggregate safety data by the sponsor's study team, there is no need for independent Safety Assessment Committee (SAC) review of anticipated events. Additional clarification of the reporting responsibilities for anticipated events to Health Authorities and Institutional Review Boards (IRB)/Independent Ethics Committees (IEC). Changed name of committee to be in alignment with company	

Applicable Section(s)	Description of Change(s)
procedures.	
Attachment 11: Anticipated Events	Anemia, neutropenia, and thrombocytopenia were deleted from the anticipated events list. The review and reporting requirements for anticipated events were clarified. Revised "Anticipated Event Review Committee" to "Safety Assessment Committee".
Rationale: To eliminate the possibility of inconsistency between the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version number referenced in the protocol and the standard AE grade descriptions outlined in the protocol.	
12.1.3. Severity Criteria	Removed definitions of severity criteria as they are specified in NCI-CTCAE Version 4.03.
Rationale: The definition of duration of response (DOR) was revised as subjects in the daratumumab SC in combination with bortezomib, lenalidomide, and dexamethasone (D-VRd) cohort received only 4 cycles of study treatment and DOR was not calculated for this cohort.	
2.1.2. Endpoints; 11.3. Efficacy Analyses	The following text was removed '~~or very good partial response (VGPR) or better for D-VRd cohort~~'. Deleted 'D-VRd'.
Rationale: To maintain consistency in presentation of order of cohorts throughout the protocol.	
Synopsis: Endpoints, Overview of Study Design, Statistical Methods; 2.1.2. Endpoints; 11.3. Efficacy Analyses	Changed the order of 'daratumumab SC in combination with bortezomib, melphalan, and prednisone (D-VMP), D-Kd' to 'D-Kd, D-VMP'.
Rationale: To align the synopsis and body of the protocol with the Time and Event table.	
Synopsis: Evaluations; 9.6. Safety Evaluations	Transthoracic echocardiogram (TTE) monitoring was added as a safety evaluation for subjects in the D-Kd cohort.
Rationale: Comparisons for primary endpoints will not be performed, p-values are not applicable.	
Synopsis: Statistical Methods; 11.3. Efficacy Analyses	Text regarding p-values for the hypothesis testing of primary endpoint for each cohort was deleted.
Rationale: To maintain consistent text throughout the protocol.	
3.2. Study Design Rationale	Added text '>90% power for D-VRd, D-VMP, and daratumumab SC in combination with lenalidomide and dexamethasone (D-Rd) cohorts and >80% power for the D-Kd cohort'.
Rationale: To align with the Centers for Disease Control (CDC) definition of hepatitis B.	
4.2. Exclusion Criteria	Criterion #5: Modified the definition of subjects seropositive for hepatitis B.
Rationale: To align with daratumumab program standard language by clarifying the reasons for continued observation on subsequent daratumumab injections and to clarify guidance regarding SC daratumumab injection.	

Applicable Section(s)	Description of Change(s)
6.3.1. Dara SC Delivery	Deleted '~~will~~' and added 'should' for administration of each dose of daratumumab SC injection at alternating locations on the abdomen. Additional text was added to keep the subjects with a higher risk of respiratory complications, subject with infusion-related reaction (IRR) with first injection of study drug, and subject with a decreased condition on day of dosing compared to prior dosing day under observation and keep the dose of daratumumab constant throughout the study.
6.4.1.1. Pre-administration Medication	The word 'within' was added to limit the duration of pre-administration medications between 1 to 3 hours. Additional clarification was added regarding pre-administration of antihistamine and dexamethasone. Deleted words '~~mandatory~~ and ~~1 to 3 hours~~ 'and maintained '3 hours'.
Rationale: To align with daratumumab program standard language.	
4.3. Prohibitions and Restrictions	Added text 'during dose interruption' to specify that subjects must not donate blood during dose interruption.
6.4.2. Management of Infusion-related Reactions	Text was added requiring extra attention to be given to recruit staff trained in daratumumab administration.
6.5. Dose Delays and Dose Modification of Daratumumab	Text was added to further clarify that it was mandatory to complete Day 1 of any cycle and if it was missed it was to be considered a cycle delay.
6.5.2. Daratumumab Interruption or Missed Doses	The following-text was added: 'Infusion-related reactions may occur upon re-initiation of daratumumab after a prolonged delay in treatment. Investigators should consider the applicable infusion reaction guidance provided in Section 6.4.2.'
8.1.4. Prophylaxis for Herpes Zoster Reactivation	Additional text was added regarding initiation of antiviral prophylaxis to prevent herpes zoster reactivation.
8.1.8. Infection Prophylaxis (new section)	Text was added regarding prophylactic use of antibiotics for infection in subjects with multiple myeloma.
8.3. Prohibited Therapies	Text was added clarifying the prohibited use of live attenuated vaccines.
10.2. Discontinuation of Study Treatment/Withdrawal from the Study	Text was added to clarify that subjects who discontinue treatment with any one component of study treatment may continue to receive treatment with the other components of study treatment.
Rationale: "Carfilzomib" was omitted in error.	
6.5.1. Daratumumab Toxicity Management	"Carfilzomib" was added to the list of background treatment where text describes daratumumab toxicity management.
Rationale: Minor errors, editorial issues, or changes for clarity/consistency noted in the protocol were corrected.	
1.2.1. Clinical Studies; 3.2. Study	Study-related use of the word 'patient' was changed to 'subject'.

Applicable Section(s)	Description of Change(s)
Design Rationale; 8.3. Prohibited Therapies; 9.6. Safety Evaluations; 10.2. Discontinuation of Study Treatment/Withdrawal from the Study; 16.1. Study-Specific Design Considerations; Attachment 6: Asthma Guidelines; Attachment 10: Interpretation of The SEBIA Hydrashift 2/4 Daratumumab IFE Interference Test	
1.2.1. Clinical Studies	Changed word ‘infusion’ to ‘injection’.
6.1.1. D-VRd Cohort; 6.4.1.1. Pre-administration Medication	Changed word ‘infusion’ to ‘administration’.
Table 8 Time and Events Schedule - Overview for the D-Kd Cohort	The use of the abbreviation ‘TTE’ (transthoracic echocardiogram) was added.
Abbreviations	Removed ‘ARC’ (anticipated event review committee) and ‘IDMC’ (Independent Data Monitoring Committee) and added ‘CD38’ (cluster of differentiation 38), ‘EOT’ (end of treatment), ‘HRT’ (hormonal replacement therapy), ‘IMP’ (investigational medicinal product), ‘NYHA’ (New York Heart Association), ‘SAC’ (Safety Assessment Committee), and ‘TTE’ (transthoracic echocardiogram).
Table 23 Dose Modification Guidelines for Bortezomib, Melphalan, and Prednisone	The following abbreviation key was added for clarity: ‘VMP= bortezomib, melphalan, and prednisone’ and ‘NCI-CTC= National Cancer Institute-Common Terminology Criteria for Adverse Events’.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 3 (31 January 2019)

The overall reason for the amendment: The overall reason for the amendment is in response to identification of a new important risk (hepatitis B virus [HBV] reactivation).

Applicable Section(s)	Description of Change(s)
Rationale: The text for identification of HBV reactivation, testing, and management of subjects with the potential for HBV reactivation was added in response to identification of a new important risk (HBV reactivation).	
Table 1: Time and Events Schedule - Overview for the D-VRd Cohort; Table 3: Time and Events Schedule - Overview for the D-VMP Cohort; Table 6: Time and Events Schedule - Overview for the D-Rd Cohort; Table 8: Time and Events Schedule - Overview for the D-Kd Cohort.	For HBV serology added a row and identified the timepoint at which HBV serology would be conducted. For HBV DNA test, changed the note from 'Only for subjects with a known history of positivity for antibodies to hepatitis B core antigen (Anti-HBc) or antibodies to hepatitis B surface antigen (Anti-HBs)' to 'For subjects with serologic evidence of resolved HBV infection (ie, positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally' and identified when the HBV DNA test would be conducted.
Section 4.2 Exclusion Criteria (Criterion # 5.1)	Clarified language to exclude subjects who are seropositive for hepatitis B. Modified the following sentence: Subjects with resolved infection (ie, subjects who are **HBsAg negative but** positive for Anti-HBc and/or Anti-HBs) must be screened using real-time polymerase chain reaction (PCR) measurement of HBV DNA levels.
Section 8.1.7 Management of Hepatitis B Virus Reactivation	Added a new section for information for the management of HBV reactivation.
Section 9.6 Safety Evaluations	Added information detailing the conduct of HBV serology and updated DNA tests.
References	Deleted reference # 9 and renumbered other references.
Rationale: To correct the frequency of end of treatment (EOT) post-treatment visit in Time and Event Schedule Tables 1 and 2 from 30 days to 4 weeks after the last dose of study drug.	
Table 1: Time and Events Schedule – Overview for the D-VRd Cohort; Table 2: Time and Events Schedule - Pharmacokinetic/Immunogenicity Sample Collection Times (D-VRd Cohort)	Corrected the frequency of EOT post-treatment visit in the EOT column heading from 30 days to 4 weeks after the last dose of study drug.
Rationale: To correct the days when pre-medications are administered and to coincide them with the days when daratumumab is administered in Time and Event Schedule Table 8.	
Table 8: Time and Events Schedule – Overview for the D-Kd Cohort	Removed the reference to the administration of pre-medications on Day 8 of Cycles 3 to 6 and on Day 8 and Day 15 of Cycles 7+.
Rationale: To add the provision of conducting a study participant experience survey at the last study visit.	

Applicable Section(s)	Description of Change(s)
Section 3.1 Overview of Study Design	Added a statement mentioning that at their last study visit, each study participant will be invited to complete an independent ethics committee (IEC)/institutional review board (IRB) approved experience survey, to share his/her experiences as a volunteer in this study.
Rationale: To simplify the language for conducting the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test.	
Attachment 10 Interpretation of The SEBIA Hydrashift 2/4 Daratumumab IFE Interference test	The language for conducting the test was simplified.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendments below are listed beginning with the most recent amendment.

Amendment 2 (12 October 2018)

The overall reason for the amendment: The overall reasons for the amendment is to add a cohort to explore the efficacy and safety of daratumumab SC in combination with carfilzomib and dexamethasone.

Applicable Section(s)	Description of Change(s)
Rationale: Information about the safety and efficacy of daratumumab for intravenous infusion (Dara IV) in combination with carfilzomib and dexamethasone (D-Kd) was added.	
1.1.1. Combination Therapy Studies	Information from Study 54767414MMY1001 was added.
Rationale: Study descriptions, design elements, treatment administration information and Time and Events Schedules were updated to include information about the D-Kd cohort.	
Time and Events Schedule, Table 8, Table 9	Time and Events Schedules were added for the D-Kd cohort.
Synopsis, Secondary Objectives; 2.1.1. Objectives	Added text to include evaluation of the D-Kd cohort for MRD negativity rate.
Synopsis, Primary Endpoints, Key Secondary Endpoints; 2.1.2. Endpoints	Added text to include evaluation of the D-Kd cohort for ORR, VGPR or better rate as defined by the IMWG response criteria, DOR, and MRD negativity rate.
Synopsis, Overview of Study Design; 3.1. Overview of Study Design	Added text for the inclusion of the D-Kd cohort in subjects in first relapse or refractory MM after initial treatment with a lenalidomide-containing regimen.
Figure 1	The schematic overview of the Phase 2 study design was updated to include the D-Kd cohort.

Applicable Section(s)	Description of Change(s)
3.2. Study Design Rationale	Included rationale for the inclusion of the D-Kd cohort; rationale for the inclusion of D-Rd was updated to include the patient population for which D-Rd was approved, namely patients with relapsed MM; rationale for the inclusion of D-VMP was updated to denote the approval of daratumumab in combination with VMP for newly diagnosed MM.
4.1. Inclusion Criteria	Criterion #4.1.d. was added to provide criteria for inclusion in the D-Kd cohort for relapsed or refractory disease; the requirements for inclusion of subjects in the D-Kd cohort were added and included hemoglobin count (Criterion #6.1.a), platelet count (Criterion #6.1.c), bilirubin values (Criterion #6.1.f), and estimated creatinine clearance values (Criterion #6.1.g); included instruction for women of childbearing potential (Criterion #7.1).
4.2. Exclusion Criteria	Criterion #1.1: Denoted prior or concurrent exposure to lenalidomide instructions for the D-Rd cohort only; added the following criterion for the D-Kd cohort: Subject has previously received carfilzomib; included the D-Kd cohort to the exclusion criterion regarding ASCT or allogeneic stem cell transplant. Criterion #4.1: Added the following exclusion criterion for subjects in the D-Kd cohort: Known infiltrative pulmonary disease or known pulmonary hypertension. Criterion #8.1: Added clinically significant cardiac disease exclusion criteria for the D-Kd cohort: transthoracic echocardiogram showing left ventricular ejection fraction (LVEF) <40% and uncontrolled hypertension, defined as an average systolic blood pressure >159 mmHg or diastolic >99 mmHg despite optimal treatment. Criterion #9.1: Added: For D-Kd cohort only: allergy, hypersensitivity, or intolerance to Captisol. Criterion #17 was added.
4.3. Prohibitions and Restrictions	Denoted that the D-Kd cohort will be administered pregnancy test as clinically indicated.
Synopsis, Dosage and Administration	The following text was added: Subjects in the D-Kd cohort will receive treatment in 28-day cycles. Treatment will consist of daratumumab SC 1800 mg weekly for Cycles 1 and 2, every 2 weeks for Cycles 3-6, and every 4 weeks thereafter for Cycles 7+. Subjects will receive carfilzomib IV 20 mg/m^2 on Cycle 1 Day 1. If tolerated, beginning with the second dose of carfilzomib, the dose will be escalated to 70 mg/m^2 on Cycle 1 Days 8 and 15. For Cycles 2+, carfilzomib IV 70mg/m^2 will be given weekly on Days 1, 8, and 15 of each cycle.
6.1.4 D-Kd Cohort	This section was added to include the treatment schedule and administration for the D-Kd cohort

Applicable Section(s)	Description of Change(s)
Synopsis, Overview of Study Design; 6.5.1. Daratumumab Toxicity Management; 6.5.2. Daratumumab Interruption or Missed Doses; 8. Prestudy and Concomitant Therapy; 9.1.3. Treatment Phase; 9.2.1.5. Bone Marrow Examination, Table 33; 9.5. Biomarkers; 10.2. Discontinuation of Study Treatment/Withdrawal from the Study; 11.3 Efficacy Analysis; 16.1. Study-Specific Design Considerations	Instruction was added for the D-Kd cohort.
6.4.1.1. Pre-administration Medication	Information about pre-administration of medications in the D-Kd cohort was added.
6.6. Bortezomib, Melphalan, Lenalidomide, Carfilzomib, and Prednisone	Denoted that the sponsor may provide carfilzomib.
6.6.1. Dose Calculation of Bortezomib, Melphalan, Carfilzomib, and Prednisone; 6.7. Dose Reductions of Bortezomib, Lenalidomide, Melphalan, Carfilzomib, Dexamethasone, and Prednisone	Information on the dose calculation and dose reduction of carfilzomib was added.
6.7.5. Carfilzomib Toxicity; 6.7.5.1. Hematologic Toxicity of Carfilzomib; 6.7.5.2. Hydration and Fluid Monitoring; 6.7.5.3. Management of Peripheral Edema, Pulmonary Edema, Congestive Heart Failure	These sections were added to inform on dose modifications for carfilzomib.
9.1.1. Overview	Text was added to inform on the total blood volume for the D-Kd treatment group.

Applicable Section(s)	Description of Change(s)
9.6 Safety Evaluations	The following evaluation was added: Participants in the D-Kd cohort must have a transthoracic echocardiogram according to the Time and Events Schedule (Table 8). Two-dimensional transthoracic echocardiogram to assess left ventricular ejection fraction for eligibility purposes will be assessed during screening and will serve as the baseline echocardiogram.
11.2. Sample Size Determination	The following text was added: … for the D-Kd cohort, the corresponding power is >80% to test the null hypothesis that the ORR is at most 65%, against the alternative hypothesis that the ORR is at least 80%.
11.2. Sample Size Determination, Table 34	The Hypothesis and Power Table was updated to include information for the D-Kd cohort.
3.1. Overview of Study Design; 11.3. Efficacy Analyses	Text was updated to denote that the timing of the analysis would be associated with enrollment of the 60th subject, not after the last subject was enrolled. Following text was added: at the time of the primary analysis, the D-Kd cohort will not be included in the analysis and will be analyzed in subsequent analyses after approximately the 60th subject is enrolled in the D Kd cohort.
Rationale: The windows were broadened for End of Treatment (EOT) visit and Follow Up (FUP) Post-Treatment Visit at 8 weeks in the daratumumab SC, bortezomib, lenalidomide, and dexamethasone (D-VRd) arm to enable flexibility for stem cell collection and autologous stem cell transplant (ASCT).	
Time and Events Schedules Table 1, Table 2	The EOT visit was changed from 30 days to 4 weeks; the EOT visit window was changed from ±1wk to ±2wk and the FUP Post-Treatment visit at 8 weeks was changed from ±1wk to -2wk/+4wk.
Rationale: Changes were made to provide consistency in visit windows between cycles.	
Time and Events Schedules Table 3	The visit window for Cycles 1 to 9 was changed to ±3d for consistency with the visit window in Cycles 10+.
Time and Events Schedules Table 6	The visit windows for Cycles 1 & 2 Day 1 and for Cycles 3 to 6 Day 1 were changed to ±3d for consistency with the visit window in Cycles 7+ Day 1.
Rationale: The assay to be used for the analysis of daratumumab interference on serum M-protein quantitation was changed.	
Attachment 10	Information about the Daratumumab Interference Reflex Assay (DIRA) was replaced with information about the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test.
Rationale: Text was updated to include instruction on disease evaluations that should be collected for subjects who discontinue treatment prior to PD.	
10.2. Discontinuation of Study Treatment/Withdrawal from the Study	The following text was added: For subjects who discontinue treatment prior to PD, disease evaluations should continue every 28 days until the Follow-up Visit is completed. For subjects in the D-VRd cohort, subsequent therapy will be collected potentially after the End-of-Treatment Visits and best response after transplant will be collected in the eCRF.
Rationale: To clarify that hepatitis serology testing will occur during screening.	
9.6. Safety Evaluations, HBV-DNA Tests	Text was added to clarify that subjects who have a history of hepatitis will undergo hepatitis serology testing during screening.
Rationale: To clarify age of subjects who will receive a specified dexamethasone dose.	
Section 6.1.3. D-Rd Cohort	Clarified that dexamethasone will be administered at a dose of 20mg/week PO for subjects ≥75 years or BMI <18.5, rather than >75 years.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify the immunogencity-evaluable analysis set.	
11.1. Subject Information	Text was updated to clarify the immunogencity-evaluable analysis set.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (06 Jun 2018)

The overall reason for the amendment: To address Health Authority (HA) requests and to correct administrative errors and inconsistencies in the original protocol.

Applicable Sections	Description of Changes
Rationale: Provided rationale for why the sponsor considers that the combination therapy should not be considered investigational medicinal products (IMPs).	
3.2 Study Design Rationale	Added text describing why the use of VMP, VRd, and Rd is considered standard of care in the proposed study and why they should not be considered IMPs. Added clarification text for VRd bullet.
Rationale: Update the study's inclusion criteria to: align with the lenalidomide and bortezomib Summary of Product Characteristics (SmPCs); clarify and align with the text in the body of the protocol; and align with the Clinical Trial Facilitation Group (CTFG) guidance to clarify the duration of contraceptive method use.	
4.1 Inclusion Criteria	Minor revisions to Criterion #4.1 for clarification purposes and changed "investigator's determination" to "investigator's evaluation". Revised Criterion #6.1 for platelet count (6c), total bilirubin (6f), and corrected serum calcium (6h) for safety purposes. Deletion in Criterion #7.1 to align with body text. For Criterion #8.1, added that contraception must continue during the study and for 3 months after receiving the last dose of daratumumab.
Rationale: To update the study exclusion criteria to: remove erroneous, duplicative text; align with instructions provided to the PI; and to align with the current protocol template and standard text across daratumumab protocols.	
4.2 Exclusion Criteria	Criterion #1.1, deleted bullet for receiving cumulative dose of corticosteroids. Criterion #2.1, revisions made to align with PI letter sent to the sites. Criterion #5.1, added clarification lead-in text of "known to be…" with further clarification for hepatitis B bullet. Criterion #6.1, added clarification lead-in text of "known to be…" with further clarification for hepatitis C bullet. Criterion #16 was added.
Rationale: To clarify the dosing instructions for the various components of the backbone regimen(s).	

Applicable Sections	Description of Changes
Synopsis, Dosage and Administration	Prednisone PO 60 mg/m^2 on Days **1-4** ~~2, 3 and 4~~ for Cycles 1 to 9. ~~and dexamethasone PO or IV at 20 mg weekly for Cycle 1, every 3 weeks for Cycles 2 to 9, and every 4 weeks for Cycles 10+.~~
6.1.1 D-VRd Cohort	Added clarification text for administration of lenalidomide, dexamethasone, and bortezomib. Also, deleted text to allow for lenalidomide administration per local label for subjects outside of the US.
6.1.2 D-VMP Cohort, Table 15 Treatment Schedule and Dosing (D-VMP-Cohort)	"Prednisone" Dose for Cycle 1 and Cycles 2-9 corrected to "Days 1-4", and "Dexamethasone" row deleted.
6.1.3 D-Rd Cohort, Table 16 Treatment Schedule and Dosing (D-Rd Cohort)	Change made from "Days 1, 8, 15, 22" to "weekly" for "Cycles 1 and 2", and footnote added at select timepoints for all cycles.
6.7 Dose Reductions of Bortezomib, Lenalidomide, Melphalan, Dexamethasone, and Prednisone, Table 17 Dose Reduction for Prednisone	Changed starting dose, first dose reduction, and second dose reduction from "…on Days 1-4" to "… on Days 2 to 4".
6.1.2 D-VMP Cohort	Paragraph added for melphalan and prednisone and for bortezomib to give instructions on dose, administration, and timing of administration.
6.1.3 D-Rd Cohort	Deleted text to allow for lenalidomide administration per local label for subjects outside of the US. Revisions made for dexamethasone administration.
Rationale: Text revised for consistency to clarify the daratumumab route of administration**.**	
6.4.1.1 Pre-administration Medication; 6.5.1 Daratumumab Toxicity Management; 8 Prestudy and Concomitant Therapy; 9.6 Safety Evaluations, Daratumumab Interference with Indirect Antiglobulin Test Results subsection; 12.3.2 Serious Adverse Events	Changed "infusion" to "administration" or "injection" as applicable.
Rationale: Clarified text concerning continuation of study treatment when one component of the regimen is discontinued due to toxicity.	
6.5.2 Daratumumab Interruption or Missed Doses	A daratumumab dose that is held for more than the permitted time (Table 14 to Table 16) 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. **If one of the components of the standard myeloma therapy is discontinued due to toxicity, the remaining components should continue as long as no dose interruption rules have been met.**
Rationale: Revised to align with current International Myeloma Working Group (IMWG) criteria. Deleted all text for "clinical relapse" footnote, as it is not accepted by the sponsor.	
9.2.1.1 Response Categories, Table 32 International Uniform Response Criteria Consensus Recommendations	For Minimal response (MR) row: removed bullet for "in subjects with relapsed refractory myeloma…". Deleted all footnote text for "clinical relapse".
Rationale: Revisions made to align with SAP and planned statistical analyses.	

Applicable Sections	Description of Changes
11.1 Subject Information	Deleted bullet for "All subjects enrolled analysis set" and revised "Treated analysis set" to "All treated analysis set" and accompanying text regarding the use and analysis set.
11.3 Efficacy Analyses (MRD Negativity Rate)	Deleted, "…or whole blood".
11.5 Immunogenicity Analyses	Text revised for immunogenicity analyses paragraph.
Rationale: To align with current template text and other recent amendments across the daratumumab compound.	
10.2 Discontinuation of Study Treatment/Withdrawal from the Study	Deleted text specifying "Relapse from CR is not considered as disease progression. Revised the text related to subjects withdrawing from the study.
12.1.1 Adverse Event Definitions and Classifications, Unlisted (Unexpected) Adverse Event/Reference Safety Information subsection; 14.1 Physical Description of the Study Drug; 15 Study-Specific Materials	Added Japan-specific text for the bortezomib Investigator's Brochure and IP classification.
12.3.1 All Adverse Events	Added text related to sponsor's responsibility for reporting anticipated events.
12.3.2 Serious Adverse Events	Added clarification text for expected disease progression.
12.3.3 Pregnancy	Deleted text concerning unknown effects of study drug on sperm.
17.3 Subject Identification, Enrollment, and Screening Logs	Added '(as allowed by local regulations)' following 2 instances of 'date of birth'.
17.11 Use of Information and Publication	Changed the time for submitting study results for publication from 'within 12 months of the availability of the final data (tables, listings, graphs)' to 'within 18 months after study end date'. Revised the text beginning 'Authorship of publications...'
Rationale: To clarify the procedures, including timing, that need to be completed and to ensure consistency with the text in the body of the protocol.	
Time and Events Schedules Table 1 through Table 7	Miscellaneous edits throughout the Time and Events Schedules.
Rationale: Miscellaneous edits made for clarity and consistency across the protocol.	
4.2 Exclusion Criteria	Criterion #8.1 revised to remove text referring to National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE, Version 4.03] Grade 2 or higher).
6.7.2 Dose Modification Guidelines for Dexamethasone	Added, "PO", as in, "The 20-mg IV or PO dose of dexamethasone…".
6.7.3.1 Hematologic Toxicity of Bortezomib Table 25 Dose Modifications for Hematologic Toxicity	"Thrombocytopenia Grade 3" row revised to add instructional text on withholding bortezomib to align with local protocol revisions.

Applicable Sections	Description of Changes
8.3 Prohibited Therapies	Revised text to, "…given as backbone therapy and IRRs…", and added text for inhibitors and inducers.
9.2.1.1 Response Categories; 16.2.3 Informed Consent Form	Since "survival status" was deleted from Time and Events Tables 1, 3, and 6, accompanying survival status text was also deleted in body text. For 9.2.1.1 only: Added missing bibliographic reference citation for Kumar 2016, and changed "determine response" to "evaluate response".
9.2.1.5 Bone Marrow Examination, Table 33 Bone Marrow Testing	For "Screening" and "CR, sCR" rows: Added clarification text concerning sample collection timing in the "Central Testing" column.
11.8 Safety Analyses, Stem Cell Collection subsection	Changed "D-Rd arm only" to "D-VRd cohort only"
Attachment 8: Antihistamines That May Be Used Pre-dose	Revised text to remove reference to Dara-IV infusion.
Attachments	In Attachment 3, corrected the e-GFR formula for creatinine in µmol/L. Added Attachment 12 for inhibitors and inducers.
Rationale: Minor errors were noted.	
Throughout document	Minor corrections for formatting, grammar, etc.

SYNOPSIS

A Multicenter Phase 2 Study to Evaluate Subcutaneous Daratumumab in Combination with Standard Multiple Myeloma Treatment Regimens

EudraCT NUMBER: 2017-004203-41

This is an open-label, international, multicenter study to demonstrate that daratumumab administered by subcutaneous (SC) injection in combination with standard treatment regimens is safe and efficacious in subjects with newly diagnosed multiple myeloma (MM) or in subjects with relapsed or refractory disease.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Primary Objective

- To evaluate the clinical benefit of SC daratumumab administered in combination with standard MM regimens in subjects with MM as measured by overall response rate (ORR) or very good partial response (VGPR) or better rate.

Secondary Objectives

- To evaluate safety and pharmacokinetics of SC administration of daratumumab in combination with standard MM regimens
- To evaluate additional clinical benefit of SC daratumumab administered in combination with standard MM regimens in subjects with MM
- To characterize the immunogenicity of daratumumab and rHuPH20 following SC administration
- To evaluate minimal residual disease (MRD) negativity rate in the D-VMP (daratumumab SC in combination with bortezomib, melphalan and prednisone), D-Rd (daratumumab SC in combination with lenalidomide and dexamethasone), and D-Kd (daratumumab SC in combination with carfilzomib and dexamethasone) cohorts

Endpoints

Primary Endpoints

- ORR, defined as the proportion of subjects with a partial response or better as defined by the International Myeloma Working Group (IMWG) response criteria (D-Kd, D-VMP, and D-Rd cohorts)
- VGPR or better rate, defined as the proportion of subjects with a VGPR or better rate as defined by the IMWG response criteria (D-VRd cohort)

Key Secondary Endpoints

- Serum concentrations of daratumumab
- Rate of infusion-related reactions
- VGPR or better rate as defined by the IMWG response criteria (D-Kd, D-VMP, and D-Rd cohort), and ORR as defined by the IMWG response criteria (D-VRd cohort)

Hypothesis

The hypothesis is that the addition of daratumumab administered SC to standard MM regimens will improve responses compared to response data observed in completed phase 3 studies without daratumumab.

OVERVIEW OF STUDY DESIGN

This study will investigate the efficacy and safety of daratumumab administered SC (Dara SC) in combination with bortezomib, lenalidomide, and dexamethasone (VRd) in subjects with newly diagnosed MM who are transplant eligible; or in combination with bortezomib, melphalan, and prednisone (VMP) in subjects with newly diagnosed MM who are ineligible for transplant; or in combination with lenalidomide and dexamethasone (Rd) in subjects with relapsed or refractory MM or in combination with carfilzomib and dexamethasone (D-Kd) in subjects in first relapse or refractory MM after initial treatment with a lenalidomide-containing regimen. Approximately 60 subjects will be treated per cohort. Subjects enrolled in the daratumumab-VRd cohort (D-VRd) will be treated for 4 cycles and will be evaluated for a VGPR or better rate. Hematopoietic stem cell collection and autologous transplant will be performed off protocol. Subjects enrolled in the D-Kd, D-VMP, and D-Rd cohorts will be evaluated for ORR and will be treated until disease progression. A study evaluation team will evaluate safety during this study.

SUBJECT POPULATION

Key eligibility criteria: ≥18 years of age; documented secretory MM based on IMWG criteria, and an Eastern Cooperative Oncology Group (ECOG) performance status grade of 0, 1, or 2. Additional criteria are defined for each treatment cohort (D-VRd, D-VMP, D-Kd, and D-Rd).

DOSAGE AND ADMINISTRATION

Subjects in the D-VRd cohort will receive treatment in 21-day cycles for a maximum of 4 cycles. Treatment will consist of daratumumab SC 1800 mg weekly for Cycles 1 to 3 and on Day 1 of Cycle 4; bortezomib SC 1.3 mg/m^2 on Days 1, 4, 8 and 11 of each cycle; lenalidomide orally (PO) at 25 mg on Days 1 to 14 of each cycle; and dexamethasone PO or intravenously (IV) 20 mg on Days 1, 2, 8, 9, 15 and 16 of each cycle.

Subjects in the D-VMP cohort will receive treatment in 42-day cycles for Cycles 1 to 9 and then 28-day cycles thereafter. Treatment will consist of daratumumab SC 1800 mg weekly for Cycle 1, every 3 weeks for Cycles 2 to 9 and every 4 weeks thereafter; bortezomib SC 1.3 mg/m^2 on Days 1, 4, 8, 11, 22, 25, 29 and 32 for Cycle 1, and Days 1, 8, 22 and 29 for Cycles 2 to 9; melphalan PO 9 mg/m^2 on Days 1-4 for Cycles 1 to 9; prednisone PO 60 mg/m^2 on Days 1-4 for Cycles 1 to 9.

Subjects in the D-Kd cohort will receive treatment in 28-day cycles. Treatment will consist of daratumumab SC 1800 mg weekly for Cycles 1 and 2, every 2 weeks for Cycles 3-6, and every 4 weeks thereafter for Cycles 7+. Subjects will receive carfilzomib IV 20 mg/m^2 on Cycle 1 Day 1. If tolerated, beginning with the second dose of carfilzomib, the dose will be escalated to 70 mg/m^2 on Cycle 1 Days 8 and 15. For Cycles 2+, carfilzomib IV 70mg/m^2 will be given weekly on Days 1, 8, and 15 of each cycle.

Subjects in the D-Rd cohort will receive treatment in 28-day cycles. Treatment will consist of daratumumab SC 1800 mg weekly for Cycles 1 and 2, every 2 weeks for Cycles 3 to 6 and every 4 weeks thereafter; lenalidomide PO 25 mg on Days 1 to 21 of each cycle; and dexamethasone PO or IV 40 mg weekly for each cycle.

The data cutoff for the final analysis and the end of data collection will occur approximately 10 months after the last subject is enrolled in the D-Kd cohort. Subsequently, the clinical database will be locked for the final analysis.

Subjects benefiting from study treatment can continue receiving the study drugs after the end of data collection until the study drugs are commercially available, available from another source (eg. via a dedicated long-term extension study), or until study completion.

The end of study will occur when all subjects discontinue study treatment or 18 months after the end of data collection, whichever occurs first.

EVALUATIONS

Assessment of disease will be conducted in accordance with the IMWG response criteria. Disease evaluations will include: measurements of myeloma proteins, bone marrow examinations, skeletal surveys and other imaging studies, and serum calcium corrected for albumin. Blood samples will be drawn from all subjects to characterize the pharmacokinetics of daratumumab and to assess for the generation of antibodies to daratumumab and to rHuPH20. Biomarkers will also be assessed. Safety evaluations include adverse event monitoring, physical examinations, electrocardiograms, transthoracic echocardiograms (TTE) for D-Kd cohort only, SC injection site evaluations, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and ECOG performance status.

STATISTICAL METHODS

Response and progressive disease will be analyzed and reported using a computerized algorithm based on the central laboratory results (unless otherwise specified). The primary efficacy endpoints of ORR (D-Kd, D-VMP, and D-Rd cohorts) or VGPR or better rate (D-VRd cohort), along with their two-sided 90% exact confidence interval, will be calculated for each treatment cohort. No formal comparisons between these treatment cohorts will be performed.

TIME AND EVENTS SCHEDULES

Table 1: Time and Events Schedule – Overview for the D-VRd Cohort

Note: Refer to Attachment 15 for a description of study procedures for subjects who continue receiving study drugs after data collection has ended.

Time and Events Schedule for the D-VRd cohort only	Notes	Study Visits						
		Screening Phase	Treatment Phase (1 Cycle = 21 d)				Post-Treatment Phase	
			Cycles 1 to 3			Cycle 4	EOT Post-treatment Visit at 4 weeks after last dose of study drug	FUP Post-treatment Visit at 8 wks (-2 wk/+4 wk) after last dose of study drug
Study Day		-28 to -1	D1	D8	D15	D1		
Visit window			±3d	±1d	±1d	±3d	±2wk	-2wk to +4wk
Unless otherwise stated, all blood and urine samples must be obtained before administration of study drug.								
Informed consent	Subjects must sign the informed consent form before any study-specific procedures							
Eligibility criteria		X						
Spirometry test (ie, FEV1) in subjects with COPD or asthma		X						
Demography/height/medical history		X						
Physical examination	Complete physical examination should be performed during the Screening Phase.	X	Only a symptom-directed physical examination is required.					
Weight	To be measured pre-dose.	X	X			X		
Chest X-ray	Acceptable if performed as part of standard of care within 28 days before the first administration or if performed as part of the skeletal survey. A full-dose chest CT is also acceptable.	X						
Vital sign measurements	To be performed as described in Section 9.6 (Safety Evaluations).	X	On Cycle 1 Day 1: immediately before the start of daratumumab administration, at end of administration, and at 0.5 and 1 hr after end of administration. For all other daratumumab administration days: immediately before the start of daratumumab administration and at the end of administration.				X	
ECOG performance status		X	X			X	X	
Electrocardiogram		X	As clinically indicated.				X	
Medication Administration								

Time and Events Schedule for the D-VRd cohort only	Notes	Study Visits						
		Screening Phase	Treatment Phase (1 Cycle = 21 d)				Post-Treatment Phase	
			Cycles 1 to 3			Cycle 4	EOT Post-treatment Visit at 4 weeks after last dose of study drug	FUP Post-treatment Visit at 8 wks (-2 wk/+4 wk) after last dose of study drug
Study Day		-28 to -1	D1	D8	D15	D1		
Visit window			±3d	±1d	±1d	±3d	±2wk	-2wk to +4wk
Daratumumab SC	Within 1 d of the scheduled dose in Cycles 1 to 4		X	X	X	X		
Bortezomib	Administered by SC injection. Dose may be delayed up to 48 hrs, however subsequent doses must be adjusted to account for delay as all bortezomib doses should be at least 72 hrs apart. Doses that need to be withheld are skipped and will not be made up later in the cycle. Individual doses within a cycle have a ±1d window		<----------Days 1, 4, 8, and 11 of each cycle---------->					
Lenalidomide			<----------Days 1 through 14 of each cycle---------->					
Dexamethasone			<----------Days 1, 2, 8, 9, 15, and 16 of each cycle ---------->					
Pre-administration medications			X	X	X	X		
Diary Review	Accountability/exposure check.		Cycles 2 and 3	X	X	X	X	
Adverse event monitoring		Continuous from the time of signing of informed consent form until 30 d after the final dose of study drug. Subjects need to be observed for 6 hrs after the first daratumumab dose. Beyond the 30 d EOT Visit, information on serious adverse events considered related to study drug will continue to be collected.						
SPM information		X						
Concomitant medication recording		Continuous from time of ICF signature until 30 d after last study drug dose.						
Subsequent myeloma therapy							X	X
Laboratory Assessments								
Blood type and indirect antiglobulin test results	To be obtained once before the first injection of daratumumab.	X						

Time and Events Schedule for the D-VRd cohort only	Notes	Study Visits						
		Screening Phase	Treatment Phase (1 Cycle = 21 d)				Post-Treatment Phase	
			Cycles 1 to 3			Cycle 4	EOT Post-treatment Visit at 4 weeks after last dose of study drug	FUP Post-treatment Visit at 8 wks (-2 wk/+4 wk) after last dose of study drug
Study Day		**-28 to -1**	**D1**	**D8**	**D15**	**D1**		
Visit window			**±3d**	**±1d**	**±1d**	**±3d**	**±2wk**	**-2wk to +4wk**
	Record on the subject's identification wallet card.							
Urine or serum pregnancy test	Women of childbearing potential only	Day -14 to Day -10	Cycle 1 Days 1, 8, and 15; then Day 1 of each subsequent cycle or Days 1 and 15 for subjects with irregular menses. See Section 4.3 (Prohibitions and Restrictions) for additional instructions on pregnancy testing during the treatment phase.				X	
Chemistry	At screening, acceptable to meet CRAB criteria if performed as part of SOC within 42 days before randomization. During the treatment phase, may be performed up to 3 days before study drug administration day. Results must be evaluated before each study drug administration.	X	X			X	X	
Hematology		X	X	X	X	X	X	
HBV Serology	All subjects will be tested locally for HBsAg, Anti-HBs, and Anti-HBc. See Section 9.6.	X						
HBV DNA test	For subjects with serologic evidence of resolved HBV infection (ie, positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. See Section 9.6.	X	X			X	X	X[a]
Whole blood (biomarker)	Pre-administration collections for PBMCs and plasma		Cycle 1 Day 1 and Cycle 3 Day 1				X	
Pharmacokinetics and immunogenicity blood samples for daratumumab and rHuPH20 characterization: See Table 2.								
Disease Evaluations (Blood/Urine) - Samples must be sent to the central laboratory.								
Serum β_2-microglobulin	SPEP and UPEP are to be	X						

Time and Events Schedule for the D-VRd cohort only	Notes	Study Visits						
		Screening Phase	Treatment Phase (1 Cycle = 21 d)				Post-Treatment Phase	
			Cycles 1 to 3			Cycle 4	EOT Post-treatment Visit at 4 weeks after last dose of study drug	FUP Post-treatment Visit at 8 wks (-2 wk/+4 wk) after last dose of study drug
Study Day		**-28 to -1**	**D1**	**D8**	**D15**	**D1**		
Visit window			**±3d**	**±1d**	**±1d**	**±3d**	**±2wk**	**-2wk to +4wk**
QIg (IgA, IgM, IgG, IgD, IgE)	performed within 14 d before Cycle 1 Day 1 and on the scheduled assessment day (±3 d).	X					X	
SPEP		X	X			X	X	
UPEP (24-hr urine sample)		X	X			X	X	
Serum calcium corrected for albumin		X	X			X	X	
Investigator evaluation of response	Per IMWG criteria (see Section 9.2.1.1)		Cycles 2-4				X	
Serum FLC & serum/urine immunofixation		X	Serum FLC and serum/urine immunofixation are to be performed for any subject when CR is suspected or maintained; for light chain MM subjects, serum FLC will also be performed on Day 1 of every cycle, and at the end of treatment					
Disease Evaluations (Other)								
Bone marrow aspirate/biopsy	For screening (up to 42 d before administration of study treatment). Disease characterization performed locally (morphology and either immunohistochemistry or immunofluorescence or flow cytometry). Cytogenetics by conventional karyotype or FISH (preferred), performed locally.	X	Samples are requested at time of suspected CR to confirm CR/sCR.					
Bone lesion assessment Skeletal survey	Screening assessment may be performed within 42 d before administration of study treatment. Low-dose whole body CT is preferred. As clinically indicated and per local practice, a skeletal survey by X-ray, MRI or PET-CT may be used as an alternative.	X	As clinically indicated					
Assess extramedullary	For screening (up to 42 d before	X	Measurable sites every 3 wks for physical examination (if applicable) and every 12 wks					

Time and Events Schedule for the D-VRd cohort only	Notes	Study Visits						
		Screening Phase	Treatment Phase (1 Cycle = 21 d)				Post-Treatment Phase	
			Cycles 1 to 3			Cycle 4	EOT Post-treatment Visit at 4 weeks after last dose of study drug	FUP Post-treatment Visit at 8 wks (-2 wk/+4 wk) after last dose of study drug
Study Day		**-28 to -1**	**D1**	**D8**	**D15**	**D1**		
Visit window			**±3d**	**±1d**	**±1d**	**±3d**	**±2wk**	**-2wk to +4wk**
plasmacytomas	administration of study treatment.) See section 9.2.1.8 for details on assessing and documenting extramedullary plasmacytomas.		for radiologic assessment (for subjects with a history of plasmacytomas or as clinically indicated for others)					

Anti-HBc=antibodies to hepatitis B core antigen; Anti-HBs=antibodies to hepatitis B surface antigen; C1D1= Cycle 1 Day 1; COPD=chronic obstructive pulmonary disease; CR=complete response; CT=computed tomography; D=day; d=days; D-VRd=Dara SC, bortezomib, lenalidomide, and dexamethasone; ECOG=Eastern Cooperative Oncology Group; EOT=End of Treatment; FISH= fluorescence in situ hybridization; FLC=free light chain; FUP=Follow-up Phase; hr(s)=hour(s); HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; ICF=informed consent form; QIg=quantitative immunoglobulins; MM=multiple myeloma; MRI=magnetic resonance imaging; PBMC=peripheral blood mononuclear cells; PCR=polymerase chain reaction; PD=progressive disease; SC=subcutaneous; sCR=stringent CR; SPEP=Serum M-protein quantitation by electrophoresis; SPM = secondary primary malignancy; UPEP=urine M-protein quantitation by electrophoresis; wk(s)=week(s).

[a] Every 12 weeks for up to 6 months after the last dose of study treatment.

Table 2: Time and Events Schedule - Pharmacokinetic/Immunogenicity Sample Collection Times (D-VRd Cohort)

PK Schedule for the D-VRd cohort only	Cycle 1		Cycle 3	Cycle 4		Post-treatment	
Day	1	4	1	1	4	EOT Post-treatment Visit at 4 weeks after last dose of study drug	FUP Post-treatment Visit at 8 wks (-2 wk/+4 wk) after last dose of study drug
Visit window d=day, wk=week	0	±1d	0	0	±1d	±2wk	-2wk to +4wk
D=study drug administered	D		D	D			
Daratumumab pharmacokinetics (serum)							
Before administration[a]	X		X	X			
After administration		X			X	X	X
Daratumumab immunogenicity (no additional blood draw; serum taken from pharmacokinetic sample)[b]							
Before administration[a]	X			X		X	X
rHuPH20 immunogenicity (plasma)[b]							
Before administration[a]	X			X		X	X

D-VRd=Dara SC, bortezomib, lenalidomide, and dexamethasone; PK=pharmacokinetic; rHuPH20=recombinant human hyaluronidase.

[a] On dosing days, sample collection may occur up to 2 hours before but not after the start of the drug administration. Samples collected on dosing days with visit windows should be collected on the actual day of study drug administration.

[b] In addition, samples for assessment of antibodies to daratumumab or antibodies to daratumumab and rHuPH20 should be drawn, if possible, any time an infusion-related reaction is reported (according to the Laboratory Manual and Section 9.3) in association with the second daratumumab administration or beyond.

Table 3: Time and Events Schedule – Overview for the D-VMP Cohort

Note: Refer to Attachment 15 for a description of study procedures for subjects who continue receiving study drugs after data collection has ended.

Time and Event Schedule for the D-VMP cohort only	Notes	Study Visits				
			Treatment Phase		Post-Treatment Phase	
		Screening Phase	Cycles 1 to 9 (1 Cycle = 42 d)	Cycles 10+ (1 Cycle = 28 d)	EOT Post-treatment Visit at 30 Days after last dose of study drug	FUP Post-treatment Visit at 8 wks after last dose of study drug
Study Day		**-28 to -1**				
Visit window			**±3d**	**±3d**	**±1wk**	**±1wk**
Unless otherwise stated, all blood and urine samples must be obtained before administration of study drug.						
Informed consent	Subjects must sign the ICF before any study-specific procedures.					
Eligibility criteria		X				
Spirometry test (ie, FEV1) in subjects with COPD or asthma		X				
Demography/height/medical history		X				
Physical examination	Complete physical examination should be performed during the Screening Phase.	X	Only a symptom-directed physical examination is required.			
Weight	To be measured pre-dose.	X	D1	D1		
Chest X-ray	Acceptable if performed as part of standard of care within 28 days before the first administration or if performed as part of the skeletal survey. A full-dose chest CT is also acceptable.	X				
Vital sign measurements	To be performed as described in Section 9.6 (Safety Evaluations).	X	On Cycle 1 Day 1: immediately before the start of daratumumab administration, at end of administration, and at 0.5 and 1 hr after end of administration. For all other daratumumab administration days: immediately before the start of daratumumab administration and at the end of administration.		X	
ECOG performance status		X	D1	D1	X	
Electrocardiogram		X	As clinically indicated		X	
Adverse event monitoring		Continuous from the time of signing of informed consent form until 30 d after the final dose of study drug. Subjects need to be observed for 6 hrs after the first daratumumab dose. Beyond the 30 d EOT Visit, information on serious adverse events considered related to study drug will continue to be collected.				
SPM information		X				
Concomitant medication recording		Continuous from time of ICF signature until 30 d after last study drug dose				
Subsequent myeloma therapy					X	X
Study Drug Administration						

Time and Event Schedule for the D-VMP cohort only	Notes	Study Visits				
		Screening Phase	Treatment Phase		Post-Treatment Phase	
			Cycles 1 to 9 (1 Cycle = 42 d)	Cycles 10+ (1 Cycle = 28 d)	EOT Post-treatment Visit at 30 Days after last dose of study drug	FUP Post-treatment Visit at 8 wks after last dose of study drug
Study Day		**-28 to -1**				
Visit window			**±3d**	**±3d**	**±1wk**	**±1wk**
Daratumumab SC			See Table 4 for details	D1		
Bortezomib						
Melphalan						
Prednisone						
Pre-administration medications				Refer to Section 6.4.1.1		
Laboratory Assessments						
Blood type and indirect antiglobulin test results	To be obtained once before the first injection of daratumumab. Record on the subject's identification wallet card	X				
Urine or serum pregnancy test	Women of childbearing potential only	-14 to C1D1	As clinically indicated			
Chemistry	At screening, acceptable to meet CRAB criteria if performed as part of SOC within 42 days before randomization. During the treatment phase, may be performed up to 3 days before study drug administration day. Results must be evaluated before each study drug administration	X	See Table 4 for details	X	X	
Hematology		X	See Table 4 for details	X	X	
HBV Serology	All subjects will be tested locally for HBsAg, Anti-HBs, and Anti-HBc. See Section 9.6.	X				
HBV DNA test	For subjects with serologic evidence of resolved HBV infection (ie, positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. See Section 9.6.	X	D1	Every 12 weeks	X	X[a]
Whole blood (biomarker)	Pre-administration collections for PBMCs and plasma		C1D1 and C3D1 only		X	
Pharmacokinetics and immunogenicity blood samples for daratumumab and rHuPH20 characterization: See Table 5						
Disease Evaluations (Blood/Urine) - Samples must be sent to the central laboratory.						

Time and Event Schedule for the D-VMP cohort only	Notes	Study Visits				
		Screening Phase	Treatment Phase		Post-Treatment Phase	
			Cycles 1 to 9 (1 Cycle = 42 d)	Cycles 10+ (1 Cycle = 28 d)	EOT Post-treatment Visit at 30 Days after last dose of study drug	FUP Post-treatment Visit at 8 wks after last dose of study drug
Study Day		**-28 to -1**				
Visit window			**±3d**	**±3d**	**±1wk**	**±1wk**
Serum β_2-microglobulin	QIg, SPEP and UPEP are to be performed within 14 d before Cycle 1 Day 1 and on the scheduled assessment day (±3 d).	X				
QIg (IgA, IgM, IgG, IgD, IgE)		X	q6 wks for Cycle 1 to 9, q8 wks thereafter until PD. Not required on Cycle 1 Day 1 if screening values were obtained from samples collected within the prior 14 d.		X	
Serum calcium corrected for albumin		X			X	
SPEP		X			X	
UPEP (24-hr urine sample)		X			X	
Serum FLC & serum/urine immunofixation		X	Serum FLC and serum/urine immunofixation are to be performed for any subject when CR is suspected or maintained; for light chain MM subjects, serum FLC will also be performed q6 wks for Cycle 1 to 9, q8 wks thereafter until PD. Not required on Cycle 1 Day 1 if screening values were obtained from samples collected within the prior 14 d, and at the end of treatment.			
Investigator evaluation of response	Per IMWG criteria (see Section 9.2.1.1)		Day 1 of Cycles 2 +			
Disease Evaluations (Other)						
Bone marrow aspirate/biopsy	Disease characterization (morphology and either immunohistochemistry or immunofluorescence or flow cytometry). Cytogenetics by conventional karyotype or FISH (preferred), performed locally. For screening (up to 42 d before administration of study treatment.) fresh aspirate or biopsy preferred. If not available, obtain non-decalcified tissue. Samples will be sent to central laboratory for MRD evaluation.	X	Samples are requested at the time of suspected CR to confirm CR/sCR and to evaluate MRD. For subjects who achieve CR and remain on study, an additional bone marrow aspirate will be obtained at 12, 18, and 24 months (±1 month) post C1D1 and every 12 months thereafter (±1 month) until disease progression. If one of these timepoints occur within 1 month of suspected CR, a repeat bone marrow will not be requested.			

Time and Event Schedule for the D-VMP cohort only	Notes	Study Visits				
		Screening Phase	Treatment Phase		Post-Treatment Phase	
			Cycles 1 to 9 (1 Cycle = 42 d)	Cycles 10+ (1 Cycle = 28 d)	EOT Post-treatment Visit at 30 Days after last dose of study drug	FUP Post-treatment Visit at 8 wks after last dose of study drug
Study Day		**-28 to -1**				
Visit window			**±3d**	**±3d**	**±1wk**	**±1wk**
Bone lesion assessment Skeletal survey	Screening assessment may be performed within 42 d before administration of study treatment. Low-dose whole body CT is preferred. As clinically indicated and per local practice, a skeletal survey by X-ray, MRI or PET-CT may be used as an alternative.	X	As clinically indicated			
Assess extramedullary plasmacytomas	For screening (up to 42 d before administration of study treatment.) See section 9.2.1.8 for details on assessing and documenting extramedullary plasmacytomas.	X	Measurable sites every 4 wks for physical examination (if applicable) and every 12 wks for radiologic assessment (for subjects with a history of plasmacytomas or as clinically indicated for others).			

Anti-HBc=antibodies to hepatitis B core antigen; Anti-HBs=antibodies to hepatitis B core surface antigen; C1D1=Cycle 1 Day 1; C3D1=Cycle 3 Day 1; COPD=chronic obstructive pulmonary disease; CR=complete response; CT=computed tomography; D=day; d=days; D--VMP=Dara SC, bortezomib, melphalan, and prednisone; ECOG=Eastern Cooperative Oncology Group; EOT=End of Treatment; FISH=fluorescence in situ hybridization; FLC=free light chain; FUP=Follow-up Phase; hr(s)=hour(s); HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; ICF=informed consent form; Qlg=quantitative immunoglobulins; MM=multiple myeloma; MRD=minimal residual disease; MRI=magnetic resonance imaging; PBMC=peripheral blood mononuclear cells; PD=progressive disease; SC=subcutaneous; sCR=stringent CR; SPEP=Serum M-protein quantitation by electrophoresis; SPM = secondary primary malignancy; UPEP=urine M-protein quantitation by electrophoresis; wk(s)=week(s).

[a] Every 12 weeks for up to 6 months after the last dose of study treatment.

Table 4: Time and Events Schedule for Study Treatment (D-VMP Treatment Phase, Cycles 1 to 9)

Note: Refer to Attachment 15 for a description of study procedures for subjects who continue receiving study drugs after data collection has ended.

Treatment Schedule Cycles 1 to 9 for the D-VMP cohort only	Notes	Week 1				Week 2		Week 3	Week 4		Week 5		Week 6
		D1	D2	D3	D4	D8	D11	D15	D22	D25	D29	D32	D36
Study treatment should be administered in the following order: prednisone, daratumumab, bortezomib, and melphalan. Cycles are based on the administration of bortezomib. The start of each cycle may occur ±3 d of the scheduled day in order to accommodate the schedule of the site or subject.													
Hematology	At screening, acceptable to meet CRAB criteria if performed as part of SOC within 42 days before randomization. During the treatment phase, may be performed up to 3 days before study drug administration day. Results must be evaluated before each study drug administration	X				C1 only		C1 only	X		C1 only		C1 only
Chemistry		X							X				
Diary Review	Accountability/exposure check. At D8 of each cycle, if diary is not available review at next possible visit.					C1-9							
Pre-administration Medications													
Pre-administration medications		Refer to Section 6.4.1.1											
Medication Administration													
Prednisone	Dispense on Day 1 for self-administration. See Section 6.1.2 for additional details. On C1-9 Day 1, prednisone will be substituted by dexamethasone as pre-administration medication as specified in Section 6.1.2.	X	X	X	X								
Bortezomib	Administered by SC injection. Dose may be delayed up to 48 hrs, however subsequent doses must be adjusted to account for delay as all bortezomib doses should be at least 72 hrs apart. Doses that need to be withheld are skipped and will not be made up later in the cycle. Individual doses within a cycle have a ±1 d window	X			C1 only	X	C1 only		X	C1 only	X	C1 only	
Melphalan	Dispense on Day 1 for self-administration.	X	X	X	X								
Daratumumab SC		X				C1 only		C1 only	X		C1 only		C1 only

C1=Cycle 1; d=days; D--VMP=Dara SC, bortezomib, melphalan, and prednisone; SC=subcutaneous; hrs=hours

Table 5: Time and Events Schedule - Pharmacokinetic/Immunogenicity Sample Collection Times (D-VMP Cohort)

Note: Refer to Attachment 15 for a description of study procedures for subjects who continue receiving study drugs after data collection has ended.

PK Schedule for the D-VMP cohort only	Cycle 1		Cycle 2		Cycle 3	Cycle 6	Cycle 9	Post-treatment	
Day	1	4	1	4	1	1	1	EOT Post-treatment Visit at 30 days after last dose of study drug	FUP Post-treatment Visit at 8 wks after last dose of study drug
Visit window d=day, wk=week	0	±1d	0	±1d	0	0	0	±1wk	±1wk
D=study drug administered	D		D		D	D	D		
daratumumab pharmacokinetics (serum)									
Before administration[a]	X		X		X	X	X		
After administration		X		X				X	X
daratumumab immunogenicity (no additional blood draw; serum taken from pharmacokinetic sample)[b]									
Before administration[a]	X				X	X	X	X	X
rHuPH20 immunogenicity (plasma)[b]									
Before administration[a]	X				X	X	X	X	X

D--VMP=Dara SC, bortezomib, melphalan, and prednisone; PK=pharmacokinetic; rHuPH20=recombinant human hyaluronidase.

[a] On dosing days, sample collection may occur up to 2 hours before but not after the start of the drug administration. Samples collected on dosing days with visit windows should be collected on the actual day of study drug administration.

[b] In addition, samples for assessment of antibodies to daratumumab or antibodies to daratumumab and rHuPH20 should be drawn, if possible, any time an infusion-related reaction is reported (according to the Lab Manual and Section 9.3) in association with the second daratumumab administration or beyond.

Table 6: Time and Events Schedule – Overview for the D-Rd Cohort

Note: Refer to Attachment 15 for a description of study procedures for subjects who continue receiving study drugs after data collection has ended.

Time and Event Schedule for the D-Rd cohort only	Notes	Study Visits									
		Screening Phase	Treatment Phase (1 Cycle = 28 d)							Post-Treatment Phase	
			Cycles 1 & 2				Cycles 3 to 6		Cycles 7+	EOT Post-treatment Visit at 30 Days after last dose of study drug	FUP Post-treatment Visit at 8 wks after last dose of study drug
Study Day		**-28 to -1**	**D1**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		
Visit window			**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±3d**	**±1wk**	**±1wk**
Unless otherwise stated, all blood and urine samples must be obtained before administration of study drug.											
Informed consent	Subjects must sign the ICF before any study-specific procedures.										
Eligibility criteria		X									
Spirometry test (ie, FEV1) in subjects with COPD or asthma		X									
Demography/height/medical history		X									
Physical examination	Complete physical examination should be performed during the Screening Phase.	X	Only a symptom-directed physical examination is required.								
Weight	To be measured pre-dose.	X	X				X		X		
Vital sign measurements	To be performed as described in Section 9.6 (Safety Evaluations).	X	On Cycle 1 Day 1: immediately before the start of daratumumab administration, at end of administration, and at 0.5 and 1 hr after end of administration. For all other daratumumab administration days: immediately before the start of daratumumab administration and at the end of administration.							X	
ECOG performance status		X	X				X		X	X	
Electrocardiogram		X	As clinically indicated.							X	
Medication Administration											
Daratumumab SC	Refer to Section 6 for details on study drug administration.		X	X	X	X	X	X	X		
Lenalidomide			<----------Days 1 through 21 of each Cycle---------->								
Dexamethasone			<----------Days 1, 8, 15, and 22---------->								
Pre- medications			X	X	X	X	X	X	X		
Diary Review	Accountability/exposure check.		Cycle 2	X	X	X	X	X	X	X	

Time and Event Schedule for the D-Rd cohort only	Notes	Study Visits									
		Screening Phase	Treatment Phase (1 Cycle = 28 d)							Post-Treatment Phase	
			Cycles 1 & 2				Cycles 3 to 6		Cycles 7+	EOT Post-treatment Visit at 30 Days after last dose of study drug	FUP Post-treatment Visit at 8 wks after last dose of study drug
Study Day		-28 to -1	D1	D8	D15	D22	D1	D15	D1		
Visit window			±3d	±1d	±1d	±1d	±3d	±1d	±3d	±1wk	±1wk
Adverse event monitoring		Continuous from the time of signing of informed consent form until 30 d after the final dose of study drug. Subjects need to be observed for 6 hrs after the first daratumumab dose. Beyond the 30d EOT Visit, information on serious adverse events considered related to study drug will continue to be collected.									
SPM information		X									
Concomitant medication recording		Continuous from time of signed ICF until 30 d after last study drug dose.									
Subsequent myeloma therapy										X	X
Laboratory Assessments											
Blood type and indirect antiglobulin test results	To be obtained once before the first injection of daratumumab. Record on the subject's identification wallet card	X									
Urine or serum pregnancy test	Women of childbearing potential only	Day -14 to Day -10	Cycle 1 Days 1, 8, and 15; then Day 1 of each subsequent cycle or Days 1 and 15 for subjects with irregular menses. See Section 4.3 (Prohibitions and Restrictions) for additional instructions on pregnancy testing during the treatment phase.							X	
Chemistry	At screening, acceptable to meet CRAB criteria if performed as part of SOC within 42 days before randomization. During the treatment phase, may be performed up to 3 days before study drug administration day. Results must be evaluated before each study drug administration	X	X				X		X	X	
Hematology		X	X	X	X	X	X	X	X	X	
HBV Serology	All subjects will be tested locally for HBsAg, Anti-HBs, and Anti-HBc. See Section 9.6.	X									
HBV DNA test	For subjects with serologic evidence of resolved HBV infection (ie, positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. See Section 9.6.	X	X				X		Every 12 weeks	X	X[a]

Time and Event Schedule for the D-Rd cohort only	Notes	Study Visits								
		Screening Phase	Treatment Phase (1 Cycle = 28 d)						Post-Treatment Phase	
			Cycles 1 & 2				Cycles 3 to 6		Cycles 7+	EOT Post-treatment Visit at 30 Days after last dose of study drug	FUP Post-treatment Visit at 8 wks after last dose of study drug
Study Day		**-28 to -1**	**D1**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		
Visit window			**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±3d**	**±1wk**	**±1wk**
Whole blood (biomarker)	Pre-administration collections for PBMCs and plasma.		Cycle 1 Day 1 and Cycle 3 Day 1							X	
Pharmacokinetics and immunogenicity blood samples for daratumumab and rHuPH20 characterization: See Table 7											
Disease Evaluations (Blood/Urine) Samples must be sent to the central laboratory.											
Serum β_2-microglobulin	SPEP and UPEP are to be performed within 14 d before Cycle 1 Day 1 and on the scheduled assessment day (±3 d).	X									
QIg (IgA, IgM, IgG, IgD, IgE)		X	Every 3 months during treatment (window of ±1 month)							X	
SPEP		X	X				X		X	X	
UPEP (24 hr urine sample)		X	X				X		X	X	
Serum calcium corrected for albumin		X	X				X		X	X	
Serum FLC & serum/urine immunofixation		X	Serum FLC and serum/urine immunofixation are to be performed for any subject when CR is suspected or maintained; for light chain MM subjects, serum FLC will also be performed on Day 1 of every cycle, and at the end of treatment.								
Investigator evaluation of response	Per IMWG criteria (see Section 9.2.1.1)		Day 1 of Cycles 2+								
Disease Evaluations (Other)											
Bone marrow aspirate/biopsy	Disease characterization (morphology and either immunohistochemistry or immunofluorescence or flow cytometry). Cytogenetics by conventional karyotype or FISH (preferred), performed locally. For screening (up to 42 d before administration of study treatment.) fresh aspirate or biopsy preferred. If not available, obtain non-decalcified tissue. Samples will be sent to central laboratory for MRD evaluation.	X	Samples are requested at the time of suspected CR to confirm CR/sCR and to evaluate MRD. For subjects who achieve CR and remain on study, an additional bone marrow aspirate will be obtained at 12, 18, and 24 months (±1 month) post C1D1 and every 12 months thereafter (±1 month) until disease progression. If one of these timepoints occur within 1 month of suspected CR, a repeat bone marrow will not be requested.								

Time and Event Schedule for the D-Rd cohort only	Notes	Study Visits								
		Screening Phase	Treatment Phase (1 Cycle = 28 d)						Post-Treatment Phase	
			Cycles 1 & 2				Cycles 3 to 6		Cycles 7+	EOT Post-treatment Visit at 30 Days after last dose of study drug	FUP Post-treatment Visit at 8 wks after last dose of study drug
Study Day		**-28 to -1**	**D1**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**		
Visit window			**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±3d**	**±1wk**	**±1wk**
Bone lesion assessment Skeletal survey	Screening assessment may be performed within 42 d before administration of study treatment. Low-dose whole body CT is preferred. As clinically indicated and per local practice, a skeletal survey by X-ray, MRI or PET-CT may be used as an alternative.	X	As clinically indicated								
Assess extramedullary plasmacytomas	For screening (up to 42 d before administration of study treatment.) See section 9.2.1.8 for details on assessing and documenting extramedullary plasmacytomas.	X	Measurable sites every 4 wks for physical examination (if applicable) and every 12 wks for radiologic assessment (for subjects with a history of plasmacytomas or as clinically indicated for others)								

Anti-HBc=antibodies to hepatitis B core antigen; Anti-HBs=antibodies to hepatitis B core surface antigen; C1D1=Cycle 1 Day 1; COPD=chronic obstructive pulmonary disease; CR=complete response; CT=computed tomography; D=day; d=days; D-Rd=Dara SC, lenalidomide, and dexamethasone, ECOG=Eastern Cooperative Oncology Group; EOT=End of Treatment; FISH=fluorescence in situ hybridization; FLC=free light chain; FUP=Follow-up Phase; hr(s)=hour(s); HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; ICF=informed consent form; Qlg=quantitative immunoglobulins; MM=multiple myeloma; MRD=minimal residual disease; MRI=magnetic resonance imaging; PBMC=peripheral blood mononuclear cells; PD=progressive disease; SC=subcutaneous; sCR=stringent CR; SPEP=Serum M-protein quantitation by electrophoresis; SPM = secondary primary malignancy; UPEP=urine M-protein quantitation by electrophoresis; wk(s)=week(s).

[a] Every 12 weeks for up to 6 months after the last dose of study treatment.

Table 7: Time and Events Schedule - Pharmacokinetic/Immunogenicity Sample Collection Times (D-Rd Cohort)

Note: Refer to Attachment 15 for a description of study procedures for subjects who continue receiving study drugs after data collection has ended.

PK Schedule for the D-Rd cohort only	Cycle 1		Cycle 3		Cycle 6	Cycle 9	Cycle 12	Post-treatment	
Day	1	4	1	4	1	1	1	EOT Post-treatment Visit at 30 Days after last dose of study drug	FUP Post-treatment Visit at 8 wks after last dose of study drug
Visit window d=day, wk=week	0	±1d	0	±1d	0	0	0	±1wk	±1wk
D=study drug administered	D		D		D	D	D		
daratumumab pharmacokinetics (serum)									
Before administration[a]	X		X		X	X	X		
After administration		X		X				X	X
daratumumab immunogenicity (no additional blood draw; serum taken from pharmacokinetic sample)[b]									
Before administration[a]	X		X		X	X	X	X	X
rHuPH20 immunogenicity (plasma)[b]									
Before administration[a]	X		X		X	X	X	X	X

D-Rd=Dara SC, lenalidomide, and dexamethasone; PK=pharmacokinetic; rHuPH20=recombinant human hyaluronidase.

[a] On dosing days, sample collection may occur up to 2 hours before but not after the start of the drug administration. Samples collected on dosing days with visit windows should be collected on the actual day of study drug administration.

[b] In addition, samples for assessment of antibodies to daratumumab or antibodies to daratumumab and rHuPH20 should be drawn, if possible, any time an infusion-related reaction is reported (according to the Lab Manual and Section 9.3) in association with the second daratumumab administration or beyond.

Table 8: Time and Events Schedule – Overview for the D-Kd Cohort

Note: Refer to Attachment 15 for a description of study procedures for subjects who continue receiving study drugs after data collection has ended.

Time and Event Schedule for the D-Kd cohort only	Notes	Study Visits															
		Screening Phase	Treatment Phase (1 Cycle = 28 d)												Post-Treatment Phase	
			Cycles 1 & 2				Cycles 3 to 6				Cycles 7+				EOT Post-treatment Visit at 30 Days after last dose of study drug	FUP Post-treatment Visit at 8 wks after last dose of study drug
Study Day		**-28 to -1**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**		
Visit window			**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±1wk**	**±1wk**
Unless otherwise stated, all blood and urine samples must be obtained before administration of study drug.																
Informed consent	Subjects must sign the ICF before any study-specific procedures.															
Eligibility criteria		X														
Spirometry test (ie, FEV1) in subjects with COPD or asthma		X														
Demography/height/medical history		X														
Physical examination	Complete physical examination should be performed during the Screening Phase.	X	Only a symptom-directed physical examination is required.													
Weight	To be measured pre-dose.	X	X				X				X					
Vital sign measurements	To be performed as described in Section 9.6 (Safety Evaluations).	X	On Cycle 1 Day 1: immediately before the start of daratumumab administration, at end of administration, and at 0.5 and 1 hr after end of administration. For all other daratumumab administration days: immediately before the start of daratumumab administration and at the end of administration. On Carfilzomib only dosing days, immediately before the start of carfilzomib infusion only.												X	
ECOG performance status		X	X				X				X				X	
Transthoracic Echocardiogram (TTE)		X	Every 6 months and as clinically indicated.													
Electrocardiogram		X	As clinically indicated.												X	
Medication Administration																
Daratumumab SC	Refer to Section 6 for details on study drug		X	X	X	X	X		X		X					
Carfilzomib			X	X	X		X	X	X		X	X	X			

Time and Event Schedule for the D-Kd cohort only	Notes	Study Visits														
		Screening Phase	Treatment Phase (1 Cycle = 28 d)												Post-Treatment Phase	
			Cycles 1 & 2				Cycles 3 to 6				Cycles 7+				EOT Post-treatment Visit at 30 Days after last dose of study drug	FUP Post-treatment Visit at 8 wks after last dose of study drug
Study Day		**-28 to -1**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**		
Visit window			**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±1wk**	**±1wk**
Dexamethasone	administration.		X	X	X	X	X	X	X	X	X	X	X	X[a]		
Pre- medications	See section 6.4.1.1		X	X	X	X	X		X		X					
Diary Review	Accountability/ exposure check.		Cycle 2	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event monitoring		Continuous from the time of signing of informed consent form until 30 d after the final dose of study drug. Subjects need to be observed for 6 hrs after the first daratumumab dose. Beyond the 30d EOT Visit, information on serious adverse events considered related to study drug will continue to be collected.														
SPM information		X														
Concomitant medication recording		Continuous from time of signed ICF until 30 d after last study drug dose.														
Subsequent myeloma therapy															X	X
Laboratory Assessments																
Blood type and indirect antiglobulin test results	To be obtained once before the first injection of daratumumab. Record on the subject's identification wallet card	X														
Urine or serum pregnancy test	Women of childbearing potential only. More frequent pregnancy tests may be conducted if required per local regulations.	Day -14 to C1D1	As clinically indicated												X	
Chemistry		X	X		X		X		X		X		X		X	

Time and Event Schedule for the D-Kd cohort only	Notes	Study Visits														
		Screening Phase	Treatment Phase (1 Cycle = 28 d)												Post-Treatment Phase	
			Cycles 1 & 2				Cycles 3 to 6				Cycles 7+				EOT Post-treatment Visit at 30 Days after last dose of study drug	FUP Post-treatment Visit at 8 wks after last dose of study drug
Study Day		**-28 to -1**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**		
Visit window			**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±1wk**	**±1wk**
Hematology	At screening, acceptable to meet CRAB criteria if performed as part of SOC within 42 days before randomization. During the treatment phase, may be performed up to 3 days before study drug administration day. Results must be evaluated before each study drug administration	X	X	X	X	X	X	X	X		X	X	X		X	
HBV Serology	All subjects will be tested locally for HBsAg, Anti-HBs, and Anti-HBc. See Section 9.6.	X														
HBV DNA test	For subjects with serologic evidence of resolved HBV infection (ie, positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. See Section 9.6.	X	Every 12 weeks for up to 6 months after the last dose of study treatment													

Time and Event Schedule for the D-Kd cohort only	Notes	Study Visits														
		Screening Phase	Treatment Phase (1 Cycle = 28 d)												Post-Treatment Phase	
			Cycles 1 & 2				Cycles 3 to 6				Cycles 7+				EOT Post-treatment Visit at 30 Days after last dose of study drug	FUP Post-treatment Visit at 8 wks after last dose of study drug
Study Day		**-28 to -1**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**		
Visit window			**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±1wk**	**±1wk**
Whole blood (biomarker)	Pre-administration collections for PBMCs and plasma.			Cycle 1 Day 1 and Cycle 3 Day 1											X	
Pharmacokinetics and immunogenicity blood samples for daratumumab and rHuPH20 characterization: See Table 9																
Disease Evaluations (Blood/Urine) Samples must be sent to the central laboratory.																
Serum β_2-microglobulin	SPEP and UPEP are to be performed within 14 d before Cycle 1 Day 1 and on the scheduled assessment day (±3 d).	X														
QIg (IgA, IgM, IgG, IgD, IgE)		X	Every 3 months during treatment (window of ±1 month)												X	
SPEP		X	X				X				X				X	
UPEP (24 hr urine sample)		X	X				X				X				X	
Serum calcium corrected for albumin		X	X				X				X				X	
Serum FLC & serum/urine immunofixation		X	Serum FLC and serum/urine immunofixation are to be performed for any subject when CR is suspected or maintained; for light chain MM subjects, serum FLC will also be performed on Day 1 of every cycle, and at the end of treatment.													
Investigator evaluation of response	Per IMWG criteria (see Section 9.2.1.1)		Day 1 of every cycle from Cycle 2 and beyond													

Time and Event Schedule for the D-Kd cohort only	Notes	Study Visits														
		Screening Phase	Treatment Phase (1 Cycle = 28 d)												Post-Treatment Phase	
			Cycles 1 & 2				Cycles 3 to 6				Cycles 7+				EOT Post-treatment Visit at 30 Days after last dose of study drug	FUP Post-treatment Visit at 8 wks after last dose of study drug
Study Day		**-28 to -1**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**		
Visit window			**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±1wk**	**±1wk**
Bone marrow aspirate/biopsy	Disease characterization (morphology and either immunohistochemistry or immunofluorescence or flow cytometry). Cytogenetics by conventional karyotype or FISH (preferred), performed locally. For screening (up to 42 d before administration of study treatment.) fresh aspirate or biopsy preferred. If not available, obtain non-decalcified tissue. Samples will be sent to central laboratory for MRD evaluation.	X	Samples are requested at the time of suspected CR to confirm CR/sCR and to evaluate MRD. For subjects who achieve CR and remain on study, an additional bone marrow aspirate will be obtained at 12, 18, and 24 months (±1 month) post C1D1 and every 12 months thereafter (±1 month) until disease progression. If one of these timepoints occur within 1 month of suspected CR, a repeat bone marrow will not be requested.													
Bone lesion assessment Skeletal survey	Screening assessment may be performed within 42 d before administration of study treatment. Low-dose whole body CT is preferred. As clinically indicated and per local practice, a skeletal survey by X-ray, MRI or PET-CT may be used as an alternative.	X	As clinically indicated													

Time and Event Schedule for the D-Kd cohort only	Notes	Study Visits														
		Screening Phase	Treatment Phase (1 Cycle = 28 d)												Post-Treatment Phase	
			Cycles 1 & 2				Cycles 3 to 6				Cycles 7+				EOT Post-treatment Visit at 30 Days after last dose of study drug	FUP Post-treatment Visit at 8 wks after last dose of study drug
Study Day		**-28 to -1**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**		
Visit window			**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±1wk**	**±1wk**
Assess extramedullary plasmacytomas	For screening (up to 42 d before administration of study treatment.) See section 9.2.1.8 for details on assessing and documenting extramedullary plasmacytomas.	X	Measurable sites every 4 wks for physical examination (if applicable) and every 12 wks for radiologic assessment (for subjects with a history of plasmacytomas or as clinically indicated for others)													

Anti-HBc=antibodies to hepatitis B core antigen; Anti-HBs=antibodies to hepatitis B core surface antigen; C1D1=Cycle 1 Day 1; COPD=chronic obstructive pulmonary disease; CR=complete response; CT=computed tomography; D=day; d=days; D-Kd=Dara SC, carfilzomib, and dexamethasone; ECOG=Eastern Cooperative Oncology Group; EOT=End of Treatment; FISH=fluorescence in situ hybridization; FLC=free light chain; FUP=Follow-up Phase; hr(s)=hour(s); HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; ICF=informed consent form; QIg=quantitative immunoglobulins; MM=multiple myeloma; MRD=minimal residual disease; MRI=magnetic resonance imaging; PBMC=peripheral blood mononuclear cells; PD=progressive disease; SC=subcutaneous; sCR=stringent CR; SPEP=Serum M-protein quantitation by electrophoresis; SPM = secondary primary malignancy; UPEP=urine M-protein quantitation by electrophoresis; wk(s)=week(s).

[a] During Cycles 7 to 9, only.

Table 9: Time and Events Schedule - Pharmacokinetic/Immunogenicity Sample Collection Times (D-Kd Cohort)

Note: Refer to Attachment 15 for a description of study procedures for subjects who continue receiving study drugs after data collection has ended.

PK Schedule for the D-Kd cohort only	Cycle 1		Cycle 3		Cycle 6	Cycle 9	Cycle 12	Post-treatment	
Day	1	4	1	4	1	1	1	EOT Post-treatment Visit at 30 Days after last dose of study drug	FUP Post-treatment Visit at 8 wks after last dose of study drug
Visit window d=day, wk=week	0	±1d	0	±1d	0	0	0	±1wk	±1wk
D=study drug administered	D		D		D	D	D		
daratumumab pharmacokinetics (serum)									
Before administration[a]	X		X		X	X	X		
After administration		X		X				X	X
daratumumab immunogenicity (no additional blood draw; serum taken from pharmacokinetic sample)[b]									
Before administration[a]	X		X		X	X	X	X	X
rHuPH20 immunogenicity (plasma)[b]									
Before administration[a]	X		X		X	X	X	X	X

D-Kd=Dara SC, carfilzomib, and dexamethasone; PK=pharmacokinetic; rHuPH20=recombinant human hyaluronidase.

[a] On dosing days, sample collection may occur up to 2 hours before but not after the start of the drug administration. Samples collected on dosing days with visit windows should be collected on the actual day of study drug administration.

[b] In addition, samples for assessment of antibodies to daratumumab or antibodies to daratumumab and rHuPH20 should be drawn, if possible, any time an infusion-related reaction is reported (according to the Lab Manual and Section 9.3) in association with the second daratumumab administration or beyond.

ABBREVIATIONS

Anti-HBc	antibodies to hepatitis B core antigen
Anti-HBs	antibodies to hepatitis B surface antigen
ASCT	autologous stem cell transplant
BMI	body mass index
CD38	cluster of differentiation 38
CI	confidence interval
C_{min}	minimum observed concentration
C_{max}	maximum observed concentration
COPD	chronic obstructive pulmonary disease
CR	complete response
CT	computed tomography
C_{trough}	trough concentration
Dara-IV	daratumumab for intravenous infusion
Dara-MD	daratumumab and recombinant human hyaluronidase for subcutaneous injection: mix and deliver
Dara SC	daratumumab and recombinant human hyaluronidase for subcutaneous injection: co-formulated
DOR	duration or response
DRd	daratumumab-IV, lenalidomide, and dexamethasone
D-Kd	daratumumab-SC, carfilzomib, and dexamethasone
D-Rd	daratumumab SC, lenalidomide, and dexamethasone
DVd	daratumumab-IV, bortezomib, and dexamethasone
D-VMP	daratumumab SC, bortezomib, melphalan, and prednisone
D-VRd	daratumumab SC, bortezomib, lenalidomide, and dexamethasone
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EOT	end of treatment
EU	European Union
FEV1	forced expiratory volume in 1 second
FFPE	formalin-fixed, paraffin-embedded
FOIA	Freedom of Information Act
FLC	free light chain
GCP	good clinical practice
HBc	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HRT	hormonal replacement therapy
IAT	indirect antiglobulin test
ICF	informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFE	immunofixation electrophoresis
IgG	immunoglobulin G
IMiD	immunomodulatory drug
IMP	investigational medicinal product

IMWG	International Myeloma Working Group
INR	international normalized ratio
IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous
IWRS	interactive web response system
LMWH	low molecular weight heparin
MDRD	modification of diet in renal disease
MDSC	myeloid-derived suppressor cell
MM	multiple myeloma
M-protein	monoclonal paraprotein
MRD	minimal residual disease
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NK	natural killer
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic
PO	orally
PQC	product quality complaint
PR	partial response
RBC	red blood cell
Rd	lenalidomide and dexamethasone
REMS	risk evaluation and mitigation strategy
rHuPH20	recombinant human hyaluronidase
SAC	Safety Assessment Committee
SC	subcutaneous
sCR	stringent complete response
SET	study evaluation team
SIPPM	Site Investigational Product and Procedures Manual
SmPC	Summary of Product Characteristics
SPEP	serum M-protein quantitation by electrophoresis
SPM	secondary primary malignancy
SUSARs	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
T_{max}	time to maximum observed concentration
TTE	transthoracic echocardiogram
ULN	upper limit of normal
UPEP	urine M-protein quantitation by electrophoresis
US	United States
Vd	bortezomib and dexamethasone
VMP	bortezomib, melphalan, and prednisone
VRd	bortezomib, lenalidomide, and dexamethasone

VGPR	very good partial response

1. INTRODUCTION

Daratumumab (JNJ-54767414) is a human immunoglobulin G (IgG) monoclonal antibody (mAb) immunotherapy that binds with high affinity to cluster of differentiation 38 (CD38), a transmembrane glycoprotein, expressed on tumor cells, and induces tumor cell death through multiple mechanisms of action. These mechanisms of action include complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis, and direct cytotoxicity by induction of apoptosis by Fc gamma receptor mediated crosslinking of tumor-bound monoclonal antibodies. Daratumumab treatment leads to the rapid and sustained elimination of highly immunosuppressive subsets of $CD38^+$ Tregs, $CD38^+$ MDSCs, and $CD38^+$ regulatory B cells (Bregs) (Krejcik 2016[15]). The elimination of these immunosuppressive cells, modulation of CD38 enzymatic activity and destruction of the malignant myeloma cells is thought to lead to the clonal expansion of CD8+ and CD4+ T cells (Chiu 2016[6]). The multiple mechanisms of actions are hypothesized to lead to the minimal residual disease (MRD) negative responses observed in some patients

The intravenous (IV) formulation of DARZALEX (daratumumab) is approved in a number of countries worldwide for the treatment of multiple myeloma (MM). DARZALEX was initially approved in the United States (US) and European Union(EU) as monotherapy for the treatment of heavily pre-treated patients with relapsed and refractory multiple myeloma and since this time, several indications have been approved for DARZALEX in combination with background therapies for both relapsed/refractory and newly diagnosed multiple myeloma patients. Most recently, the subcutaneous (SC) formulation of DARZALEX was approved in the US and EU and provides several key benefits for patients and healthcare providers as it is a flat dose that reduces the time taken to receive daratumumab treatment and reduces the incidence and severity of infusion related reactions (IRRs) in comparison to the IV formulation. For more details about current approved indications, please refer to Summary of Product Characteristics (SmPC 2020[8]) and United States Package Insert (USPI 2020[9]).

Recombinant human hyaluronidase (rHuPH20) is the active ingredient of Hylenex® recombinant (hyaluronidase human injection), which was approved for use in the US in December 2005. rHuPH20 is also approved in combination with protein therapeutics for SC administration, such as HyQvia (Immune globulin infusion 10% [human] with rHuPH20) in the US and EU, as well as anticancer medications such as Herceptin® SC (trastuzumab) in the EU and MabThera® SC (rituximab) in the EU and the US.

For the most comprehensive nonclinical and clinical information regarding daratumumab and rHuPH20, refer to the latest version of the Investigator's Brochures for daratumumab and rHuPH20[13]. The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Clinical Studies

For the results of the single agent IV daratumumab studies refer to the daratumumab Investigator's Brochure[13].

1.1.1. Combination Therapy Studies: Summary of the Results from Studies MMY3003, MMY3004, MMY3007, and MMY1001

The US and EU approval of daratumumab for the treatment of patients with MM who have received at least 1 prior therapy was based on the results of the phase 3 Study 54767414MMY3003 (hereafter referred to as Study MMY3003) and Study MMY3004 as well as the Phase 1 Study 54767414MMY1001, all of which examined the safety and efficacy of daratumumab for intravenous infusion (Dara-IV) in combination with other therapies in the treatment of relapsed MM. The results from the 3 studies are summarized below along with the interim results of the phase 3 combination Study 54767414MMY3007 comparing daratumumab SC, bortezomib, melphalan, and prednisone (D-VMP) to daratumumab SC, bortezomib, melphalan, and prednisone (VMP) in newly diagnosed MM:

- In Study MMY3003, subjects with MM received Dara-IV in combination with lenalidomide and dexamethasone (DRd). At the time of the first interim analysis, treatment with DRd resulted in a 63% reduction in the risk of disease progression or death compared to the combination of lenalidomide and dexamethasone (Rd). The median progression-free survival (PFS) was not reached in the daratumumab group; median PFS was 18.4 months in the Rd group. The overall response rates (ORRs) were 93% for the DRd group and 76% for Rd group.
- In Study MMY3004, subjects with MM received Dara-IV in combination with bortezomib and dexamethasone (DVd). At the time of the first interim analysis, treatment with DVd showed a 61% reduction in the risk for disease progression or death compared to the combination of bortezomib and dexamethasone (Vd). The median PFS was not estimable in the DVd group; median PFS was 7.2 months, in the Vd group. The ORRs were 83% for the DVd group and 63% for the Vd group.
- In Study MMY3007, subjects with MM received Dara-IV in combination with bortezomib, melphalan and dexamethasone (D-VMP). At the time of the first interim analysis, treatment with D-VMP showed a 50% reduction in the risk for disease progression or death compared to the combination of bortezomib, melphalan and dexamethasone (VMP). The median PFS was not reached for the D-VMP group and was 18.1 months for the VMP group. The ORRs were 91% for the D-VMP group and 75% for the VMP group.
- In Study MMY1001, subjects with MM received Dara-IV in combination with carfilzomib (70 mg/m^2 weekly) and dexamethasone (D-Kd). As of the clinical cutoff date of 12 Oct 2017, 85 subjects were treated with D-Kd which resulted in a 12-month PFS rate of 71%. The median PFS was not reached. The ORR was 86% (Lonial 2017[21]).

Adverse events of special interest from these studies include:

- Neutropenia in combinations of daratumumab with lenalidomide, pomalidomide, or melphalan; thrombocytopenia combinations of daratumumab with bortezomib or melphalan.
- A higher incidence of all-grade infections. However, the incidence of life-threatening and fatal infections was low and generally balanced between the 2 treatment arms.
- An increased risk of secondary primary malignancy (SPM).

The incidence of study drug discontinuation and deaths in these studies was low. For further details and the most up-to-date information about combination therapy studies, refer to the daratumumab Investigator's Brochure.

1.1.2. Study 54767414MMY1004

Study 54767414MMY1004 (hereafter referred to as Study MMY1004) is an ongoing, open-label, 2-part phase 1b study to assess the safety and pharmacokinetics (PK) of SC daratumumab in subjects with relapsed or refractory multiple myeloma who have received ≥2 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD). In Part 1, subjects (n=53) received the mix and deliver formulation of subcutaneous daratumumab (Dara-MD), and in Part 2, subjects (n=25) are receiving daratumumab co-formulated (Dara SC) with rHuPH20. Enrollment in both parts of the study has been completed.

1.1.2.1. Preliminary Data from Study MMY1004 Part 1

Dara-MD is a solution that requires mixing of the daratumumab drug product with rHuPH20 prior to delivery. In Part 1 of Study MMY1004, Dara-MD was administered subcutaneously according to the same schedule as the approved IV daratumumab regimen, ie, once weekly in Cycles 1 and 2, every 2 weeks in Cycles 3 to 6, and then every 4 weeks in subsequent cycles until disease progression or unacceptable toxicity. Subjects were enrolled in sequential cohorts at 1200 mg (n=8 subjects) and 1800 mg (n=45 subjects).

After a median treatment duration of 2.6 months for the 1200 mg cohort and 5.4 months for the 1800 mg cohort (clinical cutoff 03 Aug 2017), the key safety findings were:

- The incidence of all-grade IRRs was 13% and 24% in the 1200 mg and 1800 mg Dara-MD cohorts, respectively. In comparison, among subjects treated in single-agent or combination studies with IV daratumumab, IRRs were reported in 48% of subjects.
  - Across both cohorts, all but 1 infusion-related reaction (IRR) were mostly Grade 1 or 2. One subject (2%) in the 1200 mg Dara-MD cohort developed a Grade 3 IRR of dyspnea compared to 6% on daratumumab IV monotherapy studies.
  - All IRRs developed within 6 hours of the start of the Dara-MD infusion and did not result in treatment discontinuation.

- The most frequently reported treatment-emergent adverse events (TEAEs) (≥20% of all subjects) were upper respiratory tract infection, thrombocytopenia and insomnia (38% each) and pyrexia, fatigue, anemia, diarrhea, vomiting, headache, and cough (25% each) for the 1200 mg cohort. For the 1800 mg cohort TEAEs were anemia (33%), diarrhea, upper respiratory tract infection (22% each), pyrexia (27%), fatigue and asthenia (20% each).
- Grade 3 or 4 TEAEs were reported in 63% and 49% of subjects in the 1200 mg and 1800 mg cohorts, respectively. In studies of IV daratumumab, Grade 3 or 4 TEAEs were reported in 56% of subjects.
- Serious TEAEs were reported in 50% and 31% of subjects in the 1200 mg and 1800 mg cohorts, respectively compared to 34% on Dara-IV monotherapy studies.
- One subject in the 1800 mg cohort died due to a TEAE of depressed level of consciousness; this event occurred 20 days after last dose of Dara-MD and was considered by the investigator to be unrelated to study drug and related to progression of disease.

At the time of the clinical cutoff (03 Aug 2017), 53 subjects (8 subjects in the 1200 mg Dara-MD cohort and 45 subjects in the 1800 mg Dara-MD cohort) were evaluable for efficacy, which was defined as having C3D1 disease evaluation or demonstrated disease progression. In the 1200 mg Dara-MD cohort, the ORR was 25% (95% confidence interval (CI): 3%-65%) and 2 subjects achieved partial responses (PRs): one 8 weeks and the other 20 weeks after initiation of treatment. In the Dara-MD 1800 mg cohort, the ORR was 42% (compared to 31% for Dara-IV). The rates of greater than or equal to very good partial response (VGPR) and complete response (CR) were 20% and 9%, respectively (12% and 3% respectively for Dara-IV). The median time to first response in the 1200 mg and 1800 mg cohorts was 3.4 months (range 1.8-4.9 months) and 1 month (range 0.9-10.2 months), respectively, which is in line with what was observed for Dara-IV.

Preliminary Pharmacokinetic Data

Preliminary PK data following Dara-MD administration show a slower absorption with a later T_{max} (approximately 72 h post-infusion) compared with IV administration. Preliminary analyses indicate the bioavailability of Dara-MD is approximately 77% when administered subcutaneously. Please refer to Section 1.1.2.2, Preliminary Data from Study MMY1004 Part 2, for detailed results for Dara SC.

1.1.2.2. Preliminary Data from Study MMY1004 Part 2

The final SC daratumumab, Dara SC, which will be used in Study MMY2040 is a co-formulated drug product intended for a fixed-dose administration, containing rHuPH20 and daratumumab in a single vial. Part 2 of Study MMY1004 is a phase 1b, non-randomized, open-label study to evaluate Dara SC (referred to in the MMY1004 protocol as Dara-CF) administered subcutaneously to subjects with multiple myeloma who have received at least 2 prior lines of therapy, including a PI and an IMiD, and have measurable disease. Based on the results from Part 1 of the study, the 1800 mg dose was selected for Part 2.

After a median treatment duration of 2.3 months (clinical cutoff date of 03 Aug 2017), key safety findings for the 25 subjects who have received at least 1 dose of 1800 mg Dara SC are as follows:

- IRRs (all grades) was reported in 8% of subjects. All IRRs (chills, dyspnea, and allergic rhinitis) were Grade 1 or 2.
- Injection site reactions were reported in 2 subjects: 1 subject had a Grade 1 injection site discoloration/injection site induration (although no measurable induration was reported in this subject), and 1 subject had a Grade 1 erythema. A Grade 1 hematoma was reported for a third subject after the clinical cutoff.
- The most frequently reported TEAEs (≥3 [12%] subjects) were lymphopenia (32%); thrombocytopenia, pyrexia, fatigue, asthenia, back pain, nausea, headache, insomnia (16% each); and leukopenia, anemia, chills, and diarrhea (12% each).
- Grade 3 or 4 TEAEs were reported in 36% of subjects.
- Serious TEAEs were reported in 2 subjects (8%). The serious TEAEs were pyrexia, asthenia, fatigue, hyponatremia, febrile neutropenia, leukopenia, and thrombocytopenia; and all were Grade 3 or 4 except for pyrexia.
- No subject discontinued treatment or died due to a TEAE.

Preliminary Pharmacokinetic Data

As of the clinical cutoff date, 20 subjects had reached Cycle 3 Day 1 (C3D1). Of those, 18 subjects had received all scheduled doses of study drug in cycles 1 and 2 and had provided a pre-dose PK sample on C3D1 and were therefore considered evaluable for the PK endpoint.

The primary PK endpoint of C3D1 trough concentration (C_{trough}) mean value was 904.42 µg/mL for the Dara SC cohort (n=18) compared with 754.62 µg/mL for the 1800 mg 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 C3D1 C_{trough} values for Dara SC are similar to the 1800 mg Dara-MD formulations (798.9 and 795.5 µg/mL, respectively) and slightly higher than the 16 mg/kg IV median values from Studies MMY2002 and GEN501 (559.6 and 713.9 µg/mL, respectively). The range of C3D1 C_{trough} observations for the SC cohort is within the range observed following 16 mg/kg IV dosing and the variability appeared to be similar for the Dara SC and 16 mg/kg IV cohorts.

The observed mean maximum observed concentration (C_{max}) values following the last (8^{th}) weekly dose for the Dara SC cohort was 1012.4 µg/mL, similar to the mean C_{max} of 914.9 µg/mL observed after the C3D1 (9^{th}) dose for Dara-IV in Study MMY2002. The C3D1 C_{max} was selected for this comparison as the C_{max} was not captured following the last weekly (8^{th}) dose in Study MMY2002. The observed C_{max} values from the Dara SC cohort is within the range observed for Dara-MD and daratumumab 16 mg/kg IV.

1.2. Recombinant Human Hyaluronidase (rHuPH20)

Recombinant human hyaluronidase (rHuPH20) is a recombinantly expressed version of hyaluronidase synthesized in Chinese Hamster Ovary cells that have been transfected with a plasmid containing the DNA sequence encoding human PH20 hyaluronidase. rHuPH20 acts locally and transiently within the SC space to increase the tissue dispersion and absorption of other injected drugs and fluids. rHuPH20 cleaves the repeating disaccharide subunits (N-acetyl-D-glucosamine and D-glucuronic acid) of hyaluronan, a polymeric, gel-like glycosaminoglycan (mucopolysaccharide) that limits the movement of fluids and other molecules in the SC tissue. rHuPH20 de-polymerizes the gel-like hyaluronan, resulting in decreased resistance to fluid flow and a transient increase in permeability of the local SC tissue.

The co-formulated preparation (Dara SC) currently under study in Part 2 of Study MMY1004 has a daratumumab concentration of 120 mg/mL and rHuPH20 at a concentration of 2000 U/mL. The injection volume for daratumumab 1800 mg with Dara SC is approximately 15 mL, which contains 30,000 U rHuPH20.

1.2.1. Clinical Studies

When rHuPH20 doses of 10,000 and 30,000 U were administered IV to humans, the mean maximum concentration achieved was 2.5 and 6.8 U/mL, respectively. The half-life of plasma enzymatic activity was 3.7 and 5.6 minutes for the respective doses. It is expected that SC doses in the range of 30,000 to 45,000 U will result in levels of rHuPH20 in plasma that are well below limits of quantitation (approximately 0.3 U/mL).

In Part 1 of Study MMY1004, the concentration of rHuPH20 was 500 U/mL, which is approximately equivalent to rHuPH20 30,000 U for a 60-mL infusion of 1200 mg of daratumumab, and rHuPH20 45,000 U for a 90-mL infusion of 1800 mg of daratumumab. In Part 2, a flat-dosed, fixed co-formulated drug product containing rHuPH20 drug substance (2000 U/mL) and Generation 2 (Gen 2) daratumumab drug substance (120 mg/mL) in a single vial (Dara SC) was used. Previous clinical studies have demonstrated that SC injection of up to 96,000 U of rHuPH20 is tolerable (Halozyme data on file). Currently marketed anticancer therapeutic antibodies have achieved bioavailability of 71% (rituximab) to 87% (trastuzumab) with co-administration of <30,000 U of rHuPH20.

Phase 1 trials of rituximab SC administration in subjects with follicular lymphoma and trastuzumab SC in healthy volunteers and subjects with early breast cancer using rHuPH20 have demonstrated substantially shorter administration times, comparable tolerability, and comparable PK compared with IV (Shpilberg 2013[30]). More gradual absorption was observed with trastuzumab SC administration, with maximum observed concentrations approximately 2-fold lower for SC versus IV, and the time to maximum concentration was 4 to 6 days with SC administration versus ≤3 hours with IV administration (Wynne 2013[31]). However, the trough concentrations occurring with SC delivery are generally the same or higher as compared to IV (Bittner 2012[2]), and clinical efficacy of the 2 routes of administration is comparable (Ismael 2012[14]). In a 2-stage phase 1b study with rituximab, the fixed dose of rituximab 1400 mg

SC was confirmed to have non-inferior observed serum concentrations immediately prior to the next administration (C_{trough}) relative to rituximab 375 mg/m^2 IV, with a comparable safety profile. Local administration-related reactions, mostly mild to moderate in severity, occurred more frequently after SC administration (Salar 2014[29]). These findings were confirmed in a randomized phase 3 study (Davies 2014[7]).

1.3. Overall Rationale for the Study

A co-formulated product of daratumumab and rHuPH20 allows for the SC administration of daratumumab in 3 to 5 minutes compared to 4 to 7 hours for an IV infusion of daratumumab. Results from the phase 1 monotherapy study (MMY1004) suggest a reduction of IRRs and efficacy that is similar to what is observed with daratumumab IV monotherapy. This is an open-label, international, multicenter, phase 2 study to demonstrate that daratumumab administered by SC injection in combination with standard treatment regimens is safe and efficacious in subjects with newly diagnosed MM or in subjects with relapsed or refractory disease.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

- To evaluate the clinical benefit of SC daratumumab administered in combination with standard MM regimens in subjects with MM as measured by ORR or VGPR or better rate.

Secondary Objectives

- To evaluate safety and PK of SC administration of daratumumab in combination with standard MM regimens
- To evaluate additional clinical benefit of SC daratumumab administered in combination with standard MM regimens in subjects with MM
- To characterize the immunogenicity of daratumumab and rHuPH20 following SC administration
- To evaluate minimal residual disease (MRD) negativity rate in the D-VMP (daratumumab SC in combination with bortezomib, melphalan, and prednisone), D-Kd (daratumumab SC in combination with carfilzomib and dexamethasone), and D-Rd (daratumumab SC in combination with lenalidomide and dexamethasone) cohorts.

2.1.2. Endpoints

Primary Endpoint

- ORR, defined as the proportion of subjects with a partial response or better as defined by the International Myeloma Working Group (IMWG) response criteria (D-Kd, D-VMP, and D-Rd cohorts)
- VGPR or better rate, defined as the proportion of subjects with a VGPR or better rate as defined by the IMWG response criteria (D-VRd cohort)

Secondary Endpoints

- Serum concentrations of daratumumab
- Rate of IRRs
- VGPR or better rate as defined by the IMWG response criteria (D-Kd, D-VMP, and D-Rd cohort), and ORR as defined by the IMWG response criteria (D-VRd cohort)
- CR or better rate, as defined by the IMWG response criteria
- Duration of response (DOR), defined as the time from the date of initial documented response (PR or better for D-Kd, D-VMP, and D-Rd cohorts) to the date of first documented evidence of progressive disease or death due to PD
- Incidence of anti-drug antibodies against daratumumab or rHuPH20
- Minimal residual disease (MRD) negativity rate in the D-Kd, D-VMP, and D-Rd cohorts.

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

2.2. Hypothesis

The hypothesis is that the addition of daratumumab administered SC to standard MM regimens will improve responses compared to response data observed in completed phase 3 studies without daratumumab.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

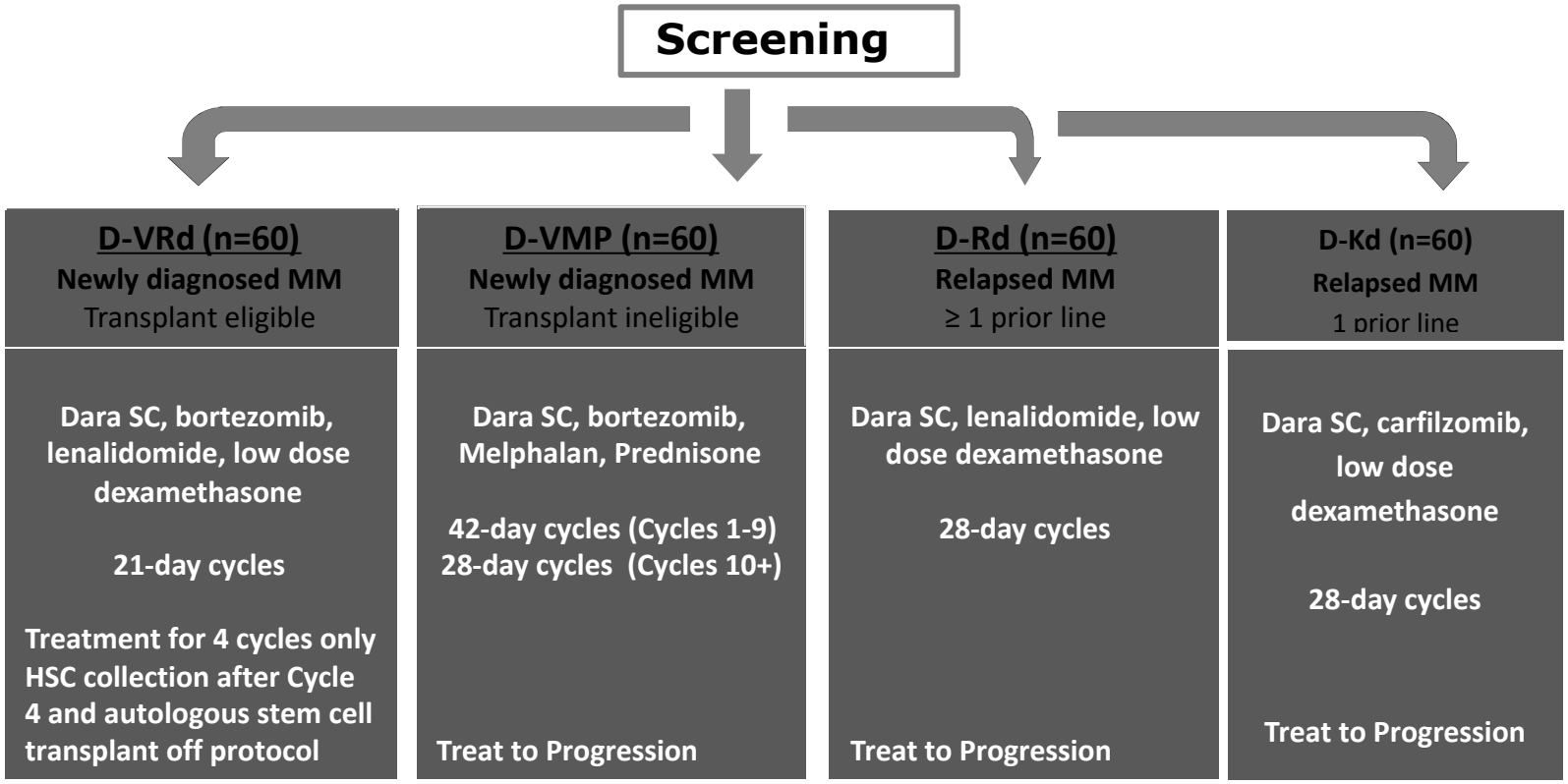
This is a multicenter, open-label, phase 2 study to investigate the efficacy and safety of Dara SC in combination with bortezomib, lenalidomide, and dexamethasone (VRd) in subjects with newly diagnosed MM who are transplant eligible; or in combination with bortezomib, melphalan, and prednisone (VMP) in subjects with newly diagnosed MM who are ineligible for transplant; or in combination with lenalidomide and dexamethasone (Rd) in subjects with relapsed or refractory MM, or in combination with carfilzomib and dexamethasone (Kd) in subjects in subjects in first relapse or refractory MM after initial treatment with a lenalidomide-containing regimen. Approximately 60 subjects will be treated in each cohort. Subjects enrolled in the daratumumab, bortezomib, lenalidomide, and dexamethasone cohort (D-VRd) will be treated for 4 cycles and will be evaluated for a VGPR or better rate thereafter. Hematopoietic stem cell collection and autologous transplant will be performed off protocol. Subjects enrolled in the D-VMP, D-Kd, and D-Rd cohorts will be treated until disease progression. A diagram of the study design is provided in Figure 1.

The data cutoff for the primary analysis for the study will occur at least 6 months after approximately the 60th subject is enrolled in the last treatment cohort (D-VRd, D-VMP, or D-Rd). All available data at the time of this data cutoff will be included in the Clinical Study Report. The cutoff for the primary analysis for the D-Kd cohort will occur at least 6 months after approximately the 60th subject is enrolled in the D-Kd cohort. The data cutoff for the final analysis and the end of data collection will occur approximately 10 months after the last subject is enrolled in the D-Kd cohort. Subsequently, the clinical database will be locked for the final analysis (see Attachment 15).

Subjects benefiting from study treatment can continue receiving the study drugs after the end of data collection until the study drugs are commercially available, available from another source (eg. via a dedicated long-term extension study), or until study completion. The end of study will occur when all subjects discontinue study treatment or 18 months after the end of data collection, whichever occurs first. An addendum to the Clinical Study Report will be generated and describe safety data, including serious adverse events and pregnancy reporting, from the end of data collection through the end of study.

A study evaluation team (SET) consisting of the participating investigators the sponsor's medical monitor, the sponsor's clinical pharmacologist (if PK data are being evaluated), the sponsor's statistician the sponsor's safety officer, and the sponsor's study manager will evaluate safety data after at least 6 toxicity-evaluable subjects complete Cycle 1 in each cohort. Additional data reviews by the SET can be scheduled as needed to support decisions on dose selection or schedule modification. The SET reviews and dose selection decisions will be documented in writing in the Trial Master File.

Figure 1: Schematic Overview of the Phase 2 Study Design



Dara SC= daratumumab and recombinant human hyaluronidase for subcutaneous injection: co-formulated; D-VRd=Dara SC, bortezomib, lenalidomide, and dexamethasone; D-VMP= Dara SC, bortezomib, melphalan, and prednisone; Dara-Rd= Dara SC, lenalidomide, and dexamethasone; D-Kd=Dara SC, carfilzomib and dexamethasone; HSC=hematopoietic stem cell; MM=multiple myeloma.

3.2. Study Design Rationale

Study MMY2040 will test Dara SC (1800 mg) in combination with the regimens that have been evaluated in several completed or ongoing daratumumab IV Phase 3 studies, for which indications are already approved or are anticipated. The regimens include: Dara SC in combination with bortezomib, lenalidomide and dexamethasone (D-VRd) in newly diagnosed subjects with MM who are eligible for transplant; in combination with bortezomib, melphalan and prednisone (D-VMP) in newly diagnosed subjects with MM who are ineligible for transplant; and in combination with lenalidomide and dexamethasone (D-Rd) in subjects with relapsed or refractory MM, or in combination with carfilzomib and dexamethasone (D-Kd) in MM subjects who had lenalidomide-containing frontline treatment and are relapse or refractory to lenalidomide.

The 4 drug combinations bortezomib/melphalan/prednisone (VMP), lenalidomide/dexamethasone (Rd), carfilzomib/dexamethasone (Kd), and bortezomib/lenalidomide/dexamethasone (VRd) are all established myeloma regimens. Per the Summary of Product Characteristics (SmPC), bortezomib is indicated in combination with melphalan and prednisone (VMP) for adult subjects with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with hematopoietic stem cell transplantation. It is also indicated in combination with an IMiD and dexamethasone as the induction treatment for adult subjects with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with hematopoietic stem cell transplant. Both the European Myeloma Network (Engelhardt 2014[11]) and the National Comprehensive Cancer Network recommend VRd as an induction therapy for transplant-eligible subjects. Per the SmPC, lenalidomide is indicated in combination with dexamethasone in adult subjects with previously treated multiple myeloma who are not eligible for high-dose chemotherapy with hematopoietic stem cell transplantation. The sponsor considers the use of VMP, VRd, Kd, and Rd in the aforementioned indications as standard of care. In the proposed study, the 4 combination regimens are used according to their indications/recommendations in combination with Dara SC. The sponsor therefore believes the combination therapies VMP, VRd, Kd, and Rd should also be considered standard of care in the proposed study and should not be considered IMPs.

The rationale for selecting the 4 combination regimens is as follows:

- To evaluate 3 classes of myeloma drugs, (IMiDs, proteasome inhibitors [PIs], alkylators) and their combinations.
- To evaluate daratumumab in combination with standard regimen in the 3 major segments of the MM disease spectrum (newly diagnosed transplant eligible MM, newly diagnosed transplant ineligible MM, and relapsed MM).
- D-Rd (1+ lines) is the regimen that was evaluated in Study MMY3003, which led to the approval of daratumumab IV in combination with Rd in subjects with relapsed MM.
- D-VMP (frontline) is the regimen evaluated in Study MMY3007, which led to the approval of daratumumab in combination with VMP for subjects with newly diagnosed MM.

- VRd (frontline) is an emerging SOC regimen commonly used as induction for newly diagnosed transplant eligible subjects with MM and D-VRd is the experimental arm in the ongoing Study MMY2004.
- Kd is an approved regimen in the United States and Europe for subjects with relapsed/refractory MM who have received 1-3 lines of therapy. Carfilzomib 70 mg/m^2 weekly dose is an approved dose schedule in the United States. The combination of Dara-IV+Kd was evaluated as a single arm and was effective in Study MMY1001.

Study MMY2040 will include 60 subjects/cohort which will provide >90% power for D-VRd, D-VMP, D-Rd cohorts and >80% power for the D-Kd cohort to reject the null hypotheses for each treatment combination.

Rationale for PK, Immunogenicity, and Biomarker Evaluations

Data obtained from the current study will provide information about the PK profile of daratumumab by SC delivery in subjects with MM in these combinations. If sufficient data are available, then population PK analysis of concentration-time data for daratumumab will be performed and reported separately.

Immunogenicity to daratumumab or rHuPH20 is possible. Therefore, samples to determine the presence of antibodies to daratumumab (immunogenicity) and samples to determine the presence of antibodies to rHuPH20 (immunogenicity) will be collected from all subjects.

Biomarkers collected in this study may provide information about daratumumab's mechanism of action of these novel combinations. Samples may be used for immunophenotyping, which would include analysis of specific subsets of immune cells, such as cytotoxic T cells, regulatory T cells, and activated natural killer (NK) cells. Refer to Section 9.5, Biomarkers for details of the biomarker analyses.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 28 days before administration of the study drug. The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed. For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

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

1. ≥18 years of age (or the legal age of consent if it is higher than 18 years of age in the jurisdiction in which the study is taking place)

2. Multiple myeloma diagnosed according to the IMWG diagnostic criteria (refer to Attachment 1) (Rajkumar 2014[28])

3. Measurable, secretory disease as defined by any of the following:

   - Serum M-protein level ≥1.0 g/dL; or
   - Urine M-protein level ≥200 mg/24 hours; or
   - Light chain MM, for subjects without measurable disease in the serum or urine: serum Ig free light chain (FLC) ≥10 mg/dL and abnormal FLC ratio

4. Criterion modified per Amendment 1 and Amendment 2:

4.1 Meets one of the sets of the following criteria:

   a. For inclusion into the D-VRd cohort for newly diagnosed disease:
      – Newly diagnosed MM by IMWG criteria and eligible/planned for high-dose therapy and autologous stem cell transplant (ASCT)
   b. For inclusion into the D-VMP cohort:
      – Newly diagnosed and previously untreated MM by IMWG criteria and not considered a candidate for high-dose chemotherapy with ASCT due to:
         - Being age ≥65 years, or
         - In subjects <65 years: presence of important comorbid condition(s) will make stem cell transplant intolerable for the subject. Sponsor review of these comorbid conditions and approval is required before the first dose of study treatment.
   c. For inclusion into the D-Rd cohort for relapsed or refractory disease:
      – Relapsed disease is defined as progression of disease after an initial response to previous treatment, more than 60 days after cessation of treatment
      – Refractory disease is defined as either <25% reduction in M-protein or confirmed progressive disease (PD) by IMWG criteria during previous treatment or ≤60 days after cessation of treatment
      – Subject must have received at least 1 prior line of therapy for MM
         - 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.

- Subjects must have progressed from or be refractory to their last line of treatment
- Subject must have achieved a response (PR or better based on investigator's evaluation of response by the IMWG criteria) to at least 1 prior treatment regimen

d. For inclusion in the D-Kd cohort for relapsed or refractory disease:

- Subject must have received only 1 prior line of therapy for MM which included at least 2 consecutive cycles of lenalidomide therapy
- 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
- Subject must have achieved a response (PR or better based on investigator's evaluation of response by the IMWG criteria) to the first treatment regimen
- Subject must have progressed from or be refractory to the first line of treatment as defined below:
  - Relapsed disease is defined as progression of disease after an initial response to previous treatment, more than 60 days after cessation of treatment
  - Refractory disease is defined as confirmed PD by IMWG criteria during previous treatment or ≤60 days after cessation of treatment (primary refractory patients are not eligible)

5. Eastern Cooperative Oncology Group (ECOG) Performance Status grade of 0, 1, or 2 (refer to Attachment 2).

6. Criterion Modified per Amendment 1 and Amendment 2

6.1 Pretreatment clinical laboratory values during the Screening Phase (all cohorts):

a) hemoglobin ≥7.5 g/dL (≥4.65 mmol/L); D-Kd cohort 8.0 g/dL (without prior red blood cell [RBC] transfusion within 7 days before the laboratory test; recombinant human erythropoietin use is permitted);

b) absolute neutrophil count ≥1.0 × 10^9/L (prior growth factor support is permitted);

c) platelet count for D-Rd, D-Kd, and D-VRd cohorts: >75 × 10^9/L for subjects in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet

count >50 × 10^9/L (transfusions are not permitted within 7 days of testing to achieve this minimum platelet count); for the D-VMP cohort: platelet count ≥70 x 10^9/L for subjects in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count >50 × 10^9/L (transfusions are not permitted within 7 days of testing to achieve this minimum platelet count;

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

e) alanine aminotransferase ≤2.5 × ULN;

f) For the D-Rd cohort: total bilirubin ≤2.0 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤2.0 × ULN is required); for the, D-Kd, D-VMP, and D-VRd cohorts: total bilirubin ≤1.5 × ULN; except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case direct bilirubin ≤1.5 × ULN is required);

g) estimated creatinine clearance ≥40 mL/min (D-VMP cohort) or ≥30 mL/min (for D-VRd and D-Rd cohorts); or ≥20 mL/min (D-Kd cohort) (refer to Attachment 3)

h) corrected serum calcium ≤13.5 mg/dL (≤3.4 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L) (refer to Attachment 4)

7. Criterion modified per Amendment 1 and Amendment 2:

7.1 D-VRd and D-Rd cohorts: A woman of childbearing potential must have 2 negative serum or urine pregnancy tests at screening, the first within 10 to 14 days prior to dosing and the second within 24 hours prior to dosing.

D-VMP and D-Kd cohorts: A woman of childbearing potential must have a negative serum or urine pregnancy test at screening within 14 days prior to dosing.

8. Criterion modified per Amendment 1:

8.1. Criterion modified per Amendment 4:

8.2. Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse, or to use 2 methods of reliable birth control simultaneously during the Treatment Period, during any dose interruptions, and for 3 months after the last dose of any component of study treatment. This birth control method must include one highly effective form of contraception (tubal ligation, intrauterine device, hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants], or partner's vasectomy with confirmation of procedure), and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing and continue for 3 months after discontinuation of study treatment. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral

oophorectomy (See Attachment 13 for further details).

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

9. Criterion modified per Amendment 4:

9.1. During the study, during dose interruptions, and for 3 months after receiving the last dose of any component of the study treatment, a female subject must agree not to donate eggs (ova, oocytes) and male subjects of reproductive potential must not donate semen or sperm during the study, during dose interruptions, or for 3 months after the last dose of any study drug.

10. Each subject (or their legally acceptable representative) must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study. Subjects must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.2. Exclusion Criteria

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

1. Criterion modified per Amendment 1 and Amendment 2:

1.1 Prior or concurrent exposure to any of the following:

- Daratumumab or other anti-CD38 therapies
- Approved or investigational treatments for MM (including but not limited to conventional chemotherapies, IMiDs, or PIs) within 2 weeks of Cycle 1 Day 1
- Maximum of 40 mg dexamethasone (or equivalent) daily for a maximum of 4 days up to 21 days prior to the 1st dose
- Investigational drug (including investigational vaccines) or an invasive investigational medical device within 4 weeks or 5 half-lives (whichever is longer) before Cycle 1 Day 1, or is currently enrolled in another investigational study
- ASCT within 12 weeks before the date of administration of study treatment, or allogeneic stem cell transplant (regardless of timing) for the D-Rd and D-Kd cohorts
- For D-Rd cohort, only: Refractory to lenalidomide, (ie, subjects who had progression of disease while receiving lenalidomide therapy or within 60 days of ending lenalidomide therapy) or who are intolerant to lenalidomide (ie, discontinued due to any drug-related adverse event) while on lenalidomide

treatment are not eligible for the lenalidomide-containing cohorts

- For D-Kd cohort, only: Subject has previously received carfilzomib

2. Criterion modified per Amendment 1:

2.1 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.

3. Exhibits clinical signs of meningeal involvement of MM.

4. Criterion modified per Amendment 2:

4.1 Either of the following:

- 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 subjects suspected of having COPD and subjects must be excluded if FEV1 is <50% of predicted normal
- Moderate or severe persistent asthma, or a history of asthma within the last 2 years, or currently has uncontrolled asthma of any classification (refer to Attachment 6). (Subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study).

For D-Kd cohort: Known infiltrative pulmonary disease or known pulmonary hypertension.

5. Criterion modified per Amendment 1.

5.1. Criterion modified per Amendment 3.

5.2. Criterion modified per Amendment 4:

5.3. Any of the following:

- Known to be seropositive for human immunodeficiency virus (HIV);
- Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative with antibodies to total hepatitis B core antigen [Anti-HBc] with or without the presence of hepatitis B surface antibody [Anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) AND a known history of prior HBV

vaccination, do not need to be tested for HBV DNA by PCR.

6. Criterion modified per Amendment 1:

6.1 Known to be seropositive for hepatitis C (Anti-HCV antibody positive or HCV-RNA quantitation positive), except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).

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

8. Criterion modified per Amendment 1 and Amendment 2:

8.1 Clinically significant cardiac disease, including:

- myocardial infarction within 6 months before Cycle 1 Day 1, or an unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV) (refer to Attachment 7);
- uncontrolled cardiac arrhythmia or clinically significant electrocardiogram (ECG) abnormalities; or screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTc) >470 msec.
- For D-Kd cohort only:
  - Transthoracic echocardiogram (TTE) showing left ventricular ejection fraction (LVEF) <40%;
  - Uncontrolled hypertension, defined as an average systolic blood pressure >159 mmHg or diastolic >99 mmHg despite optimal treatment

9. Criterion modified per Amendment 2

9.1 Allergies, hypersensitivity, or intolerance to any of the study drugs, hyaluronidase, monoclonal antibodies, human proteins, or their excipients (refer to daratumumab Investigator's Brochure and rHuPH20 Investigator's Brochure) or known sensitivity to mammalian-derived products.

For D-Kd cohort only: allergy, hypersensitivity, or intolerance to Captisol.

10. Plasma cell leukemia, Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or amyloidosis.

11. Unable to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder) or the subject has any condition for which, in the opinion of

the investigator, participation would not be in the best interest of the subject (eg, compromise their well-being) or that could prevent, limit, or confound the protocol-specified assessments.

12. Pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of any study drug.

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

14. Major surgery within 2 weeks before administration of study treatment, or has not fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study drug administration. Kyphoplasty or vertebroplasty are not considered major surgery. Note: Subjects 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 subject in the study.

15. Plasmapheresis within 28 days before Cycle 1 Day 1

16. For D-VRd and D-VMP cohorts: Received a strong CYP3A4 inducer within 5 half-lives prior to randomization (Indiana University 2016[12]) (Attachment 12).

    For D-VMP arm: neuropathy or neuropathic pain Grade 2 or higher, as defined by the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03.

17. Criterion added per Amendment 2:

17.1 For D-VMP cohort: Neuropathy or neuropathic pain Grade 2 or higher, as defined by the NCI-CTCAE Version 4.03.

    For D-Kd cohort: Neuropathy or neuropathic pain Grade 3 or higher, as defined by the NCI-CTCAE Version 4.03.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

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

4.3. Prohibitions and Restrictions

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

1. Refer to Section 8 Prestudy and Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Typically, IV contrast is NOT used in computed tomography (CT) scanning of subjects with secretory MM because of the risk to the kidney. If administration of IV contrast is necessary, then adequate precautions including hydration are indicated.

3. Subjects must not donate blood during therapy, during dose interruptions, and for at least 4 weeks following discontinuation of lenalidomide.

4. Subjects in the D-VRd and D-Rd cohorts: Due to the embryo-fetal risk of lenalidomide, all subjects must adhere to the local lenalidomide Risk Evaluation and Mitigation Strategy (REMS) program (when lenalidomide is supplied locally), or the Lenalidomide Global Pregnancy Prevention Plan (when lenalidomide is supplied centrally and no local lenalidomide REMS program exists). (See Attachment 14 for further details).

5. In the D-VRd and D-Rd cohorts: During the Treatment Phase, pregnancy tests are required weekly during Cycle 1 and then monthly in subsequent cycles in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. A pregnancy test is also required at the End-of-Treatment Visit. Additional pregnancy tests may be required, as specified in the local lenalidomide REMS program (where lenalidomide is supplied locally) or the Lenalidomide Global Pregnancy Prevention Plan (where lenalidomide is supplied centrally and no local lenalidomide REMS program exists).

6. In the D-VMP and D-Kd cohorts: During the Treatment Phase, pregnancy tests will be administered as clinically indicated.

5. TREATMENT ALLOCATION AND BLINDING

Each subject will be assigned into the treatment group for which he or she is eligible and will receive a unique subject number.

6. DOSAGE AND ADMINISTRATION

Detailed information on the composition of the study drug is in the Site Investigational Product and Procedures Manual (SIPPM), and the Investigational Product Preparation Instructions (IPPI).

6.1. Treatment Schedule and Administration for each Cohort

6.1.1. D-VRd Cohort

The Treatment Phase will consist of 4 cycles of approximately 21 days. Subjects will receive pre-and post-administration medications for prevention of IRRs (Section 6.4.1.1, Pre-administration Medication). Subjects in the D-VRd cohort will continue to receive the study drugs for a maximum of 4 cycles (see Table 10), if disease progression, unacceptable toxicity, or other reasons listed in Section 10.2 (Discontinuation of Study Treatment/Withdrawal from the Study) occur then the subject will discontinue treatment before the 4 cycles are completed.

Table 10: Treatment Schedule and Dosing (D-VRd Cohort)

Drug, Route of administration	Dose, Cycles 1-3 (21-day cycles)	Dose, Cycle 4 (21-day cycles)
Daratumumab, SC	1800 mg on Days 1, 8, 15	1800 mg on Day 1
Bortezomib, SC	1.3 mg/m^2 on Days 1, 4, 8, 11	1.3 mg/m^2 on Days 1, 4, 8, 11
Lenalidomide, PO	25 mg on Days 1-14	25 mg on Days 1-14
Dexamethasone, IV or PO	20 mg on Days 1, 2, 8, 9, 15, 16	20 mg on Days 1, 2, 8, 9, 15, 16

D-VRd=Dara SC, bortezomib, lenalidomide, and dexamethasone; PO=orally, IV=intravenous, SC=subcutaneous

Lenalidomide will be administered to subjects in the D-VRd cohort at a dose of 25 mg orally (PO) daily on Days 1 through 14 of each 21-day cycle for subjects with creatinine clearance >60 mL/min. For subjects with creatinine clearance between 30 and 60 mL/min, the dose is 10 mg every 24 hours. Creatinine clearance should be recalculated at the beginning of every cycle. Once the creatinine clearance is >60 mL/min during the course of the treatment, lenalidomide can be increased to 25 mg. On daratumumab treatment days, lenalidomide should be administered either prior to or, preferably, at the same time as the pre-administration medications. If a daily lenalidomide dose is missed, it may be taken if <12 hours have elapsed since the time that it should have been taken. If the next dose is scheduled to be taken within 12 hours, the missed lenalidomide dose should be skipped. Lenalidomide should be taken as a single dose at the same time daily. Lenalidomide can be taken with or without food. Breaking or dividing the lenalidomide capsule is strongly discouraged. Home administration of lenalidomide should be documented by the subject in a diary (provided by the site).

Bortezomib must be administered after the daratumumab administration. Bortezomib dosing may be delayed up to 48 hours, however subsequent doses must be adjusted to account for the delay. Note that there should be at least 72 hours between doses of bortezomib. Skipped doses of bortezomib will not be made up later in the cycle. Individual doses within a cycle have a ±1 day window. For subjects with unacceptable toxicity at the local injection site of bortezomib despite

dose modifications or change in injection concentration, bortezomib can be administered intravenously as a 3 to 5 sec bolus injection. Please refer to local prescribing information for further details on either SC or IV administration.

Dexamethasone will be administered at 20 mg weekly for subjects ≥75 years of age or underweight (body mass index [BMI] <18.5). If dexamethasone is given on the daratumumab dosing day, then this will serve as the pre-medication and no additional dexamethasone administration will be needed. On daratumumab dosing days, the pre-administration medication replaces the daily dose dexamethasone. Home administration of lenalidomide should be documented by the subject in a diary (provided by the site).

6.1.2. D-VMP Cohort

The Treatment Phase will consist of 9 cycles of the VMP regimen (1 Cycle = 6 weeks) with daratumumab. Thereafter, subjects will receive daratumumab monotherapy in 28-day cycles and will continue to receive study drugs until disease progression, unacceptable toxicity, or other reasons as listed in Section 10.2 (Discontinuation of Study Treatment/Withdrawal from the Study) (Table 11). Subjects will receive pre- and post-administration medications for prevention of IRRs (Section 6.4.1.1).

Table 11: Treatment Schedule and Dosing (D-VMP Cohort)

Drug, Route of Administration	Dose, Cycle 1 (42-day cycles)	Dose, Cycles 2-9 (42-day cycles)	Dose, Cycles 10+ (28-day cycles)
Daratumumab, SC	1800 mg on Days 1, 8, 15, 22, 29, 36	1800 mg on Days 1, 22	1800 mg on Day 1
Bortezomib, SC	1.3 mg/m^2 on Days 1, 4, 8, 11, 22, 25, 29, 32	1.3 mg/m^2 on Days 1, 8, 22, 29	
Melphalan, PO	9 mg/m^2 on Days 1-4	9 mg/m^2 on Days 1-4	
Prednisone, PO	60 mg/ m^2 on Days 1-4	60 mg/ m^2 on Days 1-4	

D-VMP=Dara SC, bortezomib, melphalan, and prednisone; PO=orally; SC=subcutaneous

Breaking or dividing melphalan or prednisone tablets is strongly discouraged; the total calculated dose should be rounded to the closest dose that can be administered using the tablets available. Prednisone tablets are to be taken with or immediately after a meal or snack, preferably in the morning. Home administration of melphalan and prednisone should be documented by the subject in a diary (provided by the site).

Prednisone will not be given on days that dexamethasone is given as pre-medication. Instead, dexamethasone will serve as the treatment dose of corticosteroid for Day 1 of Cycles 1 through 9 as well as the required pre-medication prior to daratumumab administration. Prednisolone may be substituted for prednisone in countries where prednisone is not available.

In exceptional circumstances, a subject may not tolerate sudden corticosteroid withdrawal at the end of 4 days of prednisone treatment. In such an instance, a tapering regimen of prednisone (30 mg/m^2 on Day 5, 20 mg/m^2 on Day 6, 10 mg/m^2 on Day 7, then stop) can be prescribed to the subject after sponsor review. Under no circumstances will melphalan administration be prolonged beyond 4 days.

Bortezomib must be administered after the daratumumab administration. Bortezomib dosing may be delayed up to 48 hours, however subsequent doses must be adjusted to account for the delay. Note that there should be at least 72 hours between doses of bortezomib. Skipped doses of bortezomib will not be made up later in the cycle. Individual doses within a cycle have a ±1 day window. For subjects with unacceptable toxicity at the local injection site of bortezomib despite dose modifications or change in injection concentration, bortezomib can be administered intravenously as a 3 to 5 sec bolus injection. Please refer to local prescribing information for further details on either SC or IV administration.

6.1.3. D-Rd Cohort

The Treatment Phase will consist of cycles of approximately 28 days and will continue to receive study drugs until disease progression, unacceptable toxicity, or other reasons as listed in Section 10.2 (Discontinuation of Study Treatment/Withdrawal from the Study) (Table 12). Subjects will receive pre- and post-administration medications for prevention of IRRs (Section 6.4.1.1).

Table 12: Treatment Schedule and Dosing (D-Rd Cohort)

Drug, Route of administration	Cycles 1 & 2 (28-day cycles)	Cycles 3-6 (28-day cycles)	Cycles 7+ (28-day cycles)
Daratumumab, SC	1800 mg on Days 1, 8, 15, 22	1800 mg on Days 1 and 15	1800 mg on Day 1
Lenalidomide, PO	25 mg on Days 1 to 21	25 mg on Days 1 to 21	25 mg on Days 1 to 21
Dexamethasone, IV or PO	40 mg on weekly*	40 mg on Days 1*, 8, 15*, 22	40 mg on Days 1*, 8, 15, 22

D-Rd=Dara SC, lenalidomide, and dexamethasone; PO=orally, IV=intravenous, SC=subcutaneous
* During weeks when the subject receives an administration of daratumumab, half the dexamethasone dose will be given on the day of administration (20 mg) and half the dose will be given via PO administration the day after the administration (20 mg). Subjects older than 75 years or underweight who may be taking the 20-mg dose should receive the entire 20 mg prior to daratumumab administration only.

Lenalidomide will be administered to subjects in the D-Rd cohort at a dose of 25 mg PO daily on Days 1 through 21 of each 28-day cycle for subjects with creatinine clearance >60 mL/min. For subjects with creatinine clearance between 30 and 60 mL/min, the dose is 10 mg every 24 hours. Creatinine clearance should be recalculated at the beginning of every cycle. Once the creatinine clearance is >60 mL/min during the course of the treatment, lenalidomide can be increased to 25 mg.

Dexamethasone (or equivalent in accordance with local standards; see Attachment 5 for conversion table) will be administered at a total dose of 40 mg weekly. For subjects 75 years or older or underweight (BMI <18.5), the dexamethasone dose may be administered at a dose of 20 mg weekly. During weeks when the subject receives an administration of daratumumab, half the dexamethasone dose will be given on the day of administration via IV or PO administration before the administration and half the dose will be given via PO administration the day after the administration. This is applicable only for subjects taking the full 40-mg dose. Subjects 75 years or older or underweight who may be taking the 20-mg dose should receive the entire 20 mg prior to daratumumab administration. During weeks when no daratumumab administration is administered, dexamethasone will be administered at a dose of 40 mg/week PO (or 20 mg/week PO for subjects ≥75 years or BMI <18.5).

6.1.4. D-Kd Cohort

The Treatment Phase will consist of cycles of approximately 28 days and subjects will continue to receive study drugs (Table 13) until disease progression, unacceptable toxicity, or other reasons as listed in Section 10.2 (Discontinuation of Study Treatment/Withdrawal from the Study). Subjects will receive pre- and post-administration medications for prevention of IRRs (Section 6.4.1.1 Pre-administration Medication).

Table 13: Treatment Schedule and Dosing (D-Kd Cohort)

Drug, Route of administration	Cycle 1 (28-day cycles)	Cycle 2 (28-day cycles)	Cycles 3-6 (28-day cycles)	Cycles 7+ (28-day cycles)
Daratumumab, SC	1800 mg on Days 1, 8, 15, 22	1800 mg on Days 1, 8, 15, 22	1800 mg on Days 1 and 15	1800 mg on Day 1
Carfilzomib, IV	20 mg/m^2 C1D1, only; 70 mg/m^2 D8, 15	70 mg/m^2 D1, 8, 15	70 mg/m^2 D1, 8, 15	70 mg/m^2 D1, 8, 15
Dexamethasone, IV or PO	40 mg on weekly[a]	40 mg on weekly[a]	40 mg on Days 1[a], 8, 15[a], 22	40 mg on Days 1[a], 8, 15, 22 (Day 22 Cycles 7-9, only)

D-Kd=Dara SC, carfilzomib, and dexamethasone; PO=orally, IV=intravenous, SC=subcutaneous
[a] During weeks when the subject receives an administration of daratumumab, half the dexamethasone dose should be given on the day of administration (20 mg) and half the dose should be given via PO administration the day after the administration (20 mg). Subjects 75 years or older or underweight (BMI <18.5) who may be taking the 20-mg dose should receive the entire 20 mg prior to daratumumab administration only.

Carfilzomib will be administered to subjects in the D-Kd cohort at a dose of 20 mg/m^2 as a 30-minute IV infusion on Cycle 1 Day 1. If a dose of 20 mg/m^2 is tolerated, carfilzomib will be administered on Cycle 1 Day 8, at a dose of 70 mg/m^2 as a 30-minute IV infusion. Please refer to the United States Package Insert (USPI 2012[17]) or Summary of Medicinal Product Characteristics (SmPC 2018[18]) for administration, precautions and reconstitution/preparation guidelines. Subjects should receive carfilzomib followed by daratumumab SC when both are given on the same day. When carfilzomib is given first, the dexamethasone dose, on carfilzomib and daratumumab SC dosing days will be given prior to administration of carfilzomib.

Subjects will receive pre-hydration prior to each carfilzomib infusion during Cycle 1. Pre-hydration will consist of oral fluids (30 mL per kg at least 48 hours before Cycle 1 Day 1) and IV fluids 250-500 mL normal saline or other appropriate IV fluid prior to each dose of carfilzomib in Cycle 1. Thereafter, carfilzomib pre-hydration should only be administered if the

subject's condition and/or risk factors require it. Monitor subjects for evidence of volume overload and adjust hydration as needed based on subjects' risk including for cardiac failure. The total volume of pre-hydration and the reason for pre-hydration after Cycle 1 will be recorded.

Dexamethasone (or equivalent in accordance with local standards; see Attachment 5 for conversion table) will be administered at a total dose of 40 mg weekly. During weeks when the subject receives an administration of daratumumab, half the dexamethasone dose should be given on the day of administration via IV or PO before the administration and half the dose should be given via PO the day after the administration. For subjects 75 years or older or underweight (BMI <18.5), the dexamethasone dose may be administered at a dose of 20 mg weekly. Subjects 75 years or older or underweight who may be taking the 20-mg dose should receive the entire 20-mg dose prior to daratumumab administration. During weeks when the subject receives an administration of carfilzomib alone, 40 mg dexamethasone will be given on the day of administration via IV or PO before the carfilzomib administration. This is applicable only for subjects taking the full 40-mg dose. Subjects aged 75 years or older or underweight who may be taking the 20-mg dose should receive the entire 20-mg dose prior to carfilzomib administration. During weeks when no daratumumab or carfilzomib is administration, dexamethasone will be administered at a dose of 40 mg/week PO (or 20 mg/week PO for subjects ≥75 years of age or BMI <18.5).

6.2. Study Drug Preparation

6.2.1. Dara SC Preparation

Dara SC is a fixed combination drug product containing rHuPH20 drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial. Detailed instructions for preparation of SC daratumumab will be supplied in the SIPPM and IPPI.

6.3. Study Drug Delivery

6.3.1. Dara SC Delivery

Dara SC will be delivered by SC injection given through a syringe and needle by a manual push over approximately 3 to 5 minutes. Each dose should be administered at alternating locations on the abdomen. The volume of the SC solution will be 15 mL for the 1800 mg dose. Refer to the IPPI for additional guidance on SC administration of Dara SC. All subjects will be observed for at least 6 hours after the end of the SC injection during Cycle 1 Day 1 and, if deemed necessary by the investigator, after consecutive injections. Reasons for continued observation on subsequent daratumumab injections may include but are not limited to the following:

- subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with COPD who have an FEV1 <80% at screening or developed FEV1 <80% during the study without any medical history),
- subjects with an IRR occurring with the first injection of study drug,

- subject with a decreased condition on day of dosing compared to prior dosing day.

The dose of daratumumab will remain constant throughout the study.

Subjects will receive pre-administration and post-administration medications as detailed in Section 6.4.1 (Prevention of Infusion-related Reactions). All subjects should have vital signs monitored as specified in the Time and Events Schedule (Table 1- Table 9). If a subject experiences a significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event.

6.4. Guidelines for Prevention and Management of Infusion-related Reactions

6.4.1. Prevention of Infusion-related Reactions due to Daratumumab Injections

6.4.1.1. Pre-administration Medication

In an effort to prevent IRRs, all subjects will receive the following medications within 1 to 3 hours prior to each study drug administration:

- An antipyretic: paracetamol (acetaminophen) 650 to 1000 mg orally (PO)
- An antihistamine: diphenhydramine 25 to 50 mg PO, or equivalent. Avoid IV use of promethazine (see Attachment 8 for a list of antihistamines that may be used).
  - After Cycle 6, if a participant has not developed an infusion-related reaction and is intolerant to antihistamines, modifications are acceptable as per investigator discretion.
- Administer 20 mg dexamethasone or equivalent prior to every administration.
  - When dexamethasone is the background regimen specific corticosteroid, the dexamethasone treatment dose (or its part) will instead serve as pre-medication on daratumumab administration days.
  - Dexamethasone is given orally or intravenously prior to the first daratumumab administration and oral administration may be considered prior to subsequent administration.

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

Pre-dose administration of a leukotriene inhibitor (montelukast 10 mg PO or equivalent) is optional on Cycle 1 Day 1 and can be administered up to 24 hours before the injection according to investigator discretion.

D-Kd cohort: When carfilzomib is given first, pre-administration medications as noted above will be given prior to the carfilzomib on the daratumumab dosing days. If any delay in administration of daratumumab following the carfilzomib, the pre-administration medications

may be repeated prior to daratumumab administration. On carfilzomib only dosing days, the dexamethasone should be given prior to the carfilzomib infusion.

6.4.1.2. Post-administration Medication

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

- Antihistamine (diphenhydramine or equivalent)
- Leukotriene inhibitor (montelukast or equivalent)
- A short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salbutamol ± inhaled corticosteroids for subjects with COPD)

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after daratumumab administration. If subjects are hospitalized, then an improvement in FEV1 should be documented prior to discharge. If these subjects are not hospitalized, then a follow-up telephone call should be made to monitor their condition within 48 hours after all daratumumab administrations. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If an at-risk subject experiences no major IRRs, then these post-administration medications may be waived after 4 doses at the investigator's discretion. Any post-administration medication will be administered after the administration has completed.

6.4.2. Management of Infusion-related Reactions

Local Injection-site Reactions

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

Infusion-related Reactions

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

If an IRR develops, then daratumumab administration should be temporarily interrupted. Please see the IPPI for further details. Subjects who experience adverse events during daratumumab administration must be treated for their symptoms. Subjects should be treated with acetaminophen, antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject.

Infusion-related Reactions of Grade 1 or Grade 2

If the investigator assesses a Grade 1 or 2 IRR adverse event to be related to administration of the study drug, then the daratumumab administration should be paused. When the subject's condition is stable, daratumumab administration may be re-started at the investigator's discretion. For instructions for re-starting administration refer to the IPPI.

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

Infusion-related Reactions of Grade 3 or Higher

For IRR adverse events (other than laryngeal edema or bronchospasm) that are Grade 3, the daratumumab administration must be stopped and the subject must be observed carefully until resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point the daratumumab administration may be re-started at the investigator’s discretion. If the intensity of the adverse event returns to Grade 3 after re-start of the daratumumab administration, then the subject must be withdrawn from daratumumab treatment. For IRR adverse events that are Grade 4, the daratumumab administration must be stopped and the subject withdrawn from daratumumab 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 daratumumab administration, the daratumumab treatment must be discontinued.

6.5. Dose Delays and Dose Modification of Daratumumab

Dose modification of daratumumab is not permitted. Day 1 of a cycle should never be skipped, however, if a Day 1 dose of any cycle is missed it should be considered a cycle delay. Dose delay is the primary method for managing daratumumab-related toxicities.

6.5.1. Daratumumab Toxicity Management

On the first day of each new treatment cycle and before each daratumumab dose, the subject will be evaluated by the treating physician for possible toxicities that may have occurred after the

previous dose(s). Toxicities are to be assessed according to NCI-CTCAE, Version 4.03. Dose modifications or delays will be made based on the toxicity experienced during the previous cycle of therapy or newly encountered on Day 1 of a cycle.

The study treatment must be held if any of the following criteria below are met, to allow for recovery from toxicity, regardless of relationship to daratumumab, bortezomib, lenalidomide, melphalan, or carfilzomib.

- Grade 4 hematologic toxicity, except for Grade 4 lymphopenia
- Grade 3 thrombocytopenia with bleeding
- Febrile neutropenia
- Neutropenia with infection, of any grade
- Grade 3 or higher non-hematologic toxicities, with the following exceptions:
  - Grade 3 nausea or Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

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

For all daratumumab doses in a treatment cycle except the first dose, if daratumumab administration does not commence within the pre-specified window for each cohort (Table 14 to Table 16) 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. The minimal time interval between daratumumab doses should be no less than 4 days.

Table 14: Daratumumab-Related Toxicity Management (D-VRd Cohort)

Cycles	Frequency	Dose Held	Dosing Re-start
1 to 3	Weekly (q1wk)	>3 days	next planned weekly dosing date

D-VRd=Dara SC, bortezomib, lenalidomide, and dexamethasone

Table 15: Daratumumab-Related Toxicity Management (D-VMP Cohort)

Cycles	Frequency	Dose Held	Dosing Re-start
1	Weekly (q1wk)	>3 days	next planned weekly dosing date
2 to 9	Every 3 weeks (q3wks)	>7 days	next planned every-third-week dosing date
Post VMP	Every 4 weeks (q4wks)	>14 days	next planned every-fourth-week dosing date

D-VMP=Dara SC, bortezomib, melphalan, and prednisone

Table 16: Daratumumab-Related Toxicity Management (D-Rd Cohort or D-Kd Cohort)

Cycles	Frequency	Dose Held	Dosing Re-start
1 and 2	Weekly (q1wk)	>3 days	next planned weekly dosing date
3 to 6	Biweekly (q2wks)	>7 days	next planned biweekly dosing date
7+	Every 4 weeks (q4wks)	>14 days	next planned every 4 weeks dosing date

D-Rd=Dara SC, lenalidomide, and dexamethasone
D-Kd=Dara SC, carfilzomib, and dexamethasone

For the D-VRd cohort: cycles may be delayed up to 4 weeks (Cycle 1 to Cycle 4). If Day 1 of a cycle is delayed, Day 1 of subsequent cycles should be adjusted accordingly to maintain the 21-day cycle duration.

For the D-VMP cohort: if the daratumumab administration cannot be given on Day 1 of a cycle, the start of the cycle should be delayed. Day 1 of a cycle should not be skipped. A maximum delay of 4 weeks is allowed in Cycle 1 to Cycle 9. Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 4 weeks will result in permanent discontinuation of daratumumab. After Cycle 9, any adverse event deemed to be related to daratumumab that requires a dose hold of 2 consecutive planned doses will result in permanent discontinuation of daratumumab.

For the D-Rd or D-Kd cohorts: cycles may be delayed up to 4 weeks (Cycle 1 to Cycle 6) or up to 6 weeks (Cycle 7 and beyond). If Day 1 of a cycle is delayed, Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration.

However, for all cohorts, if a within-cycle dose is delayed, then the dates of the subsequent within-cycle doses should not be adjusted. If a dose delay occurs, then PK and pharmacodynamic assessments should be performed on the actual administration day of daratumumab, not on the original scheduled administration day.

6.5.2. Daratumumab Interruption or Missed Doses

A daratumumab dose that is held for more than the permitted time (Table 14 to Table 16) 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. If one of the components of the standard myeloma therapy is discontinued due to toxicity, the remaining components should continue as long as no dose interruption rules have been met. Infusion-related reactions may occur upon re-initiation of daratumumab after a prolonged delay in treatment. Investigators should consider the applicable infusion reaction guidance provided in Section 6.4.2.

For the D-VRd, D-Kd, and D-Rd cohorts:

- Subjects whose dose was delayed for more than 4 weeks (D-VRd cohort: Cycle 1 to Cycle 4; D-Rd and D-Kd cohorts: Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond, D-Rd and D-Kd cohorts only) should have study treatment discontinued, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

- If a dose is interrupted for more than 28 days for any subject in the D-VRd, D-Kd, and D-Rd cohorts due to unresolved direct daratumumab toxicity, then daratumumab must be discontinued.
- If a dose is interrupted for more than 14 days and less than 21 days for any subject in the D-VRd cohort and more than 21 days and less than 28 days for any subject in the D-Rd and D-Kd cohorts due to unresolved direct daratumumab toxicity, daratumumab may be discontinued. Continued daratumumab treatment requires review by the sponsor.
- Dose interruptions of more than 21 days (D-VRd cohort) or 28 days (D-Rd and D-Kd cohorts) for other reasons, such as non-compliance, 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 drug administration, not on the original scheduled administration day.

For the D-VMP cohort:

- Subjects whose dose was delayed for more than 4 weeks (Cycle 1 to Cycle 9) or 2 consecutive planned doses (after Cycle 9) should have study drug discontinued, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

6.6. Bortezomib, Melphalan, Lenalidomide, Carfilzomib, and Prednisone

The sponsor will provide bortezomib and may provide lenalidomide and carfilzomib to the sites, if the site, for example, cannot source the drug. Sites will use commercially available melphalan, and prednisone for administration in this study unless otherwise communicated by the study team to the site. Before administering any drug, refer to the currently approved package inserts for complete prescribing information. See Section 6.1 (Treatment Schedule and Administration for each Cohort) for the dosing and schedule of administration for each cohort.

6.6.1. Dose Calculation of Bortezomib, Melphalan, Carfilzomib, and Prednisone

The amount (in mg) of bortezomib, carfilzomib, melphalan, and prednisone to be administered, will be determined by body surface area, calculated according to a standard nomogram (Attachment 9). If weight changes by more than 10% from baseline, the dose for bortezomib, carfilzomib, melphalan, and prednisone will be recalculated and adjusted accordingly. The total calculated dose of bortezomib may be rounded to the nearest decimal point (eg, a calculated dose of 2.47 mg can be rounded to 2.5 mg).

6.7. Dose Reductions of Bortezomib, Lenalidomide, Melphalan, Carfilzomib, Dexamethasone, and Prednisone

Bortezomib will be reduced or discontinued according to the guidelines presented in Table 17. If several bortezomib doses in a cycle are withheld due to bortezomib-related toxicity (≥3 doses during twice weekly administration or ≥2 doses during weekly administration), bortezomib dose should be reduced by 1 dose level. For dose modification guidelines regarding allergic reactions

and constitutional toxicities related to VMP refer to Section 6.7.1 (Dose Modification Guidelines for Bortezomib, Melphalan, and Prednisone-related Toxicities [D-VMP cohort only]). See Section 6.7.3 (Bortezomib Toxicity) for bortezomib-related hematologic, non-hematologic and neurologic toxicities.

Table 17: Dose Reduction for Bortezomib

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

Dose adjustments of lenalidomide will follow the approved labeling as follows (Table 18) and should be based on the highest grade of toxicity that is ascribed to lenalidomide. See Section 6.7.4 (Lenalidomide Toxicity) for lenalidomide toxicities.

Table 18: Dose Reduction for Lenalidomide

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
25 mg	15 mg	10 mg	5 mg

Melphalan will be reduced or discontinued according to the guidelines presented in Table 19.

Table 19: Dose Reduction for Melphalan

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
9 mg/m^2 QD on Days 1-4	6.75 mg/m^2 QD on Days 1-4	4.5 mg/m^2 QD on Days 1-4	discontinue melphalan

QD=every day

Carfilzomib will be reduced or discontinued according to the guidelines presented in Table 20. If a carfilzomib dose is reduced, the reduced dose level will be continued for at least 1 cycle. If the reduced dose level is well-tolerated, then the dose may be re-escalated to the prior dose at the investigator's discretion.

Table 20: Dose Reduction for Carfilzomib

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction	Fourth Dose Reduction
70 mg/m^2 QD	56 mg/m^2 QD	45 mg/m^2 QD	36mg/m^2	discontinue carfilzomib

QD=every day

Prednisone will be reduced or discontinued according to the guidelines presented in Table 21.

Table 21: Dose Reduction for Prednisone

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
60 mg/m^2 QD on Days 2-4	45 mg/m^2 QD on Days 2-4	30 mg/m^2 QD on Days 2-4	discontinue prednisone

QD=every day

Dexamethasone will be reduced or discontinued according to the guidelines presented in Table 22.

Table 22: Dose Reduction for Dexamethasone

First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Reduce dexamethasone by 50% from the starting dose	Skip dexamethasone on days when daratumumab is not given	discontinue dexamethasone

6.7.1. Dose Modification Guidelines for Bortezomib, Melphalan, and Prednisone-related Toxicities (D-VMP cohort only)

Once reduced due to toxicity, doses of bortezomib, melphalan, or prednisone should not be re-escalated, with the exception of melphalan re-escalation following recovery of renal function. Dose modification guidelines for bortezomib, melphalan, and prednisone are provided in Table 23.

Table 23: Dose Modification Guidelines for Bortezomib, Melphalan, and Prednisone

Body System	NCI-CTC Adverse Event and or Symptom and Category	Bortezomib	Melphalan	Prednisone
Allergic reactions	Allergic reaction or hypersensitivity Grade 2 or 3	Hold all therapy. If the toxicity resolves to ≤ Grade 1, re-start VMP. Reduce by 1 dose-level the suspected medication(s) and implement appropriate anti-allergic prophylaxis therapy. If the reaction was anaphylactic in nature, do not resume VMP. Note: If the reaction was cutaneous in nature, refer to the cutaneous category below.		
	Allergic reaction or hypersensitivity Grade 4	Discontinue VMP.		
Constitutional	Fluid Retention (ie, edema) >Grade 3 (limiting function and unresponsive to therapy or anasarca)			Administer diuretics as needed, and decrease dexamethasone or prednisone dose by 1 dose-level; if edema persists despite above measures, decrease dose another dose-level. Discontinue prednisone and do not resume if symptoms persist despite second reduction.
	Fatigue ≥ Grade 3 (ie, severe fatigue interfering with activities of daily living)	Reduce bortezomib by 1 dose level.		

VMP= bortezomib, melphalan, and prednisone, NCI-CTC= National Cancer Institute-Common Terminology Criteria for Adverse Events

6.7.2. Dose Modification Guidelines for Dexamethasone

For each treatment group, the dose of dexamethasone may be reduced if additional problems persist, at the investigator's discretion. Refer to Table 24 for recommended dose reductions, and to the dexamethasone package insert, which states that dosage requirements are variable and must be individualized. Note that Table 24 represents suggested dose modifications of

dexamethasone, but physician discretion and clinical judgment should prevail. The 20-mg IV or PO dose of dexamethasone will be continued as a prior medication before daratumumab administration. However, subjects may receive low-dose methylprednisolone (≤20 mg) PO (or equivalent in accordance with local standards) for the prevention of delayed IRRs as clinically indicated.

Table 24: Dexamethasone Dose Modification

CTCAE Category	Toxicity	Dose Change
Gastrointestinal	Grade 1-2 dyspepsia, gastric, or duodenal ulcer, gastritis requiring medical management	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measure, decrease dexamethasone dose by 50%.
	≥Grade 3 requiring hospitalization or surgery	Hold dexamethasone until symptoms adequately controlled. Re-start at 50% of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measure, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Discontinue dexamethasone and do not resume
Cardiovascular	≥Grade 3 edema limiting function and unresponsive to therapy or anasarca	Diuretics as needed and decrease dexamethasone dose by 25%. If edema persists despite above measures, decrease dose to 50% of initial dose. Discontinue dexamethasone and do not resume if symptoms persist despite 50% reduction
Neurology/ Psychiatric	≥Grade 2 interfering with function but not interfering with activities of daily living	Hold dexamethasone until symptoms adequately controlled. Re-start at 50% of current dose. If symptoms persist despite above measure, discontinue dexamethasone and do not resume.
Musculoskeletal	≥Grade 2 muscle weakness symptomatic and interfering with function but not interfering with activities of daily living	Decrease dexamethasone dose by 25%. If weakness persists despite above measures, decrease dose to 50% of initial dose. Discontinue dexamethasone and do not resume if symptoms persist despite 50%.
Metabolic	≥Grade 3 hyperglycemia	Treatment with insulin or oral hypoglycemic agents as needed. If uncontrolled despite above measure, decrease dose by 25% decrements until levels are satisfactory.

6.7.3. Bortezomib Toxicity

6.7.3.1. Hematologic Toxicity of Bortezomib

If the subject experiences neutropenia, then the investigator should consider the use of growth factors in the subject's management. If the subject's neutrophil count decreases further, or if the subject's platelet count decreases, then dose adjustments should be made according to the hematologic toxicity recommendations in Table 25. No dose adjustments are required for anemia, lymphopenia, or leukopenia.

Table 25: Dose Modifications for Hematologic Toxicity

Hematologic Toxicity	Dose Modification
Neutropenia Grade 3 (without complications)	No dose reduction, consider treatment with G-CSF
Neutropenia associated with fever (≥38.5ºC): Grade 3 or neutropenia Grade 4	Hold bortezomib until recovery to baseline or ≤ Grade 2. Upon recovery, re-start bortezomib at current dose and consider G-CSF support. If recurrence is seen, reduce bortezomib by 1 dose-level.
Thrombocytopenia Grade 3 (without complications)	Hold bortezomib until recovery to baseline or ≤Grade 2. Upon recovery, re-start bortezomib at current dose and consider G-CSF support. If recurrence is seen, reduce bortezomib by 1 dose level.
Platelet count <25,000/µL (ie, Grade 4) or Grade 3 thrombocytopenia with bleeding	Hold bortezomib until recovery to baseline or ≤ Grade 2. Upon recovery, re-start at 1 dose reduced level.

G-CSF=granulocyte-colony stimulating factor

6.7.3.2. Neurologic Toxicity Bortezomib

If the subject experiences peripheral neuropathy, then dose adjustments should be made according to the recommendations in Table 26.

Table 26: Recommended Dose Modification for Bortezomib-related Neuropathic Pain or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms*	Modification of Dose and Regimen
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living [ADL]**)	Reduce bortezomib to 1 mg/m^2 or Change bortezomib treatment schedule to 1.3 mg/m^2 once a week
Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL ***)	Withhold bortezomib treatment until symptoms of toxicity have resolved. When toxicity resolves, reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 once a week
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue bortezomib

*Grading based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) most recent version **Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc; ***Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

6.7.3.3. Other Grade 3 or 4 Non-Hematologic Toxicities Bortezomib

For other Grade 3 or 4 toxicities judged by the investigator to be related to bortezomib alone, treatment with bortezomib should be interrupted and re-started at the next lower dose level, or the administration schedule should be changed to once a week once the toxicity has resolved to Grade 2 or less.

6.7.4. Lenalidomide Toxicity

6.7.4.1. Deep Vein Thrombosis and Pulmonary Embolism

Lenalidomide has been associated with an increased incidence of deep vein thrombosis and pulmonary embolism. Therefore, prophylaxis with aspirin or low molecular weight heparin (LMWH) is strongly recommended for all subjects. The injection should be handled according to local practice.

6.7.4.2. Thrombocytopenia

If the subject's platelet count decreases, then dose adjustments should be made according to the recommendations in Table 27.

Table 27: Lenalidomide Dose Adjustment for Thrombocytopenia

Platelet Count	Recommended Course of Action
• When count first falls to < 30×10^9/L • When count returns to ≥ 30×10^9/L	• Interrupt lenalidomide treatment, follow complete blood count weekly • Resume lenalidomide at 15 mg
• For each subsequent drop in count to < 30×10^9/L • When count returns to ≥ 30×10^9/L	• Interrupt lenalidomide treatment • Resume lenalidomide at the next lower dose level (10 mg or 5 mg) once daily. Do not decrease dose below 5 mg once daily

6.7.4.3. Neutropenia

If the subject experiences neutropenia, then the investigator should consider the use of growth factors in the subject's management. If the subject's neutrophil count decreases further, then dose adjustments should be made according to the recommendations in Table 28.

Table 28: Lenalidomide Dose Adjustment for Neutropenia

Neutrophil Count	Recommended Course of Action
• When count first falls to < 1.0×10^9/L • When count returns to ≥ 1.0×10^9/L and neutropenia is the only observed toxicity	• Interrupt lenalidomide treatment, start G-CSF treatment, follow complete blood count weekly • Resume lenalidomide at 25 mg once daily
• When count returns to ≥ 1.0×10^9/L and other toxicity is observed	• Resume lenalidomide at 15 mg once daily
• For each subsequent drop in count to < 1.0×10^9/L • When count returns to ≥ 1.0×10^9/L	• Interrupt lenalidomide treatment • Resume lenalidomide at the next lower dose level (15, 10 mg, or 5 mg) once daily. Do not decrease dose below 5 mg once daily

G-CSF= granulocyte-colony stimulating factor

6.7.4.4. Renal Impairment

Lenalidomide is primarily excreted unchanged by the kidney. Therefore, adjustments to the dose of lenalidomide are recommended to provide appropriate drug exposure in subjects with moderate or severe renal impairment. Lenalidomide dose adjustment should be instituted for subjects with a creatinine clearance of 60 mL/minute or less. The recommended doses for subjects with MM and renal impairment are shown in Table 29.

Table 29: Lenalidomide Dose Adjustment for Renal Impairment

Category	Renal Function[a]	Dose
Moderate renal impairment	CrCl 30-60 mL/min	10 mg every 24 hours
Severe renal impairment	CrCl <30 mL/min (not requiring dialysis)	15 mg every 48 hours
End-stage renal disease	CrCl <30 mL/min (requiring dialysis)	5 mg once daily. On dialysis days, administer the dose after dialysis

CrCl=creatinine clearance.
[a] Estimated by creatinine clearance as calculated by the Cockcroft-Gault, modification of diet in renal disease (MDRD)

6.7.4.5. Other Grade 3 or 4 Non-Hematologic Adverse Events

For other Grade 3 or 4 toxicities judged by the investigator to be related to lenalidomide alone, treatment with lenalidomide should be interrupted and re-started at the next lower dose level once the toxicity has resolved to Grade 2 or less. Treatment with daratumumab and dexamethasone may continue, unless the toxicity meets the criteria for daratumumab dose delay as specified in Section 6.5.1 (Daratumumab Toxicity Management).

6.7.5. Carfilzomib Toxicity

Carfilzomib doses should be skipped if held longer than 2 days to ensure 5 days between carfilzomib doses. Carfilzomib treatment must be held if any of the following criteria below are met, to allow for recovery from toxicity if the toxicity is considered related to carfilzomib or contribution of carfilzomib cannot be excluded.

6.7.5.1. Hematologic Toxicity of Carfilzomib

If the subject experiences neutropenia, then the investigator should consider the use of growth factors in the subject's management. If the subject's neutrophil count decreases further, or if the subject's platelet count decreases, then dose adjustments should be made according to the hematologic toxicity recommendations in Table 30. No dose adjustments are required for anemia, lymphopenia, or leukopenia. Dose modification guidelines for non-hematologic toxicities are provided in Table 31.

Table 30: Carfilzomib Dose Modifications for Hematologic Toxicity

Hematologic toxicity	Recommended Action	
Thrombocytopenia		
When platelets fall to <30 x 10^9/L and for each subsequent drop to <30 x 10^9/L	If platelets 10 to 30 x 10^9/L without evidence of bleeding	• Hold • Restart at previous dose when platelets >30 x 10^9/L
	If evidence of bleeding or platelets <10 x 10^9/L	• Hold • Restart at one-dose level reduction when platelets >30 x 10^9/L
Neutropenia		
When ANC falls to <0.5 x 10^9/L		• Hold dose • Resume at one-dose level reduction when ANC ≥0.5 x 10^9/L
Febrile Neutropenia (ANC <0.5x10^9/L and temperature >38.5 or 2 temperatures of 38.0 within 2 hours)		Withhold dose -If recovered to baseline, continue at the same dose level

ANC = absolute neutrophil count

Table 31: Carfilzomib Dose Modification Guidelines for Non-hematologic Toxicities

Toxicity	Recommended Action
Renal Dysfunction[a]	
Creatinine ≥2xbaseline, or CrCl decreased by ≥50%, or CrCl <15 mL/min (Grade 4), or dialysis required	Hold carfilzomib - When renal function recovers to within 25% of baseline; restart at one-dose level reduction if renal dysfunction was due to carfilzomib - If toxicity is not attributed to carfilzomib dosing may resume at the discretion of the physician - If dialysis required use the maximal dose of 20 mg/m^2 and administer carfilzomib after dialysis.
Chronic dialysis stable for ≥30 days	Dose may be re-escalated up to full dose as clinically tolerated
Hepatic Dysfunction	
Mild to moderate liver dysfunction: defined as 2 consecutive values, at least 28 days apart, of: (1) total bilirubin (>33% direct) > 1x ULN to <3x ULN OR (2) an elevation of AST and/or ALT with normal bilirubin	Reduce dose by one-dose level - Dose may be re-escalated if liver function tests return to normal and drug-induced hepatotoxicity is excluded.
Grade 3 elevation in ALT and/or AST (>5x ULN)	Hold carfilzomib until resolution to baseline. - Resume carfilzomib with a 25% one-dose level reduction if drug-induced hepatotoxicity is excluded.
Grade 3 elevation in total bilirubin	Hold carfilzomib until resolution to baseline. - Resume carfilzomib dosing with a one-dose level reduction if drug-induced hepatotoxicity is excluded.
Drug-induced hepatotoxicity (attributable to carfilzomib)	Discontinue carfilzomib permanently
Cardiac Toxicities	
Congestive heart failure	Any subject with congestive heart failure, whether or not drug related, must have the dose held until resolution or return to baseline. Appropriate medical management should be initiated. Once congestive heart failure resolves or returns to baseline, treatment may continue at one dose level reduction. If no resolution after 4 weeks, **carfilzomib will be permanently discontinued**.
LVEF <40% or Reduction of LVEF >20% from baseline and absolute value <55%	Hold carfilzomib until LVEF returns to >40% or to within 15% of baseline -Resume at one-dose level reduction
Hypertension (SBP > 140 and/or DBP > 90)	
<Grade 3	Continue at same dose if initiation of appropriate treatment controls hypertension
Grade ≥3	Hold carfilzomib until resolution to normal or baseline. Initiate appropriate anti-hypertensive therapy prior to resuming carfilzomib at one-dose level reduction.
Other Non-hematologic Toxicities	
Infection (Grade 3 or 4)	Hold carfilzomib. Once infection is controlled and the subject is without infection-related symptoms resume carfilzomib at full dose.
Neuropathy (Grade 2 with emergent pain, or Grade 3)	Hold carfilzomib until resolved to ≤Grade 2 without pain; then resume carfilzomib at one-dose level reduction.
Neuropathy (Grade 4)	Permanently discontinue carfilzomib.

Table 31: Carfilzomib Dose Modification Guidelines for Non-hematologic Toxicities

Toxicity	Recommended Action
Dyspnea (Grade ≥2)	Hold carfilzomib until resolution to Grade 1 or baseline - Resume at one-dose level reduction unless related to other pulmonary or cardiac toxicity, then follow that recommended action.
Pulmonary toxicity: Non-infectious interstitial lung disease, acute respiratory failure, ARDS (≥Grade 3)	Hold carfilzomib until resolution to Grade 1 or baseline - Restart at one-dose level reduction.
Pulmonary hypertension (Grade ≥3)	Hold carfilzomib until resolution to Grade 1 or baseline and restart at one-dose level reduction
Posterior reversible encephalopathy syndrome: Headaches, altered mental status, seizures, visual loss, and hypertension	If PRES is suspected, hold carfilzomib. - Consider evaluation with neuroradiological imaging, specifically MRI, for onset of visual or neurological symptoms suggestive of PRES. - If PRES is confirmed, permanently discontinue carfilzomib. - If PRES is excluded, carfilzomib administration may resume at same dose, if clinically appropriate.
Thrombotic microangiopathy: Fever, microangiopathic hemolytic anemia, renal failure, thrombocytopenia, neurological manifestations	If the diagnosis is suspected, hold carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If TMA is confirmed, permanently discontinue carfilzomib. If the diagnosis is excluded, carfilzomib can be restarted
Venous thrombosis (≥Grade 3)	Hold carfilzomib and adjust anticoagulation regimen; resume carfilzomib at full dose once anticoagulation has been optimized per treating investigator's discretion.
Toxicity	**Recommended Action**
drug-related non-hematologic toxicity ≥Grade 3[b] Exceptions: -Grade 3 nausea, vomiting, or diarrhea (unless persisting > 3 days with adequate treatment of antiemetics or antidiarrheal agents) -Grade 3 dexamethasone-related hyperglycemia -Grade 3 fatigue (unless persisting for >14 days) -Alopecia	Hold carfilzomib dose. Restart at one-dose level reduction when toxicity has resolved to Grade 1 or less or to baseline grade.

ALT = alanine aminotransferase; ANC = absolute neutrophil count; ARDS = acute respiratory distress syndrome; AST = aspartate aminotransferase; CrCl = creatinine clearance; DBP = diastolic blood pressure; G-CSF=granulocyte-colony stimulating factor; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PRES = Posterior Reversible Encephalopathy Syndrome; SBP = systolic blood pressure; TMA = thrombotic microangiopathy; ULN = upper limit of normal.

a For a rapid fall from baseline in CrCl or an absolute fall of ≥60 mL/min, contact the medical monitor.

6.7.5.2. Management of Peripheral Edema, Pulmonary Edema, Congestive Heart Failure

Subjects may develop volume overload during the study. Management of volume overload is at the discretion of the treating physician but will likely include loop diuretics (furosemide, torsemide or equivalent), nitrate preparations, and/or ionotropic agents. Use of these medications is permissible during the protocol and should be recorded in the electronic case report form (eCRF) as concomitant medications. Dose reductions of carfilzomib and/or dexamethasone (Table 20 and Table 22, respectively) would be required in this setting.

7. TREATMENT COMPLIANCE

The study drug (Dara SC) and the components of the backbone regimens will be administered by qualified site staff, and the details of each administration will be recorded in the eCRF. Subjects will be provided with a diary to record access compliance for melphalan, lenalidomide, prednisone, and dexamethasone. Additional details are provided in the SIPPM.

8. PRESTUDY AND CONCOMITANT THERAPY

For those subjects in the D-Rd and D-Kd cohorts, all prior anti-myeloma therapies, including those since diagnosis, must be recorded at screening. Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 8.3 (Prohibited Therapies). The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. Concomitant medications related adverse events, pre- and post-administration medications, and significant medical history will be collected in the eCRF and recorded in the source documents beginning with signing of the ICF up to 30 days after the last dose of the last study treatment or until the start of subsequent anticancer treatment, if earlier.

8.1. Recommended Therapies

8.1.1. Bisphosphonate Therapy

Bisphosphonate therapy is strongly recommended for all subjects with evidence of lytic destruction of bone or with osteopenia. Bisphosphonate therapy is recommended to be continued according to treatment guidelines (Moreau 2013[24]; NCCN 2013[25]). 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 subjects with osteolytic or osteopenic myelomatous bone disease. Oral bisphosphonates may be used as alternatives if IV bisphosphonates are not available at the study site. It is preferred that investigators use the same route of bisphosphonate therapy for all subjects at their sites.

Subjects who are using bisphosphonate therapy when they enter the study should continue the same treatment. Subjects with evidence of lytic destruction of bone or with osteopenia who are not using a bisphosphonate at the time of administration of study treatment should start a

bisphosphonate as soon as possible during Cycle 1 or 2 of treatment. Investigators should not start bisphosphonate therapy during the study, unless it has been agreed with the sponsor that there is no sign of disease progression.

8.1.2. Therapy for Tumor Lysis Syndrome

Subjects should be monitored for symptoms of tumor lysis syndrome. Management of tumor lysis syndrome, including dehydration and abnormal laboratory test results such as hyperkalemia, hyperuricemia, and hypocalcemia, are highly recommended. It is also recommended that high-risk subjects (ie, those with a high tumor burden) should be treated prophylactically in accordance with local standards (eg; rehydration, diuretics, allopurinol 300 mg daily, and medication to increase urate excretion). Subjects will receive prophylactic therapy to prevent IRRs during the Treatment Phase, as described in Section 6.4.1 (Prevention of Infusion-related Reactions).

8.1.3. Therapy for Pneumocystis carinii/jirovecii

Pneumocystis carinii/jirovecii pneumonia prophylaxis should be considered, according to institutional guidelines.

8.1.4. Prophylaxis for Herpes Zoster Reactivation

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

8.1.5. Prevention of Steroid Induced Gastritis

Dexamethasone and other steroids may induce gastritis. Medications to prevent gastritis are permitted according to institutional guidelines, for example proton pump inhibitors (omeprazole or equivalent), sucralfate, or H2 blockers (ranitidine or equivalent).

8.1.6. Prevention of Deep Vein Thrombosis and Pulmonary Embolism

Lenalidomide has been associated with increased incidence of deep vein thrombosis and pulmonary embolism. Thromboprophylaxis is recommended in the D-Kd cohort due to the combination of carfilzomib and dexamethasone. Both individual and myeloma-related risks of venous thromboembolism should be taken into account in determining the type of thromboprophylaxis. In summary:

- If no risk factor, or any one risk factor is present, aspirin 81-325 mg once daily is recommended or dose according to institutional standards

- If 2 or more risk factors are present, LMWH (equivalent of enoxaparin 40 mg once daily) or full-dose warfarin, international normalized ratio (INR) 2-3, is recommended
- If any myeloma therapy-related risk factor is present, then LMWH (equivalent of 40 mg enoxaparin once daily) or full-dose warfarin (target INR 2-3) is recommended

8.1.7. Management of Hepatitis B Virus Reactivation

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation (see Section 9.6).

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

8.1.8. Infection Prophylaxis

Prophylactic use of antibiotics is highly recommended due to the susceptibility of subjects with multiple myeloma to infections. Prophylactic administration of antibiotics should be considered and dependent on institutional guidelines.

8.2. Permitted Therapies

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

- Antivirals
- Prevention of constipation (eg, adequate hydration, high-fiber diet, and stool softeners if needed)
- Prophylactic antiemetics, with the exception of corticosteroids
- Colony stimulating factors, erythropoietin, and transfusion of platelets and RBCs except those described in Section 4.1 (Inclusion Criteria)
- Loperamide is recommended for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose and regimen is according to institutional guidelines. Prophylactic loperamide is not recommended
- Adequate hydration is recommended for prevention of myeloma-related kidney disease

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

8.3. Prohibited Therapies

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. Concomitant administration of any other antineoplastic therapy for the intention of treating MM 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 treatment (during or after emergency orthopedic surgery or radiotherapy because of subject benefit) may only occur in the absence of disease progression and after consultation with and approval by the sponsor.

Emergency radiotherapy may consist of localized radiotherapy for pain control or for stabilization of an extensive bone lesion at high risk of pathologic fracture or damage to surrounding tissues in a subject for whom delay of systemic therapy is not appropriate. Radiotherapy must occur within the first 2 cycles of treatment and only if disease progression has not occurred. Before radiotherapy, the sponsor will review the evidence and confirm that disease progression has not occurred.

Concomitant administration of investigational agents and of commercially available agents with activity against or under investigation for MM are prohibited. Systemic corticosteroids (>10 mg prednisone each day or equivalent) (other than those given as backbone therapy and IRRs as described in Section 6.4.1 [Pre- and Post-administration Medications]) should be avoided. Nonsteroidal anti-inflammatory agents should be avoided to prevent myeloma-related kidney disease. Vaccination with live attenuated vaccines is prohibited.

Typically, IV contrast is not used in CT scanning of subjects with secretory MM because of the risk to the kidney. If administration of IV contrast is necessary, then adequate precautions including hydration are indicated.

Concomitant administration of strong CYP3A4 inducers is prohibited with the use of bortezomib. Administration of strong CYP3A4 inhibitors (eg, ketoconazole, ritonavir) should be avoided and is not recommended in subjects receiving bortezomib. If a strong CYP3A4 inhibitor must be given in combination with bortezomib, monitor subjects for signs of bortezomib toxicity and consider a bortezomib dose reduction. For an ongoing list of CYP3A inhibitors and inducers, see Attachment 12 [12].

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule (Table 1 to Table 9) summarizes the frequency and timing of efficacy, PK, immunogenicity, biomarker, and safety measurements applicable to this study. 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. 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 subject's participation in the study.

The total blood volume for the D-VRd treatment group is approximately 260 mL (117 mL for safety, 60 mL for efficacy, 30 mL for daratumumab PK and immunogenicity, 20 mL for rHuPH20 immunogenicity, 9 mL for biomarkers, and 24 mL for pregnancy testing [women only]). The total blood volume for the D-VMP treatment group for the first year of treatment is approximately 453 mL (167 mL for safety, 190 mL for efficacy, 40 mL for daratumumab PK and immunogenicity, 30 mL for rHuPH20 immunogenicity, 24 mL for biomarkers, and 2 mL for pregnancy testing [women only]). The total blood volume for the D-Rd treatment group for the first year of treatment is approximately 490 mL (200 mL for safety, 140 mL for efficacy, 40 mL daratumumab PK and immunogenicity, 30 mL for rHuPH20 immunogenicity, 24 mL for biomarkers, and 56 mL for pregnancy testing [women only]). The total blood volume for the D-Kd treatment group for the first year of treatment is approximately 510 mL (270 mL for safety, 140 mL for efficacy, 40 mL daratumumab PK and immunogenicity, 30 mL for rHuPH20 immunogenicity, 24 mL for biomarkers, and 2 mL for pregnancy testing [women only]). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Subjects benefiting from study treatment can continue receiving the study drugs after the end of data collection until the study drugs are commercially available, available from another source (eg, via a dedicated long-term extension study), or until study completion (see Attachment 15).

9.1.2. Screening Phase

The signed ICF must be obtained before any study-specific procedures are performed. The Screening Phase begins when the first screening assessment is conducted. During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in the Time and Events Schedule (Table 1 to Table 9). Screening procedures will be performed within 28 days before Cycle 1 Day 1; however, results of tests such as skeletal survey and other radiologic tests (eg, X-ray, CT, PET-CT, or magnetic resonance imaging [MRI]) to document baseline size of known or suspected extramedullary plasmacytomas, or bone marrow aspirate/biopsy) performed up to 6 weeks (42 days) before Cycle 1 Day 1 as routine follow-up for the subject's disease can be used.

At screening, creatinine clearance may be measured or calculated according to local practice. If calculated, use the formula according to the modification of diet in renal disease (MDRD, Levey 2006[20]). A negative pregnancy test for women of childbearing potential must be documented within 10 to 14 days prior to the first dose of any component of the treatment regimen and within 24 hours of the second dosing for subjects in the D-VRd and D-Rd cohorts.

All attempts should be made to determine eligibility of the subject based on the central laboratory results of screening blood and urine M-protein measurements. In exceptional circumstances, the local laboratory results of blood and urine M-protein measurements may be used to determine eligibility, but only if the results are clearly (eg, 25% or more) above the thresholds for measurability.

9.1.3. Treatment Phase

Details of the procedures performed during the Treatment Phase are outlined in Table 1 to Table 9. The Treatment Phase begins on Cycle 1 Day 1 and continues until disease progression in the D-VMP, D-Kd, and D-Rd cohorts, or for the other reasons outlined in Section 10.2 (Discontinuation of Study Treatment/Withdrawal from the Study). Subjects in the D-VRd cohort will be treated for 4 cycles and then will undergo ASCT as part of their standard myeloma treatment. Subjects will be monitored closely for adverse events, laboratory abnormalities, and clinical response. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. If disease progression is diagnosed in the D-VMP, D-Kd, and D-Rd cohorts, then the subject will discontinue the study drug and complete the post-treatment visits.

9.1.4. Post-treatment Phase (Follow-Up)

Unless a subject withdraws consent for study participation or is lost to follow-up, post-treatment visits will be scheduled at 30 Days and 8 weeks after the final dose of study drug. If a subject is not able to return to the site for the post-treatment visits, then the subject should be contacted (ie, via telephone call) to collect adverse events that occur within 30 days after the final dose of any component of the treatment regimen. Additional information on reporting of adverse events can be found in Section 12 (Adverse Event Reporting). Information on all new SPMs will also be collected until the end of study. If the subject has died, then the date and cause of death will be collected and documented on the eCRF.

9.1.5. Final Analysis to End of Study

The data cutoff for the final analysis and the end of data collection will occur approximately 10 months after the last subject is enrolled in the D-Kd cohort. Subsequently, the clinical database will be locked for the final analysis. Subjects benefiting from study treatment can continue receiving the study drugs after the end of data collection until the study drugs are commercially available, available from another source (eg, via a dedicated long-term extension study), or until study completion (Section 17.9.1 [End of Data Collection and End of Study]). Attachment 15 describes study procedures to be followed for subjects who continue receiving study drugs after the data collection ends.

The end of study will occur when all subjects discontinue study treatment or 18 months after the end of data collection, whichever occurs first.

9.2. Efficacy Evaluations

9.2.1. Evaluations

9.2.1.1. Response Categories

Assessment of tumor response and disease progression will be conducted in accordance with the IMWG response criteria. Disease evaluations will include measurements of myeloma proteins,

bone marrow examinations, skeletal surveys, assessment of extramedullary plasmacytomas, and measurements of serum calcium corrected for albumin.

Disease evaluations must be performed at the end of each treatment cycle as specified in the Time and Events Schedule (Table 1 to Table 9). Disease evaluations scheduled for treatment days should be collected before the study drug is administered. Disease evaluations will be performed by a central laboratory (unless otherwise specified) until disease progression or the end of treatment. This study will use the IMWG consensus recommendations for MM treatment response criteria (Durie 2006[10]; Kumar 2016[16], Rajkumar 2011[27]) presented in Table 32. For quantitative immunoglobulin at baseline, M-protein, immunofixation electrophoresis (IFE), and FLC measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory. For subjects with suspected daratumumab interference on serum M-protein quantitation by electrophoresis (SPEP) and IFE, a reflex assay will be performed (Attachment 10). Subjects with confirmed daratumumab interference who meet all other clinical criteria for CR or stringent complete response (sCR) will be considered CR/sCR.

Disease progression must be documented consistently across clinical study sites using the criteria in Table 32. For continuation of treatment, the investigator will evaluate response and assess progression according to the IMWG criteria on an ongoing basis.

Table 32: 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-hour urine M-protein by 50% to 89% • In addition to the above criteria, if present at baseline, 25% to 49% reduction in the size of soft tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
Stable disease	• Not meeting criteria for CR, VGPR, PR, MR, or progressive disease
Progressive disease (PD)†	• Increase of 25% from lowest response value in any one of the following: • Serum M-component (absolute increase must be ≥0.5 g/dL), • Urine M-component (absolute increase must be ≥200 mg/24 hours), • Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥10%) • Bone marrow plasma cell percentage: 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

FLC=free light chain; PC=plasma cell

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 stable disease categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither.

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

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

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

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

9.2.1.2. Myeloma Protein Measurements in Serum and Urine

Blood and 24-hour urine samples for M-protein measurements will be sent to and analyzed by a central laboratory. Only 1 serum and one 24-hour urine sample at each timepoint are required by the central laboratory to perform the following tests:

- Serum quantitative immunoglobulins
  - All subjects will be evaluated for IgG, IgA, IgM, IgE, and IgD as indicated in the Time and Events Schedule (Table 1 to Table 9)
- SPEP
- Serum IFE at screening and thereafter when M-protein is non-quantifiable
- Serum FLC assay
- 24-hour urine M-protein quantitation by electrophoresis (UPEP)
- Urine IFE at screening and thereafter when a M-protein is non-quantifiable

Blood and 24-hour urine samples will be collected as specified in the Time and Events Schedule (Table 1 to Table 9) until the development of confirmed disease progression. If the 24-hr urine collection (UPEP) began before informed consent was obtained as part of routine patient care, the sample can be used in this study as long as it was sent to the central laboratory for analysis after the informed consent was obtained. Disease progression based on one of the laboratory tests alone must be confirmed by at least 1 repeat investigation performed 1 to 3 weeks later. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed. Serum and urine IFE and serum FLC assay will be performed at screening and thereafter when a CR is suspected or maintained (when serum or 24-hour urine M-protein electrophoresis [by SPEP or UPEP] are 0 or non-quantifiable). For subjects with light chain MM, both serum and urine IFE test will be performed routinely.

Serum IFE assay samples will be split into 2 aliquots, with 1 reserved for potential follow-on testing if daratumumab interference with IFE is suspected. As daratumumab is a monoclonal IgG antibody, additional serum samples may be utilized to monitor for potential daratumumab interference with the IFE.

Previous studies have demonstrated potential interference of therapeutic monoclonal antibodies with detection of endogenous myeloma M-protein on serum IFE (McCudden 2015[23]). For subjects with suspected daratumumab interference on SPEP, serum IFE, or both, a follow-up test will be run utilizing antiidiotype antibodies against daratumumab to remove antibody interference. Subjects who meet all other IMWG criteria for CR or sCR, and whose positive IFE is confirmed to be daratumumab, will be considered as having a CR or sCR.

9.2.1.3. Serum Calcium Corrected for Albumin

Blood samples for calculating serum calcium corrected for albumin will be collected and analyzed centrally (as specified in the Time and Events Schedules [Table 1 to Table 9]). During the Treatment Phase, 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, Table 32). 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"). Measurement of free ionized calcium is an acceptable alternative to corrected serum calcium for determining hypercalcemia. Free ionized calcium levels greater than the ULN (local laboratory reference ranges) are considered as having achieve a CR or sCR.

9.2.1.4. 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. The central laboratory values will be used to calculate ISS stage.

9.2.1.5. Bone Marrow Examination

Bone marrow assessments to be performed locally and centrally are summarized in Table 33.

Table 33: Bone Marrow Testing

	Local Testing	Central Testing
Screening	Disease characterization (morphology and either immunohistochemistry or immunofluorescence or flow cytometry). Cytogenetics by conventional karyotype or FISH.	MRD: For D-VMP, D-Kd, and D-Rd cohorts, a portion of the bone marrow aspirate collected at screening, will be sent to the central laboratory. A fresh bone marrow aspirate is preferred, but if a fresh bone marrow aspirate is not performed at screening because a sample is available within 42 days prior to administration of study treatment, obtain non-decalcified slides (bone marrow aspirate, touch preparation or clot selection) or FFPE block (clot section only, no bone marrow biopsy).
CR, sCR	For response confirmation, additional bone marrow aspirates or biopsies (or both) will be performed locally to confirm sCR or CR. Response characterization (morphology by immunohistochemistry or immunofluorescence or flow cytometry). For sCR: Detection of kappa/lambda ratio by 2-4 color flow cytometry is strongly preferred. If flow cytometry is not available at site, either immunohistochemistry or immunofluorescence can be done, however, kappa/lambda ratio from analysis of ≥100 plasma cells is required to confirm sCR. If sCR is not met, repeat local testing for sCR with subsequent bone marrow examinations will be done.	MRD Assessment: For D-VMP, D-Kd, and D-Rd cohorts, a portion of the bone marrow aspirate collected for confirmation of CR/sCR will be sent to the central laboratory for MRD assessment. For subjects who achieve CR and remain on study, an additional bone marrow aspirate will be obtained at 12, 18, and 24 months (±1 month) post C1D1 and every 12 months thereafter (±1 month) until disease progression. If one of these timepoints occur within 1 month of suspected CR, a repeat bone marrow will not be requested.

CR=complete response; FFPE=formalin-fixed, paraffin-embedded; FISH=fluorescence in situ hybridization; MRD=minimal residual disease; sCR=stringent complete response

9.2.1.6. Minimal Residual Disease Assessment

Minimal residual disease (MRD) evaluation of the number of cells remaining after treatment by next-generation sequencing (NGS) is a relatively new and effective tool in the assessment of subjects with MM (Ladetto 2014[19]). Daratumumab containing regimens demonstrated significantly greater MRD negative rates as compared to the control group was demonstrated in the MMY3003 and MMY3004 clinical trials (Avet-Loiseau, 2016[1]). Several studies have demonstrated that MRD status is correlated with PFS and OS (Martinez-Lopez 2014[22]). In the present study, bone marrow aspirate will be collected for MRD analysis, in the D-VMP, D-Kd, and D-Rd cohorts only, when bone marrow samples are obtained at screening, confirmation of CR/sCR, and subsequent timepoints after the first dose (see Table 33).

9.2.1.7. Assessment of Lytic Disease

A complete skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease) is to be performed and evaluated by the local laboratory by roentgenography (or the local standard of care imaging, eg, low-dose whole body CT) during the Screening Phase. Please note that the same methodology used at screening should be used throughout the study for comparison purposes. During the Treatment Phase and before disease progression is confirmed, imaging should be performed whenever clinically indicated based on symptoms, to document response or progression. Magnetic resonance imaging is an acceptable method for evaluation of bone disease and may be included as an additional assessment at the discretion of the investigator (see the disease response criteria in Table 32).

Subjects may present with disease progression manifested by symptoms of pain due to bone changes. Therefore, disease progression may be documented, in these cases, by skeletal survey or other radiographs, depending on the symptoms that the subject experiences. If the diagnosis of disease progression is obvious by radiographic investigations, then no repeat confirmatory imaging is necessary. In instances where changes may be subtler, repeat imaging may be performed in 1 to 3 weeks according to investigator discretion.

9.2.1.8. Documentation of Extramedullary Plasmacytomas

Sites of known extramedullary plasmacytomas must be documented during the Screening Phase. Clinical examination or MRI may be used to document extramedullary sites of disease. Computed tomography scan evaluations are an acceptable alternative if there is no contraindication to the use of IV contrast. Positron emission tomography scan alone (ie, without a CT) or ultrasound tests are not acceptable to document the size of extramedullary plasmacytomas.

Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas or if clinically indicated at screening, by clinical examination or radiologic imaging. For subjects with a history of plasmacytomas assessed by physical examination, physical examination should be repeated on Cycle 1 Day 1 if not done within 14 days prior to administration of study treatment. Assessment of measurable sites of extramedullary disease will

be performed and evaluated locally approximately every 4 weeks (every 3 weeks in the D-VRd cohort) by physical examination or approximately every 12 weeks by imaging (if required) for subjects with a history of plasmacytomas or as clinically indicated during treatment for other subjects, until development of confirmed CR or confirmed disease progression. For every subject, the methodology used for evaluation of each disease site should be consistent across all visits. Irradiated or excised lesions will be considered not measurable and will be monitored only for disease progression.

To qualify for PR, the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have decreased by at least 50%, and new plasmacytomas must not have developed (see the disease response criteria in Table 32). To qualify for disease progression, either the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have increased by at least 50% or a new plasmacytoma must have developed. In the cases where not all existing extramedullary plasmacytomas are reported, but the sum of products of the perpendicular diameters of the reported plasmacytomas have increased by at least 50%, this will also qualify as disease progression.

9.3. Pharmacokinetics and Immunogenicity

9.3.1. Evaluations

Samples to assess both the serum concentration (PK) of daratumumab and the generation of anti-daratumumab antibodies (immunogenicity) will be obtained from all subjects according to the Time and Events Schedules (Table 2, Table 5, Table 7, and Table 9). Samples will also be collected from all subjects to evaluate the immunogenicity of rHuPH20 according to the Time and Events Schedules (Table 2, Table 5, Table 7, and Table 9). The exact dates and times of blood sampling must be documented. Refer to the Laboratory Manual or equivalent document for sample collection requirements. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the Laboratory Manual. Samples collected for determining serum concentrations/ immunogenicity of daratumumab or immunogenicity of rHuPH20 in this study may be retained to address questions about drug characteristics that may arise at a later timepoint.

9.3.2. Analytical Procedures

Samples will be analyzed to determine concentrations of daratumumab or generation of antibodies to daratumumab or rHuPH20 using validated immunoassay methods by or under the supervision of the sponsor. For the daratumumab immunogenicity assessments, serum samples will be screened for antibodies binding to daratumumab and serum titer will also be determined from confirmed positive samples. Other immunogenicity analyses (eg, assessment of neutralizing capabilities) may be performed to further characterize the immune responses that are generated. For the rHuPH20 immunogenicity assessments, plasma samples will be screened for antibodies binding to rHuPH20 and will be assessed in confirmatory and titer assays as necessary. Neutralizing antibody assessments may also be performed to further characterize immune responses that are generated.

9.3.3. Pharmacokinetic Parameters

The PK parameters are defined as:

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

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

9.3.4. Immunogenicity Assessments

Serum from venous blood samples collected from all subjects will be assessed for the generation of anti-daratumumab antibodies (immunogenicity) according to the Time and Events PK/Immunogenicity Sample Collection Tables (Table 2, Table 5, Table 7, and Table 9). Daratumumab concentration will be evaluated at all immunogenicity timepoints to ensure appropriate interpretation of immunogenicity data. When both daratumumab serum concentration and immunogenicity analyses are specified, they will be performed on aliquots from the same blood draw and no additional sampling is required. Plasma samples will also be collected from all subjects and assessed for anti-rHuPH20 antibodies.

When an IRR occurs associated with the second daratumumab administration or beyond, 2 blood samples should be obtained, if possible, for determination of both anti-daratumumab antibodies and anti-rHuPH20 antibodies. No unscheduled samples need to be collected for IRRs associated with the first administration of daratumumab. Daratumumab serum concentration will also be determined from the daratumumab IRR sample for the purpose of interpreting immunogenicity data. These samples will be stored and evaluated if deemed necessary. If an IRR results in treatment discontinuation, then a subject 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 additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period or for the evaluation of relevant biomarkers by the sponsor or sponsor's designee. Subjects who discontinue treatment or withdraw from the study before confirmation of PD should have samples collected at the time of early discontinuation. Subjects who discontinue treatment will also be asked to return for immunogenicity evaluation during the Follow-up Phase.

9.4. 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. If these analyses are performed, then the details and results will be presented in a separate report.

9.5. Biomarkers

As permitted by local rules and regulations, bone marrow aspirates in the D-VMP, D-Kd, and D-Rd cohorts will be collected at screening and following treatment as outlined in the Time and Events Schedule for MRD monitoring (Table 3, Table 6, and Table 8). Baseline bone marrow aspirate samples will be subjected to DNA sequencing to establish a MM clone for MRD monitoring. A fresh bone marrow aspirate at screening is required, if possible. By exception, non-decalcified diagnostic tissue slides (bone marrow aspirate, touch preparation or clot selection) or formalin-fixed, paraffin-embedded (FFPE) block (clot selection only, no bone marrow biopsy) may be supplied for MRD assessment. For subjects who achieve a CR, bone marrow aspirates will be utilized for assessment of MRD by NGS of Ig heavy and light chains. 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 subjects as specified in the Time and Events Schedule for processing to plasma and peripheral blood mononuclear cells. These samples may be used to evaluate the mechanism of action of subcutaneously delivered daratumumab in combination with standard of care regimens. As daratumumab has been demonstrated to have an immunomodulatory mechanism, specific subsets of immune cells such as cytotoxic T cells, regulatory T cells, and activated NK cells may be evaluated by fluorescence-activated cell sorting (FACS) or cytometry/time-of-flight mass spectrometry and T-cell receptor sequencing. Proteomic analysis may also be used to evaluate changes in proteins in circulation to evaluate potential biomarkers of response and resistance.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data. Samples for biomarker evaluations will be collected as specified in the Time and Events Schedule (Table 1 to Table 9).

Additional Collections

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

9.6. Safety Evaluations

Safety will be measured by adverse events, laboratory test results, ECGs, vital sign measurements, physical examination findings, SC injection-site assessments, and assessment of ECOG performance status score. In addition, TTE monitoring will be performed in subjects in the D-Kd cohort only. All toxicities will be graded according to the NCI-CTCAE Version 4.03. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event 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 endpoint is reached.

Based on the previous clinical experience with daratumumab, in vitro studies, and animal toxicological findings, IRRs/allergic reactions, hemolysis, infection, neutropenia, and thrombocytopenia will be closely monitored. As a biologic agent, immunogenicity also will be monitored. Any of the safety monitoring assessments may be performed more frequently, and adverse events should be evaluated by the investigator according to the standard practice, if clinically indicated. Details regarding the SET are provided in Section 11.9 (Study Evaluation Team).

The study will include the following evaluations of safety and tolerability according to the timepoints provided in the Time and Events Schedule (Table 1 to Table 9):

Adverse Events

Adverse events (with the exception of progression of MM) will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) from the time a signed and date informed consent is obtained until 30 days following the final dose of daratumumab. Adverse events will be followed by the investigator as specified in Section 12 (Adverse Event Reporting). After the data collection has ended, only serious adverse events will be collected, as described in Attachment 15.

Clinical Laboratory Tests

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

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

- Hematology panel

  -hemoglobin
  -white blood cell (WBC) count
  -absolute neutrophil count (ANC)
  -absolute lymphocyte count (ALC)
  -platelet count

- Serum chemistry panel

  -AST
  -ALT
  -total bilirubin[a]
  -glucose
  -creatinine
  -sodium
  -alkaline phosphatase
  -uric acid
  -blood urea nitrogen or urea
  -calcium and albumin-adjusted calcium[b]
  -lactic acid dehydrogenase
  -potassium

  [a] If Gilbert's disease, assessment of direct bilirubin.
  [b] These parameters will be part of the efficacy evaluations as specified in Section 9.2.1.3, Serum Calcium Corrected for Albumin, and will be analyzed at a central laboratory.

Pregnancy Testing

Serum beta-human chorionic gonadotropin (β-hCG) or urine pregnancy testing for women of childbearing potential will be collected as specified in the Time and Events Schedule (Table 1 to Table 9).

For women of childbearing potential only: lenalidomide is a thalidomide analogue and is contraindicated for use during pregnancy. Birth defects have been observed in preclinical studies of lenalidomide similar to thalidomide in humans. Therefore, strict monitoring for pregnancy must be conducted during Screening and throughout the Treatment Phase, as specified in the Time and Events Schedule. Where lenalidomide is supplied locally, subjects must adhere to the local lenalidomide REMS program. Where lenalidomide is supplied centrally and no local lenalidomide REMS program exists, then subjects must adhere to the Lenalidomide Global Pregnancy Prevention Plan in Attachment 14.

If pregnancy or positive pregnancy test does occur, then study treatment should be discontinued immediately, and the subject should be referred to an obstetrician experienced in reproductive toxicity for further evaluation and counseling.

Daratumumab Interference with Indirect Antiglobulin Test Results

Daratumumab interferes with the indirect antiglobulin test (IAT), which is a routine pre-transfusion test performed to identify a subject's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a subject identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT) determined before the first administration of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab IAT interference by treating reagent RBCs with dithiothreitol (DTT) (Chapuy 2015[4], Chapuy 2016[5]).

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

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

Uncrossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed urgently according to 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 Investigator's Brochure for daratumumab[13].

FEV1 Test

Subjects with known or suspected COPD or asthma must have a FEV1 test during screening. Refer to Section 6.4.1.2 (Post-administration Medication) for details on subjects with higher risk of respiratory complications.

HBV Serology

Subjects in the D-Kd cohort will be tested locally for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) at Screening. Additionally, subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment when Protocol Amendment 3 is implemented will be required to have HBV serology performed locally upon signing the updated ICF. For subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment, HBV serology is not required if this was performed as part of standard of care within 3 months prior to first dose.

HBV DNA Tests

Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for hepatitis B DNA by PCR. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. During study treatment and within 6 months of the last dose of daratumumab, subjects who have history of HBV infection will be closely monitored by the investigator for clinical and laboratory signs of reactivation of HBV as specified in the Time and Events Schedule (Table 1, Table 3, Table 6, and Table 8). eviWhere required by local law, the results of HBV testing may be reported to the local health authorities.

Electrocardiogram (ECG)

Electrocardiograms will be performed as specified in the Time and Events Schedule (Table 1 to Table 9). Whenever possible, ECGs should be performed immediately before chemistry and PK assessments. During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same timepoint as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Transthoracic Echocardiogram

Participants in the D-Kd cohort must have a TTE according to the Time and Events Schedule (Table 8). Two-dimensional TTE to assess left ventricular ejection fraction for eligibility purposes will be assessed during screening and will serve as the baseline echocardiogram.

Vital Signs

Vital signs (temperature, pulse/heart rate, respiratory rate, and blood pressure) will be performed as specified in the Time and Events Schedule (Table 1 to Table 9). 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).

Physical Examination

A complete physical examination should be performed during the Screening Phase. Thereafter, only a symptom-directed physical examination is required. Abnormalities will be recorded in the appropriate section of the eCRF.

Eastern Cooperative Oncology Group (ECOG) Performance Status

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

9.7. Sample Collection and Handling

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. Samples for PK and immunogenicity testing must not be taken from the same arm as drug administration.

Refer to the Time and Events Schedule (Table 1 to Table 9) for the timing and frequency of all sample collections. Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

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

10.1. Completion

A subject will be considered to have completed the study if he or she has completed all protocol-specified procedures before the end of the study, has not been lost to follow-up, or has not withdrawn consent for study participation before the end of the study, or has transitioned to study drugs which are commercially available or available from another source.

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

The sponsor's medical monitor will review the provided documentation and confirm PD has occurred according to IMWG criteria (see Section 9.2.1.1, Response Categories) and that study treatment should be discontinued. After confirmation of PD by the sponsor, the subject will discontinue study treatment and enter the Follow-up Phase.

Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the study if he or she must discontinue treatment before the end of the treatment regimen. The End-of-Treatment Visits and Follow-up visit assessments should continue as specified in the Time and Events Schedule (Table 1 to Table 9).

Subjects who discontinue treatment with any one component of study treatment (daratumumab or bortezomib, melphalan, prednisone [D-VMP]; lenalidomide, dexamethasone [D-Rd]; carfilzomib, dexamethasone [D-Kd]) may continue to receive treatment with the other components of study treatment, as assigned.

A subject's study treatment (daratumumab and combination therapy) must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- If the subject becomes pregnant or a positive pregnancy test does occur and she is enrolled in a lenalidomide containing cohort, lenalidomide must be discontinued immediately. Continuation of other drugs may be considered if the subject (or the subject's legally acceptable representative), investigator, and sponsor agree the benefits to the subject outweigh the risks to the fetus and continuation of treatment is in the best interests of the subject. If the male participant’s partner becomes pregnant and is enrolled in a lenalidomide containing cohort, they must immediately inform the investigator.
- The subject (or the subject’s legally acceptable representative) withdraws consent for administration of the study drug
- The subject initiates treatment with a prohibited medication
- The subject received concurrent (non-protocol) treatment for MM
- The subject experiences unacceptable toxicity, including IRRs described in Section 6.4, Management of Injection-site and Infusion-related Reactions
- The subject’s dose of daratumumab is held for a prolonged period (unless sponsor approves continuation). See Section 6.5 for a description of the management of dose delays for each cohort
- The subject experiences disease progression (see below).
- A subject who experiences a second primary malignancy that cannot be treated by surgery or radiotherapy alone must be withdrawn from the study. However, a subject who develops a malignancy that can be cured surgically or with definitive radiotherapy may continue to receive the assigned study treatment and should continue to be followed for subsequent progression of MM.

Study treatment will continue for 4 cycles in the D-VRd cohort, or until confirmation of PD in the D-VMP, D-Kd, and D-Rd cohorts. Before subjects are discontinued from study treatment because of suspected PD, the investigator (or designee) will provide documentation of disease progression (for example, by completing a disease progression form or by contacting the

interactive web response system [IWRS]) as soon as possible and within 48 hours of confirmation of disease progression. Documentation of PD status into IWRS is not required after end of data collection (see Attachment 15).

If a subject's study treatment must be discontinued, then this will not result in automatic withdrawal of the subject from the study; instead, the subject will enter the Post-treatment Follow-up Phase. For subjects who discontinue treatment prior to PD, disease evaluations should continue every 28 days until the Follow-up Visit is completed. For subjects in the D-VRd cohort, subsequent therapy will be collected potentially after the End-of-Treatment Visits and best response after transplant will be collected in the eCRF. The End-of-Treatment Visit and Follow-up Visit assessments should continue as specified in the Time and Events Schedule (Table 1 to Table 9). For additional clarification regarding continued assessments for subjects who continue receiving study drugs after data collection ends, see Attachment 15.

Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent for study participation
- Death
- Sponsor terminates the study

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

When a subject withdraws consent before completing the study, the reason for study end should be recorded as ‘withdrawal of consent’ and all data collection should stop immediately. Study drug assigned to the withdrawn subject may not be assigned to another subject. If subjects withdraw from the study after Cycle 1, additional subjects will not be enrolled. Subjects who withdraw from the study during Cycle 1 for reasons other than toxicity may be replaced at the discretion of the sponsor. If a subject discontinues study drug and withdraws from the study before the end of treatment, assessments outlined in the End-of-Treatment Visit should be obtained (Table 1). If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

10.3. Withdrawal From the Use of Research Samples

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

11. STATISTICAL METHODS

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

11.1. Subject Information

The analysis sets for this study include:

- All treated analysis set: defined as all subjects who receive at least 1 dose of study treatment. This analysis set will be used for analyses of disposition, demographic and baseline disease characteristics, treatment exposure, safety and efficacy. All subjects in the all treated analysis set will be analyzed according to the treatment that they actually received.
- PK analysis set: defined as subjects who received at least 1 administration of study drug and have at least 1 PK sample concentration value after the first dose. All PK parameters will be analyzed based on the PK analysis set.
- Immunogenicity-evaluable analysis set is defined as all subjects who receive at least 1 dose administration of daratumumab SC and have at least 1 immunogenicity sample for detection of anti-daratumumab antibodies after the first dose.
- Immunogenicity-evaluable analysis set for rHuPH20 is defined as all subjects who receive at least 1 dose of daratumumab SC and have appropriate plasma samples for detection of antibodies to rHuPH20 (at least 1 sample after the start of the first dose of daratumumab SC).

Descriptive statistics will be used to summarize data. For continuous parameters, number of observations, mean, standard deviation, median, and range will be used. For discrete parameters, frequency will be summarized. For time-to-event parameters, Kaplan-Meier estimates will be produced. When sample sizes are small, sample listings may be provided instead.

11.2. Sample Size Determination

For the D-VMP cohort, 60 subjects will be required to test the null hypothesis that the ORR is at most 70%, against the alternative hypothesis that the ORR is at least 90% with a 1-sided alpha of 0.05 and at least 98% power (Table 34). For the D-Rd cohort, 60 subjects will be required to test the null hypothesis that the ORR is at most 75% against the alternative hypothesis that the ORR is at least 90% with a 1-sided alpha of 0.05 and at least 90% power. Similarly, for the D-Kd cohort, the corresponding power is >80% to test the null hypothesis that the ORR is at most 65%, against the alternative hypothesis that the ORR is at least 80%. For the D-VRd cohort, 60 subjects will achieve a power of at least 93% to test the null hypothesis that the response rate of

VGPR or better is at most 50%, against the alternative hypothesis that the ORR is at least 70% with a 1-sided alpha of 0.05.

Table 34: Hypothesis and Power Table

Cohort	N	H_0	H_1	Power
D- VRd	60	VGPR or better rate ≤50%	VGPR or better rate ≥70%	>93%
D-VMP	60	ORR ≤70%	ORR ≥90%	>98%
D- Rd	60	ORR ≤75%	ORR ≥90%	>90%
D-Kd	60	ORR ≤65%	ORR ≥80%	>80%

D-VRd=Dara SC, bortezomib, lenalidomide, and dexamethasone; D-VMP=Dara SC, bortezomib, melphalan, and prednisone; D-Rd=Dara SC, lenalidomide, and dexamethasone; ORR=overall response rate; D-Kd=Dara SC, carfilzomib, and dexamethasone

11.3. Efficacy Analyses

A computerized algorithm will be used to derive the response and disease progression based on the central laboratory results (unless otherwise specified) for the analysis and reporting. The primary analysis for the study will occur at least 6 months after approximately the 60th subject is enrolled in the last treatment cohort (D-VRd, D-VMP, or D-Rd). The cutoff for the primary analysis for the D-Kd cohort will occur at least 6 months after approximately the 60th subject is enrolled in the D-Kd cohort. No formal comparisons between the treatment cohorts will be performed.

Primary Endpoint

The primary efficacy endpoint for the D-Kd, D-VMP, and D-Rd cohorts is ORR, which is defined as the proportion of subjects who achieve a response of PR or better according to IMWG response criteria. The ORR, along with its 2-sided 90% exact CI, will be calculated.

At the time of the primary analysis for the study, the D-Kd cohort will not be included in the analysis and will be analyzed in subsequent analyses at least 6 months after approximately the 60th subject is enrolled in the D-Kd cohort.

The primary efficacy endpoint for the D-VRd cohort is VGPR or better rate, which is defined as the proportion of subjects who achieve a response of VGPR or better according to IMWG response criteria. The VGPR or better rate, along with its 2-sided 90% exact CI, will be calculated.

Secondary Endpoints

VGPR or Better Rate (D-Kd, D-VMP, and D-Rd cohorts)

The proportion of subjects who achieve a response of VGPR or better according to the IMWG response criteria and its two-sided exact 90% CI will be calculated for D-Kd, D-VMP, and D-Rd cohorts.

ORR (D-VRd cohort)

The proportion of subjects who achieve a response of PR or better according to the IMWG response criteria and its two-sided exact 90% CI will be calculated for D-VRd cohort.

CR or Better Rate

The proportion of subjects who achieve a response of CR or better according to the IMWG response criteria and its two-sided 90% exact CI will be calculated for each treatment cohort.

Duration of Response

Duration of response is calculated from the date of initial documented response (PR or better for D-Kd, D-VMP, and D-Rd cohorts) to the date of first documented evidence of progressive disease as defined according to IMWG criteria or death due to PD, whichever occurs first, for the subjects who had achieved a response (PR or better for D-Kd, D-VMP, and D-Rd cohorts). Median DOR with 90% CI will be estimated based on the Kaplan-Meier method for each treatment cohort.

MRD Negativity Rate

Minimal residual disease (MRD) negativity rate is defined as the proportion of subjects who are considered MRD negative after MRD testing at any timepoint after first dose by bone marrow aspirate. The MRD negative rate will be calculated for cohorts D-VMP, D-Kd, and D-Rd. The corresponding two-sided 90% exact CI will be provided.

Exploratory Analysis

Best overall response based on the IMWG criteria will be collected after autologous stem cell transplantation for the D-VRd cohort after 4 cycles of treatment. These data may be used in an exploratory analysis.

11.4. Pharmacokinetic Analyses

Daratumumab Pharmacokinetic Analysis

Pharmacokinetic analyses will be performed on the PK-evaluable analysis set, defined as subjects who have received at least 1 dose of daratumumab and have at least 1 post-dose sample. 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 timepoint. C_{min} is defined as the minimum concentration observed immediately before daratumumab administration and C_{max} is defined as the maximum concentration observed following daratumumab administration, as presented in the summary of serum concentration by sampling timepoint. Other PK parameters, if available, may also be summarized.

If sufficient data are available, population-PK analysis of serum concentration-time data of daratumumab may be performed and may be combined with 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. Exposure-response analyses may also be performed and may use data from other studies; if performed, details will be provided in a separate analysis plan and report.

11.5. Immunogenicity Analyses

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

11.6. Pharmacodynamic Analyses, and Biomarker Analyses

Biomarker studies are designed to identify markers predictive of response (or resistance) to daratumumab. Analyses will be stratified by clinical covariates using the appropriate statistical methods (eg, parametric or non-parametric, univariate or multivariate, analysis of variance [ANOVA], or survival analysis, depending on the endpoint). Baseline level and changes in expression patterns of specific cell types (NK, T, and B cells), CD38 expression in MM cells, and complement inhibitory proteins expression in MM cells will be evaluated for association with PK, clinical response, and disease parameters. Other biomarker parameters may be evaluated in a similar fashion.

Any pharmacodynamic measures will be listed, tabulated, and where appropriate, plotted. Subjects may be grouped by cohort, dose, or clinical response. Results of biomarker and pharmacodynamic analyses may be presented in a separate report. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information.

11.7. Pharmacokinetic/Pharmacodynamic Analyses

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 performed, details and results of the analysis will be presented in a separate report.

11.8. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the Treatment Phase or that are a consequence of a

pre-existing condition that has worsened since baseline. All reported adverse events with onset during the treatment phase (ie, TEAEs, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized for each treatment cohort. The proportion of subjects who have an IRR and its two-sided 90% exact CI will be calculated for each treatment cohort.

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

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 each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled timepoint. A listing of subjects with any laboratory results outside the reference ranges will be provided.

Parameters with predefined NCI-CTCAE (Version 4.03) toxicity grades will be summarized. Worst toxicity grade during treatment will be presented. Change from baseline to the worst adverse event grade experienced by the subject during the study will be provided as shift tables.

Electrocardiogram (ECG)

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

Vital Signs

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 timepoint.

Stem Cell Collection (D-VRd cohort only)

Descriptive statistics of number of stem cells collected, number of days of autologous stem cell collection, drugs used for autologous stem cell mobilization, and requirement special stem cell mobilizing agent (eg, mozobil) will be summarized.

11.9. Study Evaluation Team

A SET consisting of the participating investigators, the sponsor's medical monitor, the sponsor's clinical pharmacologist (if PK data are being evaluated), the sponsor's statistician the sponsor's safety officer, and the sponsor's study manager will evaluate safety data after at least 6 toxicity-evaluable subjects complete Cycle 1 in each cohort. Additional data reviews by the SET can be scheduled as needed to support decisions on dose selection or schedule modification. The SET reviews and dose selection decisions will be documented in writing.

12. ADVERSE EVENT REPORTING

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event 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 according to 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 adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse 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 subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be

immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include second primary malignancy. These should usually be considered serious.

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For daratumumab, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure[13]. Anticipated events will be recorded and reported as described in Attachment 11. In Japan, the Investigator's Brochure of bortezomib will be referred for the expectedness of an adverse event.

Adverse Event Associated With the Use of the Drug

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

12.1.2. Attribution Definitions

Not Related

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

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.

Possible

An adverse event that might be due to the use of the drug. 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 drug. 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).

12.1.3. Severity Criteria

The severity assessment for an adverse event or serious adverse event should be completed using the NCI-CTCAE Version 4.03. Any adverse event or serious adverse event not listed in the NCI-CTCAE Version 4.03 will be graded according to investigator clinical judgment by using the standard grading outlined in the NCI-CTCAE Version 4.03.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

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

- Overdose of a sponsor study drug. No MTD has been reached for daratumumab. However, if the dose exceeds the maximum tested dose of 2000 mg, then it will be considered as an overdose in this study.
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

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

12.3. Procedures

12.3.1. All Adverse Events

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 11. (Note: Some countries require reporting of all adverse events to the health authorities, eg, Japan will not identify anticipated events for the health authorities).

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the final dose of study drug. The only exception is for subjects who have withdrawn informed consent for study

participation or for subjects who have received additional treatment with therapeutic intent for MM within 30 days after the final dose of any component of the treatment regimen. For subjects who have received additional treatment with therapeutic intent for MM during the adverse event reporting period, only adverse events that are considered to be possibly, probably, or definitely related to the study drug or any part of the backbone treatment regimen must be reported (unless the subject has been withdrawn from the study).

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the final dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate safety information that is spontaneously reported by an investigator beyond the timeframe specified in the protocol.

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

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

The sponsor assumes responsibility for appropriate reporting of adverse events 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 serious adverse events 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 investigational 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.

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

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All serious adverse events 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 serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted electronically or by facsimile (fax).

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

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

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

- If the subject has not experienced a significant medical event but is hospitalized overnight only for observation following administration of study drug, then the hospitalization should not be reported as a serious adverse event.

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience, the investigator may choose to hospitalize the subject for the duration of the treatment period. Note: This should not be considered a serious adverse event.

Expected progression of disease should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements (see Section 12, Adverse Event Reporting).

Refer to Attachment 15 for details on serious adverse event reporting after the end of the data collection.

12.3.3. Pregnancy

All initial reports of pregnancy 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, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant or experiences a positive pregnancy test during the study must discontinue further study treatment. The subject should be referred to a physician experienced in teratology for evaluation and advice. Investigators should follow the local label for guidance on subject education and ensure that all subjects adhere to the local lenalidomide REMS program (when lenalidomide is supplied locally), or the Lenalidomide Global Pregnancy Prevention Plan provided in Attachment 14 (when lenalidomide is supplied centrally and no local lenalidomide REMS program exists). Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Because the effect of the study drug on sperm is unknown, pregnancies or positive pregnancy tests in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Pregnancy reporting will continue as described above after the end of the data collection until the end of study (see Attachment 15).

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event. If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. 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.

14. STUDY DRUG INFORMATION

14.1. Physical Description of the Study Drug

The daratumumab supplied for SC injection (Dara SC) in this study is a colorless to yellow liquid and sterile concentrate of 120 mg/mL daratumumab + 2000 U/mL rHuPH20 as a liquid in vial. The study agent should be essentially free of visible particulate matter at the time of syringe preparation and drug product administration. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients (Note: In some countries, both daratumumab and rHuPH20 are treated as an investigative product. In this study, the study drug refers to the co-formulation of daratumumab and rHuPH20)[13]. In Japan, bortezomib is treated as an investigative product and will be provided by the sponsor.

14.2. Packaging

Dara SC is supplied in glass vials containing daratumumab at a concentration of 120 mg/mL and rHuPH20 at a concentration of 2000 U/mL (~20 μg/mL). It will be supplied to the site/pharmacy as open-label supply.

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

14.4.1. Dara SC Formulation

Dara SC must be stored in the original carton in a refrigerator at controlled temperatures ranging from 2°C to 8°C until it is removed for dose preparation. The study drug must not be utilized after the expiry date printed on the label. Dara SC must be protected from light and must not be frozen. The product does not contain preservatives; therefore, any unused portion remaining in the vial must be discarded. Refer to the IPPI for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

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

Study drug must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return to the sponsor of unused study drug will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed onsite, this must also be documented on the drug return form.

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

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The

investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure for daratumumab
- Investigator's Brochure for rHuPH20
- Investigator's Brochure for bortezomib (in Japan only)
- Investigational Product Preparation Instructions
- Investigational Product and Procedures Manual
- Laboratory Manual
- IWRS Manual
- eCRF completion guidelines
- Sample ICF
- Subject identification wallet card, including space for blood type and IAT result
- Subject diaries for recording pre-dose and post-dose medications that are administered at home
- Other manuals and guidance documents as needed

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

As discussed in Section 1.1.2.2, Preliminary Data from Study MMY1004 Part 2, preliminary efficacy data suggest that SC administration of Dara SC may provide comparable or better response rates compared with IV administration of Dara-IV. Additional benefits of Dara SC compared with Dara-IV include:

- Potential reduction in the incidence rate and severity of IRRs (compared with IV infusion), due to slower absorption of daratumumab into systemic circulation
- Shorter administration time (approximately 3 to 5 minutes compared with 4 to 7 hours for IV infusion)
- Reduced administration volume (SC administration of approximately 15 mL instead of 500 mL to 1000 mL IV infusion), which may be clinically meaningful for elderly subjects with comorbid cardiac or renal insufficiency

Based on the mechanism of action of daratumumab, a potential risk could be infection; therefore, the protocol requires the review of hematological laboratory results prior to daratumumab administration. CD38 is distributed in erythrocytes and platelets. Safety data from a phase 3 clinical study (Study MMY3004) in subjects with relapsed or refractory MM comparing

daratumumab, bortezomib and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd), showed daratumumab may increase thrombocytopenia associated with bortezomib-based regimens. Additionally, safety data from the phase 3 clinical study (Study MMY3003) in subjects with relapsed or refractory MM comparing daratumumab, lenalidomide and dexamethasone (DRd) vs bortezomib and dexamethasone (Rd), showed daratumumab may increase neutropenia associated with lenalidomide-based regimens. However, bleeding events were low and the majority of events were minor (less than 1% of subjects experienced Grade 3 or 4 bleeding events). Anemia, all grades and Grade 3 or 4 in the MMY3004 study, were similar among the 2 treatment groups. Routine safety laboratory measurement of hemoglobin and platelets will be closely monitored in this study. Safety data from the phase 2 Study MMY1001, evaluating the combination of daratumumab in combination with carfilzomib and dexamethasone, showed a safety profile consistent with the individual agents. Carfilzomib has been associated with cardiac toxicity, thus additional monitoring of cardiac function with echocardiograms will be performed to monitor for cardiac safety in the D-Kd cohort of the study.

In a previous study with SC administration of daratumumab (MMY1004), a lower incidence of IRRs was observed compared to the IRR rate reported from studies with IV infusion of daratumumab. However, IRRs may still occur and may develop at a later timepoint than previously observed with IV infusion due to the more gradual absorption (see Section 6.4 for guidelines for prevention and management of IRRs). Subjects will therefore be observed for at least 6 hours on their first day of SC daratumumab administration. Apart from IRRs, a similar toxicity profile has been shown for SC versus IV infusion for anemia, thrombocytopenia, and other toxicities. During this study, local tolerability at the SC injection site will be closely monitored as well.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled. Note that as specified in Section 16.2.3, Informed Consent, a legally acceptable representative may provide consent on behalf of the subject.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of

study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)

- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

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

16.2.3. Informed Consent Form

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

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

the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

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

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

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

16.2.4. Privacy of Personal Data

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

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

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

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

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

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

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

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

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

in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

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

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

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

- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth (as allowed by local regulations). In cases where the subject is not enrolled into the study, the date seen and date of birth (as allowed by local regulations) will be used.

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

17.4. Source Documentation

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

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document). The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

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

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

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically

extracted for use by the sponsor. If the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

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

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

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

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

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

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.
- There will be no data collection in the eCRF after the database is closed for the final analysis. Attachment 15 describes study procedures for subjects who continue receiving study drugs after the end of the data collection.

17.6. Data Quality Assurance/Quality Control

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

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

17.7. Record Retention

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

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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

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

17.8. Monitoring

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

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

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site. Central monitoring may take place for data identified by the sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. End of Data Collection and End of Study

The end of data collection will be approximately 10 months after the last subject is enrolled in the D-Kd cohort or when the sponsor decides to stop the study. Subjects benefiting from study treatment can continue receiving the study drugs after the end of data collection until the study drugs are commercially available, available from another source (eg, via a dedicated long-term extension study), or until study completion. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

After the end of the data collection, the clinical database will be closed, and no additional data will be collected in the eCRF. Attachment 15 describes study procedures for subjects who continue receiving study drugs after the end of the data collection.

The end of study will occur when all subjects discontinue study treatment or 18 months after the end of data collection, whichever occurs first.

17.9.2. Study Termination

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

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

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

- Discontinuation of further study drug development

17.10. On-Site Audits

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

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

17.11. Use of Information and Publication

All information, including but not limited to information regarding daratumumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The 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 Clinical Study Report generated by the sponsor and will contain eCRF data from all study sites that participated in the study according to the 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. Results of biomarker analyses performed after the Clinical Study Report has been issued may be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (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 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 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.

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ATTACHMENTS

Attachment 1: International Myeloma Working Group Diagnostic Criteria

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

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

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

(Rajkumar 2014[28])

Attachment 2: Eastern Cooperative Oncology Group Performance Status Grade

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 MD, Group Chair (Oken 1982[26])

Attachment 3: Modified Diet in Renal Disease Formula

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

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

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

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

(Levey 2006[20])

Attachment 4: 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])

Attachment 5: Conversion Table for Glucocorticosteroid Dose

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

Attachment 6: Asthma Guidelines

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

Attachment 7: New York Heart Association (NYHA) 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.

Attachment 8: Antihistamines That May Be Used Pre-dose

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

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

* The IV use of promethazine should be avoided.

Attachment 9: Body Surface Area Nomogram

Body surface area should be calculated according to the following formula:

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

or

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

Attachment 10: Interpretation of The SEBIA Hydrashift 2/4 Daratumumab IFE Interference Test

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

Implementation: To mitigate this interference, the sponsor will use the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test. 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 subject 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 subject 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 subject 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 subject 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 subject is not in a complete response (CR), because the CR response criteria requires a negative SPEP and serum IFE.

Attachment 11: Anticipated Events

Anticipated Event

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

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

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

Reporting of Anticipated Events

All AEs will be recorded in the eCRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described in Section 12.3.2. Each anticipated event will be assessed by the investigator at the individual case level and if considered to be drug-related will undergo expedited reporting (if appropriate) as per applicable clinical trial legislation to Health Authorities and IRB/ECs. If an anticipated event is considered disease-related or not related to study drug the event will be exempt from expedited reporting.

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

Safety Assessment Committee (SAC)

A 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 cohort.

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.

Attachment 12: Inhibitors and Inducers of CYP3A

Examples of inhibitors and inducers of CYP3A are as shown below[12]:

Inhibitors of CYP3A

Strong inhibitors:
INDINAVIR
TIPRANAVIR
COBICISTAT
INDINAVIR
TROLEANDOMYCIN
TELAPRAVIR
DANOPREVIR
ELVITEGRAVIR
SAQUINAVIR
LOPINAVIR
NELFINAVIR
RITONAVIR
CLARITHROMYCIN
MIBEFRADIL
LCL161
ITRACONAZOLE
KETOCONAZOLE
POSACONAZOLE
NEFAZODONE
TELITHROMYCIN
CONIVAPTAN
BOCEPREVIR
VORICONAZOLE
SUBOXONE
GRAPEFRUIT JUICE DS[b]

Moderate inhibitors:
amiodarone
chloramphenicol
boceprevir
ciprofloxacin
delavirdine
diethyl-dithiocarbamate
fluoxetine
fluvoxamine
atazanavir/RIT
gestodene
imatinib
mifepristone
norfloxacin
norfluoxetine
star fruit
voriconazole
Darunavir
dronedarone
crizotinib
casopitant
amprenavir
imatinib
tofisopam
cyclosporine

Moderate inhibitors:
aprepitant
erythromycin
diltiazem
fluconazole
grapefruit juice
Seville oranges
verapamil
cimetidine

a. Azithromycin is unique in that it does not inhibit CYP3A
b. 240 mL GFJ double-strength administered TID for 3 days

Inducers of CYP3A

Potent inducers	Moderate inducers
rifampin	ritonavir and St. Johns wort
mitotane	[semagacestat]
avasimibe	efavirenz
phenytoin	tipranavir and ritonavir
carbamazepine	bosentan
enzalutamide	genistein
St John's Wort	thioridazine
rifabutin	
phenobarbital	nafcillin
	[talviraline]
	lopinavir
	modafinil
	etravirine
	lersivirine

Attachment 13: Contraceptive (and Barrier) Guidance and Collection of Pregnancy Information

Subjects must follow contraceptive measures as outlined in Section 4.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 9.6 Safety Evaluations (Pregnancy Testing).

Definitions:

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

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

  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, 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.) Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding,

DARATUMUMAB specific

Participants must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation. For restrictions related to concomitant medications, please refer to Section 8.3 Prohibited Therapies

1. Female subjects of reproductive childbearing potential (defined as post-menarche until post-menopause unless permanently sterilized) must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously during the Treatment Period, during any dose interruptions, and for 3 months after the last dose of any study drug. Sexual abstinence is considered a highly effective method only if defined as refraining from

heterosexual intercourse during the entire period of risk associated with the study drug and is consistent with the usual lifestyle of the subject. This birth control method must include one highly effective form of contraception (tubal ligation, intrauterine device [IUD], hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy with confirmation of procedure) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy.

- A woman of childbearing potential must have 1 negative serum or urine pregnancy tests at Screening. For requirements during the Treatment Phase, refer to Section 4.1.
- 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 study drug.
- Male subjects of reproductive potential who are sexually active with females of reproductive potential must always use a latex or synthetic condom during the study and for 3 months after discontinuing daratumumab (even after a successful vasectomy).
- Male subjects of reproductive potential must not donate semen or sperm during the study, during dose interruptions, or for 3 months after the last dose of any study drug.

2. Typically, IV contrast is not used in CT scanning of subjects with secretory multiple myeloma because of the risk to the kidney. If administration of IV contrast is necessary, then adequate precautions including hydration are indicated.

For Lenalidomide studies

For women of childbearing potential, adequate contraception, without interruption, must begin 28 days before starting lenalidomide and continue during the Treatment Phase, during any dose interruptions, and for at least 4 weeks after the last dose of lenalidomide. All women must not donate ova during the study and for at least 4 weeks after the last dose of lenalidomide. All women must not breastfeed while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

Prior to starting lenalidomide, 2 negative pregnancy tests are required. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide.

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

A man who is sexually active with a pregnant woman or a woman of childbearing potential must always use a latex or synthetic condom during the study and for at least 4 weeks after discontinuing lenalidomide (even if he has undergone a successful vasectomy). All men must not donate semen or sperm during the study, during dose interruptions, or for 3 months after the last dose of any study drug.

Because of the embryo-fetal risk of lenalidomide, all subjects must adhere to the local lenalidomide REMS program (when lenalidomide is supplied locally), or the Lenalidomide Global Pregnancy Prevention Plan provided in Attachment 14 (when lenalidomide is supplied centrally and no local lenalidomide REMS program exists).

Subjects must not donate blood during therapy, during dose interruptions, and for at least 4 weeks following discontinuation of lenalidomide.

For Carfilzomib studies

1. Women of childbearing potential should be advised to avoid becoming pregnant while being treated with carfilzomib. Given that carfilzomib was clastogenic in the in vitro chromosomal aberration test in peripheral blood lymphocytes, as a precaution, women of childbearing potential and/or their male partners should use highly effective contraception methods or abstain from sexual activity during treatment and for 30 days after treatment with carfilzomib and for 3 months after cessation of daratumumab treatment.
2. 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 1 additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). It cannot be excluded that the efficacy of oral contraceptives may be reduced during carfilzomib treatment. In addition, due to an increased risk of venous thromboembolic events associated with carfilzomib, females should avoid the use of hormonal contraceptives that are associated with a risk of thrombosis during treatment with carfilzomib. Female subjects 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 non-hormonal method of highly effective contraception. Contraception must begin 4 weeks prior to dosing. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy.
3. Women of childbearing potential must have a negative urine or serum pregnancy test at screening within 14 days prior to randomization.
4. 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 month after receiving the last dose of carfilzomib.
5. Male subjects of reproductive potential who are sexually active with females of reproductive potential or pregnant must always use a latex or synthetic condom during the study and for 3 months after discontinuing study treatment (even after a successful vasectomy).
6. Male subjects of reproductive potential must not donate semen or sperm during the study, during dose interruptions, or for 3 months after the last dose of any study drug.

Attachment 14: Lenalidomide Global Pregnancy Prevention Plan

Where lenalidomide is supplied locally, subjects must adhere to the local lenalidomide REMS program. Where lenalidomide is supplied centrally and no local lenalidomide REMS program exists, then subjects must adhere to the lenalidomide Global Pregnancy Prevention Plan provided in this attachment.

Within this attachment only, use of the phrase "study drug" refers to lenalidomide.

1.1 Pregnancy Prevention Risk Management Plans

1.1.1 Lenalidomide Pregnancy Prevention Risk Management Plan

1.1.1.1 Lenalidomide Pregnancy Risk Minimisation Plan for Celgene Clinical Trials

This attachment applies to all subjects receiving lenalidomide therapy. The following Pregnancy Risk Minimisation Plan documents are included:

1) Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods (Section 1.1.1.2);
2) Lenalidomide Education and Counseling Guidance Document (Section 1.1.1.3);
3) Lenalidomide Information Sheet (Section 1.1.1.4).

1. The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 1.1.1.2) provides the following information:
   - Potential risks to the fetus associated with lenalidomide exposure
   - Definition of Female of Childbearing Potential
   - Pregnancy testing requirements for subjects receiving Lenalidomide who are females of childbearing potential
   - Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving Lenalidomide in the study
   - Requirements for counseling of all study subjects receiving Lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide
2. The Lenalidomide Education and Counseling Guidance Document (Section 1.1.1.3) must be completed and signed by either a trained counselor or the Investigator at the participating clinical center prior to each dispensing of lenalidomide study treatment. A copy of this document must be maintained in the subject records.
3. The Lenalidomide Information Sheet (Section 1.1.1.4) will be given to each subject receiving lenalidomide study therapy. The subject must read this document prior to starting lenalidomide study treatment and each time they receive a new supply of study drug.

1.1.1.2 Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods)

Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Counseling

For a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (ie, all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol (Section 1.1.1.2)
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

The investigator must ensure that for females of childbearing potential:

- Complies with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, lenalidomide is contraindicated unless all of the following are met (ie, all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

Traces of lenalidomide have been found in semen. Male subjects taking lenalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) dose interruptions; and 4) for at least 28 days after study treatment discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in subjects with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a subject is currently using combined oral contraception the subject should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female Subjects:

FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10 to 14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The subject may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Subjects:

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Subjects:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a study subject, study drug must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Subjects:

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study subject during study participation, the investigator must be notified immediately.

Additional precautions

- Subjects should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.

- Female subjects should not donate blood during therapy, during dose interruptions, and for at least 28 days following discontinuation of study drug.
- Male subjects should not donate blood, semen or sperm during therapy, during dose-interruptions, or for at least 28 days following discontinuation of study drug.
- Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.

1.1.1.3 Lenalidomide Education and Counseling Guidance Document

To be completed prior to each dispensing of study drug.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (mm/dd/yyyy)

(Check the appropriate box to indicate risk category)

Female: □

If female, check one:

- □ FCBP (Female of childbearing potential): sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)
- □ NOT FCBP

Male: □

Do Not Dispense study drug if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual contact) [at least 28 days prior to therapy, during therapy and during dose interruption].**

FCBP:

1. I verified that the required pregnancy tests performed are negative.
2. I counseled FCBP regarding the following:
   - Potential risk of fetal exposure to lenalidomide: If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. The teratogenic potential of lenalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking lenalidomide.

- Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to therapy, during therapy, during dose interruption and 28 days after discontinuation of study drug].
- That even if she has amenorrhea, she must comply with advice on contraception
- Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
  - Highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants)
    - Tubal ligation
    - Partner's vasectomy
  - Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical Cap
- Pregnancy tests before and during treatment, even if the subject agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10 to 14 days and the second within 24 hours of the start of study drug.
- Frequency of pregnancy tests to be done:
  - Every week during the first 28 days of this study and a pregnancy test every 28 days during the subject's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
  - If the subject missed a period or has unusual menstrual bleeding.
  - When the subject is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.
- Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug, during dose interruptions, and for 28 days after stopping study drug.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
- Do not break, chew, or open study drug capsules.

- Return unused study drug to the study doctor.

3. Provide Lenalidomide Information Sheet to the subject.

FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):

1. I counseled the female NOT of child bearing potential regarding the following:
   - Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP)
   - NEVER share study drug with anyone else.
   - Do not donate blood while taking study drug, during dose interruptions, and for 28 days after stopping study drug.
   - Do not break, chew, or open study drug capsules
   - Return unused study drug capsules to the study doctor.
2. Provide Lenalidomide Information Sheet to the subject.

MALE:

1. I counseled the Male subject regarding the following:
   - Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP).
   - To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 28 days after stopping study drug.
   - Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant.
   - NEVER share study drug with anyone else.
   - Do not donate blood, semen or sperm while taking study drug, during dose interruptions, and for 28 days after stopping study drug.
   - Do not break, chew, or open study drug capsules.
   - Return unused study drug capsules to the study doctor.
2. Provide Lenalidomide Information Sheet to the subject.

Investigator/Counselor Name (Print): _____

(circle applicable)

Investigator/Counselor Signature: _____ Date: _____/_____/_____

(circle applicable)

Maintain a copy of the Education and Counseling Guidance Document in the subject records.

1.1.1.4 Lenalidomide Information Sheet

FOR SUBJECTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Lenalidomide Information Sheet before you start taking study drug and each time you get a new supply. This Lenalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about lenalidomide?

1. **Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Lenalidomide has not been tested in pregnant women but may also cause birth defects. Findings from a monkey study indicate that lenalidomide caused birth defects in the offspring of female monkeys who received the drug during pregnancy**.**

   If you are a female who is able to become pregnant:

   - **Do not take study drug if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting study drug
     - while taking study drug
     - during dose interruptions of study drug
     - for 28 days after stopping study drug
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days and again 24 hours prior to the first dose of study drug
     - weekly for the first 28 days
     - every 28 days after the first month or every 14 days if you have irregular menstrual periods
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of study drug (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking study drug if you become pregnant during treatment**
     - If you suspect you are pregnant at any time during the study, you must stop study drug immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation
   - **Do not breastfeed while taking study drug**
   - The study doctor will be able to advise you where to get additional advice on contraception.

   If you are a female not of childbearing potential:

   In order to ensure that an unborn baby is not exposed to lenalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

Lenalidomide is detected in trace quantities in human semen. The risk to the foetus in females of child bearing potential whose male partner is receiving lenalidomide is unknown at this time.

- Male subjects (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking study drug
  - During dose interruptions of study drug
  - For 28 days after you stop taking study drug
- **Male subjects should not donate sperm or semen** while taking study drug and for 28 days after stopping study drug.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they get pregnant.**

2. **Restrictions in sharing study drug and donating blood:**
   - **Do not share study drug with other people. It must be kept out of the reach of children and should never be given to any other person.**
   - **Do not donate blood** while you take study drug, during dose interruptions, and for 28 days after stopping study drug.
   - **Do not break, chew, or open study drug capsules.**
   - You will get no more than a 28-day supply of study drug at one time.
   - Return unused study drug capsules to your study doctor.

   Additional information is provided in the informed consent form and you can ask your study doctor for more information.

Attachment 15: Continuation of Treatment After Clinical Cutoff for the Final Analysis (End of the Data Collection)

Protocol Amendment 5 will allow those subjects who are benefiting from study treatment to continue receiving study drugs after the end of data collection until the study drugs are commercially available, available from another source (eg. via a dedicated long-term extension study), or until study completion. The following limited schedule is applicable.

Documentation of assessments performed is required only in the subject file/source notes.

Dosage and Administration

Daratumumab will be administered according to the regimen established prior to Amendment 5 (see Section 6 [Dosage and Administration]).

Treatment Period

Once the sponsor has notified investigators that the clinical cutoff for the final analysis has been achieved (end of the data collection), subjects may continue treatment with daratumumab until PD per investigator evaluation, unacceptable toxicity, withdrawal of consent, the investigator decides to stop treatment, or the start of subsequent anticancer therapy. Post-treatment follow-up is not applicable for subjects who discontinue study treatment in this period, except for HBV DNA testing as described below.

Efficacy Evaluations

Investigators should monitor and assess subjects for response to treatment or disease progression according to local institutional practice and make decisions if treatment should be continued based on benefit /risk evaluation. The assessments and outcome should be entered in the subject file/source notes.

Safety Evaluations

Once the data collection has ended, local hematology laboratory assessments, chemistry laboratory assessments, and assessment of vital signs should still be performed on Day 1 of each dosing cycle for consistency with previous cycles and to guide safe use of study treatment. For patients in D-Kd cohort transthoracic echocardiogram should still be performed every 6 cycles. These local results do not need to be reported to the sponsor.

Safety Reporting

Once the data collection has ended, serious adverse events that occur while the subject is receiving study drug and within 30 days after the last dose of study drug will be collected and reported to the sponsor's global medical safety database only via the same serious adverse event reporting process used over the course of the study (see Section 12.3.2 [Serious Adverse Events]). Serious adverse events should also be documented in the subject file/source notes.

Pregnancy reporting should continue as described in Section 12.3.3 [Pregnancy]. The pregnancy should be documented in the subject file/source notes.

HBV DNA Tests

Subjects who are positive for anti-HBc or anti-HBs will undergo testing for HBV DNA by PCR every 12 weeks (±1 month) after entering this treatment period. Testing will continue for 6 months after the last dose of study treatment. Subjects with serologic findings suggestive of HBV vaccination (anti-HBs

positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV by PCR. Results of the HBC-DNA tests should be documented in the subject's file.

Sample Collection and Handling

There are no PK, immunogenicity, or biomarker assessments during this treatment period, and any sample collection or test for safety or disease evaluation should comply with standard local institution practice.

Case Report Form Completion

No data will be collected in the eCRF during this treatment period.

Source Documentation

At a minimum, the type and level of detail of source data collected should be consistent with that commonly recorded at the site as a basis for standard medical care. This should include subject identification and study identification, study discussion, documentation of the informed consent process including the date, dates of visits, drug dispensing/return records, and study drug administration information.

INVESTIGATOR AGREEMENT

JNJ-54767414 (daratumumab)
Clinical Protocol 54767414MMY2040 Amendment 5

INVESTIGATOR AGREEMENT

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

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, 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): Ming Qi, MD, PhD.

Institution: Janssen Research & Development

Signature: MING QI Date: _____
(Day Month Year)

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

Approved, Date: 30 September 2020

Approved, Date: 30 September 2020