Janssen Research & Development *

Clinical Protocol

A Randomized Study of Daratumumab Plus Lenalidomide Versus Lenalidomide Alone as Maintenance Treatment in Patients with Newly Diagnosed Multiple Myeloma Who Are Minimal Residual Disease Positive After Frontline Autologous Stem Cell Transplant

AURIGA

Protocol 54767414MMY3021; Phase 3
Amendment 4

DARZALEX® (daratumumab)

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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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DOCUMENT HISTORY	
Document	**Date**
Amendment 4	12 August 2024
Amendment 3	24 June 2021
Amendment 2	08 July 2020
Amendment 1	09 December 2019
Original Protocol	13 February 2019

Amendment 4 (12 August 2024)

Overall Rationale for the Amendment: Protocol clarification and revision to allow for additional IMWG response assessments per the investigator during Follow-up visits after study treatment completion.

The changes made to the clinical protocol 54767414MMY3021 as part of Protocol Amendment 4 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Attachment 4: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
Time And Event Schedule – Part 1: Overall Study Procedures	Revised the time and events schedule to include IMWG response evaluation per investigator's assessments during study conduct and for follow-up visits.	To clarify when response assessments need to be performed.
6.2.1 Preparation and Administration 7 Study Treatment(s) Compliance 14.3 Preparation, Handling, and Storage	Updated language to "…Commercial Prescribing Instruction for drug preparation and administration…"	Investigational Product Preparation Instructions are no longer applicable due to a shift in the daratumumab commercial supply.
9.1 Study Procedures	Revised language to include the bolded language, "Every effort should be made to keep patients on the study schedule as planned from C1D1. At each visit, **whether in-person or via telemedicine,** study assessments should be completed before the administration of study treatment. **Daratumumab administration and study-specific tests/procedures must be completed by study staff**"	To clarify that study visits during study conduct can be in-person or conducted via telemedicine.
9.3.1 Response	Added language to clarify that investigator assessment of IMWG response after completion or premature discontinuation of study treatment is to be performed based on local laboratory results.	To clarify that local laboratory results will be utilized for IMWG assessments during Follow-up visits after completion or premature discontinuation of study treatment.

SYNOPSIS

STUDY TITLE

A Randomized Study of Daratumumab Plus Lenalidomide Versus Lenalidomide Alone as Maintenance Treatment in Patients with Newly Diagnosed Multiple Myeloma Who Are Minimal Residual Disease Positive After Frontline Autologous Stem Cell Transplant

DARATUMUMAB MAINTENANCE TREATMENT

Daratumumab (JNJ-54767414) is a human immunoglobulin G1 kappa monoclonal antibody that binds with high affinity to a unique epitope on CD38. The addition of daratumumab to bortezomib and dexamethasone or to lenalidomide and dexamethasone in the CASTOR and POLLUX studies, respectively, tripled the minimal residual disease (MRD) negative rate in patients with relapsed multiple myeloma, and patients who attained MRD negativity had significantly longer progression-free survival (PFS) than patients who remained positive. Similarly, in newly diagnosed myeloma patients, addition of daratumumab to standard of care regimens such as bortezomib plus melphalan and prednisone, bortezomib plus thalidomide and dexamethasone, as well as lenalidomide and dexamethasone, improved the MRD negativity rate and PFS significantly, as observed in the ALCYONE, CASSIOPEIA, and MAIA studies, respectively. Maintenance therapy with lenalidomide is the standard of care following frontline autologous stem cell transplant (ASCT) for multiple myeloma. Attainment of MRD negativity following ASCT and maintenance therapy has been shown to improve long-term outcomes. However, lenalidomide alone may not be sufficient to convert MRD positive patients post-transplant to MRD negativity. Therefore, to improve the likelihood of converting patients to MRD negativity, addition of subcutaneous (SC) daratumumab to lenalidomide maintenance treatment will be evaluated in Study MMY3021. We expect that the benefits of addition of SC daratumumab to lenalidomide, as maintenance treatment, will outweigh the risks, even among patients who may achieve a complete response (CR) or better after transplant. Prolonged administration of daratumumab in conjunction with lenalidomide does not result in an increased total risk of adverse events (AEs). In the MAIA study of IV daratumumab and Rd versus Rd alone in newly diagnosed patients with myeloma, the incidence of serious treatment-emergent (TE) AEs was similar in both treatment groups (62.9% in the DRd group and 62.7% in the Rd group). Of the most frequently reported (>10%) Grade 3 or 4 adverse events, higher rates of neutropenia (DRd: 50.0%; Rd: 35.3%), lymphopenia (DRd: 15.1%; Rd: 10.7%), leukopenia (DRd: 11.0%; Rd: 4.9%), and pneumonia (DRd: 13.7%; Rd: 7.9%) were observed in the DRd group, while Grade 3 or 4 anemia occurred more frequently in the Rd group (DRd: 11.8%; Rd: 19.7%). Although Grade 4 TEAEs were reported in a higher percentage of patients in the DRd group compared with the Rd group, fewer patients in the DRd group (7.1%) discontinued study treatment due to a TEAE compared with the Rd group (15.9%); however, the percentage of patients discontinuing lenalidomide was similar in both arms.

We hypothesize that the addition of daratumumab to lenalidomide maintenance therapy following frontline ASCT may increase the MRD negativity rate and improve clinical outcomes. The proposed study will evaluate improvement in MRD negativity rate in newly diagnosed multiple myeloma patients following maintenance treatment with SC daratumumab and lenalidomide in comparison with maintenance treatment with lenalidomide alone.

HYPOTHESIS

The addition of daratumumab to lenalidomide maintenance treatment in anti-CD38 treatment naïve, newly diagnosed multiple myeloma patients who are MRD positive following high-dose therapy (HDT) and ASCT will improve the conversion rate to MRD negativity.

OBJECTIVES AND ENDPOINTS

The objectives and endpoints of this study are shown below.

Objectives	Endpoints
Primary	
To evaluate conversion rate to MRD negativity following the addition of daratumumab to lenalidomide relative to lenalidomide alone, when administered as maintenance treatment to anti-CD38 treatment naïve patients with newly diagnosed multiple myeloma who are MRD positive as determined by NGS at screening, following HDT and ASCT.	The MRD conversion rate from baseline to 12 months after maintenance treatment (defined as the proportion of patients who have achieved MRD negative status [at 10^{-5}] by 12 months after maintenance treatment) as determined by NGS.
Secondary	
To further evaluate the efficacy, health-related quality of life, and safety of daratumumab in combination with lenalidomide as maintenance treatment for patients with newly diagnosed multiple myeloma.	**Major secondary endpoint:** • PFS, defined as the duration from the date of randomization to either PD or death, whichever occurs first. Disease progression will be determined according to IMWG 2016 criteria. For patients who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy. **Other secondary endpoints:** • The overall MRD negative conversion rate at any time after the date of randomization. • Durable MRD negativity rate, defined as the proportion of patients who have achieved MRD negative status (at 10^{-5}) in 2 bone marrow aspirate examinations that are a minimum of 1 year apart, without any examination showing MRD positive status in between assessments. • Response rates by IMWG 2016 criteria including rate of CR and sCR, defined as the proportion of patients who achieve the respective responses prior to the first subsequent anti-myeloma therapy in accordance with the IMWG criteria, during or after the study treatment. • OS, measured from the date of randomization to the date of the patient's death due to any cause. If the patient is alive and vital status is unknown, then the patient's data will be censored at the date the patient was last known to be alive. • Duration of CR, calculated from the date of initial documentation of a response of CR or sCR to the date of first documented evidence of PD (as defined in the IMWG criteria), or death due to PD, whichever occurs first. • Change in HRQoL based on the PROs utilized in this study. • Safety/Tolerability.

Note: Exploratory objectives, endpoints, and analysis of the exploratory endpoints will be detailed in the SAP.

Key: ASCT = autologous stem cell transplant; CR = complete response; HRQoL = health-related quality of life; HDT = high-dose therapy; IMWG = International Myeloma Working Group; MRD = minimal residual disease; NGS = next generation sequencing; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PRO = patient-reported outcome; SAP = Statistical Analysis Plan; sCR = stringent complete response.

OVERVIEW OF STUDY DESIGN

This is a Phase 3, randomized, open-label, active-controlled, multicenter study to be conducted at sites in the United States (US) and Canada to primarily evaluate the conversion rate to MRD negativity following 12 months of maintenance treatment with SC daratumumab in combination with lenalidomide relative to treatment with lenalidomide alone in patients with newly diagnosed multiple myeloma who have received a minimum of 4 cycles of induction, have undergone HDT and ASCT within 12 months of the start of induction therapy, are within 6 months of ASCT on the date of randomization, have very good partial response or better, are MRD positive at the time of screening, and are anti-CD38 treatment naïve.

The study includes a Screening Period; a Maintenance Phase; an End of Treatment (EOT) Visit; and a Follow-up Phase as described below.

- Screening Period: Screening is to be conducted within 60 days prior to randomization; randomization must occur within 6 months of the transplant date. Eligible patients must have undergone HDT and a single ASCT within 12 months of the start of induction treatment and be MRD positive at the time of screening. Adaptive Biotechnologies' next generation sequencing (NGS)-based MRD assay will be used to assess MRD positivity during screening for enrollment and randomization of treatment. Residual bone marrow sample, if available, will be banked for future tests, if required. Note that, if results of post-ASCT NGS assay (ie, Adaptive Biotechnologies' NGS-based MRD assay) conducted previously as part of institutional standards are available at screening, these results are to be recorded in the electronic case report form (eCRF).

- Maintenance Phase: Comprised of up to thirty-six, 28-day cycles. Patients will be randomized to receive maintenance treatment with SC daratumumab in combination with lenalidomide or lenalidomide alone. Study treatment will continue until confirmed progressive disease (PD), unacceptable toxicity, withdrawal from study or the end of study maintenance phase.

- EOT Visit: An EOT visit is to be scheduled 30 days (± 7 days) after the last dose of study treatment(s) or, if a patient begins new therapy for multiple myeloma, as soon as possible prior to the start of next-line therapy.

- Follow-up Phase: After the EOT visit, patients will continue to be followed until the end of the study, every 6 months. The end of the study is defined as 36 months from the date of randomization of last patient.

Planned enrollment includes a total of 214 patients to be randomly allocated in a 1:1 ratio to one of the two treatment arms, with randomization stratified by cytogenetic risk (high versus standard/unknown).

PATIENT POPULATION

Key entry criteria include the following. A patient must:

1. Be 18 to 79 years of age,
2. Have newly diagnosed multiple myeloma with a history of a minimum of 4 cycles of induction therapy, have received HDT and ASCT within 12 months of the start of induction therapy, and be within 6 months of the date of ASCT at the time of randomization.

3. Have a very good partial response or better assessed per the International Myeloma Working Group (IMWG) 2016 criteria at the time of randomization.
4. Have archived bone marrow samples collected before induction treatment (ie, at diagnosis) or before transplant (eg, at the end of induction) or have existing results on the index MM clone based on Adaptive Biotechnologies' NGS-based MRD assay. Archived bone marrow samples will be used for calibration of myeloma clonal cells to facilitate assessment of the primary endpoint by NGS. Any one of the following archived bone marrow samples are required:
    - Greater than 1 mL viable frozen bone marrow aspirated aliquot (preferred) collected in an ethylenediaminetetraacetic acid tube, and stored at a temperature of −80°C, **or**
    - Non-decalcified diagnostic bone marrow aspirate clot sections (block or slides) for MRD assessment:
        - A Formalin fixed paraffin embedded (FFPE) block of bone marrow aspirate clot, or slides (preferably 5 slides, if available), 5 μm each, of non-decalcified bone marrow, **or**
        - Slides (preferably 5 slides, if available), bone marrow aspirate smear.
        - Please note: bone marrow core sections are not acceptable samples for analysis.
        - In exceptional circumstances when index myeloma clone cannot be identified from the archived bone marrow sample, a post-transplant sample can be used to identify myeloma clone with permission from the Sponsor.
    - If an existing result on index myeloma clone is available from Adaptive Biotechnologies' NGS-based MRD assay, conducted as part of institutional procedures, then archived bone marrow sample is not required as long as Adaptive Biotechnologies is able to retrieve historical results on the index myeloma clone from the clinical database.
5. Have residual disease as defined by detectable MRD by NGS (Adaptive Biotechnologies' NGS-based MRD assay). If this assay was conducted post ASCT as part of institutional procedures and MRD results are available during screening, then patients who were MRD positive at 10^{-5} based on existing NGS test result are also eligible to participate in the study (such patients will NOT be required to undergo MRD assessment by NGS again at the time of screening),
6. Be anti-CD38 treatment naïve.

DOSAGE AND ADMINISTRATION

The 2 treatment arms comprise of daratumumab in combination with lenalidomide or lenalidomide alone as follows (each treatment cycle will be 28 days, with a maximum duration of maintenance treatment of 36 cycles):

1. Daratumumab 1800 mg administered by SC injection:
    - Weekly during C1 and C2,
    - Every 2 weeks during C3 to C6, and
    - Every 4 weeks from C7 onwards until confirmed PD, unacceptable toxicity, or until end of study treatment.
2. Lenalidomide 10 mg PO:
    - Days 1 to 28 (continuously) of each 28-day cycle until confirmed PD, unacceptable toxicity, or until end of study treatment. If a patient experiences toxicity to lenalidomide, dose and/or schedule may be modified per institutional standard.

- After 3 cycles of maintenance therapy, if well tolerated, the lenalidomide dose may be increased to 15 mg daily, at the discretion of the investigator.

STUDY EVALUATIONS

Study evaluations will include the following:

- Standard baseline screening evaluations for this patient population, including assessment of MRD status by NGS assay (Adaptive Biotechnologies' NGS-based MRD assay), and treatments to be administered
- Calibration by NGS on archived bone marrow samples collected before induction treatment or before transplant.
- Efficacy: MRD assessment by NGS at 12, 18, 24, and 36 months during maintenance treatment, myeloma proteins, bone marrow examinations, skeletal surveys, and extramedullary soft tissue plasmacytomas. Disease status will be assessed in accordance with IMWG 2016 response criteria.
- Patient-reported outcomes (PROs): European Organization for Research and Treatment of Cancer Quality of Life Questionnaires-C30 (EORTC QLQ-C30) and -Multiple Myeloma Module (EORTC QLQ-MY20), and the European Quality of Life Five Dimensions Questionnaire-5-level (EQ-5D-5L) scale (questionnaire).
- Safety/tolerability: Adverse events, clinical laboratory evaluations (to include pregnancy screening), vital signs, and Eastern Cooperative Oncology Group (ECOG) performance status.

In addition, patients will be followed for onset of other malignancy, next-line therapy, including date of PD on next-line therapy, and survival.

STATISTICAL METHODS

Datasets for Analysis

- Intent-to-treat Population: Includes all randomized patients.
- Safety Population: Includes all treated patients who receive at least 1 dose of randomized therapy.

Sample Size Determination

Based on previous reports of MRD negativity rate in lenalidomide-treated myeloma patients, the anticipated MRD (at 10^{-5}) negativity conversion rate is estimated to be 20% for patients treated with lenalidomide alone following post ASCT. Assuming a 20% absolute increase in MRD negativity rate (40% daratumumab plus lenalidomide versus 20% lenalidomide alone) by the end of 12-month maintenance treatment, a sample size of 214 patients (ie, 107 patients per treatment group at a 1:1 randomization) will be needed to achieve at least 85% power to detect such a treatment difference at a 2-sided alpha of 0.05 using continuity corrected chi-squared test.

Statistical Methods

Data will be summarized using descriptive statistics as appropriate, ie, continuous variables will be summarized using mean, standard deviation, and range. Categorical variables will be summarized using frequency tables. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries. All statistical testing will be conducted at 2-sided alpha level of 0.05 without multiplicity

adjustments. Response to study treatment and PD will be evaluated by a validated computer algorithm based on IMWG 2016 criteria.

Primary Endpoint Analysis

The primary endpoint will be compared between the 2 treatment groups in the intent-to-treat population using the stratified Cochran Mantel-Haenszel test with baseline cytogenetic risk (high versus standard/unknown) as stratification factor. A Mantel-Haenszel odds ratio along with its 2-sided 95% confidence intervals (CIs) will be calculated.

The primary analysis will be performed after all randomized patients have completed 12 months of maintenance treatment, have disease progression, died, or have been discontinued from study treatment by this time point. Afterwards, an annual analysis will be performed to update secondary endpoints and safety. A final analysis will occur at the end of study ie, 36 months from the date of randomization of last patient.

Secondary Endpoints and Analysis

- **PFS, OS, MRD, and clinical response:**

Time-to-event secondary endpoints including PFS and OS will be analyzed using a stratified log-rank test for the comparison of the distribution between the 2 treatment groups. The Kaplan-Meier method will be used to estimate the distribution for each treatment. The treatment effect (hazard ratio) and its 2-sided 95% CIs are to be estimated using a stratified Cox regression model. The stratification factor is baseline cytogenetic risk (high versus standard/unknown).

The overall MRD negativity rate at any time after randomization and MRD negative durability will be analyzed.

The binary secondary endpoints including rate of CR and stringent CR (sCR) will be analyzed similarly to MRD negativity rate.

A descriptive summary for duration of response will be provided. No statistical comparison will be made.

- **Patient-reported Outcomes**

The EORTC QLQ-C30 and EORTC QLQ-MY20 scale scores and EQ-5D-5L utility and visual analog scores will be descriptively summarized by treatment group at each time point. Within-group and between-group treatment effects of the PRO endpoints will be assessed by change from baseline using mixed models for repeated measures. Full details on meaningful change thresholds and statistical analyses will be provided in the Statistical Analysis Plan.

Safety Analyses

Safety data will be summarized using descriptive statistics and/or listed as appropriate; no inferential statistical analyses are planned for safety data.

TIME AND EVENT SCHEDULE – PART 1: OVERALL STUDY PROCEDURES

Procedure	Study Phases/Visits [a]				
	Screening	Maintenance (Cycles 1 – 36)	EOT	Follow-up (from the date of last study treatment until the end of study)	Notes
Informed consent	X	-	-	-	Must be signed before any study-related procedures are performed.
Eligibility criteria	X	-	-	-	For further details refer to Section 4.
Demographics and medical history	X	-	-	-	Clinically significant medical history, within the past 2 years, including surgery or procedures planned prior to randomization. History of malignancy at any time in the past prior to randomization should also be entered in the eCRF.
Height	X	-	-	-	-
Chest x-ray or full chest CT scan	X	As clinically indicated	-	-	Not required if performed as part of standard of care within 30 days prior to screening.

[a] Study Phases/Visits:

- Screening Phase: Screening is to be conducted within 60 days prior to randomization; randomization must be within 6 months of the transplant date. Patients must have undergone HDT and ASCT within 12 months of the start of induction therapy. Tandem transplants are not allowed.
- Maintenance Phase: Comprised of up to thirty-six, 28-day cycles. Patients are to receive study treatment (ie, daratumumab in combination with lenalidomide or lenalidomide alone), until confirmed PD, unacceptable toxicity, or the end of study treatment.

  Note: PD based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation performed at least 1 day later. Clinical judgment should prevail; however, repeat assessments within 3 weeks can be used as a general guideline.
- EOT Visit: An EOT visit is to be scheduled 30 days (± 7 days) after the last dose of study treatment(s) or, if a patient begins new therapy for the treatment of multiple myeloma, as soon as possible prior to the start of next-line therapy.

  In this study, in accordance with the IMWG 2016 criteria consensus recommendations, a line of subsequent therapy is defined as one or more cycles of a planned treatment program. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) because of PD, relapse, or toxicity.
- Follow-up Phase: After the EOT visit, patients will continue to be followed until the end of the study. The end of the study is defined as 36 months from the date of randomization of the last patient. If a patient has died, the date and cause of death will be collected and documented in the eCRF.
  - After confirmed PD or the start of a new treatment for multiple myeloma, patients will be contacted by telephone for follow-up information on secondary primary malignancy, next-line therapy, date of PD on next-line therapy, and/or survival (all patients). Written documentation of information obtained via telephone call must be available for review in source documents.

Procedure	Study Phases/Visits [a]				
	Screening	Maintenance (Cycles 1 – 36)	EOT	Follow-up (from the date of last study treatment until the end of study)	Notes
Spirometry test (ie, FEV1) (only in patients with known or suspected COPD or asthma)	X	As clinically indicated	-	-	Spirometry (ie, measurement of FEV1) is required at screening in patients with known or suspected COPD or asthma, unless if performed as part of standard of care anytime from 60 days prior to transplant up to randomization.
ECOG performance status	X	D1 of odd cycles (ie, C1, C3, C5, C7, and so on)	X	-	ECOG performance status assessments should be obtained prior to any other study procedures planned for the same day whenever possible.
12-Lead ECG	X	As clinically indicated	-	-	-
Physical examination	X	Symptom and disease directed exam as clinically indicated	-	-	During screening, a complete physical examination is to be conducted with measurement of height. Thereafter, only a symptom and disease directed physical examination is required as clinically indicated.
Weight	X	On C1D1	-	-	-
Vital signs	X	• Lenalidomide only arm: − D1 of odd cycles (ie, C1, C3, C5, C7, and so on). • Daratumumab + lenalidomide arm: − C1D1: Up to 30 minutes before administration; at end of administration; and at 0.5 and 1 hour (+/- 5 minutes) after end of administration. − C3 onwards: Immediately before and at the end of daratumumab administration on D1 of odd cycles (ie, C3D1 C5D1, C7D1, etc.	-	-	To include pulse, temperature, and blood pressure measured in a sitting position after approximately 5 minutes of rest

Procedure	Study Phases/Visits [a]				Notes
	Screening	Maintenance (Cycles 1 – 36)	EOT	Follow-up (from the date of last study treatment until the end of study)	
Blood type/indirect antiglobulin test (all patients)	X	-	-	-	A wallet card with the patient's blood type is to be provided to patients receiving daratumumab.
Safety and Laboratory Assessments (To be conducted at local laboratory)					
Pregnancy test (women of childbearing potential only)	X	←X→			• Serum β-hCG pregnancy test: – Within 10-14 days before the first dose on C1D1; – Within 24 hours before the first dose on C1D1; and – Each month thereafter beginning with C2. • Serum β-hCG or urine pregnancy test at the EOT visit. For patients remaining on lenalidomide after the EOT visit, testing must continue as per standard of care in the Follow-up Phase. Test may be repeated as clinically indicated.
Hematology and serum chemistry*	X	• Hematology: Lenalidomide only arm: D1 of every cycle, ie, C1D1, C2D1, C3D1, C4D1, C5D1, C6D1, C7D1, C8D1, C9D1, C10D1, C11D1, C12D1, etc, up to C36D1. Lenalidomide + Daratumumab Arm: D1, D8, D15, D22 of Cycles 1 and 2; D1, D15 of Cycles 3, 4, 5, and 6; D1 of every cycle from C7 onwards (ie, C7D1, C8D1, C9D1, C10D1, C11D1, C12D1, C13D1, C14D1, C15D1, C16D1, etc.) • Serum chemistry: Lenalidomide only arm: D1 of Cycles 1 through 6 (ie, C1D1, C2D1, C3D1,	X	-	On-site or accredited local laboratory must be used for hematology laboratory assessments. Results of local hematology tests must be evaluated before each study treatment administration to guide treatment decisions. Hematology panel to include: • Hgb, WBCs with absolute neutrophils and lymphocytes, RBCs, and platelet count. Serum chemistry panel to include: • Sodium, potassium, serum creatinine and creatinine clearance (CrCl) (must be calculated as described in Section 9.2.2), glucose, AST, ALT, total bilirubin, alkaline phosphatase, BUN, calcium and albumin-adjusted calcium (see Section 9.2.3), and albumin. Note that albumin and serum calcium corrected for albumin will also be obtained on C1D1 from the central laboratory as described below under Disease evaluations, laboratory evaluations.

Procedure	Study Phases/Visits [a]				
	Screening	Maintenance (Cycles 1 – 36)	EOT	Follow-up (from the date of last study treatment until the end of study)	Notes
		C4D1, C5D1, C6D1), and every 3rd cycle thereafter (ie, C9D1, C12D1, C15D1 C18D1, C21D1, C24D1, C27D1, C30D1, C33D1 and C36D1) Lenalidomide + Daratumumab arm: D1, D8, D15, D22 of Cycles 1-2; D1, D15 of Cycles 3-6; D1 of every 3rd cycle thereafter (ie, C9D1, C12D1, C15D1, C18D1, C21D1, C24D1, C27D1, C30D1, C33D1 and C36D1) On C1D1 and D1 of subsequent cycles, there is no need to repeat the tests if performed within the past 3 days. In addition, tests may be repeated as clinically indicated. Results must be evaluated before each daratumumab administration or beginning of new cycle of lenalidomide administration.			

Procedure	Study Phases/Visits [a]				Notes
	Screening	Maintenance (Cycles 1 – 36)	EOT	Follow-up (from the date of last study treatment until the end of study)	
HCV viral load (patients with prior history of HCV only)	X	Every 4th cycle, (ie, C4D1, C8D1, C12D1, C16D1, C20D1, C24D1, C28D1, C32D1, C36D1)	-	-	Patients who completed treatment for HCV at least 6 months prior to screening and have no detectable circulating HCV during screening, may participate in the study. Such patients will be required to undergo assessment for HCV reactivation as shown and will be withdrawn from the study if they test positive at any time during the study.
HBV serology	X	-	-	-	All patients will be tested for HBsAg, antibody to antiHBs, and antibody to antiHBc assessments performed locally prior to the first dose.
HBV-DNA testing	X	Q12W during treatment	X	Q12W for up to 6 months after the last dose of study treatment	Only required for patients (in all treatment arms) with serologic evidence of prior HBV infection (ie, positive Anti-HBs or positive Anti-HBc). Performed locally by PCR at screening, every 12 weeks during treatment, at EOT, and Q12W for up to 6 months after the last dose of study treatment. Not required at C1D1 if performed at screening. Patients with serologic findings suggestive of HBV vaccination (antiHBs 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.
Study Drug Randomization					
Randomization	-	X	-	-	To be performed up to 3 business days before the first dose of study treatment on C1D1. Patients will be randomly allocated in a 1:1 ratio to receive daratumumab in combination with lenalidomide or lenalidomide alone
Study Treatment Administration	-	←X→ (thirty-six, 28-day cycles) All patients treated with daratumumab will be observed for at least 6 hours after the end of the SC injection on C1D1. If	-	-	• Daratumumab 1800 mg SC: – Weekly during C1 and C2, – Every 2 weeks during C3-C6, and – Every 4 weeks from C7 onwards until confirmed PD, unacceptable toxicity, or until end of study treatment – Refer to Section 6.2.2 related to Pre-Administration and Post-

Procedure	Study Phases/Visits [a]				
	Screening	Maintenance (Cycles 1 – 36)	EOT	Follow-up (from the date of last study treatment until the end of study)	Notes
		deemed necessary by the investigator, patients may also be observed after subsequent injections.			Administration Medications for patients treated with daratumumab • Lenalidomide 10 mg PO: – Days 1 to 28 (continuously) of each 28-day cycle until confirmed PD, unacceptable toxicity, or until end of study treatment. If a patient experiences toxicity to lenalidomide, dose and/or schedule may be modified per institutional standard. – After 3 cycles of maintenance therapy, if well tolerated, the lenalidomide dose may be increased to 15 mg daily, at the discretion of the investigator. – The start of each cycle may occur ±3 days of the scheduled day to accommodate the schedule of the site or patient. Day 1 of subsequent cycles should be adjusted accordingly to maintain the intended cycle duration. Any delays ≥4 days of the scheduled day will need to be discussed with the sponsor.

Procedure		Study Phases/Visits [a] Screening	Maintenance (Cycles 1 – 36)	EOT	Follow-up (from the date of last study treatment until the end of study)	Notes
PROs						
EORTC QLQ-C30, EORTC QLQ-MY20, and EQ-5D-5L		-	At C1D1, and at the end of 6, 12, 24, and 36 months of treatment, (ie, C1D1, C7D1, C13D1, C25D1 and EOT). PROs should be administered at specified timepoints even after patient discontinues the study treatment.			PROs must be completed prior to conducting any other study-specific procedures. PROs should be completed at EOT if the patient discontinues early.
Disease evaluations						
Laboratory evaluations (tests to be conducted at the central laboratory)						
IMWG Response Evaluation per Investigator Assessment		X	D1 of every 3rd cycle (ie, every 3 months) beginning with C1D1, during the first Year (ie, C1D1, C3D1, C6D1, C9D1, C12D1), followed by every 6th cycle (ie, C18D1, C24D1, C30D1, C36D1) during Year 2 and Year 3	X	Every 6 months	IWMG Response Assessments during the Follow-up visits will be done for participants who have completed study treatment (36 cycles) or who have prematurely discontinued study treatment (due to reasons other than progressive disease). These assessments are to be performed based on local efficacy laboratory results. Assessments can stop after confirmation of Progressive Disease by the investigator. Determination of progressive disease, as well as other response assessments (VGPR, CR, or sCR) per investigator assessments are to follow the IMWG criteria for assessment of progressive disease and disease response, as outlined in Table 7.
β_2-microglobulin and LDH		X	-	X	-	-
Albumin and serum calcium corrected for albumin		-	C1D1 only	-	-	Refer to Section 9.2.3 for the calculations of serum calcium corrected for serum albumin.
Blood and 24-hour urine samples**	SPEP	X* (see Note in next column)	D1 of every 3rd cycle (ie, every 3 months) beginning with C1D1, during the first Year (ie, C1D1, C3D1, C6D1, C9D1, C12D1), followed by every 6th cycle (ie, C18D1, C24D1, C30D1, C36D1) during Year 2 and Year 3	X	-	Only 1 blood sample and 1, 24-hour urine sample are required to perform these tests. Note that • If daratumumab interference is suspected based on SPEP and IFE results, additional reflex IFE testing will be performed by the central laboratory. • All patient's samples will be tested for IgG, IgA, and IgM. Patients with IgE or IgD
	UPEP	X* (see Note in		X	-	

Procedure		Study Phases/Visits [a]				
		Screening	Maintenance (Cycles 1 – 36)	EOT	Follow-up (from the date of last study treatment until the end of study)	Notes
		next column)				myeloma will have samples tested for IgE or IgD. • Note that screening SPEP, UPEP, serum IFE, and urine IFE must be done within 21 days before randomization. • For patients with light chain multiple myeloma, both serum and urine immunofixation tests will be performed at D1 of every 3rd cycle (ie, every 3 months) during the first year, followed by every 6th cycle (ie, every 6 months) during Year 2 and Year 3.
	Serum QIg (IgG, IgA, IgM, IgD, and IgE)	X		X	-	
	Serum IFE	X* (see Note in next column)	D1 of every 3rd cycle (ie, every 3 months) beginning with C1D1, during the first Year (ie, C1D1, C3D1, C6D1, C9D1, C12D1), followed by every 6th cycle (ie, C18D1, C24D1, C30D1, C36D1) during Year 2 and Year 3 and whenever CR or sCR is suspected or maintained. Note: SPEP, UPEP, serum IFE, and urine IFE assays must be done during screening (21 days before C1D1) as well as on C1D1.	X	-	
	Urine IFE	X* (see Note in next column)		X	-	
	Serum FLC assay	X	D1 of every 3rd cycle, beginning with C1D1 (ie, C1D1, C3D1, C6D1, C9D1, C12D1, C15D1, C18D1, C21D1, C24D1, C27D1, C30D1, C33D1, C36D1) and whenever CR or sCR is suspected or maintained	X	-	

Procedure	Study Phases/Visits [a]				
	Screening	Maintenance (Cycles 1 – 36)	EOT	Follow-up (from the date of last study treatment until the end of study)	Notes
					Note: All attempts should be made to determine eligibility of the patient based on the central laboratory results of screening blood and urine M-protein measurements. During the COVID-19 pandemic, local laboratory results can be used to determine eligibility of the patient on a temporary basis and with Sponsor approval before laboratory results are collected. Local laboratory results should be reported in eCRF as an unscheduled visit. After the COVID-19 situation improves, all attempts should be made to determine eligibility of the patient based on the central laboratory results. In exceptional circumstances, the local laboratory results of blood and urine M-protein measurements may be used to determine eligibility, but only if the results are clearly (eg, 25% or more) above the thresholds for measurability. In such cases, central laboratory results are still required to be obtained to establish baseline values and confirm the results from the local laboratory. On C1D1 and D1 of subsequent cycles, there is no need to repeat the tests if performed within the past 3 days of scheduled visit. In addition, tests may be repeated as clinically indicated. Results must be evaluated before each daratumumab administration or beginning of new cycle of lenalidomide administration.
Bone marrow aspirate/biopsy (tests to be conducted at the central laboratory) (additional details in the Time and Events Schedule – Part 2)					
PC clonality assay (flow cytometry)	X	At the end of 12, 18, 24, and 36 months, (ie.,	X	-	• Bone marrow biopsy and/or aspirate, as indicated in the first column on the left, are required during screening and aspirate will be requested at time of PD, if feasible. For all
Morphology (aspirate and/or biopsy)	X·		X	-	

Procedure	Study Phases/Visits [a]				
	Screening	Maintenance (Cycles 1 – 36)	EOT	Follow-up (from the date of last study treatment until the end of study)	Notes
		C13D1, C19D1, C25D1 and at the EOT visit)			other assessments, only bone marrow aspirates are required. • PC clonality and morphology assessments to be conducted at the central laboratory. • Bone marrow aspirate collected within ±30 days of the scheduled visit during the maintenance phase is acceptable. • If a bone marrow biopsy was conducted up to 30 days prior to the start of screening AND a positive MRD result based on Adaptive Biotechnologies' NGS-based MRD assay is available, a repeat biopsy during screening is not required. In this situation, local PC clonality and morphology may be used.

Procedure	Study Phases/Visits [a]				
	Screening	Maintenance (Cycles 1 – 36)	EOT	Follow-up (from the date of last study treatment until the end of study)	Notes
Cytogenetics - FISH aspirate (performed centrally)	X	-	-	-	• Central cytogenetics assessment is not required during screening if local laboratory assessment included del(17p), t(4;14), and t(14;16) performed as part of standard of care at any time from the time of diagnosis of multiple myeloma to randomization. • Central FISH testing to include del(1p), gain of 1q, del(17p), t(11;14), t(4;14), t(14;16), and t(14;20). Any existing cytogenetics results from the local laboratory, if available, should be entered in the eCRF. Note: Stratification will be based on central laboratory results or local laboratory results, if available. For stratification purposes, if central cytogenetic results are not available (ie, due to technical reasons), or if central cytogenetic testing was not conducted due to availability of local cytogenetic results, then local cytogenetics may be used with the approval of the medical monitor. If central and local cytogenetic results are unavailable, the patient will be stratified with patients with standard cytogenetics.

MRD (aspirate) by NGS	X (NGS)	At the end of 12, 18, 24, and 36 months (NGS), (ie, C13D1, C19D1, C25D1 and at the EOT visit)	X	-	• **<u>During Screening</u>**: NGS assay (Adaptive Biotechnologies' NGS-based MRD assay) to be done on bone marrow aspirate collected during screening to determine eligibility for study entry. Residual samples, if available, will also be banked for future tests. Two sequential NGS assays will be done during screening. The first NGS assay will be conducted on archived bone marrow samples for calibration and identification of the index myeloma clone. Obtain archived bone marrow samples as described in Inclusion Criterion #4. If an existing result on index myeloma clone is available from Adaptive Biotechnologies' NGS-based MRD assay, conducted as part of institutional procedures, then archived bone marrow sample is not required as long as Adaptive Biotechnologies is able to retrieve historical results on the index myeloma clone from the clinical database. Following index clone calibration (or verification of existing index clone results from a previously conducted Adaptive Biotechnologies' NGS-based MRD assay), MRD will be assessed by NGS (Adaptive Biotechnologies' NGS-based MRD assay), using fresh bone marrow aspirate sample collected during screening. *Note: If Adaptive Biotechnologies' NGS-based MRD assay was conducted post-ASCT as part of institutional procedures and MRD results are available at screening, these results are to be recorded in the eCRF. Patients who are MRD positive at 10^{-5} based on an existing post-ASCT NGS assay conducted by Adaptive Biotechnologies, are eligible to participate. Such patients will not be required to undergo NGS based MRD assessment again during screening.* • **<u>After the start of study treatment (after C1D1):</u>**

Procedure	Study Phases/Visits [a]				
	Screening	Maintenance (Cycles 1 – 36)	EOT	Follow-up (from the date of last study treatment until the end of study)	Notes
					NGS is to be conducted at 12, 18, 24, and 36 months: During the bone marrow aspirate procedure, the first aspirate sample that is drawn will be sent to the central laboratory to determine MRD by NGS. All bone marrow aspirates to be sent to the central laboratory should be at least 3 mL. Additional bone marrow aspirate samples may be taken and used for local laboratory testing. Bone marrow aspirate collected within ±30 days of the scheduled visit during the maintenance phase is acceptable.
Assessment of lytic bone disease	X	As clinically indicated to document response or progression.	X	-	• The same methodology used during screening should be used throughout the study for comparison purposes • Not required during screening if performed as part of standard of care within 30 days before screening.
Extramedullary soft tissue plasmacytomas (in patients with history of extramedullary soft tissue plasmacytoma, physical or radiologic examination to be done as applicable)	X	As applicable, by physical exam every 4 weeks, or by radiologic exam every 12 weeks; to be conducted within 14 days before a scheduled visit.	-	-	
Other malignancy (other primary or recurrent malignancy diagnosed after initiation of study treatment)	-	X	X	Every 6 months	Data on other malignancy, survival status, date of PD on next line of therapy, next line of therapy along with start/stop date should be entered in eCRF at each study visit, as applicable, during the maintenance treatment and, every 6 months (24 weeks) during follow-up phase.
Next-line therapy and start/stop date	-	X	X		-
Survival	-	X	X		-
Date of PD on next-line therapy	-	X	X		-
Ongoing patient review					
Adverse events	Continuous from the time of signing of the informed consent form until 30 days (± 7 days) after last dose of any study treatment(s).				Note: If a patient is unable to return to the site for the EOT Visit, then he/she should be contacted to collect adverse events and

Procedure	Study Phases/Visits [a]				Notes
	Screening	Maintenance (Cycles 1 – 36)	EOT	Follow-up (from the date of last study treatment until the end of study)	
Concomitant medications					concomitant therapies that occur within 30 days (± 7 days) after the last dose of study treatment(s). See Section 8 and Section 11.1 for detailed instructions regarding concomitant medication use and reporting adverse events, respectively.

Key: β-hCG = beta hormone human chorionic gonadotropin; ALT = alanine aminotransferase; antiHBc = antibody to hepatitis B core antigen; antiHBs = antibody to hepatitis B surface antigen; ASCT = autologous stem cell transplant; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C = cycle (cycle number); COPD = chronic obstructive pulmonary disease; CR = complete response; CT = computed tomography; D = day (day number of cycle); ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; EORTC QLQ-MY20 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Multiple Myeloma Module EOT = end of treatment; EQ-5D-5L = EuroQoL Group-5D-5-level scale (questionnaire); FEV1 = forced expiratory volume (in 1 second); FISH = fluorescence in situ hybridization; FLC = free light chain; HBV = hepatitis B virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; Hgb = hemoglobin; IFE = immunofixation electrophoresis; Ig = immunoglobulin; IMWG = International Myeloma Working Group; LDH = lactic acid dehydrogenase; M-protein = myeloma protein; MRD = minimal residual disease; NGS = next generation sequencing; PC = plasma cell; PCR = polymerase chain reaction; PD = progressive disease; PRO = patient-reported outcome; RBC = red blood cell (count); SC = subcutaneous; SPEP = serum M-protein quantitation by electrophoresis; UPEP = urine M-protein quantitation by electrophoresis; VGPR = very good partial response; WBC = white blood cell (count). Note:

*Local and central laboratory tests should be conducted within 3 days of Day 1 of each lenalidomide cycle (control arm) OR within 3 days of each daratumumab administration.
**Urine sample collected and refrigerated up to 3 days prior to visit are acceptable for disease evaluation.

TIME AND EVENTS SCHEDULE – PART 2: DETAILS FOR BONE MARROW TESTING

Test to Perform	Lab	During Screening: Collect bone marrow aspirate and/or Biopsy	During the Maintenance Phase (Cycles 1 to 36): In addition, aspirate will be requested at time of PD if feasible.
PC clonality assay: Flow cytometry **Morphology (aspirate and/or biopsy)**	Central	PC clonality assay and morphology to be conducted during screening	At the end of 12, 24, and 36 months, (ie, C13D1, C25D1 and EOT visit). Bone marrow aspirate collected within ±30 days of the scheduled visit during the maintenance phase is acceptable.
Cytogenetics FISH aspirate to include del(1p), gain of 1q, del(17p), t(4;14), t(11;14), t(14;16), and t(14;20)	Central	• Central cytogenetics assessment is not required during screening if local laboratory assessment included del(17p), t(4;14) and t(14;16) performed as part of standard of care at any time from the time of diagnosis of multiple myeloma to randomization. • Central FISH testing to include del(1p), gain of 1q, del(17p), t(11;14), t(4;14), t(14;16), and t(14;20). Any existing cytogenetics results from the local laboratory, if available, should be entered in the eCRF. Note: Stratification will be based on central laboratory results or local laboratory results, if available. For stratification purposes, if central cytogenetic results are not available (ie, due to technical reasons), or if central cytogenetic testing was not conducted due to availability of local cytogenetic results, then local cytogenetics may be used with the approval of the medical monitor. If central and local cytogenetic results are not available, the patient will be assumed to have normal cytogenetics.	Cytogenetics not required
MRD (aspirate) by NGS	Central	MRD by (Adaptive Biotechnologies' NGS-based MRD assay) on bone marrow aspirate obtained during screening. Note that archived samples collected prior to induction therapy or prior to transplant will also be obtained as described in Inclusion Criterion #4 for calibration of MRD by NGS. If an existing result on index myeloma clone is available from Adaptive Biotechnologies' NGS-based MRD assay, conducted as part of institutional procedures, then archived bone marrow sample is not required as long as Adaptive Biotechnologies is able to retrieve historical results on the index myeloma clone from the clinical database. In addition, if Adaptive Biotechnologies' NGS-based MRD assay was conducted post ASCT as part of institutional procedures and MRD results are available at screening, then this information is to be recorded in the eCRF. Patients who are MRD positive at 10^{-5} based on an existing post-ASCT NGS assay conducted by Adaptive Biotechnologies, are eligible to participate. Such patients will not be required to undergo NGS based MRD assessment again during screening.	Bone marrow aspirate collected within ±30 days of the scheduled visit during the maintenance phase is acceptable. MRD by NGS to be conducted at the end of 12, 18, 24, and 36 months (NGS), (ie., C13D1, C19D1, C25D1 and EOT visit)

Key: ASCT = autologous stem cell transplant; C = cycle (cycle number); CR = complete response; D = day (day number of cycle); eCRF = electronic case report form; FISH = fluorescence in situ hybridization; Lab = laboratory; MRD = minimal residual disease; NGS = next generation sequencing; PC = plasma cell; PD = progressive disease; sCR = stringent complete response; VGPR = very good partial response.

ABBREVIATIONS

ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
antiHBc	antibody to hepatitis B core antigen
antiHBs	antibody to hepatitis B surface antigen
ASCT	autologous stem cell transplantation
C	Cycle
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COPD	chronic obstructive pulmonary disease
CR	complete response
CrCl	creatinine clearance
CSR	Clinical Study Report
CT	computed tomography
D(s)	Day(s)
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaires-C30
EORTC QLQ-MY20	European Organization for Research and Treatment of Cancer Quality of Life Questionnaires-Multiple Myeloma Module
EQ-5D-5L	European Quality of Life Five Dimensions Questionnaire-5-level
EOT	end of treatment
FEV1	forced expiratory volume in 1 second
FLC	free light chain
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDT	high-dose therapy
HR	hazard ratio
HRQoL	health-related quality of life
IAT	indirect antiglobulin test (also known as indirect Coombs test)
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IFE	immunofixation electrophoresis
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IRR	injection-related reactions
ISR	injection-site reactions
IV	intravenous(ly)
IWRS	interactive web response system
LMWH	low molecular weight heparin
mAb	monoclonal antibody
MFC	multiparametric flow cytometry
M-protein	myeloma protein
MDRD	Modification of Diet in Renal Disease
MRD	minimal residual disease
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NGF	next generation flow
NGS	next generation sequencing

OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PO	per os (by mouth; orally)
PQC	product quality complaint
PR	partial response
PRO	patient-reported outcome
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
rHuPH20	recombinant human hyaluronidase
SAC	Safety Assessment Committee
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
sCR	stringent complete response
SIPPM	Site Investigational Product Procedures Manual
SPE	serum protein electrophoresis
SUSAR	suspected unexpected serious adverse reactions
ULN	upper limit of normal
VGPR	very good partial response
VTE	venous thromboembolism

1. INTRODUCTION

Despite advances in treatment, multiple myeloma remains a challenging disease to cure. The addition of the anti-CD38 monoclonal antibody (mAb), daratumumab, to standard of care regimens has been associated with a 44% to 68% significant reduction in the risk of death or progression in multiple myeloma compared with standard of care, as observed in 5 randomized controlled studies: the POLLUX and CASTOR Phase 3 clinical studies in relapsed or refractory myeloma and the ALCYONE, CASSIOPEIA[16,29], and MAIA Phase 3 clinical studies in newly diagnosed myeloma. Recently, daratumumab was approved in combination with bortezomib, melphalan, and dexamethasone for frontline treatment of newly diagnosed multiple myeloma patients who are ineligible for transplant. Maintaining remission and improving the duration of response after successful induction, high-dose therapy (HDT) followed by autologous stem cell transplant (ASCT) and consolidation therapy are important goals in treating patients with newly diagnosed multiple myeloma.[1]

Despite these treatment modalities, most multiple myeloma patients relapse after ASCT. Conventional means of assessing response (ie, measurement of serum and urine M-proteins) are not sufficiently sensitive to measure low-levels of residual bone marrow disease or minimal residual disease (MRD), and the attainment of MRD negativity (ie, MRD is not detectable by highly sensitive next generation flow [NGF] cytometry of sequencing) is associated with improved long-term outcomes. Therefore, achievement of MRD negativity is evolving as an important clinical efficacy endpoint in multiple myeloma, particularly in the maintenance setting following frontline ASCT.

The addition of daratumumab to bortezomib and dexamethasone or lenalidomide and dexamethasone in the CASTOR and POLLUX studies, respectively, tripled the MRD negative rate in patients with relapsed multiple myeloma, and patients who attained MRD negativity had significantly longer progression-free survival (PFS) than patients who remained positive. Similarly, addition of daratumumab to standard of care regimens in newly diagnosed transplant ineligible myeloma patients tripled the MRD negative rate and significantly improved PFS in the ALCYONE, CASSIOPEIA, and MAIA Phase 3 clinical studies. In the CASSIOPEIA study[16,29], a higher rate of MRD negativity was observed in newly diagnosed transplant eligible patients treated with daratumumab based regimen versus standard of care treatment (64% vs. 44%, $p<0.0001$). Maintenance therapy with lenalidomide is standard of care following frontline ASCT for multiple myeloma. However, lenalidomide alone may not be sufficient to convert MRD positive patients post-transplant to MRD negativity, as it is expected that most patients would have previously been treated with lenalidomide as part of induction therapy. Attainment of MRD negativity following ASCT and maintenance therapy has been shown to improve long-term outcomes.[21,29] Therefore, to improve the likelihood of converting patients to MRD negativity, addition of SC daratumumab to lenalidomide maintenance treatment will be evaluated in Study MMY3021. We expect that the benefits of addition of SC daratumumab to lenalidomide, as maintenance treatment, will outweigh the risks, even among patients who may achieve a complete response (CR) or better after transplant. Prolonged administration of daratumumab in conjunction with lenalidomide does not result in an increased total risk of adverse event (AEs). In the MAIA study of IV daratumumab and Rd versus Rd alone in newly diagnosed patients with myeloma, the incidence of serious

treatment-emergent adverse events (TEAEs) was similar in both treatment groups (62.9% in the DRd group and 62.7% in the Rd group). Of the most frequently reported (>10%) Grade 3 or 4 adverse events, higher rates of neutropenia (DRd: 50.0%; Rd: 35.3%), lymphopenia (DRd: 15.1%; Rd: 10.7%), leukopenia (DRd: 11.0%; Rd: 4.9%), and pneumonia (DRd: 13.7%; Rd: 7.9%) were observed in the DRd group, while Grade 3 or 4 anemia occurred more frequently in the Rd group (DRd: 11.8%; Rd: 19.7%). Although Grade 4 TEAEs were reported in a higher percentage of patients in the DRd group compared with the Rd group, fewer patients in the DRd group (7.1%) discontinued study treatment due to a TEAE compared with the Rd group (15.9%); however, the percentage of patients discontinuing lenalidomide was similar in both arms.

The current study is being conducted to evaluate the MRD negativity conversion rate following the addition of daratumumab (compound number JNJ-54767414) to lenalidomide, when administered as maintenance treatment to patients with newly diagnosed multiple myeloma who have received a minimum of 4 cycles of induction therapy, have undergone HDT and ASCT within 12 months of the start of induction, are MRD positive at the time of screening, and have never been treated with an anti-CD38 antibody (ie, are anti-CD38 naïve). Further details on the overall rationale for the study, study design, assessments chosen for evaluation, and the potential risks and benefits are described in Section 3.2.

Throughout the protocol, the term “study treatment” refers to the treatments being administered for multiple myeloma and the term "sponsor" refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

The objectives and endpoints of this study are shown in Table 1.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate conversion rate to MRD negativity following the addition of daratumumab to lenalidomide relative to lenalidomide alone, when administered as maintenance treatment to anti-CD38 treatment naïve patients with newly diagnosed multiple myeloma who are MRD positive as determined by NGS at screening, following HDT and ASCT.	The MRD conversion rate from baseline to 12 months after maintenance treatment (defined as the proportion of patients who have achieved MRD negative status [at 10^{-5}] by 12 months after maintenance treatment) as determined by NGS.
Secondary	
To further evaluate the efficacy, health-related quality of life, and safety of daratumumab in combination with lenalidomide as maintenance treatment for patients with newly diagnosed multiple myeloma.	**Major secondary endpoint:** • Progression-free survival (PFS), defined as the duration from the date of randomization to either PD or death, whichever occurs first. Disease progression will be determined according to the IMWG 2016 criteria. For patients who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy. **Other secondary endpoints:** • The overall MRD negative conversion rate at any time after the date of randomization. • Durable MRD negativity rate, defined as the proportion of patients who have achieved MRD negative status (at 10^{-5}) in 2 bone marrow aspirate examinations that are a minimum of 1 year apart, without any examination showing MRD positive status in between assessments. • Response rates by IMWG 2016 criteria including rate of CR and sCR, defined as the proportion of patients who achieve the respective responses prior to the first subsequent anti-myeloma therapy in accordance with the IMWG criteria, during or after the study treatment. • Overall survival (OS), measured from the date of randomization to the date of the patient's death due to any cause. If the patient is alive and vital status is unknown, then the patient's data will be censored at the date the patient was last known to be alive. • Duration of CR, calculated from the date of initial documentation of a CR or sCR to the date of first documented evidence of PD (as defined in the IMWG criteria), or death due to PD, whichever occurs first. • Change in HRQoL based on the PROs utilized in this study. • Safety/Tolerability.

Note: Exploratory objectives, endpoints, and analysis of the exploratory endpoints will be detailed in the SAP.

Key: ASCT = autologous stem cell transplant; CR = complete response; HRQoL = health-related quality of life; HDT = high-dose therapy; IMWG = International Myeloma Working Group; MRD = minimal residual disease; NGS = next generation sequencing; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PRO = patient-reported outcomes; SAP = Statistical Analysis Plan; sCR = stringent complete response.

2.2. Hypothesis

The addition of daratumumab to lenalidomide maintenance treatment in anti-CD38 treatment naïve, newly diagnosed multiple myeloma patients who are MRD positive following HDT and ASCT will improve the conversion rate to MRD negativity.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a Phase 3, randomized, open-label, active-controlled, multicenter study to be conducted at sites in the United States (US) and Canada to primarily evaluate the MRD conversion rate following 12 months of maintenance treatment with SC daratumumab in combination with lenalidomide relative to lenalidomide alone in patients with newly diagnosed multiple myeloma who have received a minimum of 4 cycles of induction therapy, have undergone HDT and ASCT within 12 months of the start of induction, are within 6 months of the ASCT date at the time of randomization, are MRD positive at the time of screening, and are anti-CD38 treatment naïve.

The study includes a Screening Period; a Maintenance Phase comprised of thirty-six, 28-day cycles; an End of Treatment (EOT) Visit; and a Follow-up Phase as described in the Time and Events Schedule – Part 1 (see footnote a).

Planned enrollment includes a total of 214 patients to be randomly allocated in a 1:1 ratio to 1 of 2 treatment arms, with randomization stratified by cytogenetic risk (high versus standard/unknown).

For inclusion in the study, a patient must:

1. Be 18 to 79 years of age,
2. Have newly diagnosed multiple myeloma, with a history of a minimum of 4 cycles of induction therapy, have received HDT and ASCT within 12 months of the start of induction therapy, and are within 6 months of ASCT on the date of randomization,
3. Have a very good partial response (VGPR) or better assessed per International Myeloma Working Group (IMWG) 2016 criteria at the time of randomization,
4. Have archived bone marrow samples collected before induction treatment (ie, at diagnosis) or before transplant (eg, at the end of induction) or have existing results on the index MM clone based on Adaptive Biotechnologies' next generation sequencing (NGS)-based MRD assay. Archived bone marrow samples will be used for calibration of myeloma clonal cells to facilitate assessment of the primary endpoint by NGS. Any one of the following archived bone marrow samples are required:
    - Greater than 1 mL viable frozen bone marrow aspirated aliquot (preferred), collected in a ethylenediaminetetraacetic acid tube, and stored at a temperature of −80°C **or**
    - **Non-decalcified diagnostic** bone marrow aspirate clot sections (block or slides) for MRD assessment:

  - A Formalin fixed paraffin embedded (FFPE) block of bone marrow aspirate clot, or slides (preferably 5 slides, if available), 5 μm each, of non-decalcified bone marrow, **or**
  - Slides (preferably 5 slides, if available), bone marrow aspirate smear.
  - Please note, bone marrow core sections are not acceptable samples for analysis.
  - In exceptional circumstances when index myeloma clone cannot be identified from the archived bone marrow sample, a post-transplant sample can be used to identify myeloma clone with permission from the Sponsor.
- If an existing result on index myeloma clone is available from Adaptive Biotechnologies' NGS-based MRD assay, conducted as part of institutional procedures, then archived bone marrow sample is not required as long as Adaptive Biotechnologies is able to retrieve historical results on the index myeloma clone from the clinical database.

5. Have residual disease as defined by detectable MRD by NGS (Adaptive Biotechnologies' NGS-based MRD assay) at the time of screening. If this assay was conducted post ASCT as part of institutional procedures and MRD results are available during screening, then patients who were MRD positive at 10^{-5} based on the existing NGS test result are also eligible to participate in the study (such patients will NOT be required to undergo MRD assessment by NGS again at the time of screening),
6. Be anti-CD38 treatment naïve

   Refer to Section 4 for a complete list of entry criteria.

The 2 treatment arms comprise of daratumumab in combination with lenalidomide or lenalidomide alone as follows (each treatment cycle will be 28 days for a maximum duration of 36 cycles):

1. Daratumumab 1800 mg administered by subcutaneous (SC) injection:
   - Weekly during Cycle (C)1 and C2,
   - Every 2 weeks during C3 to C6, and
   - Every 4 weeks from C7 onwards until confirmed progressive disease (PD), unacceptable toxicity, or until end of study treatment
2. Lenalidomide 10 mg PO:
   - Days (D)1 to 28 (continuously) of each 28-day cycle until confirmed PD, unacceptable toxicity, or until end of study treatment. If a patient experiences toxicity to lenalidomide, dose and/or schedule may be modified per institutional standard.
   - After 3 cycles of maintenance therapy, if well tolerated, the lenalidomide dose may be increased to 15 mg daily, at the discretion of the investigator.

Study assessments include the following:

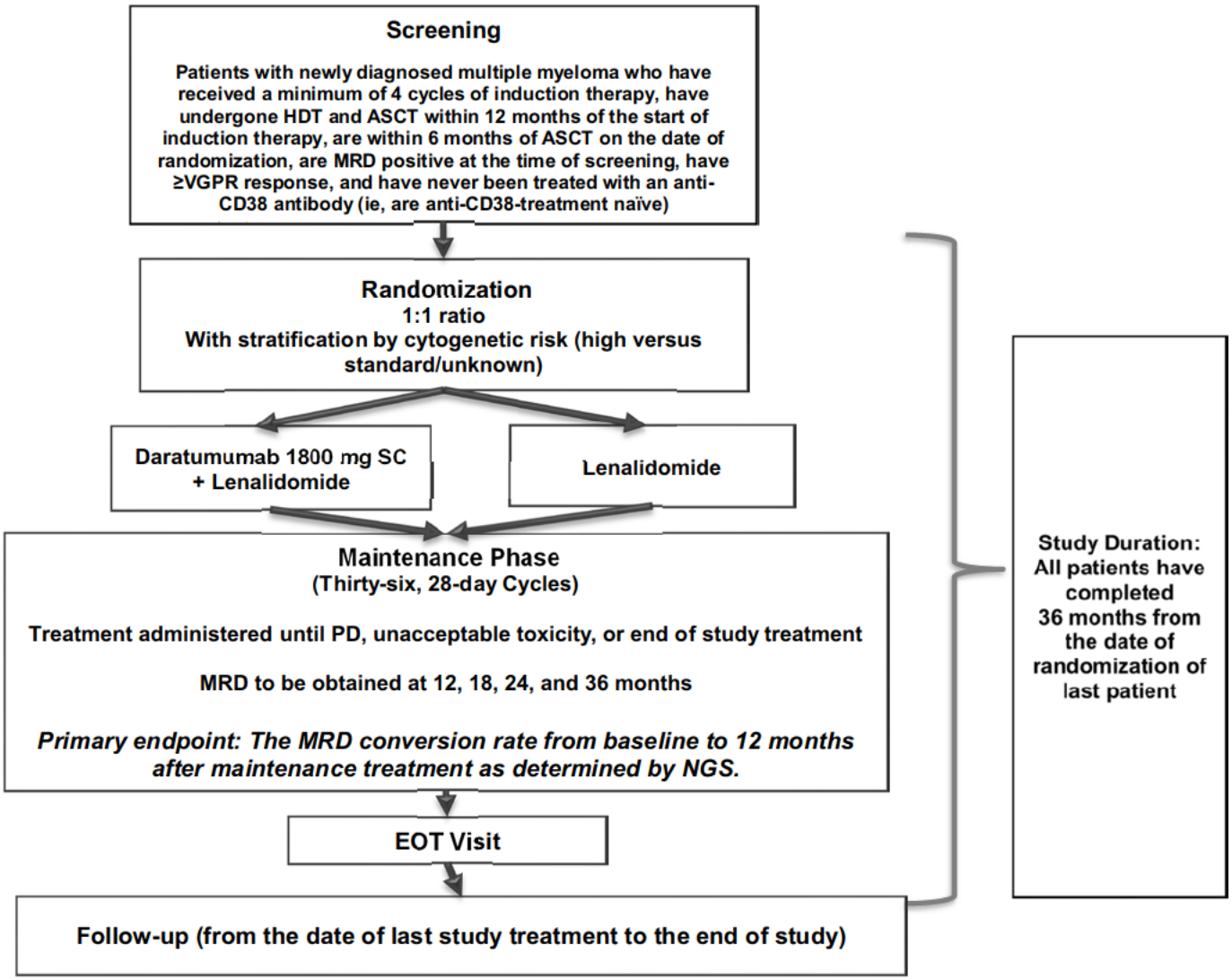
- Standard baseline screening evaluations for this patient population, including assessment of MRD status by NGS assay (Adaptive Biotechnologies' NGS-based MRD assay), and treatments to be administered.
- Calibration by NGS on archived bone marrow sample collected before induction treatment.

- Disease evaluations including MRD by NGS at the end of 12, 18, 24, and 36 months after the start of study treatment(s) (ie, after C1D1), myeloma proteins (M-proteins), bone marrow examinations, skeletal surveys, and extramedullary soft tissue plasmacytomas. Disease status will be assessed in accordance with IMWG 2016 response criteria.
- Patient-reported Outcomes (PROs), including the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires-C30 (EORTC QLQ-C30), European Organization for Research and Treatment of Cancer Quality of Life Questionnaires-Multiple Myeloma Module (EORTC QLQ-MY20), and European Quality of Life Five Dimensions Questionnaire-5-level (EQ-5D-5L).
- Safety/tolerability evaluated by AEs, clinical laboratory evaluations, vital signs, and Eastern Cooperative Oncology Group (ECOG) performance status.

In addition, patients will be followed for onset of other malignancy, next-line therapy, including date of PD on next-line therapy, and survival. Refer to the Time and Events Schedule – Part 1 for full details on study assessments to be performed.

The end of the study is defined as 36 months from the date of randomization of last patient. If a patient has died, the date and cause of death will be collected and documented in the electronic case report form (eCRF). A diagram of the study design is provided in Figure 1. An Independent Data Monitoring Committee will be commissioned for this study. Refer to Section 11.7 for details.

Figure 1: Schematic Overview of the Study



Abbreviations: ASCT = autologous stem cell transplant; EOT =end of treatment; HDT = high-dose therapy; MRD = minima residual disease; PD = progressive disease; NGS = next generation sequencing; SC = subcutaneous; VGPR = very good partial response.

3.2. Study Design Rationale

3.2.1. Overall Rationale for Study Design

Multiple myeloma, a malignant clonal disorder of plasma cells, is characterized by uncontrolled and progressive proliferation. Patients with multiple myeloma can produce a monoclonal paraprotein, otherwise known as a myeloma protein (M-protein), as well as a monoclonal free light chain (FLC), which is a fragment of immunoglobulin that is non-functional. The proliferation of myeloma cells causes displacement of the normal bone marrow. Normal immunoglobulin levels are compromised, leading to susceptibility to infections. Other frequently reported sequelae of multiple myeloma include hypercalcemia, renal insufficiency or failure, anemia, and neurological complications.

According to data from the National Cancer Institute, Surveillance, Epidemiology, and End Results Program in 2018, multiple myeloma accounted for 1.8% of all new cancer cases and 2.1% of all cancer deaths. In addition, there were approximately 30,770 new cases of multiple myeloma with approximately 12,770 deaths due to this disease in 2018. Based on data from 2008 to 2014, the 5-year survival rate is 50.7%.

Treatment choices for multiple myeloma have advanced in recent years and vary with age, performance status, comorbidity, aggressiveness of the disease, and related prognostic factors. The standard treatment approach for newly diagnosed patients who are considered eligible for HDT includes multiple phases of therapy: induction, HDT and ASCT, and consolidation and maintenance.

The current standard of care in the maintenance setting includes treatment with lenalidomide after ASCT, based on randomized Phase 3 studies showing improvement in clinical outcomes with the use of maintenance therapy[1,27] (see also the lenalidomide package insert). As of 2018, according to the National Cancer Comprehensive Network (NCCN), continuous treatment with lenalidomide is the preferred choice for maintenance treatment of multiple myeloma.[18] For the most comprehensive nonclinical and clinical information on lenalidomide refer to the most current package insert.

Lenalidomide is an immunomodulatory agent that is thought to mediate antimyeloma activity by 3 main mechanisms: 1) direct antitumor effect; 2) inhibition of the microenvironment support for tumor cells; and 3) an immunomodulatory role.[17] Direct tumor effect is described both as growth inhibition of myeloma cell lines and induction of apoptosis. The microenvironment support is affected by downregulation of cell adhesion molecules (eg, intercellular adhesion molecule), thus inhibiting stromal cell interaction with tumor cells, and inhibition of growth factors (eg, insulin growth factor 1 and vascular endothelial growth factor) induced by myeloma cell adhesion. Finally, lenalidomide exhibits immunomodulatory activity including inhibition of proinflammatory signaling molecules (cytokines) such as TNFα, IL-1β, and IL-6, the latter of which is a known growth factor for myeloma cells.[43]

Importantly, it has also been shown that lenalidomide causes upregulation of natural killer cells in myeloma[17] and enhances the effector cells of antibody-dependent cell-mediated cytotoxicity (ADCC), a known mechanism of action of daratumumab as demonstrated in preclinical studies.[41,42] This effect has also been demonstrated in patients during or just after lenalidomide treatment where peripheral blood mononuclear cells isolated from patients showed a significantly increased capacity to mediate daratumumab-dependent ADCC against multiple myeloma cells alone.[44] Additionally, the upregulation of CD38 by pomalidomide or lenalidomide can enhance the activity of anti-CD38 antibodies including daratumumab.[5]

Despite these treatment modalities, most multiple myeloma patients relapse after ASCT. However, improved depth of response, as measured by eradication of MRD, has been observed in multiple myeloma patients treated with a daratumumab-based combination therapy. For example, the addition of daratumumab to standard of care regimens has been associated with a 44% to 68% significant reduction in the risk of death or progression in multiple myeloma compared with

standard of care, as observed in 5 randomized controlled studies: the POLLUX and CASTOR Phase 3 clinical studies in relapsed or refractory myeloma and, the ALCYONE, CASSIOPEIA[16,29], and MAIA Phase 3 clinical studies in newly diagnosed myeloma. The addition of daratumumab to bortezomib and dexamethasone or lenalidomide and dexamethasone in the CASTOR and POLLUX studies, respectively, tripled the MRD negative rate in patients with relapsed multiple myeloma, compared with the control arm. In addition, patients who attained MRD negativity had significantly longer PFS than patients who remained MRD positive.[4,26] Similarly, addition of daratumumab to standard of care regimens in newly diagnosed transplant ineligible myeloma patients tripled the MRD negative rate in the ALCYONE, CASSIOPEIA[16,29], and MAIA Phase 3 clinical studies. Maintenance therapy with lenalidomide is standard of care following frontline ASCT for multiple myeloma. However, lenalidomide alone may not be sufficient to convert MRD positive patients post-transplant to MRD negativity, as it is expected that most patients would have previously been treated with lenalidomide as part of induction therapy. Attainment of MRD negativity following ASCT and maintenance therapy has been shown to improve long-term outcomes.[21,29] Therefore, to improve the likelihood of converting patients to MRD negativity, addition of SC daratumumab to lenalidomide maintenance treatment will be evaluated in Study MMY3021. We expect that the benefits of addition of SC daratumumab to lenalidomide, as maintenance treatment, will outweigh the risks, even among patients who may achieve a CR or better after transplant. Prolonged administration of daratumumab in conjunction with lenalidomide does not result in an increased total risk of AEs. In the MAIA study of IV daratumumab and Rd versus Rd alone in newly diagnosed patients with myeloma, the incidence of serious TEAEs was similar in both treatment groups (62.9% in the DRd group and 62.7% in the Rd group). Of the most frequently reported (>10%) Grade 3 or 4 adverse events, higher rates of neutropenia (DRd: 50.0%; Rd: 35.3%), lymphopenia (DRd: 15.1%; Rd: 10.7%), leukopenia (DRd: 11.0%; Rd: 4.9%) and pneumonia (DRd: 13.7%; Rd: 7.9%) were observed in the DRd group, while Grade 3 or 4 anemia occurred more frequently in the Rd group (DRd: 11.8%; Rd: 19.7%). Although Grade 4 TEAEs were reported in a higher percentage of patients in the DRd group compared with the Rd group, fewer patients in the DRd group (7.1%) discontinued study treatment due to a TEAE compared with the Rd group (15.9%); however, the percentage of patients discontinuing lenalidomide was similar in both arms.

The current study is being conducted to evaluate the MRD negativity rate following the addition of daratumumab to lenalidomide, when administered as maintenance treatment to patients with newly diagnosed multiple myeloma who have received a minimum of 4 cycles of induction therapy, have undergone HDT and ASCT within 12 months of the start of induction therapy, are within 6 months of ASCT on the date of randomization, are MRD positive at the time of screening, and have never been treated with an anti-CD38 antibody (ie, are anti-CD38 naïve).

3.2.2. Daratumumab

Daratumumab (JNJ-54767414) is a human immunoglobulin G1 kappa (IgG1κ) mAb that binds with high affinity to a unique epitope on CD38. It is a targeted immunotherapy that attacks tumor cells that overexpress CD38, a transmembrane glycoprotein, in a variety of hematological malignancies including multiple myeloma. Daratumumab induces lysis of CD38-expressing tumor cells, including multiple myeloma tumor cells that were freshly isolated from patients, by a wide

spectrum of mechanisms including complement-dependent cytotoxicity, ADCC, and antibody-dependent cellular phagocytosis, through activation of complement proteins, natural killer cells, and macrophages, respectively.[12,35] Furthermore, daratumumab has immunomodulatory properties, including inhibition of CD38 positive T regulatory cells and myeloid-derived suppressor cells and stimulation of helper and cytotoxic T cells.

3.2.2.1. Intravenous Daratumumab Administration

In the European Union (EU), daratumumab, administered as a 16 mg/kg intravenous (IV) infusion, is approved for the following indications:

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

In the US, daratumumab, administered as a 16 mg/kg IV infusion, is approved for the following indications:

- As monotherapy for the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy. including a proteasome inhibitor and an immunomodulatory agent or who are double refractory to a proteasome inhibitor and an immunomodulatory agent.
- In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.
- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for ASCT and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.
- In combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including lenalidomide and a proteasome inhibitor.
- In combination with bortezomib, melphalan, and prednisone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for ASCT.
- In combination with bortezomib, thalidomide and dexamethasone for adult patients with newly diagnosed multiple myeloma who can receive an ASCT.

Daratumumab administered as an IV infusion has been generally well tolerated. The most common side effect has been infusion-related reactions, with approximately half of patients receiving a daratumumab IV infusion-based regimen experiencing one or more of these events. Most infusion-related reactions (>90%) have occurred during the first infusion. Due to the risk of these reactions, the IV infusion requires a large volume (500 mL to 1000 mL), and the median infusion

time for the first infusion is 7 hours (up to 23.5 hours); subsequent infusions are approximately 3 to 4 hours.

3.2.2.2. Rationale for Subcutaneous Daratumumab Administration

To mitigate the risk of infusion-related reactions as well as the long infusion time that frequently requires hospitalization with IV infusions of daratumumab, the sponsor has developed a new formulation of daratumumab for SC administration.

Daratumumab for SC administration is a co-formulated product of daratumumab and recombinant human hyaluronidase (rHuPH20). The rHuPH20 cleaves the repeating disaccharide subunits (N-acetyl-D-glucosamine and D-glucuronic acid) of hyaluronan, a polymeric, gel-like glycosaminoglycan (mucopolysaccharide) that are present in the SC tissue matrix. The HuPH20 acts locally and transiently within the SC space to increase the tissue dispersion and absorption of other injected drugs and fluids.

The SC route of administration for daratumumab was first evaluated by the sponsor in Study MMY1004 (PAVO), a Phase 1b, open-label, multicenter, 2-part dose escalation study in patients with relapsed or refractory multiple myeloma. In this ongoing study, SC daratumumab is being administered according to the approved monotherapy schedule (ie, weekly for 8 weeks, every 2 weeks for an additional 16 weeks, and every 4 weeks thereafter until PD or unacceptable toxicity). The PAVO study assessed the safety, pharmacokinetics, and efficacy of SC administration of daratumumab plus rHuPH20 (DARA-PH20). After a median follow-up of 6.5 months (clinical cutoff date of 13 Dec 2017), 25 patients received at least 1 dose of 1800 mg SC daratumumab in Study MMY1004.[9] The injection-related reaction rate was 16% and consisted of Grade 1 or 2 chills, dyspnea, sneezing, and allergic rhinitis, and two Grade 3 events of hypertension. None of the injection-related reaction (IRR) events led to treatment discontinuation. Injection-site reactions (ISRs) occurred in 12% (n=3) of patients, all were Grade 1. The events were discoloration/injection site induration, hematoma, and erythema. The overall response rate (ORR) was 52% with 28% VGPRs. Median PFS has not been reached. The efficacy and adverse event profile are consistent with that of IV daratumumab with a lower rate of injection-related reactions. Based on these clinical data and supported by the pharmacokinetic profile of Dara-SC, the safety and efficacy of Dara-SC appear equivalent to and may be better than Dara-IV. Together these findings suggest that co-formulated SC daratumumab 1800 mg plus rHuPH20 is well tolerated and achieves response rates similar to those observed with daratumumab administered by IV infusion. In addition, the daratumumab SC administration has an added benefit of shorter administration time (3 to 5 minutes for SC daratumumab injection versus a median duration of 7 hours when administered by IV infusion).

Following results observed in PAVO study, 6 studies are ongoing that utilize SC administration of daratumumab, including COLUMBA, AQUILA, APOLLO, PERSEUS, CEPHEUS, and ANDROMEDA.

In the randomized Phase 3 COLUMBA study of SC versus IV daratumumab, the infusion-related reaction rate was significantly lower with SC daratumumab compared with IV daratumumab (12.7% vs. 34.5%). Furthermore, SC daratumumab was associated with only a 1.5% incidence of

Grade 3 infusion reactions. The safety profile (Grade ≥3 AEs other than infusion reactions, AEs leading to treatment discontinuation) was similar between SC and IV daratumumab. In addition, IRRs (erythema, induration) occurred in 6.9% of patients and these were all Grade 1-2 and fully reversible.[24]

For the most comprehensive nonclinical and clinical information regarding daratumumab, refer to the latest version of the Investigator's Brochure (IB) and Addenda as well as the most current product label.

DARZALEX Faspro™ (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use, received FDA approval on 01 May 2020 to be administered at a dose of 1800 mg of daratumumab and 30,000 units hyaluronidase per 15 mL (120 mg and 2000 units/mL) solution in a single-dose vial.

3.2.3. Subcutaneous Daratumumab Dosing and rHuPH20 Concentration Chosen for This Study

The dosed concentration of rHuPH20 in daratumumab in this study will be 2000 U/mL. This is the same concentration and total amount of rHuPH20 administered in Part 2 of PAVO study and other ongoing Phase 3 studies using SC administration of daratumumab.

In the proposed study, daratumumab 1800 mg SC will be administered in 28-day cycles using the standard dosing schedule for daratumumab monotherapy (ie, weekly during Cycles 1 and 2, every 2 weeks during Cycles 3 through 6, and every 4 weeks from Cycle 7 onward for a maximum of 36 cycles) to quickly achieve and maintain effective daratumumab concentrations. Patients will be randomized in a 1:1 ratio to maintenance therapy with SC daratumumab and lenalidomide or lenalidomide alone.

3.2.4. Minimal Residual Disease Conversion Rate as the Primary Endpoint

Minimal residual disease negativity has been associated with improvement in PFS and overall survival (OS). In 2 recent meta-analyses, [21,30] the achievement of MRD negativity correlated with improvement in PFS and OS regardless of transplant eligibility in patients with newly diagnosed multiple myeloma or treatment regimen. In the meta-analysis by Landgren et al, 4 studies consisting of transplant-eligible patients were evaluated; results showed that patients who achieved MRD negativity (versus those who remained MRD positive) had better PFS (hazard ratio [HR]=0.35; 95% confidence interval [CI]: 0.27, 0.46; p <0.001). In the meta-analysis by Munshi et al, 14 studies provided data on the impact of MRD status on PFS (1,273 patients, 660 MRD negative and 613 MRD positive), and 12 studies provided data on the impact of MRD status on OS (1,100 patients, 599 MRD negative and 501 MRD positive). Compared with MRD positivity, MRD negativity was associated with better significantly improved PFS (HR=0.41; 95% CI: 0.36, 0.48; p <0.001) and OS (HR=0.57; 95% CI: 0.46, 0.71; p <0.001) outcomes.

In addition, in a recent pooled analysis,[20] the achievement of MRD negativity has been correlated with improvement in PFS and OS regardless of transplant eligibility or treatment regimen. Three Spanish studies in newly diagnosed patients with multiple myeloma were pooled and analyzed for correlation of MRD negativity to PFS and OS. In this report, 609 transplant-eligible patients from

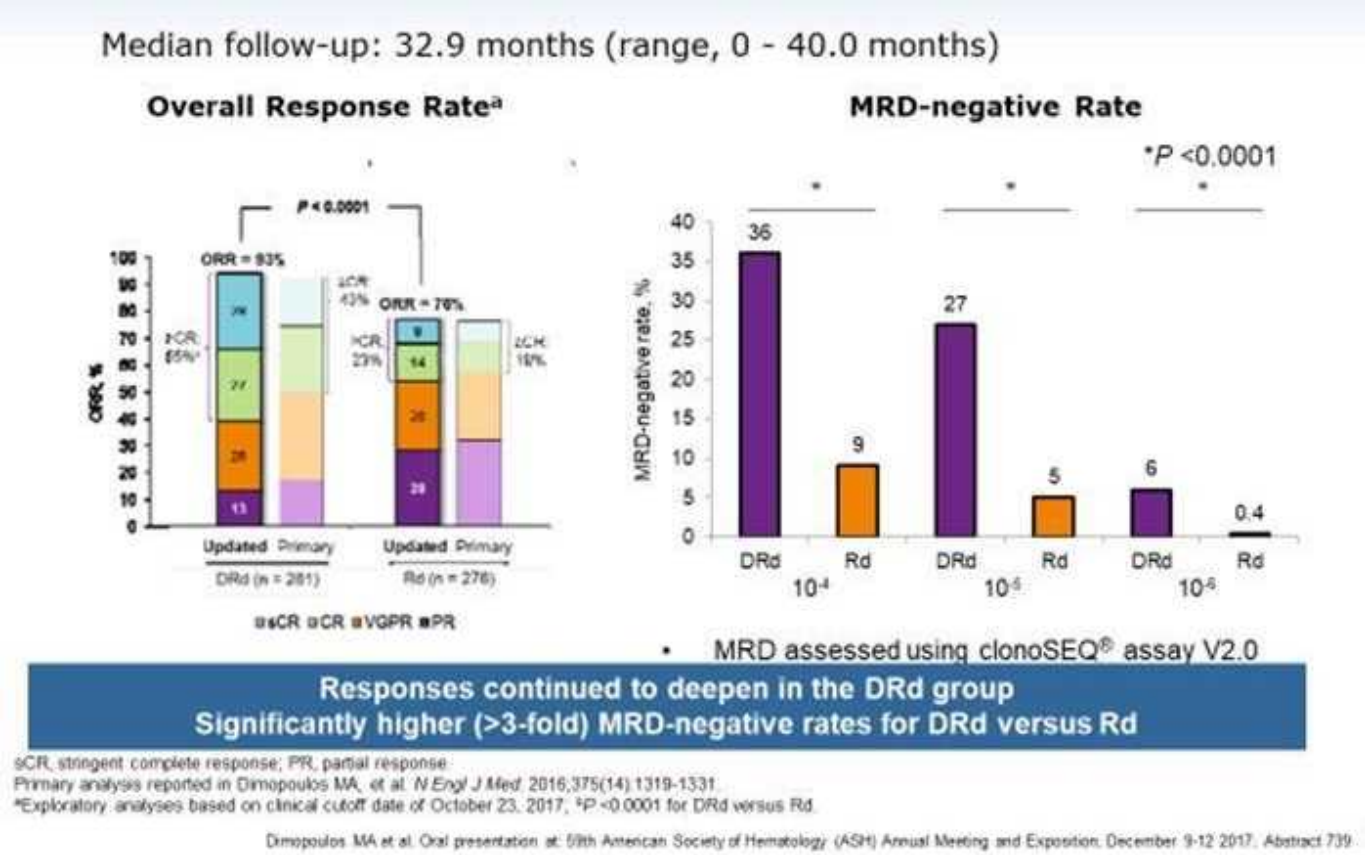
Studies GEM2000 (n=256) and GEM2005 (n=226) and 127 transplant-ineligible patients from Study GEM2010 (n=127) were analyzed for MRD at 9 months after study enrollment, regardless of the treatment regimen. The MRD negative status measured by flow cytometry (10^{-4} to 10^{-5}) was strongly associated with prolonged PFS (median: 63 months; $p<0.001$) compared with patients with CR (median: 49 months) and OS (median: not reached; $p<0.001$) compared with patients with CR (median: 128 months). Importantly, this analysis was independent of prior transplantation, ISS stage, cytogenetic risk category, or conventional response category. In fact, for patients who had achieved CR but remained MRD positive, their outcomes were similar to those patients with near complete response VGPR, and partial response (PR) with median PFS of 27, 27, and 29 months, respectively; and median OS of 59, 64, and 64 months, respectively.

Among multiple myeloma patients treated with bortezomib, lenalidomide, and dexamethasone followed by 1 year of lenalidomide maintenance, 48.3% of multiple myeloma patients were negative for MRD assessed using NGS.[3] In a prospective analysis of 50 myeloma patients with at least a VGPR, who were treated with ASCT or cyclophosphamide-lenalidomide-dexamethasone, followed by lenalidomide-based maintenance, 19 (38%) patients achieved MRD-negativity (assessed by flow cytometry after consolidation), including 12 patients in the ASCT group and 7 in the cyclophosphamide-lenalidomide-dexamethasone group. During maintenance, 7 (14%) additional patients achieved MRD negativity (2 patients in the lenalidomide-prednisone group and 5 patients in the lenalidomide group).[34]

The addition of daratumumab to standard of care treatment regimens has been found to improve MRD negativity rates. For example, data from 2 studies (POLLUX and CASTOR) utilizing daratumumab in combination with either lenalidomide and dexamethasone (MMY3003/POLLUX) or bortezomib (Velcade) and dexamethasone (MMY3004/CASTOR) in patients with relapsed/refractory multiple myeloma have shown improvement in both the number of patients achieving MRD negativity as compared to the control arms, as well as improvement in PFS for patients who achieved MRD negative status.[2] Similarly, addition of daratumumab to standard of care regimens in newly diagnosed transplant ineligible myeloma patients tripled the MRD negative rate in the ALCYONE[25] and MAIA[13] Phase 3 clinical studies. In the Phase 3 CASSIOPEIA[16,29] study, higher rate of MRD negativity was observed in newly diagnosed transplant eligible patients treated with daratumumab based regimen versus standard of care treatment (64% vs. 44%, $p<0.0001$).

These studies (CASTOR, POLLUX, ALCYONE, and MAIA) utilized NGS, and data shown below (Figure 2) reflect a sensitivity of 10^{-5}. Furthermore, in the Phase 3 POLLUX study of previously treated multiple myeloma patients, addition of daratumumab to lenalidomide and dexamethasone treatment was associated with >3-fold MRD negativity rate (30% versus 5% at the 10^{-5} threshold) compared to treatment with lenalidomide and dexamethasone alone.[4] In the MAIA study, 24% of patients in the DRd arm achieved MRD negativity at 10^{-5}, compared with only 7% of patients in the Rd arm. More importantly, daratumumab treatment was associated with durable MRD negative response (DRd: 6.0%, Rd: 1.1%). Thus, addition of daratumumab to lenalidomide significantly improved the depth of response in previously treated multiple myeloma patients.

Figure 2: POLLUX Updated Analysis: Overall Response Rate and Minimal Residual Disease-negative Rates



Abbreviations: CR = complete response; MRD = minimal residual disease; ORR = overall response rate; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.

Therefore, the sponsor proposes that the addition of daratumumab to lenalidomide maintenance treatment in newly diagnosed multiple myeloma patients who are MRD positive post ASCT will improve the MRD conversion rate by ≥20%.

3.2.5. MRD Assessment Using NGS

The most commonly used sensitive methods to monitor MRD include allele-specific oligonucleotide polymerase chain reaction (PCR) and multiparametric flow cytometry (MFC).[38,40] Each method offers distinct advantages and disadvantages. The MFC has been widely applied in the diagnostic and prognostic evaluations of patients with myeloma and may have value in response assessment, particularly in the context of patients undergoing ASCT.[36,40] The Adaptive Biotechnologies' NGS-based assay approved by the Food and Drug Administration (FDA) for assessment of MRD in acute lymphoblastic leukemia or multiple myeloma, is the most sensitive validated assay available with the ability to detect one malignant cell in the background of a million normal cells.

In this study, MRD will be assessed using Adaptive Biotechnologies' NGS-based MRD assay for rapid determination of study participation eligibility during screening. Residual samples collected during screening will also be banked for future tests. Two sequential NGS assays will be conducted

during screening. The first NGS assay will be conducted on archived bone marrow sample for calibration of index myeloma clone. If an existing result on index myeloma clone is available from Adaptive Biotechnologies' NGS-based MRD assay, conducted as part of institutional procedures, then archived bone marrow sample is not required as long as Adaptive Biotechnologies is able to retrieve historical results on the index myeloma clone from the clinical database. Following index clone calibration (or verification of existing index clone results from a previously conducted Adaptive Biotechnologies' NGS-based MRD assay), MRD will be assessed by NGS (Adaptive Biotechnologies' NGS-based MRD assay), using fresh bone marrow aspirate sample collected during screening. Note that if patients had an NGS assay (Adaptive Biotechnologies' NGS-based MRD assay) performed post ASCT as part of institutional procedures, then those who tested positive for MRD at 10^{-5} based on these results are eligible to participate in the study and such patients will not be required to undergo MRD assessment by NGS again at the time of screening. If a bone marrow biopsy was conducted up to 30 days prior to the start of screening AND a positive MRD result based on Adaptive Biotechnologies' NGS-based MRD assay is available, a repeat biopsy during screening is not required. In this situation, local PC clonality and morphology may be used.

After the start of study treatments (ie, after C1D1), MRD will be assessed by NGS at the end of 12, 18, 24, and 36 months using NGS. The primary endpoint for evaluation is the rate of MRD conversion at 12 months. During the bone marrow aspirate procedure, the first aspirate sample that is drawn will be sent to the central laboratory to determine MRD by NGS. All bone marrow aspirates to be sent to the central laboratory should be at least 3 mL. Additional bone marrow aspirate samples may be taken and used for local laboratory testing.

Other parameters chosen for evaluation of efficacy (eg, best response, OS, PFS, time-to-new treatment, etc.) as well as safety/tolerability measures are standard for these study treatment(s) and/or oncology studies.

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

3.2.6. Summary of Anticipated Benefits and Risks

The combination of lenalidomide with SC administration of daratumumab is anticipated to have a positive benefit-risk profile when used for maintenance treatment of patients with newly diagnosed multiple myeloma who are MRD positive and anti-CD38 antibody naïve. Please refer to Section 3.2.1 for additional information. This assessment is based on the following:

- Strategies directed at improving and/or maintaining depth of response are needed to improve clinical outcomes for patients with newly diagnosed multiple myeloma.

- The addition of daratumumab to the standard of care lenalidomide, which is the current a standard of care regimen for maintenance treatment in patients with newly diagnosed multiple myeloma, may improve long-term outcomes through improvement in MRD conversion rate.
- Given the potential advantages of SC administration of daratumumab (refer to Section 3.2.2.2 for detailed information), including shorter time of administration, fewer injection-related reactions, and comparable clinical response rates when compared with administration of daratumumab via IV infusion, the SC route of administration will be used in this study.
- The assessment of primary endpoint of MRD negativity at 12 months post-maintenance will be conducted using a sensitive NGS (sensitivity cutoff of 10^{-5}) assay (Adaptive Biotechnologies' NGS-based MRD assay), thus providing valuable data on the depth of response achieved with the combination of daratumumab and lenalidomide maintenance treatment in newly diagnosed multiple myeloma patients.
- We expect that the benefits of addition of SC daratumumab to lenalidomide, as maintenance treatment, will outweigh the risks, even among patients who may achieve a CR or better after transplant. As discussed in Section 3.2.1, prolonged administration of daratumumab in conjunction with lenalidomide does not result in an increased total risk of AEs based on data from ongoing trials.
- The potential risks for the study will be mitigated by monitoring via the Independent Data Monitoring Committee and the sponsor's medical monitor during the conduct of the study.

In summary, there is a strong rationale for evaluating SC daratumumab in combination with lenalidomide as maintenance treatment for patients with newly diagnosed multiple myeloma who are anti-CD38 naïve and MRD positive after frontline ASCT.

4. PATIENT POPULATION

Screening for eligible patients will be performed within 60 days before randomization.

The inclusion and exclusion criteria for enrolling patients 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 patient in the study. Waivers are not allowed.

4.1. Inclusion Criteria

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

1. Must be 18 to 79 years of age.
1. Must have newly diagnosed multiple myeloma with a history of a minimum of 4 cycles of induction therapy, have received HDT and ASCT within 12 months of the start of induction therapy, and be within 6 months of ASCT on the date of randomization.
2. Must have a VGPR or better response assessed per IMWG 2016 criteria at the time of randomization.
3. Must have archived bone marrow samples collected before induction treatment (ie, at diagnosis) or before transplant (eg, at the end of induction) or have existing results on the

index MM clone based on Adaptive Biotechnologies' NGS-based MRD assay. Archived bone marrow samples will be used for calibration of myeloma clonal cells to facilitate assessment of the primary end point by NGS. If an existing result on index myeloma clone is available from Adaptive Biotechnologies' NGS-based MRD assay, as part of institutional procedures, an archived bone marrow sample is not required as long as Adaptive Biotechnologies is able to retrieve historical results on the index myeloma clone form the clinical database. Any one of the following archived samples are required:

a. Greater than 1 mL viable frozen bone marrow aspirated aliquot (preferred) collected in an EDTA tube, frozen, and stored at a temperature of −80°C, **or**

b. **Non-decalcified diagnostic** bone marrow aspirate clot sections (block or slides) for MRD assessment:

i. An FFPE block of bone marrow aspirate clot, or slides (preferably 5, if available), 5 μm each, of non-decalcified bone marrow, **or**

ii. Slides (preferably 5, if available), bone marrow aspirate smear,

iii. Please note, bone marrow core sections are not acceptable samples for analysis.

iv. In exceptional circumstances when index myeloma clone cannot be identified from the archived bone marrow sample, a post-transplant sample can be used to identify myeloma clone with permission from the Sponsor.

4. Must have residual disease as defined by detectable MRD (Adaptive Biotechnologies' NGS-based MRD assay). If this assay was conducted post ASCT as part of institutional procedures and MRD results are available during screening, then patients who were MRD positive at 10^{-5} based on the existing NGS test result are also eligible to participate in the study (such patients will NOT be required to undergo MRD assessment by NGS again at the time of screening).
5. Must have an ECOG performance status score of 0, 1, or 2 (see Section 9.2.1).
6. Must have pretreatment clinical laboratory values meeting the following criteria during screening (laboratory tests should be repeated if not done within 3 days of C1D1):

Adequate bone marrow function:

a. Hemoglobin ≥7.5 g/dL (≥4.65 mmol/L). Prior red blood cell (RBC) transfusion or recombinant human erythropoietin use is permitted, however transfusions are not permitted within 7 days of randomization to achieve this minimum hemoglobin count.

b. Absolute neutrophil count $\geq 1.0\times10^9$/L. Granulocyte colony stimulating factor use is permitted.

c. Platelet count $\geq 75\times10^9$/L for patients in whom <50% of bone marrow nucleated cells are plasma cells. Otherwise, $\geq 50\times10^9$/L (transfusions are not permitted within 7 days of testing to achieve this minimum platelet count).

Adequate liver function:

a. Aspartate aminotransferase ≤2.5 folds of the upper limit of normal (ULN).

b. Alanine aminotransferase ≤2.5 folds of the ULN.

c. Total bilirubin ≤2.0 folds of the ULN (except in patients with congenital bilirubinemia, such as Gilbert syndrome, direct bilirubin ≤2.0 folds of the ULN)

Adequate renal function:

a. Estimated creatinine clearance ≥30 mL/min. Creatinine clearance may be calculated using Cockcroft-Gault, estimated glomerular filtration rate (Modification of Diet in Renal Disease [MDRD]), or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; refer to Section 9.2.2.

b. Corrected serum calcium ≤14 mg/dL (≤3.5 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L); refer to Section 9.2.3.

7. If a female:

a. Must not be of childbearing potential: defined as premenarchal; postmenopausal (>45 years of age with amenorrhea for at least 12 months or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone level >40 IU/L); permanently sterilized (eg, bilateral tubal occlusion [which includes tubal ligation procedures as consistent with local regulations], hysterectomy, bilateral salpingectomy, bilateral oophorectomy); or otherwise be incapable of pregnancy.

or

b. If of childbearing potential:

i. Must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously during the treatment period.

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.

Methods of reliable birth control include 1 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).

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.

and

ii. Must have 2 negative serum or urine pregnancy tests during screening, first within 10 to 14 days prior to dosing and the second within 24 hours prior to dosing.

and

iii. Must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 4 weeks after the last dose of lenalidomide and for 3 months after the last dose of daratumumab

8. If a man who is sexually active with a female of childbearing potential:
    a. Must agree to use a latex or synthetic condom, even if he had a successful vasectomy.

    and

    b. Must agree to not donate sperm during the study and for 4 weeks after the last dose of lenalidomide and for 3 months after the last dose of daratumumab.
9. Must sign (or have his/her legally acceptable representative sign) an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.
10. Is able, and agrees, to the prohibitions and restrictions specified in this protocol.

4.2. Exclusion Criteria

Any potential patient who meets any of the following criteria will be excluded from participating in the study. Each patient must not:

1. A 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 before the date of randomization. Exceptions are squamous and basal cell carcinomas of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years.

2. Must not have progressed on MM therapy at any time prior to screening.

3. Have had prior treatment/therapy with:

    a. Daratumumab or any other anti-CD38 therapies,

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

    c. Plasmapheresis within 28 days of randomization.

4. Be exhibiting clinical signs of meningeal or central nervous system involvement due to multiple myeloma.

5. Have known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal.

    Note that FEV1 testing is required for patients with suspected COPD or asthma. Patients with FEV1 <50% of predicted normal (or for patients ≥65 years of age, old FEV1 <50% or Diffusing capacity of the lung [DLCO] <50%) on screening assessment must be excluded.

6. Have known moderate or severe persistent asthma within the past 2 years (see Section 9.2.4), or current uncontrolled asthma of any classification. Note that patients who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study, provided that FEV1 is ≥50% of predicted normal.

7. Have any of the following:

    a. Known history of seropositivity for human immunodeficiency virus (HIV).

    b. Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Patients with resolved infection (ie, patients who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time PCR measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Patients with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.

    c. Seropositive for hepatitis C (anti- hepatitis C virus [HCV] antibody positive or HCV-RNA quantitation positive), except in the setting of a sustained virologic response, defined as aviremia at least 12 weeks after completion of antiviral therapy).

    Note, patients who completed treatment for hepatitis C at least 6 months prior to screening and have no detectable circulating HCV during screening may participate in the study. Such patients will be required to undergo regular assessments for HCV reactivation during the study and are to be withdrawn from the study if he/she test positive at any time during the study.

8. Have a concurrent medical or psychiatric condition or disease (eg, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease, Waldenström's macroglobulinemia, POEMS syndrome [polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and/or skin changes], or light chain amyloidosis) 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 and/or current or history of CNS involvement by the disease under investigation.

9. Have any of the following:

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

    b. Uncontrolled cardiac arrhythmia

10. Have known allergies, hypersensitivity, or intolerance to boron or mannitol, sorbitol, corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to the IB) or known sensitivity to lenalidomide.

11. Be known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder).

12. Have any condition for which, in the opinion of the investigator, participation would not be in the best interest of the patient (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. Patient is taking any prohibited concomitant therapy per Section 8.3.

13. Be pregnant, or breast-feeding, or planning to become pregnant or breast-feed while enrolled in this study or within 3 months after the last dose of study treatment(s). Or, if male, planning to father a child while enrolled in this study or within 3 months after the last dose of study treatment(s).

14. Have had major surgery within 2 weeks before randomization or will not have fully recovered from surgery, or has surgery planned during the time the patient is expected to participate in the study or within 2 weeks after the last dose of study treatment. Note, patients with planned surgical procedures to be conducted under local anesthesia may participate. Kyphoplasty or vertebroplasty are not considered major surgery.

15. Have received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks or 5 pharmacokinetic half-lives, whichever is longer, before randomization or is currently enrolled in an interventional investigational study.

16. Have contraindications to the use of lenalidomide or daratumumab, per local prescribing information.

17. Have gastrointestinal disease that may significantly alter the absorption of oral drugs.

18. Have received vaccination with live attenuated vaccines within 4 weeks of first study agent administration

19. Be unable or unwilling to undergo antithrombotic prophylactic treatment.

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

4.3. Prohibitions and Restrictions

Potential patients 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.

1. A woman of childbearing potential must remain on a highly effective method of birth control (see inclusion criteria). Contraception must begin 4 weeks before initiating treatment with daratumumab and continue during the Treatment Phase, during dose interruptions and continuing for 4 weeks after the last dose of lenalidomide and 3 months following of the last dose of daratumumab.

   Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. In addition, women must not donate ova during the study, for 4 weeks after the last dose of lenalidomide, and for 3 months after the last dose of daratumumab.

2. A man who has not had a vasectomy and who is sexually active with a woman of childbearing potential must agree to use a barrier method of birth control (eg, condom with spermicidal foam/gel/film/cream/suppository), and all men must not donate sperm during the study, for 4 weeks after the last dose of lenalidomide, and for 3 months after the last dose of daratumumab. The exception to this restriction is that if the patient's female partner is surgically sterile, a second method of birth control is not required.

3. All patients 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) in Attachment 3.

4. During the Treatment Phase, pregnancy test requirements during the study are shown in the Time and Event Schedule - Part 1. 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 (where lenalidomide is supplied centrally, and no local lenalidomide REMS program exists).

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

6. Patients must not donate blood during therapy and for at least 4 weeks following discontinuation of lenalidomide.

5. STUDY TREATMENT AND ALLOCATION AND BLINDING

Treatment Allocation

Patients will be assigned in a randomized manner to receive either 1800 mg SC daratumumab in combination with lenalidomide or lenalidomide alone as maintenance therapy and will be stratified prior to randomization by cytogenetic risk (standard risk/unknown versus high risk as defined by presence of del17p, t(4;14), or t[14;16]).

For stratification purposes, if central cytogenetic results are not available (ie, due to technical reasons) or if central cytogenetics assessment was not conducted due to availability of local results, local cytogenetic results may be used with the approval of the medical monitor. If central and local cytogenetic results are not available, the patient will be assumed to have normal/standard cytogenetics. The investigator will screen patients for enrollment and if eligible, randomize each patient using an interactive web response system (IWRS). Each patient will be assigned a unique patient number. For enrollment and treatment randomization, MRD status will be assessed using the Adaptive Biotechnologies' NGS-based MRD assay, if available.

Blinding

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

6. DOSAGE AND ADMINISTRATION

6.1. Daratumumab and Lenalidomide Dosing and Supply

Maintenance treatment regimens in this study comprise of SC daratumumab in combination with lenalidomide or lenalidomide alone as follows (each cycle will be 28 days in duration with a total of 36 cycles, the planned maximum duration of treatment; every effort should be made to keep patients on the planned dosing schedule):

Daratumumab 1800 mg administered by SC injection:

- Weekly during C1 and C2,
- Every 2 weeks during C3 to C6, and
- Every 4 weeks from C7 onwards until confirmed PD, unacceptable toxicity, or until end of study treatment.

Lenalidomide 10 mg PO:

- D1 to D28 (continuously) of each 28-day cycle until confirmed PD, unacceptable toxicity, or until end of study treatment. If a patient experiences toxicity to lenalidomide, dose and/or schedule may be modified per institutional standard.
- After 3 cycles of maintenance therapy, if well tolerated, the lenalidomide dose may be increased to 15 mg daily, at the discretion of the investigator.

The start of each cycle may occur ±3 days of the scheduled day to accommodate the schedule of the site or patient. Day 1 of subsequent cycles should be adjusted accordingly to maintain the intended cycle duration. Any delays ≥4 days of the scheduled day will need to be discussed with the sponsor.

Daratumumab will be prepared and administered on site, on an out-patient basis, as described in Section 6.2. Guidelines for the prevention and management of daratumumab administration reactions are also described in this section. For further instructions on dose delays due to daratumumab toxicity, please refer to Section 6.3.2.

Lenalidomide will be obtained and administered in accordance with the requirements of the REVLIMID REMS® program or the lenalidomide Global Pregnancy Prevention Plan (when lenalidomide is supplied centrally and no local lenalidomide REMS program exists) in Attachment 3. Patients will self-administer lenalidomide and be instructed as follows:

- To swallow capsules whole with water once a day; preferably at the same time each day. Lenalidomide may be taken with or without food.
- To **not** open, break, or chew capsules.
- To **not** handle capsules any more than needed. If a broken lenalidomide capsule or the medicine inside the capsule is touched, the patient should wash the area of his/her body with soap and water.
- If a dose is missed and it has been less than 12 hours since the prior dose, the patient should take lenalidomide as soon as remembered. If it has been more than 12 hours, he/she should skip the missed dose. Two doses should not be taken at the same time.
- How to store lenalidomide for at-home use.
- How to document lenalidomide intake in the diary provided by the site.

Guidelines for dose adjustment of lenalidomide in the event of toxicity or for renal impairment are provided in Section 6.3.3, Lenalidomide.

For patients receiving both daratumumab and lenalidomide, it is recommended that lenalidomide be taken either prior to or at the same time (preferred) as the daratumumab pre-administration medications that are to be taken within 1 to 3 hours prior to daratumumab administration (see Section 6.2.2.1).

6.2. Daratumumab

6.2.1. Preparation and Administration

Detailed instructions for preparation, administration, and storage of daratumumab will be supplied in study reference materials; please refer to the Commercial Prescribing Instructions for drug preparation and administration. An overview of this information is provided below.

In the SC daratumumab group, daratumumab will be provided as a fixed-dosed (1800 mg), combination drug product containing rHuPH20 drug substance (2000 U/mL) and daratumumab

drug substance (120 mg/mL) in a single vial. Manuals with detailed descriptions for preparation and administration of daratumumab will be supplied to each pharmacy and site.

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

Table 2: Daratumumab Dosing Schedule

Cycles	Schedule
Cycles 1 to 2	weekly (total of 8 doses)
Cycles 3 to 6[a]	every two weeks (total of 8 doses)
Cycle 7 onwards until confirmed disease progression, unacceptable toxicity, or end of study treatment[b]	every four weeks
[a]First dose of the every-2-week dosing schedule is given at Week 9 [b]First dose of the every-4-week dosing schedule is given at Week 25	

All daratumumab administrations will be in an outpatient setting. Patients will receive pre-injection medications and post-injection medications as outlined in Section 6.2.2.1 and Section 6.2.2.2, respectively.

As noted in the Time and Event Schedule, vital signs should be monitored extensively on Cycle 1 Day 1 before, and after the first administration of daratumumab. For all other administrations, vital signs should be measured before the start of injection and at the end of the injection as shown in the Time and Events Schedule – Part 1. If the patient experiences any significant medical event, then the investigator should assess whether the patient should stay overnight for observation. If the patient has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a SAE. Patients will be provided with a diary to record intake of pre- and post-administration medications taken while off-site; sites will use information to complete exposure information in the eCRF.

If an IRR develops, then the injection should be temporarily interrupted or slowed down. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or anaphylactic reaction, SC daratumumab should be discontinued, and no additional SC daratumumab should be administered to the patient. See Section 6.2.3 for instructions on the management of IRR and local ISRs.

Every effort should be made to keep patients on the planned dosing schedule; however, doses given ±3 days of the scheduled dose are permitted. Any delays ≥4 days of the scheduled day will need to be discussed with the sponsor.

6.2.2. Daratumumab Pre- and Post-administration Medications and Patient Observation

The following subsections provide information on medications to be administered prior to and after daratumumab administration to prevent or ameliorate potential administration reactions. Instructions for patient observation following daratumumab administration are also described.

If an IRR develops, then the injection should be temporarily interrupted or slowed down. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or anaphylactic reaction, SC daratumumab should be discontinued and no additional SC daratumumab should be administered to the patient. For management of administration reactions related to daratumumab refer to Section 6.2.3, and for instructions on dose delays due to other toxicities assessed as related to daratumumab or lenalidomide, refer to Section 6.3.

6.2.2.1. Pre-administration Medications

In an effort to prevent IRR, on daratumumab administration days, patients will receive the following medications 1 to 3 hours prior to administration of daratumumab:

Acetaminophen (paracetamol)	650 - 1000 mg IV or per os (PO)
Antihistamine	Diphenhydramine 25 - 50 mg IV or PO, or equivalent (eg, cetirizine, fexofenadine, loratadine, clemastine, dexchlorpheniramine, or promethazine [note: avoid using IV promethazine]). Antihistamine may be discontinued after Cycle 2 at the investigator's discretion if the patient has side effects or does not tolerate.

Corticosteroids (Long-acting or Intermediate-acting)	Administer 20 mg dexamethasone (or equivalent) prior to daratumumab injection during Cycle 1 (first 4 doses of daratumumab). Beginning in Cycle 2, corticosteroids may be tapered over 3 consecutive daratumumab injections to discontinuation at the investigator's discretion. The following dexamethasone taper should be used: 12, 8, and 4 mg over 3 daratumumab injections (for example, 12 mg on C2D1, 8 mg on C2D8, and 4 mg on C2D15, with no dexamethasone being given on C2D22 and beyond). Dexamethasone is given orally or intravenously prior to the first daratumumab injection and oral administration may be considered prior to subsequent injections. An equivalent intermediate-acting or long-acting corticosteroid may be substituted as shown below.
Leukotriene inhibitor	Predose administration of a leukotriene inhibitor (Montelukast 10 mg PO or equivalent) is optional on C1D1 and can be administered up to 24 hours before daratumumab injection as per investigator discretion.

Glucocorticoid		Approximate Equivalent Dose (mg)	Half-life (Biologic) hours
Intermediate	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

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

6.2.2.2. Post-administration Medications

Consider administering low-dose oral methylprednisolone (≤20 mg) or equivalent on the day after daratumumab injection.

For patients with a higher risk of respiratory complications (eg, patients with mild asthma or patients with COPD who have an FEV1 <80% during screening or developed FEV1 <80% during the study without any medical history), the following medications should be considered following SC daratumumab injection:

- Antihistamine (diphenhydramine or equivalent)
- Leukotriene inhibitor (montelukast or equivalent)
- 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 patients with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for patients with COPD).

In addition, these at-risk patients may be hospitalized for monitoring for up to 2 nights after an injection of daratumumab.

- If hospitalized, FEV1 should be measured and documented before discharge.
- If not hospitalized, then a follow up telephone call should be made to monitor the patient's condition within 48 hours after daratumumab injection.

Note: If the patient does not experience 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 if bronchospasm occurs after a patient is released from the hospital/clinic. If an at-risk patient experiences no major injection-related reactions, then these post-injection medications may be waived after 4 doses at the investigator's discretion.

Any post-injection medication will be administered after the injection has completed.

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

6.2.3.1. Local Injection-site Reactions

Injection-site Reactions

In clinical studies, SC administration of daratumumab was associated with local injection site reactions, such as induration and erythema, in some patients. The reactions usually resolved within 60 minutes. Local ISRs should be managed per institutional standards.

6.2.3.2. Daratumumab Injection-related Reactions

Patients should be carefully observed during daratumumab administration. Trained study staff at the clinic should be prepared to intervene in case of any injection-related reactions, 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 at the bedside. Attention to staffing should be considered when multiple patients will be dosed at the same time.

Patients who experience AEs during daratumumab administration must be treated for their symptoms:

- Treatment with acetaminophen, antihistamine, or corticosteroids, may be administered as needed.
- IV saline may be indicated.
- For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids, or bronchodilators.
- For hypotension, patients may require vasopressors.

In the event of a life-threatening reaction (which may include pulmonary or cardiac events) or anaphylactic reaction, daratumumab-SC should be discontinued, and no additional daratumumab should be administered to the patient; and the patient must be permanently withdrawn from daratumumab treatment.

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

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

If the patient 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 patient must be permanently withdrawn from daratumumab SC treatment.

6.2.3.2.2. Injection-related Reactions of Grade 3 or Higher

For injection-related reactions (other than laryngeal edema or bronchospasm) that are Grade 3, the daratumumab SC administration must be stopped, and the patient 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 SC administration may be restarted at the investigator’s discretion. Refer to the SIPPM for further details regarding continuation of daratumumab SC administration.

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

For injection-related AEs that are Grade 4, the daratumumab SC administration must be stopped, and the patient permanently discontinued from daratumumab SC treatment.

6.2.3.2.3. Recurrent Injection-related Reactions

If a Grade 3 injection-related reaction (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 patient must be permanently discontinued from daratumumab treatment.

6.3. Dose Delays and Dose Modifications

Dose modification of 1800 mg SC daratumumab (increase or decrease) is not permitted. Dose delay is recommended as the only method for managing daratumumab-related toxicities. Lenalidomide dose may be reduced, or the treatment schedule may be modified for the management of drug-related toxicities, per the investigator’s discretion, according to lenalidomide prescribing guidelines.

Toxicities should be attributed, whenever possible, to a specific study drug so that treatment modifications can be made rationally. If multiple toxicities are attributed to an individual study

drug, dose adjustment (for lenalidomide only) should be made according to the guidelines for the most severe toxicity.

Modifications to the planned dosing regimen (lenalidomide only) should be overseen by medically-qualified study-site personnel (principal or sub-investigator unless an immediate safety risk appears to be present).

Study drug administration must be captured in the source documents and the eCRF.

6.3.1. Cycle Delay

Day 1 of a cycle should never be skipped, instead it should be considered a cycle delay. A minimum of 4 days between daratumumab doses must be observed.

On the first day of each new treatment cycle and before each daratumumab dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5. Dose modifications (for lenalidomide only) 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 or lenalidomide.

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

The parameters in Table 3 must be met on the first day of a new cycle (ie, the following represent baseline inclusion criteria levels).

Table 3: Re-treatment Criteria Before the Start of Each Cycle

Laboratory Parameter	Requirements Before Each Study Drug Administration
Absolute neutrophil count	$\geq 1.0\times10^9$/L
Platelet count	$\geq 75\times10^9$/L
Hemoglobin	≥7.5 g/dL (≥4.96 mmol/L)

Any dose holds of more than 28 days due to toxicity will result in permanent discontinuation of daratumumab. If a patient permanently discontinues study treatment(s), procedures should be performed as outlined in Section 10.2.1.

If the above parameters are not met, the start of the next cycle will be held for a minimum of 1 week and a maximum of 28 days until recovery to the specified levels. During the cycle delay, daratumumab and lenalidomide must be held. Dose holds of more than 28 days for other reasons should be discussed with the sponsor. If a dose delay occurs, then pharmacokinetic and

pharmacodynamic assessments should be performed on the actual day of study drug administration, not on the original scheduled administration day.

A study drug dose held for more than 3 days from the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the sponsor at the earliest possible time. Patients missing ≥3 consecutive planned doses of study drug for reasons other than toxicity should be withdrawn from treatment, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

6.3.2. Daratumumab

6.3.2.1. Daratumumab Dose Modification

Individual dose modification of daratumumab is not permitted, but dose delay is recommended as the primary method for managing daratumumab-related toxicities, as described in Sections 6.2.3 and 6.3.2.2.

6.3.2.2. Daratumumab-related Toxicity Management

Refer to Section 6.2.3 for details on management of daratumumab injection-related reactions.

If any of the following criteria are met and the toxicity is more than expected for lenalidomide or underlying multiple myeloma, daratumumab injection must be held to allow for recovery from toxicity. If attribution is unclear, then daratumumab should be held until recovery from toxicity as noted below.

The criteria for a dose delay are:

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

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered. Other than on Day 1 of a cycle, if any "within-cycle" daratumumab administration does

not commence within the prespecified window of the scheduled administration date (Table 4), then the dose will be considered a missed dose. Administration may resume at the next planned dosing date.

Table 4: Daratumumab-related Toxicity Management

Daratumumab Dosing Frequency	Dose Missed	Dosing Resumption
Weekly	>3 days	Next planned weekly dosing date
Every 2 weeks	>7 days	Next planned every-2-weeks dosing date
Every 4 weeks	>21 days	Next planned every-4-weeks dosing date

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

If a dose is delayed, then the dates of all subsequent doses must be adjusted. If a dose delay occurs, then blood samples should be collected on the actual day of study drug administration, not on the original scheduled drug administration day. Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 28 days will result in permanent discontinuation of daratumumab, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

6.3.2.3. Daratumumab Interruption or Missed Doses

A daratumumab dose that is held for more than the permitted time (Table 4) 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. Patients whose dose is delayed or missed for 3 or more consecutive doses should be withdrawn from study treatment, unless, upon consultation with the sponsor and the review of safety and efficacy, continued treatment is agreed upon.

6.3.3. Lenalidomide

The lenalidomide dose may be reduced, or the treatment schedule may be modified for the management of study drug-related toxicities. For example, if a patient develops a drug-related toxicity that requires a dose or schedule modification while receiving lenalidomide 10 mg on D1 to D28 (continuously) of each 28-day cycle, the dose of lenalidomide may be reduced to ≤10 mg on D1 to D28 of each 28-day cycle. Alternatively, the dose and treatment schedule may be modified to ≤10 mg on D1 to D21 of each 28-day cycle, per institutional standard.

6.4. Overdose

6.4.1. Daratumumab

The maximum tolerated dose has not been established for daratumumab. However, if the dose exceeds the maximum tested dose of 2000 mg, then it will be considered as an overdose in this study. In the event of an overdose, the investigator or treating physician should:

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

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

6.4.2. Lenalidomide

According to the latest prescribing information for lenalidomide at the time of this protocol (October 2019), "There is no specific experience in the management of lenalidomide overdose in patients with MM, MDS, MCL, FL, or MZL. In dose-ranging studies in healthy patients, some were exposed to up to 200 mg (administered 100 mg BID) and in single-dose studies, some patients were exposed to up to 400 mg. Pruritus, urticaria, rash, and elevated liver transaminases were the primary reported AEs. In clinical studies, the dose-limiting toxicity was neutropenia and thrombocytopenia."

Please refer to the most current product label for lenalidomide overdose information.

7. STUDY TREATMENT(S) COMPLIANCE

Study drug (daratumumab) will be administered by qualified staff, and the details of each administration will be recorded in the eCRF. Refer to the Commercial Prescribing Instructions for drug preparation and administration.

Patients will be provided with a diary to record intake of lenalidomide as well as pre- and post-daratumumab administration medications, if required; sites will use information to complete exposure information in the eCRF.

8. PRE-STUDY AND CONCOMITANT THERAPY

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study treatments must be recorded in the eCRF. Recorded information will include the type of therapy, duration of use, dosing regimen, route of administration, and indication.

Pre-study therapies administered up to 30 days (± 7 days) before first dose of study treatment(s) must be recorded. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a patient into the study.

Concomitant therapies will be collected in the eCRF and source documents beginning with signing of the ICF to 30 days (± 7 days) after the last dose of study treatment or until the start of subsequent anticancer treatment, if earlier.

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 8.3. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. Concomitant medications to manage adverse events and serious adverse events will be recorded as per guidelines provided in Section 12.3.2.

The following subsections provide guidelines on recommended, permitted, and prohibited concomitant therapies during administration of study treatments (Sections 8.1, 8.2, and 8.3, respectively), as well as guidelines on therapies to be administered after the end of study treatments (Section 8.4).

8.1. Recommended Therapies

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

Routine systemic use of concomitant medications will be collected in the eCRF and recorded in the source documents beginning with signing of the ICF up to 30 days after the last dose of the last study treatment or until the start of subsequent anticancer treatment, if earlier.

8.1.1. Prevention of Deep Venous Thrombosis and Pulmonary Embolism

Lenalidomide has been associated with an increased risk of deep vein thrombosis and pulmonary embolism. Therefore, prophylaxis of venous thromboembolism (VTE) for all patients is recommended according to IMWG criteria as shown in (Figure 3).[37]

Figure 3: Individual and Myeloma-related Risk Factors

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

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

In summary:

Both individual and myeloma related risks of VTE 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 to 325 mg once daily is recommended or dose per institutional standards.
- If 2 or more risk factors are present, low molecular weight heparin (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.

8.1.2. Therapy for Tumor Lysis Syndrome

Patients should be monitored for symptoms of tumor lysis syndrome. Management of tumor lysis syndrome, including increasing hydration and treating hyperkalemia, hyperuricemia, and hypocalcemia, is highly recommended. It is also recommended that high-risk patients, ie, those with a high tumor burden, be treated prophylactically in accordance with local standards (eg, increased hydration; diuretics, allopurinol 300 mg daily; and medication to increase urate excretion).

8.1.3. Prophylaxis Against *Pneumocystis carinii* Pneumonia

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

8.1.4. Prophylaxis for Herpes Zoster Reactivation

Prophylaxis for herpes zoster reactivation is recommended during treatment as per 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),
- Famciclovir (eg, 125 mg given, twice a day or per institutional standards), or
- Valacyclovir (eg, 500 mg given orally, twice a day or per institutional standards).

8.1.5. Prevention 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 patients at risk for HBV reactivation.

In patients who develop reactivation of HBV while on study treatment, suspend treatment with study treatment and any concomitant steroids, chemotherapy, and institute appropriate treatment. Resumption of study treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

8.1.6. Prevention of Steroid-induced Gastritis

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

8.1.7. Drugs Affecting Bone Structure and Mineralization

Drugs affecting bone structure and mineralization like bisphosphonate therapy or monoclonal antibodies are strongly recommended for all patients with evidence of lytic destruction of bone or with osteopenia. Therapy is recommended to be continued per treatment guidelines.[29,31] 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 patients with osteolytic or osteopenic myeloma associated 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 patients at their sites.

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

8.2. Permitted Therapies

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

- Antivirals.
- Colony stimulating factors, erythropoietin, and transfusion of platelets and red blood cells.
- Loperamide is recommended for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose and regimen are according to institutional guidelines. Prophylactic loperamide is not recommended.
- Prevention of constipation (eg, adequate hydration, high-fiber diet, and stool softeners, if needed).
- Adequate hydration is recommended for prevention of myeloma-related kidney disease.
- Prophylactic antiemetics, except for corticosteroids.
- An emergency short course of corticosteroid (equivalent of dexamethasone 40 mg/day for a maximum 4 days) is permitted before treatment.

Other symptoms may be managed according to institutional guidelines provided prohibited therapies are not administered as described in the following section (see Section 8.3).

8.3. Prohibited Therapies

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

- Other agents that target CD38.
- Medications used for other indications that have anti-myeloma properties (for example, interferon and clarithromycin).[14,32,39]
- Approved or investigational treatments for multiple myeloma (including but not limited to conventional chemotherapies, immunomodulatory drugs, or proteasome inhibitors).
- Concomitant administration of other investigational agents is prohibited, including administration of commercially available agents with activity against or under investigation

for multiple myeloma.

- Systemic corticosteroids (>10 mg dexamethasone per day or equivalent; other than those given as pre-/post-medication for the study treatment regimen and for daratumumab injection-related reactions as described in Section 6.2).
- Vaccination with live attenuated vaccines.
- In the absence of PD, should a patient require emergency orthopedic surgery or radiotherapy, upon recovery, the patient may continue treatment after consultation with, and approval by the sponsor's medical monitor. Such emergency radiotherapy may consist of localized radiotherapy for pain control or for stabilization of an extensive bone lesion at high risk of pathologic fracture or damage to surrounding tissues in a patient in whom delay of systemic therapy is not appropriate. Such radiotherapy is to occur within the first 2 cycles of treatment, and the absence of evidence of PD is to be reviewed and approved by the sponsor.

8.4. Subsequent Therapies

Administration of any other anti-myeloma therapy to patients who discontinue study treatment for reasons other than PD should be monitored for PD according to the Time and Events Schedule – Part 1. It is not permissible to start other anti-myeloma therapy until PD is confirmed by IMWG criteria.

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

9. STUDY EVALUATIONS

9.1. Study Procedures

The Time and Events Schedules – Parts 1 and 2 summarize the frequency and timing of measurements applicable to this study. The signed ICF must be obtained before any study-specific procedures are performed.

Every effort should be made to keep patients on the study schedule as planned from C1D1. At each visit, whether in-person or via telemedicine, study assessments should be completed before the administration of study treatment. Daratumumab administration and study-specific tests/procedures must be completed by study staff. Any missed visits, tests not performed, or examinations that are not conducted must be reported as such in the appropriate section of the eCRF.

For study assessments that require sample collection, the actual dates and times of sample collection must be recorded on the laboratory requisition form. Instructions for the collection, handling, storage, and shipment of samples can be found in study reference materials. Urine and blood collections should be kept as close to the specified time as possible. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. In addition, 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 patient's participation in the study.

The total blood volume for the study is estimated at approximately 45 mL during screening, approximately 180 mL in Year 1 of the Maintenance Phase, and approximately 90 mL annually in Year 2 and beyond of the Maintenance Phase. This includes laboratory assessments associated with safety, efficacy, as well as scientific research samples. At the EOT visit, approximately 10 mL of blood will be collected. Unscheduled samples may be taken for safety reasons (eg, daratumumab injection-related reactions) or repeat samples may be taken due to technical issues with the samples.

9.2. Evaluations Specific to Entry Criteria and/or Other Study Measures

Additional information required to evaluate entry criteria and/or efficacy and safety evaluations are provided in the following subsections.

9.2.1. ECOG Performance Status

The ECOG performance status score is assessed as shown in Table 5.[33]

Table 5: ECOG Performance Status Scale

Grade	ECOG performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work and 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 and confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry on any self-care, and totally confined to bed or chair
5	Dead

Key: ECOG = Eastern Cooperative Oncology Group.

9.2.2. Calculated Creatinine Clearance

Calculated creatinine clearance may be done using the Cockcroft-Gault formula[10] or the MDRD or the CKD-EPI formula[22,23] as described below.

Cockcroft-Gault formula

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

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

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

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

MDRD or CKD-EPI

For online calculators, please go to https://www.kidney.org/professionals/KDOQI/gfr_calculator.

9.2.3. Serum Calcium Corrected for Albumin

Please use the following formulas for serum calcium corrected for albumin[6]:

Table 6: Serum Calcium Corrected for Albumin

If calcium is in mg/dL and albumin is in g/dL:	Corrected calcium (mg/dL) = serum calcium (mg/dL) + 0.8 × (4 - serum albumin [g/dL])
If calcium is in mmol/L and albumin is in g/L:	Corrected calcium (mmol/L) = serum calcium (mmol/L) + 0.02 × (40 - serum albumin [g/L])

9.2.4. Asthma Guidelines

Please use the guidelines in Attachment 1 for patients with asthma.

9.3. Efficacy Evaluations

Assessment of response will be assessed in accordance with the IMWG 2016 response criteria. Efficacy evaluations will include measurements of residual disease, myeloma proteins, bone marrow examinations, skeletal surveys, and extramedullary soft tissue plasmacytomas.

As applicable, procedures for sample collection, preparation, identification, storage, and shipment will be provided in study reference materials.

9.3.1. Response

Disease evaluations must be performed on the scheduled assessment day (±7 days). Disease evaluations scheduled for treatment days should be carried out before study drug is administered. Testing of specimens used for disease evaluation will be performed by a central laboratory (unless otherwise specified).

This study will use the IMWG consensus recommendations for multiple myeloma treatment response criteria presented in Table 7.[19] For M-protein and immunofixation measurements in serum and 24-hour urine and FLC measurements, the investigator will use results provided by the central laboratory. After completion of study treatment (36 cycles) or premature discontinuation of study treatment (due to reasons other than progressive disease), disease evaluations will no longer be performed by the central laboratory, and local laboratory results of blood and urine M-protein measurements should be used by investigators to determine response and progression. IMWG assessments can stop after confirmation of Progressive Disease by the investigator. Criteria for loss of responses is presented in Table 8. Determination of progressive disease, as well as other response assessments (VGPR, CR, or sCR) per investigator assessments are to follow the IMWG criteria for assessment of progressive disease and disease response, as outlined in Table 7.

Table 7: IMWG Consensus Recommendations for Multiple Myeloma Treatment Response Criteria

Response	Response criteria
sCR	• CR as defined below, *plus* • Normal FLC ratio[a], *and* • Absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)[b]
CR	• Negative immunofixation on the serum and urine, *and* • Disappearance of any soft tissue plasmacytomas, *and* • <5% PCs in bone marrow aspirates
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis, *or* • ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours
PR	• ≥50% reduction of serum M-protein plus 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 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 (SPD)[c] of soft tissue plasmacytomas is also required
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, a 25% to 49% reduction in the size (SPD)[c] of soft tissue plasmacytomas also is required
SD	• Not meeting criteria for CR, VGPR, PR, MR, or PD
PD[d,e]	Any 1 or more of the following criteria: • Increase of 25% from lowest response value in any one of the following: • Serum M-protein (absolute increase must be ≥0.5 g/dL) • Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL • Urine M-protein (absolute increase must be ≥200 mg/24 hours) • Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • Only in patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow PC percentage irrespective of baseline status (absolute increase must be ≥10%) • Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating PCs (minimum of 200 cells/μL) if this is the only measure of disease

Notes: (1) When the only method to measure disease is by serum FLC levels: CR can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the complete response criteria listed above. Very good PR in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive, new bone lesions, or extramedullary soft tissue plasmacytomas if radiographic studies were performed.

(2) Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

a. All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test.

b. Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

c. Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

d. Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a CR and are MRD-negative should be evaluated using the criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

Table 7: IMWG Consensus Recommendations for Multiple Myeloma Treatment Response Criteria

Response	Response criteria
e.	In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.
Key:	Response categories: CR = complete response; MR = minimal response; sCR = stringent complete response; SD = stable disease; PD = progressive disease; PR = partial response; VGPR = very good partial response. Other abbreviations: CT = computed tomography; FLC = free light chain; IMWG = International Myeloma Working Group; M-protein = monoclonal paraprotein; MRD = minimal residual disease; MRI = magnetic resonance imaging; PC = plasma cell; PET = positron emission tomography; SPD = sum of the products of the maximal perpendicular diameters of measured lesions.

Table 8: Criteria for Loss of Complete Response Without Disease Progression

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

Key: M-protein = monoclonal paraprotein.

9.3.2. β_2-microglobulin and Lactic Acid Dehydrogenase

Blood samples for β_2-microglobulin and lactic acid dehydrogenase, indicators of prognosis with high levels associated with more advanced disease and a potentially worse prognosis, will be collected and analyzed by a central laboratory.

9.3.3. Myeloma Protein Measurements in Serum and Urine

Blood and 24-hour urine samples will be collected and sent to the central laboratory for myeloma protein measurements. Urine and blood collections should be kept as close to the specified time as possible. Note, urine sample collected and refrigerated up to 3 days prior to visit are acceptable for disease evaluation.

Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation performed at least 1 day later. Disease evaluations will continue beyond loss of CR until PD is confirmed.

Serum and urine immunofixation tests will be performed during screening and thereafter when serum or 24-hour urine M-protein electrophoresis (serum M-protein quantitation by electrophoresis or urine M-protein quantitation by electrophoresis) is negative or non-quantifiable, at suspected CR, stringent complete response (sCR), and at suspected progression (clinical or biochemical). For patients with light chain multiple myeloma, both serum and urine immunofixation tests will be performed at on D1 of every 3rd cycle in year 1 and thereafter on D1 of every 6th cycle in year 2 and year 3 of maintenance treatment.

As an IgG1κ immunoglobulin, daratumumab has been shown to interfere with serum protein electrophoresis (SPE) and immunofixation electrophoresis (IFE).[28] This interference can be mitigated through a reflex assay using the anti-idiotype antibody to bind daratumumab, shift it on SPE and IFE, and confirm interference. This reflex assay will be implemented as part of response criteria. Patients who meet all other clinical criteria for CR/sCR, with confirmed daratumumab interference on SPE/IFE, will be considered CR/sCR, respectively.

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

9.3.4. Bone Marrow Examination and Minimal Residual Disease Assessment

Bone marrow aspirate and/or biopsy will be performed at screening and bone marrow sample will be sent to central laboratory for MRD assessment by Adaptive Biotechnologies' NGS-based MRD assay, central fluorescence in situ hybridization evaluation of high-risk cytogenetic anomalies, plasma cell clonality assessment and morphology, in the order of priority. First draw of bone marrow aspirate should be collected to ensure quality of sample for MRD assessment. High risk cytogenetics will be defined as presence of del17p, t(4;14), or t(14;16). Please refer to Time and Events Schedule – Part 2: Details for Bone Marrow Testing. If cytogenetic evaluation was conducted any time from the time of multiple myeloma diagnosis to randomization, cytogenetic assessment by central laboratory is not required, however, the results of the local cytogenetic evaluation should be recorded in the eCRF.

During screening, MRD will be assessed (Adaptive Biotechnologies' NGS-based MRD assay) at 12, 18, 24, and 36 months after the start of study treatment(s) (ie, after C1D1). Two sequential NGS assays will be conducted during screening. The first assay will be conducted on archived bone marrow sample for calibration of index myeloma clone. If an existing result on index myeloma clone is available from Adaptive Biotechnologies' NGS-based MRD assay, conducted as part of institutional procedures, then archived bone marrow sample is not required as long as Adaptive Biotechnologies is able to retrieve historical results on the index myeloma clone from the clinical database. Following index clone calibration (or verification of index clone results from a previously conducted NGS assay), MRD will be assessed by Adaptive Biotechnologies' NGS-based assay, using fresh bone marrow aspirate sample collected during screening. Residual bone marrow samples obtained during screening will be banked for future tests. Note that if post-transplant NGS results, based on Adaptive Biotechnologies' NGS-based MRD assay conducted as per institutional standards, are available at the time of screening and the patient is positive for MRD (at 10^{-5} based on the existing NGS test result), the patient may be eligible for study participation. Such patients will not be required to undergo MRD testing by NGS, again, at the time of screening.

During the bone marrow aspirate procedure, at screening and during maintenance treatment, the first aspirate sample that is drawn will be sent to the central laboratory to determine MRD (by Adaptive Biotechnologies' NGS-based MRD assay). The second aspirate sample will be sent to the central laboratory to determine cytogenetics (at screening only, if local cytogenetic evaluation was not conducted at any time from multiple myeloma diagnosis to randomization), plasma cell clonality and morphology. Additional bone marrow aspirate samples may be taken and used for local laboratory testing.

9.3.5. Assessment of Lytic Disease

A complete skeletal survey (including the skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease) is to be performed and evaluated by the local radiologist. An alternative (eg, low-dose CT) may be used in accordance with local standard of care. Please note that the same methodology used during screening should be used throughout the study for comparison purposes.

During the Maintenance Phase and before PD is confirmed, imaging should be performed whenever clinically indicated based on symptoms, to document response or progression. Magnetic resonance imaging (MRI) or low-dose CT scan is an acceptable method for evaluation of bone disease and may be included at the discretion of the investigator (see the disease response criteria in Table 7). If a radionucleotide bone scan was used during screening in addition to the complete skeletal survey, then both methods must be used to document disease status. These tests must be performed at the same time. However, a radionucleotide bone scan does not replace a complete skeletal survey.

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

9.3.6. Documentation of Extramedullary Plasmacytomas

Sites of known extramedullary soft tissue plasmacytomas must be documented during screening. Clinical examination or MRI may be used to document extramedullary sites of disease. CT and/or PET/CT scan evaluations are an acceptable alternative if there is no contraindication to the use of IV contrast. Positron emission tomography scan or ultrasound tests are not acceptable to document the size of extramedullary plasmacytomas. Post-screening assessments are to continue to be performed until confirmed CR or PD, during the maintenance phases. 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 PD.

To qualify for PD (see Table 7), 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 PD.

9.4. Patient-Reported Outcomes

The PRO measures will be completed by the patient at the clinical site. All visit-specific PRO assessments should be completed before any tests, procedures, or other consultations for that visit to prevent influencing patient perceptions. If the patient is unable to complete the PRO assessments, the reason for not completing the questionnaires will be documented in the eCRF (ie, too ill, patient refused, etc).

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

Three PRO measures will be utilized in this study: the EORTC QLQ-C30, EORTC QLQ-MY20 module, and the EQ-5D-5L. These measures will be administered according to the Time and Events Schedule – Part 1 to understand how patients self-reported health state changes over time and the difference between-treatment arms during maintenance treatment and post-progression.

EORTC QLQ-C30 Version 3 includes 30 items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 Global Health Status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The recall period is 1 week ("past week item") and responses are reported using a verbal rating scale. The item and scale scores are transformed to a 0 to 100 scale. A higher score represents greater health-related quality of life (HRQoL), better functioning, and more (worse) symptoms. The EORTC QLQ-C30 has been widely used among patients with multiple myeloma. Reliability, validity, and clinically meaningful change have been demonstrated.[45,46]

The EORTC QLQ-MY20 has been designed to be used alongside the EORTC QLQ-C30 to address issues of more relevance to myeloma patients.[11] The 20 items make up 4 scales: disease symptoms, side effects of treatment, future perspective, and body image. Recall, response options, and interpretation are similar to the EORTC QLQ-C30. Together the EORTC QLQ-C30 and the EORTC QLQ-MY20 administration time is less than 30 minutes. Key PRO endpoints include the Global Health Status, physical functioning, fatigue, and pain scales from the EORTC QLQ-C30 and the Disease Symptoms scale from the EORTC QLQ-MY20.

The EQ-5D-5L is a generic measure of health status. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression plus a visual analog scale rating "health today" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).[15] The scores for the 5 separate questions are categorical and cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. The EQ-5D-5L asks respondents to select their response based on their current health ("today") and takes less than 5 minutes to complete.

9.5. Safety Evaluations

Screening and ongoing measurements of safety in this study include adverse event monitoring, clinical laboratory tests (hematology, chemistry, pregnancy, HCV viral load, HBV infection [HBV serology and/or HBV-DNA testing], and indirect antiglobulin tests), electrocardiograms (ECGs), chest x-ray or full chest CT scan, physical examination, spirometry (FEV1), vital sign measurements including weight, and ECOG performance status as details in the Time and Events Schedule – Part 1.

All toxicities will be graded according to the NCI-CTCAE Version 5. Clinically relevant changes that occur during the study must be recorded in the Adverse Event eCRF page. Clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

Based on previous experience with daratumumab in humans, in vitro studies, and animal toxicological findings, injection-related reactions/allergic reactions, and hemolysis will be closely monitored. Any of the safety monitoring assessments may be performed more frequently as clinically indicated, and adverse events should be evaluated by the investigator according to the standard practice.

9.5.1. Adverse Events

Adverse events (excluding progression of multiple myeloma) will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally acceptable representative) from the time a signed and dated informed consent is obtained until 30 days (± 7 days) following the last dose of any component of study treatment(s). Adverse events will be followed by the investigator as specified in Section 11.1.

9.5.2. Clinical Laboratory Tests

9.5.2.1. Hematology, Chemistry, Pregnancy, HCV, and HBV Tests

Hematology, serum chemistry, and pregnancy tests (for women of childbearing potential) will be conducted by an on-site accredited local laboratory. The specific tests and the timing of these tests are detailed in the Time and Events Schedule – Part 1 (refer to the rows for hematology, serum chemistry, and pregnancy testing).

Note: 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 Schedules. Where lenalidomide is supplied locally, patients must adhere to the local lenalidomide REMS program. Where lenalidomide is supplied centrally and no local lenalidomide REMS program exists, then patients must adhere to the lenalidomide Global Pregnancy Prevention Plan in Attachment 3. If pregnancy does occur, then study treatment should be discontinued immediately, and the patient should be referred to an obstetrician experienced in reproductive toxicity for further evaluation and counselling.

In patients with a prior history of HCV, HCV viral load will be tested in a local laboratory throughout the study as specified in the Time and Events Schedule – Part 1 rows for HCV viral load testing.

All patients will be tested for HBsAg, anti-HBs, and anti-HBc assessments performed locally prior to the first dose. For patients (in all treatment arms) with serologic evidence of prior HBV infection, HBV-DNA testing will be performed locally at screening, every 12 weeks during treatment, at EOT, and every 12 weeks for up to 6 months after last dose of study treatment. HBV-

DNA is not required at C1D1 if performed at screening. Patients with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV-DNA by PCR. See Time and Events Schedule – Part 1 rows for HBV testing.

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.

9.5.2.2. Indirect Antiglobulin Test

Blood type, Rh, and indirect antiglobulin test (IAT) should be done for all patients. Patient RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first daratumumab injection.

Daratumumab interferes with the IAT, which is a routine pre-transfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends.

Patients receiving daratumumab will receive an identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first injection of daratumumab along with information on the IAT interference for healthcare providers/blood banks.

Patients are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab–interference with IAT by treating reagent RBCs with dithiothreitol (DTT).[7,8]

Possible methods for blood banks to provide safe RBCs for transfusion to patients receiving daratumumab include the following:

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

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

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

9.5.3. ECGs, Chest Imaging, Physical Examination, and Spirometry

A 12-lead ECG is required during screening and may be performed during the study as clinically indicated. During the collection of 12-lead ECGs, patients should be in a quiet setting without distractions (eg, television and cell phones). Patients should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

A chest x-ray or full chest CT scan is required during screening if not conducted within 30 days prior to screening.

A complete physical examination with measurement of height will be required during screening. Thereafter, only a symptom- and disease-directed physical examination is required as clinically indicated.

Patients with known or suspected COPD or asthma must have an FEV1 test during screening if not performed as part of standard of care anytime from 60 days prior to transplant up to randomization; refer to Section 6.2.2.2 for details on patients with higher risk of respiratory complications.

9.5.4. Vital Signs Including Weight

Vital signs and weight will be measured regularly as specified in the Time and Events Schedule – Part 1; abnormalities will be recorded as adverse events (refer to Section 12).

9.5.5. Eastern Cooperative Oncology Group Performance Status

The ECOG performance status will be conducted to evaluate the effect of the disease status on the activities of daily living (see Table 5). When scheduled, ECOG performance status assessments should be obtained prior to any other study procedures planned for the same day whenever possible.

9.6. Benefit-risk Evaluation

The benefit-risk assessment of daratumumab in combination with lenalidomide relative to lenalidomide alone will be conducted by comparing between-treatment differences of key efficacy and safety endpoints. Additional details on the benefit-risk assessment will be provided in a separate analysis plan. Please refer to Section 3.2.1 for additional information on anticipated benefit-risk profile.

10. PATIENT COMPLETION/DISCONTINUATION OF TREATMENT(S)/ WITHDRAWAL FROM THE STUDY

10.1. Study Completion

A patient will be considered to have completed the study if he or she has finished all protocol-specified procedures, including 36 cycles of maintenance treatment, or, if he or she has completed all protocol-specified procedures before the end of the study and has not been lost to

follow-up, and has not withdrawn consent for study participation before the end of the study or has transitioned to commercial drug product.

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

10.2.1. Discontinuation of Study Treatment

A patient will not be automatically withdrawn from the study if he or she must discontinue study treatment before the end of the treatment regimen; instead, the patient will enter the Follow-up Phase. The EOT Visits and Follow-up visit assessments should continue as specified in the Time and Events Schedules.

A patient's study treatment must be discontinued if the following occurs:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the patient to discontinue study treatment.
- The patient becomes pregnant.
- The patient (or the patient's legally acceptable representative) withdraws consent for administration of study drug.
- The patient experiences unacceptable toxicity, including daratumumab injection-related reactions described in Section 6.2.3.
- If 3 consecutive planned doses of daratumumab are missed for reasons other than toxicity unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.
- The patient experiences PD (please see below); loss of CR is not considered as PD.
- The patient experiences a malignancy other than multiple myeloma that cannot be treated by surgery alone (however, a patient who develops a malignancy that can be cured surgically may continue to receive the assigned study treatment and should continue to be followed for subsequent progression of multiple myeloma).

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

Study treatment will continue until PD/unacceptable toxicity or until the end of study treatment, whichever occurs first. Before patients are discontinued from study treatment because of suspected PD:

1. The investigator (or designee) will provide documentation of PD (eg, by completing a PD form or by contacting the IWRS) as soon as possible and within 48 hours of confirmation of PD.
2. The sponsor's medical monitor will review the provided documentation and confirm that PD has occurred per IMWG criteria (see Section 9.3.1) and that study treatment should be discontinued.
3. After confirmation of PD by the sponsor, the patient will discontinue study treatment and enter the Follow-up Phase.

10.2.2. Withdrawal From the Study

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

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

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

When a patient withdraws consent before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study treatment assigned to the withdrawn patient may not be assigned to another patient. Patients who withdraw will not be replaced. If a patient discontinues study treatment and withdraws from the study before the EOT Phase, EOT assessments should be obtained. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

10.3. Withdrawal From the Use of Samples In Future Research

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

11. STATISTICAL METHODS

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

11.1. Patient Information

The primary and secondary efficacy analysis will be performed based on the intent-to-treat population, which will include all randomized patients.

Safety will be evaluated for the safety population, which includes all treated patients who receive at least 1 dose of randomized therapy. Subgroup analyses will be performed as appropriate, and details will be specified in the SAP.

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

The primary analysis will be conducted at 2-sided alpha level of 0.05.

11.2. Sample Size Determination

Based on previous reports of MRD negativity rate in lenalidomide-treated myeloma patients, as discussed in Section 3.2.1, the anticipated MRD (at 10^{-5}) negativity conversion rate is estimated to be 20% for patients treated by lenalidomide alone following post ASCT. Assuming a 20% absolute increase in MRD negativity rate (40% daratumumab plus lenalidomide versus 20% lenalidomide alone) by the end of 12-month maintenance treatment, a sample size of 214 patients (ie, 107 patients per treatment group at a 1:1 randomization) will be needed to achieve at least 85% power to detect such a treatment difference at a 2-sided alpha of 0.05 using continuity corrected chi-squared test.

Disease assessments for each patient will continue until 36 months from the date of randomization of last patient. It is anticipated that this will yield 64 PFS events and provide approximately 79% power to detect a 50% reduction in the risk of progression or death (HR=0.50, translating to an improvement in median PFS from 60 months to 120 months) with a log-rank test at a 2-sided alpha of 0.05 with an accrual period of 1 year. One interim analysis using Obrien-Fleming alpha spending function is planned at the time of primary endpoint analysis when approximately 32 events are anticipated.

11.3. Efficacy Analyses

Response to study treatment and PD will be evaluated by a validated computer algorithm based on IMWG 2016 criteria. There is no imputation planned for missing efficacy endpoint values.

11.3.1. Primary Endpoint and Analysis

The primary endpoint is the MRD conversion rate from baseline to 12 months after maintenance treatment as determined by NGS, which is the proportion of patients who have achieved MRD negative status [at 10^{-5}] by 12 months after maintenance treatment prior to progressive disease (PD) or subsequent anti-myeloma therapy. Patients who have achieved MRD negative status on or after PD or switch to subsequent anti-myeloma therapy before PD, will not be considered MRD negative in the primary endpoint analysis.

The MRD conversion rate will be compared between the 2 treatment groups based on the intent-to-treat population using the stratified Cochran Mantel-Haenszel test with baseline cytogenetic risk (high versus standard/unknown) as stratification factor. A Mantel-Haenszel odds ratio along with its 2-sided 95% CIs will be calculated.

11.3.2. Secondary Endpoints and Analysis

11.3.2.1. Progression-free Survival, Overall Survival, and Minimal Residual Disease

Time-to-event secondary endpoints including PFS and OS will be analyzed through a stratified log-rank test for the comparison of the distribution between the 2 treatment groups. The Kaplan-Meier method will be used to estimate the distribution for each treatment. The treatment effect (HR) and its 2-sided 95% CIs are to be estimated using a stratified Cox regression model

with treatment as the sole explanatory variable stratified by baseline cytogenetic risk (high versus standard/unknown).

The overall MRD negativity rate at any time after randomization and MRD durability will be analyzed.

The binary secondary endpoints including rate of CR and sCR will be analyzed similarly to MRD negativity rate.

A descriptive summary for duration of response will be provided. No statistical comparison will be made.

11.3.2.2. Patient-reported Outcomes

The EORTC QLQ-C30 and EORTC QLQ-MY20 scale scores and EQ-5D-5L utility and visual analog scores will be descriptively summarized by treatment group at each time point. Within-group and between-group treatment effects of the PRO endpoints will be assessed by change from baseline using mixed models for repeated measures. Full details on meaningful change thresholds and statistical analyses will be provided in the SAP.

11.4. Safety Analyses

Adverse Events

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

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

Clinical Laboratory Tests

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

Vital Signs

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

11.5. Benefit-risk Analyses

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

11.6. Interim Analyses

No interim analysis is planned for the primary endpoint of the study. The primary analysis will be performed after all randomized patients have completed 12 months of maintenance treatment, have disease progression, died, or have been discontinued/withdrawn from study treatment by this time point. Afterwards, an annual analysis will be performed to update secondary endpoints and safety. A final analysis will occur at the end of study 36 months from the date of randomization of last patient.

An interim analysis, at the time of primary endpoint analysis, and a final analysis will be conducted for PFS. Obrien-Fleming alpha spending function will be used to control overall alpha at 0.05.

11.7. Independent Data Monitoring Committee

An Independent Data Monitoring Committee, consisting of at least 2 clinicians and 1 statistician, will be established to review safety data before the primary analysis of the MRD negativity rate, which will be conducted by the sponsor. The Independent Data Monitoring Committee will start their review after the first 100 patients have been treated for at least 4 cycles or discontinued and subsequently perform their review every 6 months. Details will be provided in a separate Independent Data Monitoring Committee charter. Emerging data from all ongoing SC daratumumab studies will be communicated to the Independent Data Monitoring Committee, where applicable.

12. ADVERSE EVENT REPORTING

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

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the patient is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events

Solicited adverse events are predefined local and systemic events for which the patient is specifically questioned.

Unsolicited Adverse Events

Unsolicited adverse events are all adverse events for which the patient is specifically not questioned.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

12.1.1.1. Adverse Event

An adverse event is any untoward medical occurrence in a clinical study patient administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. 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 per International Conference on Harmonisation [ICH])

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

Note: The sponsor collects 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).

12.1.1.2. 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 patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- 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 patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study treatment(s) 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).

12.1.1.3. 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 or package insert.

12.1.1.4. Adverse Event Associated With the Use of the Intervention

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

12.1.1.5. Adverse Event Associated With Progression of Disease

Expected progression of disease should not be considered an adverse event (or serious adverse event). 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.

12.1.2. Attribution Definitions

Each adverse event is to be assigned an attribution definition, as shown below.

Not Related

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

Doubtful

An adverse event for which an alternative explanation is more likely, for example, concomitant drug(s) and 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 study treatment(s). An alternative explanation, eg, concomitant drug(s) and 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 study treatment(s). The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s) and 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) and 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 NCI-CTCAE Version 5. Any adverse event or serious adverse event not listed in the NCI-CTCAE will be graded according to investigator clinical judgment by using general guideline in the introduction of CTCAE Version 5:

Grade 1 (Mild): Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 (Moderate): Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL*.

Grade 3 (Severe): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

***** Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

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

12.2. Special Reporting Situations

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

- Overdose of sponsor study treatment. No maximum tolerated dose has been reached for daratumumab. However, if the dose exceeds the maximum tested dose of 2000 mg, then it will be considered as an overdose in this study.
- Suspected abuse/misuse sponsor study treatment
- Accidental or occupational exposure to sponsor study treatment
- Any failure of expected pharmacologic action (ie, lack of effect) of sponsor study treatment
- Unexpected therapeutic or clinical benefit from use of a sponsor study treatment
- Medication error involving a sponsor product (with or without patient/patient exposure to the sponsor study intervention, eg, name confusion)
- Exposure to sponsor study treatment from breastfeeding
- Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

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 (± 7 days) after the last dose of study treatment(s). The only exceptions are as follows (whichever occurs first):

- Patients who have withdrawn informed consent for study participation
- Patients who have received additional treatment with therapeutic intent for multiple myeloma within 30 days (± 7 days) after the last dose study treatment(s). For these patients, only adverse events that are considered to be possibly, probably, or definitely related to the study drug must be reported (unless the patient has been withdrawn from the study).

Serious adverse events, including those spontaneously reported to the investigator within 30 days (± 7 days) after the last dose of study treatment(s), must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Death and PD 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 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 2.

All adverse events, regardless of seriousness, severity, or presumed relationship to study treatment(s), must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the 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 that 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. The investigator (or sponsor, where required) must report SUSARs to the appropriate Institutional Review Board (IRB) that approved the protocol unless otherwise required and documented by the IRB.

For all studies with an outpatient phase, including open-label studies, the patient 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 patient 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
- Patient 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 eCRF, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a 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 patient'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 treatment(s) or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information or 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 patient's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- If the patient has not experienced a significant medical event but is hospitalized overnight only for observation following administration of daratumumab, 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 eCRF).

  Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered 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 patient for the duration of the treatment period.

As previously described, disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Section 12.1.1).

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 patient who becomes pregnant during the study must discontinue further study treatment. The patient should be referred to a physician experienced in teratology for evaluation and advice. Investigators should follow the local label for guidance on patient education and ensure that all patients adhere to the local lenalidomide REMS program (when lenalidomide is supplied locally), or the lenalidomide Global Pregnancy Prevention Plan provided in Attachment 3 (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 in partners of male patients 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.

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, that is, 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 patients, 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 TREATMENT INFORMATION

For the purposes of this study, study drug refers to daratumumab.

14.1. Physical Description and Packaging of Daratumumab

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

14.2. 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.

14.3. Preparation, Handling, and Storage

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

Refer to the Commercial Prescribing Instructions for drug preparation and administration and Pharmacy Manual for details regarding dose preparation, storage, and handling of diluted solutions.

14.4. Study Treatment 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 patient must be documented on the drug accountability form. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

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

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

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

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Study protocol
- Investigator's Brochure for daratumumab
- Investigational Product Manual
- Laboratory manual and laboratory kits
- Electronic data capture (eDC) manual
- Sample ICF Trial Center file and corresponding site-specific documentation
- Patient study tools (patient diaries) and emergency ID card
- Investigator study tools and quick reference cards, as required
- NCI-CTCAE Version 5
- PRO questionnaires and user manuals: PRO questionnaires will include the EORTC QLQ-C30, EQ-5D-5L, and EORTC QLQ-MY20
- IWRS manual and codes

16. ETHICAL ASPECTS

16.1. Study-specific Design Considerations

The safety profile of daratumumab, primarily consists of infusion-related reactions. Based on the mode of action of daratumumab, a potential risk could be infection; therefore, review of hematological laboratory results prior to daratumumab administration is required per protocol. CD38 is distributed in erythrocytes and platelets. A significant reduction of platelets was reported in an animal study. In addition, in a human clinical study (Study GEN501), thrombocytopenia was also reported. However, safety laboratory monitoring has not shown a clinically meaningful reduction of platelets. No bleeding events were observed. Anemia was also reported in Study GEN501. Free hemoglobin was mildly elevated, but other parameters did not support hemolysis.

Routine safety laboratory measurement of RBCs and platelets will be closely monitored in this study. In addition, an Independent Data Monitoring Committee will be established to review safety data on a regular basis throughout the duration of the study.

Potential patients will be fully informed of the risks and requirements of the study and, during the study, patients 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 patients 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, a legally acceptable representative may provide consent on behalf of the patient.

The total blood volume to be collected during the course of the study is considered to be acceptable for patients participating in a cancer clinical study and reasonable over the time frame of the study.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide 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 patients)
- Investigator's Brochure for daratumumab (or equivalent information) and amendments/addenda
- Sponsor-approved patient recruiting materials
- Information on compensation for study-related injuries or payment to patients for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for patients
- Any other documents that the IRB requests to fulfill its obligation

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for patients, data, or study conduct)
- Revision(s) to ICF and any other written materials to be provided to patients
- If applicable, new or revised patient recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to patients 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 IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the patients or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the patients
- Report of deaths of patients 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 IRB

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

At least once a year, the 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 IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

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

The patient 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 the patient'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 patient.

If the patient 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 patient or legally acceptable representative is obtained.

When prior consent of the patient is not possible and the patient's legally acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IRB to protect the rights, safety, and well-being of the patient and to ensure compliance with applicable regulatory requirements. The patient 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 patients 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 patients confidential.

The informed consent obtained from the patient (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, IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The patient 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.

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 patients 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 till the end of the study (or according to local regulations) for additional research. Samples will only be used to understand daratumumab, to understand multiple myeloma, to understand differential intervention responders, and to develop tests/assays related to daratumumab and multiple myeloma. The research may begin at any time during the study or the post-study storage period.

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

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 IRB approval or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the patients, in which case the amendment must be promptly submitted to the IRB and relevant competent authority. Documentation of amendment approval by the investigator and IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (where required) only needs to be notified.

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

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Pre-study Documentation

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

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IRB approval of the protocol, amendments, ICF, any recruiting materials, and, if applicable, patient compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee
- Name and address of the IRB, including a current list of the 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 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 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 patient:

- Completed investigator financial disclosure forms from all sub-investigators
- Documentation of sub-investigator 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. Patient Identification, Enrollment, and Screening Logs

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

The patient identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure patient confidentiality, no copy will be made. All reports and communications relating to the study will identify patients by patient identification and date of birth (as allowed by local regulations). In cases where the patient 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 patient screening log, which reports on all patients 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: patient 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; intervention receipt/dispensing/return records; study treatment(s) administration information; and date of study completion and reason for early discontinuation of study treatment(s) 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 documents). 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 patient 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. These data are electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system, but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

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

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

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

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

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

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

17.6. Data Quality Assurance/Quality Control

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

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

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each patient, 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 use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study-site visit log that will be kept at the study site. The first post-initiation visit be scheduled within two to three weeks of the first patient's screening visit. Subsequent on-site monitoring visits will be scheduled as established in the monitoring frequency for the study and will be communicated by the site manager. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

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

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

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The end of the study is defined as 36 months from the date of randomization of last patient. If a patient has died, the date and cause of death will be collected and documented in the eCRF. Patients benefiting from treatment with daratumumab and/or lenalidomide may continue receiving treatment after the end of the study treatment period of 36 months and after the end of the study, per the investigator's discretion. However, because the study specified treatment is for 36 months, the sponsor will not provide daratumumab and/or lenalidomide after the end of the study, unless required by local health regulatory authorities. The final data from the study site will be sent to the sponsor (or designee) after completion of the final patient assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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

The investigator may initiate study-site closure at any time, provided that 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 the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further daratumumab 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. Patient 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, and formulation information) supplied by the sponsor to the investigator and not previously published and any 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 (CSR) generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. As applicable, results of analyses performed after the CSR has been issued will be reported in a separate report and will not require a revision of the CSR. Study patient 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 that there will be no multicenter study publication. Authorship of publications resulting from this study will be based on guidelines 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; drafted the work or revised it critically for important intellectual content; given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

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

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Attachment 1: 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	≤2×/month		1-2×/ month	3-4x/month		3-4×/month	>1×/week but not nightly		>1×/month	Often 7×/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 1× on any day	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 FEV1 FEV1/FVC	N/A	Normal FEV1 between exacerbations >80% >85%	Normal FEV1 between exacerbations >80% Normal	N/A	>80% >80%	>80% Normal	N/A	60-80% 75-80%	60-80% Reduced 5%	N/A	<60% <75%	<60% Reduced 5%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥2/year Relative annual risk may be related to FEV_1.	≥2/year Relative annual risk may be related to FEV_1.	≥2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥2/year Relative annual risk may be related to FEV_1.	≥2/year Relative annual risk may be related to FEV_1.	≥2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥2/year Relative annual risk may be related to FEV_1.	≥2/year Relative annual risk may be related to FEV_1.
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.											

Recommended Step for Initiating Treatment	Step 1	Step 2	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3: medium dose 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	≤1×/month		≤2×/month	>1×/month	≥2×/month	1-3×/week	>1×/week	≥2×/week	≥4×/week
	Interference with normal activity	None			Some limitation			Extremely limited		
	SABA use for symptom control (not prevention of EIB)	≤2 days/week			>2 days/week			Several times per day		
	Lung function FEV1 or peak flow FEV1/FVC	N/A	>80% >80%	>80%	N/A	60-80% 75-80%	60-80%	N/A	<60% <75%	<60%
	Validated questionnaires ATAQ ACQ ACT			0 ≤0.75 ≥20			1-2 ≥1.5 16-19			3-4 N/A ≤15
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥2/year					
		Consider severity and interval since last exacerbation								
	Reduction in lung growth/ Progressive loss of lung function	Evaluation requires long-term follow-up								
		• Maintain current step			Step up 1 step	Step up at least 1 step	• Step up 1 step • Re-evaluate	• Consider short course of oral steroids		• Consider short

Recommended Action for Treatment	• Regular follow-up every 1 to 6 months • Consider step down if well controlled for at least 3 months	• **Before step up**: Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step. • **Re-evaluate the level of asthma control in 2 to 6 weeks to achieve control**. 0 to 4 years: If no clear benefit is observed in 4 to 6 weeks, consider alternative diagnoses or adjusting therapy. 5 to 11 years: Adjust therapy accordingly. • **For side effects**, consider alternative treatment options.	in 2-6 weeks • For side effects, consider alternative treatment options	• Step up 1 to 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. • **Re-evaluate the level of asthma control in 2 to 6 weeks to achieve control**. 0 to 4 years: If no clear benefit is observed in 4 to 6 weeks, consider alternative diagnoses or adjusting therapy. 5 to 11 years: Adjust therapy accordingly. • **For side effects**, consider alternative treatment options.	course of oral steroids • Step up 1 to 2 steps • Re-evaluate in 2 weeks • For side effects, consider alternative treatment options

ACQ = asthma control questionnaire; ACT = asthma control test; ATAQ = asthma therapy assessment questionnaire; EIB = exercise-induced bronchoconstriction; FEV1 = forced expiratory volume (in 1 second); FVC = forced vital capacity; ICS = inhaled corticosteroids; N/A = not applicable; SABA = short-acting beta agonist.

Attachment 2: 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, All Adverse Events. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described in Section 12.3.2, Serious Adverse Events. 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

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

Statistical Analysis

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

Attachment 3: Contraceptive (and Barrier) Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 4.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 12.3.3, Pregnancy and Section 12.1.1 Adverse Events: Definitions and Classifications.

Refer to Guidance for Contraceptive and Barrier Use below.

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 the use of contraceptive methods for participants in clinical studies.

For Lenalidomide studies
Lena website: http://www.revlimidrems.com/
Further information about the REMS programs is available at: www.celgeneriskmanagement.com

1.	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.
2	Prior to starting lenalidomide, two 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.
3	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 3 (where lenalidomide is supplied centrally and no local lenalidomide REMS program exists).
4	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 at least 4 weeks after the last dose of lenalidomide.
5	Because of the embryo-fetal risk of lenalidomide, all patients must adhere to the local lenalidomide REMS program (when lenalidomide is supplied locally), or the lenalidomide Global Pregnancy Prevention Plan provided in Attachment 3 (when lenalidomide is supplied centrally and no local lenalidomide REMS program exists).
6	Patients must not donate blood during therapy, during dose interruptions, and for at least 4 weeks following discontinuation of lenalidomide.

Lenalidomide Global Pregnancy Prevention Plan

Where lenalidomide is supplied locally, patients must adhere to the local lenalidomide REMS program. Where lenalidomide is supplied centrally and no local lenalidomide REMS program exists, then patients 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 patients 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 patients receiving Lenalidomide who are females of childbearing potential
- Acceptable birth control methods for both female of childbearing potential and male patients receiving Lenalidomide in the study
- Requirements for counseling of all study patients 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 patient records.
    3. The Lenalidomide Information Sheet (Section 1.1.1.4) will be given to each patient receiving lenalidomide study therapy. The patient 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 (i.e., 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 patients 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 patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception, the patient should switch to one of the effective methods 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 patients 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 Patients:

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 patient may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Patients:

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 Patients:

- 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 patient, study drug must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient 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 Patients:

- 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 patient during study participation, the investigator must be notified immediately.

Additional precautions

- Patients 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 patients should not donate blood during therapy, during dose interruptions and for at least 28 days following discontinuation of study drug.
- Male patients should not donate blood, semen or sperm during therapy, during dose interruptions and 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: _____
Patient 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 (i.e., has had menses at any time during the preceding 24 consecutive months)

□ NOT FCBP

Male: □

Do Not Dispense study drug if:

- **The patient is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The patient 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 patient 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 patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
    - If the patient missed a period or has unusual menstrual bleeding.
    - When the patient 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 patient.

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 childbearing 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 patient.

MALE:

1. I counseled the Male patient 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 patient.

Investigator/Counselor Name (Print): _____
(circle applicable)

Investigator/Counselor Signature: _____ Date: _____/_____/_____
(circle applicable)

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

1.1.1.4 Lenalidomide Information Sheet

FOR PATIENTS 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 childbearing potential whose male partner is receiving lenalidomide is unknown at this time.

- Male patients (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 patients 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 4: Protocol Amendment History

Amendment 3 (24 June 2021)

Overall Rationale for the Amendment: Administrative protocol clarifications and updates to allow for Canadian sites to join the study, and clarify the discrepancy in inclusion/exclusion criteria.

Section number and Name	Description of Change	Brief Rationale
SYNOPSIS: OVERVIEW OF STUDY DESIGN; 3.1 Overview of Study Design	Revised study design and overview to include the addition of Canada. "Phase 3, randomized, open-label, active-controlled, multicenter study to be conducted at sites in the United States (US) **and Canada**…"	Added language to allow for the addition of Canadian sites to the study
4.1 Inclusion Criteria	Revised language to remove the below bullet points from Inclusion Criterion #2. a. For patients who have not received consolidation therapy, the patient must be within 180 days post-transplant at the time of randomization. b. For patients treated with consolidation therapy, the patient must be within 90 days of the last dose of consolidation therapy at the time of randomization.	Removed bullets a) and b) from Inclusion Criterion 2 to align with changes made during Amendment 2.
6.1 Daratumumab and Lenalidomide Dosing and Supply	Revised the language within Daratumumab and Lenalidomide dosing to include the following statement. "… or the lenalidomide Global Pregnancy Prevention Plan (when lenalidomide is supplied centrally and no local lenalidomide REMS program exists) in Attachment 3."	Added language to align with lenalidomide reporting requirements for Canadian sites.
6.2.2.1 Pre-administration Medications	Revised the language to indicate correct cycle for dexamethasone step down dosing. "(for example, 12 mg on C**2**D1, 8 mg on C**2**D8, and 4 mg on C**2**D15, with no dexamethasone being given on C**2**D22 and beyond)."	Updated language to align with Time and Events Schedule for step down dosing of dexamethasone.
14. STUDY TREATMENT INFORMATION	Revised the language to remove "Daratumumab will be supplied by the sponsor. Lenalidomide is commercially available." The following language was added in its place, "For the purposes of this study, study drug refers to daratumumab".	Removed prior language to align protocol with Canadian drug provision requirements.
17.9.1 Study Completion/End of Study	Revised the language to include the bolded language, "… daratumumab **and/or lenalidomide** may continue receiving treatment after **the end of the study treatment period of 36 months and after** the end of the study, per the	Added language to align protocol with Canadian drug provision requirements.

Section number and Name	Description of Change	Brief Rationale
	investigator's discretion. However, **because the study specified treatment is for 36 months, the** sponsor will not provide daratumumab **and/or lenalidomide** after the end of the study**, unless required by local health regulatory authorities**."	
Attachment 3	Revised the language to include the Lenalidomide Global Pregnancy Prevention Plan.	Added the Lenalidomide Global Pregnancy Prevention Plan for Canadian sites joining the study.

Amendment 2 (08 July 2020)

Overall Rationale for the Amendment: Protocol clarification and revision of inclusion/exclusion criteria, including removal of the 8-cycle upper limit, and extension of screening window to 60 days.

Section number and Name	Description of Change	Brief Rationale
SYNOPSIS: HYPOTHESIS; OBJECTIVES AND ENDPOINTS – Primary Objective, OVERVIEW OF STUDY DESIGN, PATIENT POPULATION; 1 Introduction; Table 1. Objectives and Endpoints – Primary Objective; 2.2 Hypothesis; 3.1 Overview of Study Design; 3.2.1 Overall Rationale for Study Design; 3.2.3 Subcutaneous Daratumumab Dosing and rHuPH20 Concentration Chosen for This Study; 4.1 Inclusion Criteria; Figure 1. Schematic Overview of the Study	Revised language to remove "with or without consolidation therapy."	To align with changes in inclusion criteria.
SYNOPSIS: OBJECTIVES AND ENDPOINTS – Primary Objective, OVERVIEW OF STUDY DESIGN; 1 Introduction; Table 1. Objectives and Endpoints – Primary Objective; 3.1 Overview of Study Design; 3.2.1 Overall	Revised study objectives and inclusion criterion #5 to require that enrolled patients have MRD positivity, as determined by NGS, **at the time of screening** (revised from "post-transplant" in some sections).	To clarify that MRD positivity must be documented no earlier than 30 days before the start of the screening period.

Section number and Name	Description of Change	Brief Rationale
Rationale for Study Design; Figure 1. Schematic Overview of the Study		
SYNOPSIS: OVERVIEW OF STUDY DESIGN; 3.1 Overview of Study Design	Strikethrough text was removed: "This is a Phase 3, randomized, open-label, active-controlled, multicenter study to be conducted at ~~approximately 50 to 60~~ sites in the United States (US)…"	To remove language specifying approximate number of study sites.
SYNOPSIS: OVERVIEW OF STUDY DESIGN, PATIENT POPULATION; 1 Introduction; 3.1 Overview of Study Design; 3.2.1. Overall Rationale for Study Design; 4.1 Inclusion Criteria; Figure 1. Schematic Overview of the Study	Revised study design and inclusion criterion #2 to replace "4 to 8 cycles of induction" with "**a minimum of** ~~4 to 8~~ cycles of induction **therapy**."	To remove the 8-cycle upper limit to allow for additional therapy prior to transplant for patients whose transplant is delayed due to COVID-19 pandemic.
SYNOPSIS: OVERVIEW OF STUDY DESIGN, PATIENT POPULATION; TIME AND EVENT SCHEDULE – PART 1: OVERALL STUDY PROCEDURES; 1 Introduction; 3.1 Overview of Study Design; 3.2.1. Overall Rationale for Study Design; 4.1 Inclusion Criteria; Figure 1. Schematic Overview of the Study	Revised study design and inclusion criterion #2 to replace the description of the interval between transplant and randomization—"within 180 days post-transplant"—with "within 6 months of ASCT" on the date of randomization.	To make this eligibility criterion easier for sites to accurately determine eligibility window between transplant date and randomization.
	Revised study design and inclusion criterion #2 to include that patients must "have undergone HDT and ASCT within 12 months of the start of induction therapy."	To limit the amount of time elapsed between induction and HDT/ASCT in light of removal of 8-cycle upper limit for induction therapy.
SYNOPSIS: PATIENT POPULATION; 3.1 Overview of Study Design; 4.1 Inclusion Criteria	Revised inclusion criterion #4 sub-bullets to reflect the following changes (bolded text was added; strikethrough text was removed): o Non-decalcified diagnostic bone marrow aspirate clot sections (block or slides) for MRD assessment: ▪ A Formalin fixed paraffin embedded (FFPE) block of bone marrow aspirate clot, or ~~5~~ slides **(preferably 5 slides, if available)**, 5 µm each, of non-decalcified bone marrow, **or** ▪ ~~5 s~~Slides **(preferably 5 slides, if available)**, bone marrow aspirate smear. ▪ **Please note, bone marrow core sections are not acceptable samples for analysis.** ▪ **In exceptional circumstances when**	For clarification purposes and to allow option of post-transplant archived bone marrow sample for MRD analysis for patients whose pre-induction or pre-transplant bone marrow samples do not provide an informative clone due to poor specimen quality.

Section number and Name	Description of Change	Brief Rationale
	index myeloma clone cannot be identified from the archived bone marrow sample, a post-transplant sample can be used to identify myeloma clone with permission from the Sponsor.	
SYNOPSIS: OVERVIEW OF STUDY DESIGN; TIME AND EVENT SCHEDULE – PART 1: OVERALL STUDY PROCEDURES; 4 Patient Population	Expanded screening window from "42 days" to "60 days" prior to randomization.	To expand the timeframe for screening window necessitated by the switch to NGS method for MRD screening and the COVID-19 pandemic.
TIME AND EVENT SCHEDULE – PART 1: OVERALL STUDY PROCEDURES	Revised Screening Phase footnote to include the following language: "Tandem transplants are not allowed."	For clarification purposes.
	Revised Notes for chest x-ray or full chest CT scan to indicate that scan is not required if performed as part of standard of care within 30 days prior to screening.	For clarification purposes and to simplify screening procedure.
	Revised Study Phases/Visits (Maintenance) for ECOG performance status to include the following language (bold text has been added): "D1 of odd cycles **(ie, C1, C3, C5, C7, and so on)."**	To provide further clarification around "D1 of odd cycles" schedule.
	Revised Notes for 12-lead ECG to remove the following language: "~~Not required if an ECG was performed as part of standard of care within 42 days prior to randomization~~."	For clarification purposes and to simplify screening procedure.
	Revised Study Phases/Visits (Maintenance) for weight to remove the following language: On C1D1~~, immediately before daratumumab SC administration~~	To clarify a definitive timeframe (C1D1).
	Revised Study Phases/Visits (Maintenance) for vital signs (bolded text was added; strikethrough text was removed): ▪ Daratumumab + lenalidomide arm: – C1D1: ~~Immediately~~**Up to 30 minutes** before administration; at end of administration; and at 0.5 and 1 hour **(+/-5 minutes)** after end of administration.	To clarify definitive timeframes.
	Revised Study Phases/Visits (Maintenance) for hematology and serum chemistry to include the following language (bold text has been added): On C1D1 **and D1 of subsequent cycles**, there is no need to repeat the tests if performed within the past 3 days.	For clarification purposes.
	Revised Notes for randomization to replace "72	To clarify that

Section number and Name	Description of Change	Brief Rationale
	hours" with "3 business days" in describing the interval between randomization and first dose of study treatment on C1D1.	randomization timeframe refers to business, and not calendar, days in case randomization occurs after a weekend.
TIME AND EVENT SCHEDULE – PART 1: OVERALL STUDY PROCEDURES (BONE MARROW ASPIRATE/BIOPSY)— Procedure: Assessment of lytic bone disease, Extramedullary soft tissue plasmacytomas (in patients with history of extramedullary soft tissue plasmacytoma, physical or radiologic examination to be done as applicable)	Revised Notes as follows (bolded text was added; strikethrough text was removed): Not required during screening if performed as part of standard of care within ~~42~~**30** days before ~~randomization~~ **screening**.	For clarification purposes and to simplify screening procedure.
	Revised Procedures as follows (bolded text was added): Extramedullary soft tissue plasmacytomas (in patients with history of **extramedullary soft tissue** plasmacytoma, physical or radiologic examination to be done as applicable)	For clarification purposes.
TIME AND EVENT SCHEDULE – PART 1: OVERALL STUDY PROCEDURES (BONE MARROW ASPIRATE/BIOPSY)— Procedure: Cytogenetics - FISH aspirate (performed centrally)	Revised Notes as follows (bolded text was added; strikethrough text was removed): If central and local cytogenetic results are **un**~~not~~ available, the patient will be ~~assumed to have normal~~ **stratified with patients with standard** cytogenetics.	To clarify language regarding cytogenetic risk stratification.
TIME AND EVENT SCHEDULE – PART 1: OVERALL STUDY PROCEDURES— Procedure: Blood and 24-hour urine samples	Revised Screening and Notes for SPEP, UPEP, Serum IFE, Urine IFE (bolded text was added; strikethrough text was removed): "Note that screening SPEP, UPEP, serum IFE, and urine IFE must be done within ~~14~~ **21** days before ~~C1D1~~**randomization**."	To allow greater flexibility in collecting laboratory samples in light of COVID-19 pandemic.
	Revised Study Phases/Visits (Maintenance) for Urine IFE (bolded text was added; strikethrough text was removed): Note: ~~*Please note:~~ SPEP, UPEP, serum IFE, and urine IFE assays must be done during screening (~~14~~**21** days before C1D1) as well as on C1D1.	To allow greater flexibility in collecting laboratory samples in light of COVID-19 pandemic.
	Revised Notes to include the following language: "During the COVID-19 pandemic, local laboratory results can be used to determine eligibility of the patient on a temporary basis and with Sponsor approval before laboratory results are collected. Local laboratory results should be reported in eCRF as an unscheduled visit. After the COVID-19 situation improves, all attempts should be made to determine eligibility of the patient based on the central laboratory results."	To provide clarification regarding local vs. central laboratory results use in relation to COVID-19 situation.

Section number and Name	Description of Change	Brief Rationale
	Revised Notes to include the following language: On C1D1 and D1 of subsequent cycles, there is no need to repeat the tests if performed within the past 3 days of scheduled visit. In addition, tests may be repeated as clinically indicated. Results must be evaluated before each daratumumab administration or beginning of new cycle of lenalidomide administration.	For clarification purposes.
TIME AND EVENT SCHEDULE – PART 1: OVERALL STUDY PROCEDURES– Footnote	Revised footnote to include language in relation to central laboratory tests: Local **and central** laboratory tests should be conducted within 3 days of Day 1 of each lenalidomide cycle (control arm) OR within 3 days of each daratumumab administration.	To provide clarification regarding local vs. central laboratory tests.
TIME AND EVENTS SCHEDULE – Part 2, Cytogenetics	Revised Lab column text (strikethrough text has been removed): Central ~~and Local~~	
3.2.2.2. Rationale for Subcutaneous Daratumumab Administration	Revised text to include the following details related to subcutaneous daratumumab administration: "DARZALEX Faspro™ (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use, received FDA approval on 01 May 2020 to be administered at a dose of 1800 mg of daratumumab and 30,000 units hyaluronidase per 15 mL (120 mg and 2000 units/mL) solution in a single-dose vial."	To provide further detail and clarification on subcutaneous daratumumab administration following US FDA approval on 01 May 2020.
TIME AND EVENT SCHEDULE – PART 1: OVERALL STUDY PROCEDURES (BONE MARROW ASPIRATE/BIOPSY); 3.2.5. MRD Assessment Using NGS	Revised text to add the following language: "If a bone marrow biopsy was conducted up to 30 days prior to the start of screening AND a positive MRD result based on Adaptive Biotechnologies' NGS-based MRD assay is available, a repeat biopsy during screening is not required. In this situation, local PC clonality and morphology may be used."	To clarify interval between bone marrow biopsy and screening that allows for avoidance of repeat biopsy during screening.
3.2.3. Subcutaneous Daratumumab Dosing and rHuPH20 Concentration Chosen for This Study	Strikethrough text was removed: In the proposed study, daratumumab 1800 mg SC will be administered in 28-day cycles using the standard dosing schedule for daratumumab monotherapy (ie, weekly during Cycles 1 and 2, every 2 weeks during Cycles 3 through 6, and every 4 weeks from Cycle 7 onward for a maximum of 36 cycles) to quickly achieve and maintain effective daratumumab concentrations. ~~Newly diagnosed multiple myeloma p~~Patients ~~treated with induction with or without consolidation~~ will be randomized ~~after transplant~~ in a 1:1 ratio to maintenance therapy with SC daratumumab and lenalidomide or lenalidomide	To align with changes in inclusion criteria and other language changes in reference to consolidation therapy.

Section number and Name	Description of Change	Brief Rationale
	alone.	
4.2 Exclusion Criteria	Added new exclusion criterion #2 and renumbered exclusion criteria accordingly. Exclusion criterion #2 (bolded text was added): **Must not have progressed on MM therapy at any time prior to screening.**	For clarification purposes.
6.2.2.1. Pre-administration Medications	Expanded language on pre-administration corticosteroid dosing (bolded text was added; strikethrough text was removed): Corticosteroids (Long-acting or Intermediate-acting): Administer 20 mg dexamethasone (or equivalent) prior to ~~every~~ daratumumab injection **during Cycle 1 (first 4 doses of daratumumab). Beginning in Cycle 2, corticosteroids may be tapered over 3 consecutive daratumumab injections to discontinuation at the investigator's discretion. The following dexamethasone taper should be used: 12, 8, and 4 mg over 3 daratumumab injections (for example, 12 mg on C1D1, 8 mg on C1D8, and 4 mg on C1D15, with no dexamethasone being given on C1D22 and beyond).**	To change pre-administration steroid requirement in light of emerging data on safety of discontinuing steroids.
	Expanded language on pre-administration antihistamine administration to include the following: "Antihistamine may be discontinued after Cycle 2 at the investigator's discretion if the patient has side effects or does not tolerate."	To modify pre-administration antihistamine requirement to allow for discontinuation after Cycle 2.
6.3.1. Cycle Delay	Revised language as follows (strikethrough text was removed): On the first day of each new treatment cycle and before each daratumumab dose, the patient will be evaluated ~~by the treating physician~~ for possible toxicities that may have occurred after the previous dose(s).	To expand language on evaluation for possible toxicities such that this can be done by chemotherapy nurses.
6.3. Dose Delays and Dose Modifications; 17.2.2 Required Pre-study Documentation	Replaced all uses of "subinvestigator" with "sub-investigator."	Minor errors, editorial issues, or changes for clarity/consistency noted in the protocol were corrected.
6.4.2. Lenalidomide	Updated the date provided for most recent prescribing information for lenalidomide from "January 2019" to "October 2019."	
TIME AND EVENTS SCHEDULE – PART 2: DETAILS FOR BONE MARROW TESTING – MRD (aspirate) by NGS	Revised "During Screening: Collect bone marrow aspirate and/or biopsy" language (bolded text was added; strikethrough text was removed): Note that archived samples collected prior to induction therapy or **prior to** ~~after~~ transplant will also be obtained as described in Inclusion Criterion #4 for calibration of MRD by NGS.	

Section number and Name	Description of Change	Brief Rationale
ABBREVIATIONS; Throughout the protocol	Updated all uses of "CRF" to "eCRF" and removed "CRF" and its definition from the abbreviations list.	
9.3.6. Documentation of Extramedullary Plasmacytomas	Revised language as follows (bolded text was added): CT **and/or PET/CT** scan evaluations are an acceptable alternative if there is no contraindication to the use of IV contrast.	To clarify option for use of PET/CT scan evaluations.
9.5.3. ECGs, Chest Imaging, Physical Examination, and Spirometry	Revised as follows (bolded text was added; strikethrough text was removed): A 12-lead ECG is required during screening and ~~if not conducted within the previous 42 days and~~ may be performed during the study as clinically indicated. A chest x-ray or full chest CT scan is required during screening if not conducted within ~~the previous 42~~ **30** days **prior to screening.**	For clarification purposes and to simplify screening procedure.

Amendment 1 (09 December 2019)

Overall Rationale for the Amendment: Protocol clarification and revision of inclusion/exclusion criteria, including MRD assessment by NGS assay during screening and to align with standard clinical practice for multiple myeloma patients receiving maintenance treatment.

Section number and Name	Description of Change	Brief Rationale
SYNOPSIS TIME AND EVENT SCHEDULE – PART 1: OVERALL STUDY PROCEDURES	Revised screening window in Synopsis and footnote in T&E Schedule Part 1 Table from '28 days' to '42 days'.	To allow time for 2 sequential NGS assays (MM index clone calibration and MRD assessment) during screening.
SYNOPSIS TIME AND EVENT SCHEDULE – PART 1: OVERALL STUDY PROCEDURES 3.1. Overview of Study Design 4.1 Inclusion Criteria	Revised Screening Phase footnote in T&E Schedule Part 1 Table and inclusion criterion #2a to extend the interval between transplant and randomization from '60 to 100 days' to 'within 180 days' post-transplant in patients who have not received consolidation therapy.	To align with institutional best practice to avoid the need for multiple bone marrow sample collection and to align the time at which screening activities, including MRD assessment of the screening bone marrow biopsy, must start with institutional clinical practice timelines
	Revised inclusion criterion #2b to extend the interval between last dose of consolidation therapy post-autologous stem cell transplant (ASCT) and randomization from '60 days' to 'within 90 days' of the last dose of consolidation therapy.	
	Revised inclusion criterion #4 to indicate that existing results from Adaptive Biotechnologies' NGS-based MRD assay, conducted post-ASCT may be used for identification of index myeloma clone and in that case, an archived sample is not required.	
	Revised inclusion criterion #4b and #4b(i) to clarify acceptable archived samples (eg, aspirate clot).	To align with the clot collection and dispatch of whole block (formalin fixed paraffin embedded bone marrow aspirate clot) at US sites.
	Revised inclusion criterion #5 to conduct screening of MRD status by NGS assay.	Since Adaptive Biotechnologies' NGS-based MRD assay has received FDA clearance, it will be used for MRD assessment during screening.
	Revised inclusion criterion#7c (adequate bone marrow function) to clarify platelet count criteria from '$\geq 50\times10^9$/L' to '$\geq 75\times10^9$/L'.	To align with other daratumumab protocols.
	Revised inclusion criterion#7c (adequate liver function) total and direct bilirubin criteria from '≥1.5 folds of ULN to '≥2.0 folds of ULN.	
	Revised inclusion criterion#7b (adequate renal function) serum calcium from '≤13.5 mg/dL (≤3.4 mmol/L)' to '≤14 mg/dL (≤3.5 mmol/L)'.	

Section number and Name	Description of Change	Brief Rationale
SYNOPSIS TIME AND EVENT SCHEDULE – PART 1: OVERALL STUDY PROCEDURES 11.6. Interim Analyses 17.9.1. Study Completion/End of Study	Added 'confirmed progression of disease' and 'changed treatment due to study drug toxicity' to the end of study definition.	To be consistent with the rest of the protocol.
SYNOPSIS TIME AND EVENT SCHEDULE – PART 1: OVERALL STUDY PROCEDURES 3.2.5. MRD Assessment Using NG 9.3.4. Bone Marrow Examination and Minimal Residual Disease Assessment	Deleted the MRD assessment by NGS at 6 months during maintenance treatment.	To reduce the frequency of bone marrow collection for patient's convenience.
TIME AND EVENT SCHEDULE – PART 1: OVERALL STUDY PROCEDURES	Revised timeline for an acceptable spirometry test from '42 days prior to screening' to 'up to '60 days prior to transplant'.	To accept spirometry test conducted up to 60 days prior to transplant as these results are unlikely to change significantly during screening.
TIME AND EVENT SCHEDULE – PART 1: OVERALL STUDY PROCEDURES	Added details for the timing and assessment of vital signs, hematology, serum chemistry, HCV viral load, blood and 24-hour urine samples, PC clonality assay, and morphology. Specified that PROs should be completed at EOT visit if the patient discontinues early and at other specified timepoints even after the patient discontinues the study treatment.	To clarify the timing and assessment of the evaluations.
TIME AND EVENT SCHEDULE – PART 1: OVERALL STUDY PROCEDURES TIME AND EVENT SCHEDULE – PART 2: DETAILS FOR BONE MARROW TESTING 9.3.4. Bone Marrow Examination and Minimal Residual Disease Assessment	Revised the time of cytogenetics assessment from 'within 42 days of randomization' to 'at any time from the time of multiple myeloma diagnosis to randomization'.	To allow for the utilization of historical cytogenetics data and ensure that patients' cytogenetics profiles are captured as accurately as possible.
SYNOPSIS TIME AND EVENT SCHEDULE – PART 1: OVERALL STUDY PROCEDURE 1.INTRODUCTION 3.2 Study Design Rationale	Added details of 3rd study CASSIOPEIA.	To add new study data in the context of PFS.
3.1. Overview of Study Design	Updated '40 sites' to '50 to 60 sites'.	To facilitate enrollment.
4.2 Exclusion Criteria	Deleted exclusion criterion#1 regarding peripheral neuropathy or neuropathic pain.	Because study treatment does not contain medications that

Section number and Name	Description of Change	Brief Rationale
		may exacerbate neuropathy, and patients may have residual neuropathy from their induction/consolidation regimen that requires additional time to recover should not be excluded from the study.
	Revised exclusion criterion#2 to further clarify on history of any concurrent malignancy.	To align with other daratumumab protocols.
	Revised exclusion criterion#7a from 'seropositivity for HIV' to 'have no known history of seropositivity for HIV'.	To modify the language for clarification.
	Revised exclusion criterion#8 to add current or history of CNS.	To align with other daratumumab protocols.
	Revised exclusion criterion#9b and deleted exclusion criteria#9c and #9d.	
	Added sorbitol to exclusion criterion#10.	
	Revised exclusion criteria#12, #14, #15.	
6.2 Daratumumab	Revised instructions on preparation, dosing schedule, administration, and storage of daratumumab.	To align with other daratumumab protocols.
	Revised text on pre-and post-administration medications.	
	Revised text on injection-related reactions.	
6.3.1 Cycle Delay	Revised text on delay of any treatment cycles and re-treatment criteria.	To align with other daratumumab protocols.
8 Pre-study and Concomitant Therapy	Revised text on recommended, permitted, and prohibited therapies.	To align with other daratumumab protocols.
9.5.2 Clinical Laboratory Tests	Revised text on effect of lenalidomide on WOCBP and pregnancy.	To align with other daratumumab protocols.
	Revised text on indirect antiglobulin tests.	
10 Patient Completion/Discontinuation of Treatment/Withdrawal From the Study	Revised text to be more specific per latest daratumumab protocol template requirements.	To align with other daratumumab protocols.
11.2 Sample Size Determination	Revised power from '80%' to 'at least 85%'.	Since NGS assay will be used for screening MRD status, assumption of 15% non-evaluable archived bone marrow samples will be applied for estimation of screening population, and not for estimation of final sample size. Despite this change, the original sample size of 214 was retained, which increased power from 80% to 85% for this Phase 3 study.
11.3 Efficacy Analysis	Added text on missing data and clarification on patients with MRD negative status.	To clarify handling of missing data and sensitivity analyses.
11.6 Interim Analyses	Added a paragraph on interim and final analysis of PFS.	To address PFS analysis.
12.3.3 Pregnancy	Revised text to be more specific on reporting of pregnancy.	To align with other daratumumab protocols.

Section number and Name	Description of Change	Brief Rationale
Attachment 2	Deleted anemia, neutropenia, and thrombocytopenia from the list of anticipated events; revised conditions of their reporting period; and renamed review committee from 'Anticipated Event Review Committee' to 'Safety Assessment Committee' with its purpose to review aggregate data by treatment arm.	To update the language on anticipated events as provided by R&D.
Attachment 3	Added details on local lenalidomide REMS program or the lenalidomide Global Pregnancy Prevention Plan.	To align with other daratumumab protocols.

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Scientific Affairs

Signature: [electronic signature appended at the end of the protocol] Date: _____
(Day Month Year)

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

Signature

User	Date	Reason
PPD	23-Aug-2024 17:19:25 (GMT)	Document Approval