Janssen Research & Development*

Clinical Protocol

Phase 2, Randomized, Open-Label Study Comparing Daratumumab, Lenalidomide, Bortezomib, and Dexamethasone (D-RVd) Versus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Subjects With Newly Diagnosed Multiple Myeloma Eligible for High-Dose Chemotherapy and Autologous Stem Cell Transplantation

Protocol 54767414MMY2004; Phase 2
Amendment 3

JNJ-54767414 (daratumumab)

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

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Date:	10 January 2019
Prepared by:	Janssen Research & Development
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	4 April 2016
Amendment 1	24 May 2017
Amendment 2	5 Feb 2018
Amendment 3	10 Jan 2019

Please note that the following summary describes changes implemented in Protocol Amendment 3. Details of the changes implemented in Protocol Amendments 1 and 2 have been moved to Attachment 9; please refer to Attachment 9 for further details on the first 2 amendments.

Amendment 3 (10 Jan 2019)

The major reason for this amendment was to allow an accelerated infusion time of daratumumab during the maintenance phase of the study based on new information. Other edits were made for clarity and are described below.

Applicable Section(s)	Description of Change(s)
Rationale: Based on a study by Barr et al,[1] it has been shown that daratumumab may be administered via rapid infusion while maintaining efficacy, safety, and tolerability. Accordingly, as all subjects in the study have now entered the maintenance phase, the protocol has been amended to allow subjects the option to receive a rapid infusion of daratumumab, if clinically feasible, beginning in Cycle 7 and continuing.	
Synopsis, Objectives Synopsis, Dosage and Administration Study Drug Dosing Schedule, Daratumumab Section 2.1.1, Objectives Section 3.2.2, Rationale for Daratumumab Dose Selection Section 6.1.2, Daratumumab Treatment Schedule Table 2, Daratumumab Infusion Rates	As part of this change, information was added to the protocol related to the following: • To give subjects the option to receive daratumumab via rapid infusion, • The rationale as to why the rapid infusion was added, • New objectives related to the rapid infusion, • When the rapid infusion of daratumumab is to begin, • Instructions on how the rapid infusion is to be administered including volumes and infusion times, and • Notification to investigators that a new informed consent form (ICF) must be signed prior to modification of daratumumab administration. Note: References were updated accordingly. In addition, no changes were made to endpoints for evaluation or statistical methods as monitoring of safety, serum concentrations, and infusion-related reactions (IRRs) related to daratumumab administration were already included in the protocol.

Applicable Section(s)	Description of Change(s)
Rationale: The following changes were made throughout the protocol as applicable for clarity or to correct inadvertent errors.	
Changes were made throughout the protocol as applicable. For specific details on sections impacted, refer to the document compare version of the protocol.	Per Protocol Amendment 2, subjects were given the option to receive maintenance treatment with daratumumab every 4 weeks (the preferred treatment regimen based on new information) instead of every 8 weeks as originally planned (refer to Protocol Amendment 2 in Attachment 9). As this was an optional change, for transparency, text in reference to daratumumab administration during the maintenance phase was modified from every 4 weeks to read every 4 or 8 weeks in the current protocol. As part of this change, the Dara-RVd Time and Events Schedule was updated such that procedures to be performed on Day 1 of each cycle during the maintenance phase now reads, "*Day 1 of each cycle when daratumumab is administered"* to emphasize that subjects will not be required to return to the study site when daratumumab is not being administered. In addition, although already being conducted at study sites, text was added to clarify that subjects must sign a new ICF prior to changing the frequency of daratumumab administration in the maintenance phase.
	Text was modified to allow for a dose delay in the event of exceptional circumstances, while noting that every effort should be made to keep subjects on schedule with dosing.
	ASCT was removed as a timepoint for assessment from the minimal residual disease (MRD) objective for accuracy as shown below: • To assess negative minimal residual disease (MRD) rate following induction, ~~ASCT,~~ post-ASCT consolidation, and maintenance treatment
	The following endpoint was modified as shown below because relapse from stringent complete response (sCR) is not defined in the International Myeloma Working Group (IMWG) criteria: • Duration of CR (and sCR) is the duration from the date of initial documentation of a CR (or sCR) response, according to the IMWG criteria, to the date of first documented evidence of progressive disease, or relapse from CR ~~(or sCR)~~.
	The endpoint describing time to recovery (previously defined as absolute neutrophil count >1.0 x 10^9/L and platelet count >100 x 10^9/L), was split into 2 separate endpoints and modified to be in accordance with the Center for International Blood and Marrow Transplant Research criteria as follows: • To assess time to absolute neutrophil count (ANC) recovery, defined as the date of the first of 3 consecutive laboratory values (obtained on different days) where the ANC is > 0.5 x 10^9/L • To assess time to platelet count recovery, defined as the date of the first of 3 consecutive laboratory values (obtained on different days) where the platelet count is > 20 x 10^9/L and at least 7 days after the most recent prior platelet transfusion
	The definition of high risk cytogenetic subgroups was modified to match the most current scientifically accepted definition, as shown below: • To evaluate the clinical efficacy of D-RVd in high-risk cytogenetic subgroups ***currently defined as***: ~~del(1p), gain of 1q,~~ del(17p), t(4;14), and t(14;16), ~~t(14;20)~~

	The definition of progression-free survival after next-line therapy was modified for accuracy as shown below: • Progression-free survival after next-line therapy will be measured from ~~the start of the next therapy~~ ***randomization*** to the date of the progressive disease on the next line of treatment or death, whichever comes first. Subjects who are still alive and have not yet progressed on the next line of treatment will be censored on the last date of follow-up.
	In the overall study description, text was presented to describe study endpoints. This information was already reported in the objectives and endpoints section and was deleted here to avoid repetitiveness. Full details of study endpoints will be provided in the Statistical Analysis Plan.
	Treatment regimens were modified for clarity as follows: • D-RVd group: RVd with daratumumab 16 mg/kg IV weekly during induction treatment (Days 1, 8, and 15 of Cycles 1 through 4) and every 3 weeks during consolidation treatment (Day 1 of Cycles 5 and 6), followed by every 4 ***or 8*** weeks during maintenance treatment. ~~plus oral lenalidomide 10 mg (D-R) daily on Days 1-21 throughout each 28-day cycle. Beginning at Cycle 10, the lenalidomide dose will be increased to 15 mg unless there is a tolerability concern.~~ Subjects will receive pre- and postinfusion medications for each dose of daratumumab as described in Sections 6.1.3.1 and 6.1.3.2, respectively. • RVd group: RVd alone as induction and consolidation treatment (Cycles 1 through 6: lenalidomide 25 mg orally on Days 1 through 14, bortezomib 1.3 mg/m^2 subcutaneously on Days 1, 4, 8, and 11, and oral dexamethasone 40 mg weekly [20 mg on Days 1, 2,8, 9, 15, and 16]) followed by maintenance treatment with oral lenalidomide 10 mg daily on Days 1-21 throughout each 28-day cycle ***on Cycles 7 through 9***. Beginning at Cycle 10, the lenalidomide dose will be increased to 15 mg unless there is a tolerability concern. In addition, as part of this change, the description of treatment regimens in the synopsis was changed to be identical to that described in the body of the report.
	Dose delay for toxicity management of daratumumab with respect to neutropenia was clarified as follows: • Grade 4 Neutropenia with ***any grade*** infection~~, of any grade~~
	Text was clarified with respect to MRD assessment as follows: ***At the time the original protocol was originally written, MRD*** ~~Minimal residual disease~~ assessment ~~is~~ ***was*** a relatively new tool in the assessment of patients with multiple myeloma.

Note: Other minor editorial changes were made. None of these changes impacted the conduct of the study and therefore are not summarized here.

ABBREVIATIONS

ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
AUC	area under the curve
β-hCG	β-human chorionic gonadotropin
BM-MNC	bone marrow mononuclear cell
BUN	blood urea nitrogen
C	Cycle
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CR	complete response
CrCl	creatinine clearance
CRF	case report form(s) (paper or electronic as appropriate for this study)
CT	computed tomography
CYP	cytochrome P450
DC	Discontinuation
DKd	daratumumab+carfilzomib+dexamethasone
DKRd	daratumumab+carfilzomib+lenalidomide+dexamethasone
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
D-R	daratumumab-lenalidomide
DRC	Data Review Committee
DRd	daratumumab-lenalidomide-dexamthasone
D-RVd	daratumumab-lenalidomide-bortezomib-dexamethasone
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4th edition)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDC	electronic data capture
EOT	end of treatment
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FISH	fluorescence in situ hybridization
FLC	free light chain
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
HCV	hepatitis C virus
HDT	high-dose chemotherapy
IAT	indirect antiglobulin test
IB	Investigator Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFE	Immunofixation
Ig	Immunoglobulin
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	Intravenous
IMWG	International Myeloma Working Group
IWRS	interactive web response system
KRd	carfilzomib-lenalidomide-dexamethasone
Kd	carfilzomib -dexamethasone
M-protein	monoclonal paraprotein
MDS	myelodysplastic syndrome
MDSC	myeloid-derived suppressor cells

MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRU	medical resource utilization
N	number of subjects
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not estimable
NK	natural killer
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PC	plasma cell
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	by mouth
Pom-dex	pomalidomide-dexamethasone
PQC	Product Quality Complaint
PR	partial response
PRO	patient-reported outcome
RBC	red blood cell
Rd	lenalidomide and dexamethasone
Reg	Regulatory cells
RVd	lenalidomide-bortezomib-dexamethasone
sCR	stringent complete response
SPEP	serum M-protein quantitation by electrophoresis
SUSAR	suspected unexpected serious adverse reaction
TTP	time to progression
ULN	upper limit of normal
UPEP	urine M-protein quantitation by electrophoresis
US	United States
Vd	bortezomib-dexamethasone
VGPR	very good partial response
VMP	bortezomib-melphalan-prednisone
VTd	bortezomib-thalidomide-dexamethasone

SYNOPSIS

Title: Phase 2, Randomized, Open-Label Study Comparing Daratumumab, Lenalidomide, Bortezomib, and Dexamethasone (D-RVd) Versus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Subjects With Newly Diagnosed Multiple Myeloma Eligible for High-Dose Chemotherapy and Autologous Stem Cell Transplantation

Daratumumab (JNJ-54767414) is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that binds CD38 expressed on the cell surface in a variety of hematological malignancies, including myeloma cells, lymphomas, and leukemias, as well as on other cell types and tissues with various expression levels. Daratumumab can induce complement dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cell phagocytosis, direct apoptosis after cross-linking, and can modulate CD38 enzymatic activity. CD38 is highly expressed on myeloma cells but is expressed at relatively low levels on normal lymphoid and myeloid cells and in some tissues of non-hematopoietic origin, making it a relevant target for the treatment of multiple myeloma.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives

Primary Objective

The primary objective is to determine if the addition of daratumumab to lenalidomide, bortezomib, and dexamethasone (D-RVd) will increase the proportion of subjects achieving stringent complete response (sCR), as defined by the International Myeloma Working Group (IMWG) criteria, by the time of completion of post-autologous stem cell transplantation (ASCT) consolidation treatment, compared with RVd alone.

Secondary Objectives

- To evaluate complete response (CR) and sCR rate following induction, ASCT, post-ASCT consolidation, and maintenance treatment
- To evaluate overall response rate (ORR) and rate of very good partial response (VGPR) or better following induction, ASCT, post-ASCT consolidation, and maintenance treatment
- To evaluate duration of and time to sCR and time to CR
- To evaluate time to VGPR or better
- To evaluate time to partial response (PR) or better
- To assess negative minimal residual disease (MRD) rate following induction, post-ASCT consolidation, and maintenance treatment
- To evaluate clinical outcomes including:
  - Time to progression (TTP)
  - Progression-free survival (PFS)
  - Overall survival (OS)
  - Duration of response
- To assess the safety and tolerability of D-RVd
- To assess the pharmacokinetics of daratumumab
- To assess the immunogenicity of daratumumab

- To evaluate patient-reported outcomes (PROs)
- To evaluate stem cell yield after mobilization
- To assess time to absolute neutrophil count (ANC) recovery, defined as the date of the first of 3 consecutive laboratory values (obtained on different days) where the ANC is > 0.5 x 10^9/L
- To assess time to platelet count recovery, defined as the date of the first of 3 consecutive laboratory values (obtained on different days) where the platelet count is > 20 x 10^9/L and at least 7 days after the most recent prior platelet transfusion
- To evaluate the tolerability of daratumumab when administered as a rapid infusion during maintenance treatment (ie, an accelerated infusion rate whereby 20% of the daratumumab dose is administered over 30 minutes and the remaining 80% is administered over 60 minutes for a total dose administration time 90 minutes)

Exploratory Objectives

- To evaluate PFS on next-line therapy
- To evaluate the clinical efficacy of D-RVd in high-risk cytogenetic subgroups currently defined as del(17p), t(4;14), and t(14;16)
- To explore immune modulatory effects of D-RVd as compared with RVd through immune profiling (NK, T, and B cells) and T-cell receptor sequencing
- To collect medical resource utilization (MRU) data that may be used in future economic modeling (the construction and reporting of the economic model will be conducted separately from this study)
- To evaluate serum concentrations and potential immunogenicity of daratumumab with respect to infusion-related reactions (IRRs) in the setting of rapid infusion during maintenance.

Endpoints

Primary Endpoint

The primary endpoint is the sCR rate by the end of post-ASCT consolidation treatment, defined as the proportion of subjects who have achieved sCR, according to the IMWG criteria, by the end of post-ASCT consolidation treatment.

Secondary Endpoints

The secondary efficacy endpoints include:

- Following induction treatment (prior to high-dose chemotherapy [HDT]/ASCT), ASCT (prior to start of consolidation treatment), post-ASCT consolidation (after Cycle 6), and maintenance treatment:
  - Overall CR and sCR rate is defined as the proportion of subjects who achieve CR (or sCR), according to the IMWG criteria, by the respective time point.
  - ORR is defined as the proportion of subjects who achieve PR or better, according to the IMWG criteria, by the respective time point.
  - VGPR or better rate is defined as the proportion of subjects achieving VGPR or better, according to the IMWG criteria, by the respective time point.
  - MRD negative rate is defined as the proportion of subjects who achieve MRD negative status by the respective time point.

    Note: A subject not tested for MRD will be considered as MRD positive.

- Duration of CR (and sCR) is the duration from the date of initial documentation of a CR (or sCR) response, according to the IMWG criteria, to the date of first documented evidence of progressive disease, or relapse from CR.
- Time to CR (and sCR) is the duration from the date of randomization to the date of initial documentation of CR (or sCR), which was confirmed by a repeated measurement as required by the IMWG criteria.
- Time to VGPR or better is the duration from the date of randomization to the date of initial documentation of VGPR or better, which was confirmed by a repeated measurement as required by the IMWG criteria.
- Time to PR or better is the duration from the date of randomization to the date of initial documentation of PR or better, which was confirmed by a repeated measurement as required by the IMWG criteria.
- Time to progression is defined as the duration from the date of randomization to the date of first documented evidence of progressive disease according to the IMWG criteria.
- Progression-free survival is defined as the duration from the date of randomization to the date of first documented evidence of progressive disease or death, whichever comes first.
- Overall survival is measured from the date of randomization to the date of the subject's death.
- Duration of response is defined as the duration from the date of initial documentation of a response (PR or better) according to the IMWG criteria to the date of first documented evidence of progressive disease according to the IMWG criteria.

Predefined data censoring rules will be applied.

Exploratory Endpoint

- Progression-free survival after next-line therapy will be measured from randomization to the date of the progressive disease on the next line of treatment or death, whichever comes first. Subjects who are still alive and have not yet progressed on the next line of treatment will be censored on the last date of follow-up.

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

Hypothesis

The primary hypothesis of this study is that D-RVd will improve the sCR rate by the end of post-ASCT consolidation treatment compared with RVd alone.

OVERVIEW OF STUDY DESIGN

This is a multicenter, randomized, open-label, active-controlled, Phase 2 study in subjects with newly diagnosed multiple myeloma eligible for HDT and ASCT. Initially, there will be a safety run-in phase in up-to-16 subjects to assess potential dose-limiting toxicities (DLTs) that may be associated with the addition of daratumumab to the RVd regimen. The main study consists of 4 phases: a 28-day screening phase; an induction/consolidation phase (which is inclusive of four 21-day induction treatment cycles followed by stem cell mobilization, HDT, and ASCT, followed by two 21-day consolidation treatment cycles); a 24-month maintenance phase that starts after the post-ASCT consolidation disease evaluation; and a long-term follow-up phase. All subjects will be followed in the long-term follow-up phase for at least 1 year after last dose of study treatment and will continue until death, withdrawal of consent for study participation, or the end of study definition is met. The end of study is defined as when all subjects have completed at least 1 year of long-term follow up, or until death or withdrawal of consent for study participation, whichever occurs first.

Initially, a safety run-in phase will be performed at selected study sites. In this safety run-in phase, a total of 8 to 16 subjects will be enrolled and assigned to receive D-RVd to assess potential DLTs during Cycle 1 of treatment. Subjects who are enrolled in the safety run-in phase will have all procedures indicated in the TIME AND EVENTS SCHEDULE performed except PRO assessments and MRU data collection.

Dose-limiting toxicities are defined as:

- Grade 4 neutropenia lasting more than 7 days.
- Grade 4 thrombocytopenia lasting more than 7 days despite transfusion support.
- Grade 3 or higher nonhematological toxicity except:
  - Grade 3 nausea, vomiting or diarrhea that can be controlled within 48 hours with maximal supportive care.
  - Grade 3 hyperglycemia that can be controlled within 48 hours with appropriate supportive care.
  - Asymptomatic Grade 3 or higher electrolyte disturbances that can be controlled with repletion within 24 hours.
  - Grade 3 maculopapular rash attributable to lenalidomide.
- Infusion-related reactions (IRRs):
  - Any Grade 4 IRR occurring within 48 hours of the infusion of daratumumab.
  - Any Grade 3 IRR occurring within 48 hours of the infusion of daratumumab that does not resolve with a reduced infusion rate or temporarily stopping the infusion, as well as administration of supportive care and symptomatic therapy such as a steroid and an antihistamine.

Alopecia, lymphopenia, and anemia will not be part of DLT determination.

Up to 16 subjects (minimum 8) will be enrolled in the safety run-in phase. Subjects will be monitored according to stopping boundaries specified in the Statistical Methods section. Subjects who experience a DLT during the safety run-in will be withdrawn from the study (based on investigator's judgment and best clinical practice). If the stopping boundaries are crossed after 8, 12, or 16 subjects, all subjects will be withdrawn from the study, and the study will be stopped. Unless the study is stopped due to DLTs, subjects enrolled in the safety run-in phase will continue in the study and follow the visit schedule and procedures described for the main study (except PRO assessments and MRU data collection).

Following successful completion of the safety run-in phase, approximately 200 subjects will be randomly assigned to 1 of 2 treatment groups (100 per treatment group) in the main study:

- D-RVd group: RVd with daratumumab 16 mg/kg intravenous (IV) weekly during induction treatment (Days 1, 8, and 15 of Cycles 1 through 4) and every 3 weeks during consolidation treatment (Day 1 of Cycles 5 and 6), followed by every 4 or 8 weeks during maintenance treatment.
- RVd group: RVd alone as induction and consolidation treatment (Cycles 1 through 6: lenalidomide 25 mg orally on Days 1 through 14, bortezomib 1.3 mg/m^2 subcutaneously on Days 1, 4, 8, and 11, and oral dexamethasone 40 mg weekly [20 mg on Days 1, 2, 8, 9, 15, and 16]) followed by maintenance treatment with oral lenalidomide 10 mg daily on Days 1-21 throughout each 28-day cycle on Cycles 7 through 9. Beginning at Cycle 10, the lenalidomide dose will be increased to 15 mg unless there is a tolerability concern.

Subjects will be stratified at randomization by International Staging System Stage I, II, or III disease (β-2 microglobulin and albumin) and creatinine clearance (CrCl [30-50 mL/min and >50 mL/min]).

Daratumumab and RVd are to be administered as described in Dosage and Administration and in the Study Drug Dosing. After 4 cycles of induction study treatment, subjects will undergo stem cell mobilization and then proceed to HDT and ASCT, which will be performed according to institutional standards. If the decision is made by the investigator not to pursue HDT and ASCT, subjects will be discontinued from study treatment and enter the long-term follow-up phase; subjects who do not undergo HDT and ASCT will not receive consolidation or maintenance treatment on protocol.

Consolidation treatment may commence when engraftment is complete and when in the opinion of the investigator the subject is fit enough to tolerate subsequent systemic therapy (60-100 days post-ASCT). At the start of consolidation treatment, both groups will receive the same dosages of lenalidomide, bortezomib, and oral dexamethasone that were tolerated at the end of induction treatment. Subjects will be evaluated for the primary endpoint (post-ASCT consolidation sCR). MRD will be assessed by next-generation sequencing, regardless of treatment group, as detailed in the TIME AND EVENTS SCHEDULE. After the post-ASCT consolidation disease evaluation, subjects will enter the 24-month maintenance phase of the study. Following completion of the last cycle of the maintenance phase, subjects may continue lenalidomide as per local standard of care.

Subjects will receive study treatment through completion of the 24-month maintenance phase, or until confirmed disease progression, discontinuation of study treatment due to an unacceptable drug toxicity, or other reasons. Unless a subject withdraws consent for study participation, or is lost to follow-up, an EOT visit is to be scheduled 30 days after the last dose of all components of the study treatment have been discontinued, or as soon as possible before the start of next-line therapy. After completion of the EOT visit, subjects will enter the long-term follow-up phase of the study. Subjects who enter the long-term follow-up phase before disease progression will return to the site every 12 weeks for disease evaluation and other follow-up assessments (ie, other malignancies, start of next-line therapy, and survival), until confirmed disease progression, death, the start of a new treatment for multiple myeloma, withdrawal of consent for study participation, or the end of study, whichever occurs first (see TIME AND EVENTS SCHEDULE). After confirmed disease progression or the start of a new treatment for multiple myeloma, subjects will return to the site or be contacted by telephone every 12 weeks for follow-up assessments (ie, other malignancies, next-line therapy, progressive disease on next-line therapy, and survival, as applicable). Following disease progression on the next-line therapy, subjects will only be followed for survival.

Throughout the study, subjects will be monitored closely for adverse events, laboratory abnormalities, and clinical response.

To measure functional status, well-being, and symptoms, the EORTC QLQ-C30, EORTC QLQ-MY20, and the EQ-5D-5L instruments will be completed by subjects throughout the study. Medical resource utilization data will also be collected.

A Data Review Committee will be established to review safety data after 8, 12, and 16 subjects in the safety run-in phase complete Cycle 1 (or discontinue before the end of Cycle 1) and will use stopping boundaries described in the Statistical Methods section. If the study is not stopped due to DLTs in the safety run-in phase, one interim safety analysis is planned for the safety run-in cohort after all subjects are treated for at least 4 cycles or discontinue study participation.

An independent Data Monitoring Committee (DMC) will meet periodically to review interim safety data during the main study. One planned interim safety analysis will occur after at least 50 subjects are treated for at least 4 cycles and undergo stem cell mobilization (or are evaluated for mobilization feasibility) in the main study or have discontinued before completing 4 cycles / stem cell mobilization / feasibility.

SUBJECT POPULATION

Potential subjects, 18 to 70 years of age, inclusive, who are eligible for HDT and ASCT, have documented multiple myeloma, have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0,

1, or 2, and have not had prior systemic therapy for multiple myeloma, are eligible for enrollment. Potential subjects will not be eligible if they have been diagnosed or treated for malignancy other than multiple myeloma (with exception of malignancies treated with curative intent and no known disease for ≥3 years or adequately treated non-melanoma skin cancer, lentigo maligna, or in situ malignancies [including but not limited to, cervical, breast] with no evidence of disease), are exhibiting clinical signs of or have a known history of meningeal or central nervous system involvement by multiple myeloma, have known chronic obstructive pulmonary disease with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal, have known moderate or severe persistent asthma within the past 2 years or currently have uncontrolled asthma of any classification, have clinically significant cardiac disease, or have plasma cell leukemia, Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and/or skin changes), or light-chain amyloidosis.

DOSAGE AND ADMINISTRATION

All induction and consolidation cycles are 21 days (Cycles 1-6). All subjects will receive RVd with or without daratumumab, based on random assignment, during induction and consolidation cycles. At the start of the consolidation phase (ie, Cycle 5 Day 1), both groups will receive the same dosages of lenalidomide, bortezomib, and oral dexamethasone that were tolerated at the end of induction treatment. Maintenance treatment cycles are 28 days in duration with lenalidomide given on Days 1-21; the D-RVd group will receive daratumumab every 4 or 8 weeks. Maintenance treatment will continue until disease progression or up to a maximum of 2 years. The start of a cycle will be the day of the first full dose of either daratumumab or lenalidomide, depending on the treatment group and study phase. The start of each cycle may occur within ±3 days (induction), ±14 days (consolidation), or ±14 days (maintenance) of the scheduled day to accommodate the schedule of the site or subject. Every effort should be made to keep a subject on schedule with dosing; however, in exceptional circumstances, dose delay may be considered.

Daratumumab (16 mg/kg) will be administered as an IV infusion weekly during induction treatment in Cycles 1 to 4 (Days 1, 8, and 15), every 3 weeks during consolidation treatment in Cycles 5 and 6 (Day 1), and every 4 or 8 weeks during maintenance treatment in Cycle 7 and beyond for 24 months. Beginning on Cycle 7 Day 1 and onward, if clinically feasible, subjects in the D-RVd will be given the option to be converted from the standard infusion rate of daratumumab to the accelerated infusion rate (90-minute rapid infusion) of daratumumab. For each daratumumab standard infusion or accelerated infusion, protocol specified pre- and post-infusion medications will be administered. No daratumumab dose modification (increase or decrease) will be permitted; dose delays are allowed to recover from toxicity. Subjects who miss ≥3 consecutive planned doses of daratumumab for reasons other than toxicity will be withdrawn from treatment.

In Cycles 1 through 6, lenalidomide will be administered at a dose of 25 mg orally each day on Days 1 through 14 of each 21-day cycle. During maintenance treatment in Cycle 7 and beyond, lenalidomide 10 mg will be administered daily on Days 1-21 throughout each 28-day cycle. Beginning at Cycle 10, the lenalidomide dose will be increased to 15 mg unless there is a tolerability concern. Following completion of the last cycle of the 24-month maintenance phase, subjects may continue lenalidomide as per local standard of care. Lenalidomide dose adjustment should be instituted for subjects with a CrCl ≤50 mL/min. To be enrolled in the study, subjects must have CrCl ≥30 mL/min. If during treatment a subject's renal status changes, the dose should be adjusted accordingly.

Bortezomib 1.3 mg/m^2 will be administered as a subcutaneous injection twice weekly (Days 1, 4, 8, and 11) during the 21-day induction and consolidation cycles (Cycles 1-6). On daratumumab infusion days, bortezomib will be administered at the end of the daratumumab infusion. Neither group will receive bortezomib after the first 6 cycles of D-RVd or RVd.

Oral dexamethasone will be administered at a total dose of 40 mg weekly (ie, 20 mg on Days 1, 2, 8, 9, 15, and 16) during the 21-day induction and consolidation cycles (Cycles 1-6). For subjects in the D-RVd group, the dexamethasone 20 mg oral or IV (only if oral is not available) dose administered as a

preinfusion medication on daratumumab infusion days (Days 1, 8, and 15) replaces the oral dexamethasone dose for that day. In the maintenance phase, dexamethasone, 20 mg orally (or IV), will be administered to subjects in the D-R group as a pre-infusion medication prior to daratumumab.

Subjects who need to temporarily interrupt treatment due to toxicity or discontinue treatment with any one component of study treatment (lenalidomide, bortezomib, dexamethasone, or daratumumab, as applicable depending on the study phase) may continue to receive treatment with the other components of study treatment, as assigned.

EFFICACY EVALUATIONS

Disease evaluations must be performed on Day 1 of every cycle according to the TIME AND EVENTS SCHEDULE. Note that an additional disease evaluation occurs on Day 21 of Cycle 4 and the day after Day 21 of Cycle 6 (with a 7-day window) to assess end of Cycle 4 and end of Cycle 6 response, respectively. Disease response and progression will be based on assessments according to the IMWG guidelines. Efficacy evaluations include: monoclonal paraprotein (M-protein) measurements (serum and urine), immunofixation (IFE; serum and urine), serum free light chain (FLC), serum calcium corrected for albumin, examination of bone marrow aspirate or biopsy, skeletal survey (assessment of lytic bone disease), and documentation of extramedullary plasmacytomas. Minimal residual disease in the bone marrow aspirate will also be assessed.

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

For all subjects who receive daratumumab (D-RVd during induction/consolidation and/or D-R during maintenance), serum concentration of daratumumab as well as the immunogenicity (anti-daratumumab antibodies) will be determined from venous blood samples collected according to the TIME AND EVENTS SCHEDULE.

BIOMARKER EVALUATIONS

Blood and bone marrow aspirate samples for biomarker studies will be collected from all subjects. Biomarker evaluations will focus on the assessment of MRD (in bone marrow aspirates). Minimal residual disease will be evaluated in subjects who achieve CR or sCR (including subjects with VGPR or better and suspected daratumumab interference). In addition to evaluating MRD, biomarker assessments may also monitor changes in immune cell subpopulations in bone marrow aspirates and whole blood.

Blood and bone marrow aspirate samples will be collected at screening and following treatment, as detailed in the TIME AND EVENTS SCHEDULE. Baseline bone marrow aspirate samples will be subjected to DNA and RNA sequencing to establish the myeloma clone for MRD monitoring. In addition to evaluating MRD, a whole blood sample will be collected from subjects, as outlined in the TIME AND EVENTS SCHEDULE for processing to plasma and PBMCs and monitoring changes in immune cell subpopulations.

SAFETY EVALUATIONS

Safety evaluations will include adverse event monitoring, clinical laboratory parameters (hematology and serum chemistry; testing for hepatitis C virus reactivation for subjects with a history of hepatitis C), pregnancy testing, electrocardiogram monitoring, vital sign measurements, physical examinations, and ECOG performance status. Since daratumumab interferes with the indirect antiglobulin test (IAT), subjects in the daratumumab group will receive an identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks.

STATISTICAL METHODS

Sample Size Determination

Historical data suggest that the post-consolidation sCR rate is approximately 35% for RVd therapy. To detect an absolute 15% increase in post-consolidation sCR rate with 80% power using a 1-sided likelihood ratio test at the 10% significance level, 200 subjects need to be randomized with a 1:1 randomization ratio, assuming a 5% non-evaluable rate.

Efficacy Analyses

Analysis of the primary and secondary efficacy variables will be based on the response-evaluable population, which includes all randomized subjects who have measurable disease, receive at least 1 dose of study treatment, and have at least 1 efficacy evaluation assessment.

Response to study treatment and progressive disease will be evaluated by a validated computer algorithm to calculate IMWG response. Rate of sCR achieved after post-ASCT consolidation will be tabulated. Treatment comparison will be made using the Cochran-Mantel-Haenszel test. The difference in post-ASCT consolidation sCR rate and its 2-sided 95% confidence interval will be provided. Other binary endpoints, including overall CR, sCR, ORR, VGPR or better rate following induction, ASCT, post-ASCT consolidation, and maintenance, and MRD-negative rate after consolidation, will be analyzed similarly.

Time-to-event efficacy endpoints, including duration of CR, sCR, TTP, PFS, OS, and time to next-line anti-myeloma treatment, will be descriptively summarized using the Kaplan-Meier method. Except for duration of CR and sCR, treatment comparisons will be made via a log-rank test, and treatment effects, measured by hazard ratios, will be estimated via a Cox regression model with treatment as the sole explanatory variable in the model.

The primary analysis will be performed after all randomized subjects have completed the post-ASCT consolidation disease evaluation or have been discontinued from study treatment by this time point. A second analysis will be performed after all randomized subjects complete the maintenance phase or have been discontinued from study treatment by this time point. A final data cutoff and analysis, to update secondary endpoints and safety, will occur at the end of study when all subjects have completed at least 1 year of long-term follow up, or until death or withdrawal of consent for study participation, whichever occurs first.

All data, including efficacy and safety, from subjects enrolled in the safety run-in phase during the study will be summarized and presented separately from the randomized portion of the study (main study) using similar methods.

Safety Analyses

During the safety run-in phase for D-RVd, DLTs in Cycle 1 will be monitored in cohorts of 4 subjects, after the first 8 subjects have completed Cycle 1 or discontinued due to DLT, using the Bayesian approach of Thall, Simon, Estey as extended by Thall and Sung. The prior probability of DLT in Cycle 1 for the D-RVd regimen is modeled by beta distribution (*Beta*(0.25, 0.75)). This distribution has the same *mean* as the maximum acceptable DLT in Cycle 1 of 0.25, and an Effective Sample Size of 1. The decision criteria applied will be to stop if Prob{p(DLT) >0.25| data}>0.95; ie, the posterior probability of the unknown DLT rate being >0.25 given the observed data is more than 0.95.

Subjects will be monitored according to the following stopping boundaries for DLT.

Number of Subjects (in complete cohorts of 4)	Stop the study if there are this many toxicities total: Number of Toxicities
8	≥5
12	≥6
16	≥8

All safety analyses will be based on the safety analysis set, which includes all randomized subjects who receive at least 1 dose of study treatment.

Treatment-emergent adverse events are adverse events with onset during the induction/consolidation or maintenance treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

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

TIME AND EVENTS SCHEDULE – DARA-RVD

		Screening Phase Within 28 days before randomization	Induction/Consolidation Phase					Maintenance Phase[a] (Cycles 7[e]-32)	EOT[f] (30 days [±7 days] after last dose)	FU[g,h] Phase	
			Induction[a] (Cycles 1-4)		ASCT[b]	Consolidation (Cycles 5-6)[a,c] (start 60-100 days post-ASCT)	Post-ASCT Consolidation Disease Evaluation[d] (+7 day window after C6D21)			Pre-PD	Post-PD
			D1 (Cycles 1-4)	D21 (C4 only)		D1					
Procedures											
Informed consent[l]		X									
Eligibility criteria		X									
Demographics/Medical History[j]		X									
Height		X									
Chest x-ray		X[k]									
Spirometry (FEV1)		X[k,l]									
ECOG performance status		X	X			X	X	D1 of each cycle when daratumumab is administered (ie, D1 every 4 weeks or D1 every 8 weeks depending on the subject's daratumumab dosing cycle)	X		
12-lead ECG		X[k]				C5 only		As clinically indicated			
Physical examination		X	X			X		D1 of each cycle when daratumumab is administered			
Neurological examination[m]		X	X			X		As clinically indicated			
Weight[n]		X	X			X	X	D1 of each cycle when daratumumab is administered			
Vital signs[o]		X	D1, D8, D15			X		D1 of each cycle when daratumumab is administered			
Blood type/indirect antiglobulin test			X[q]								
Laboratory Assessments For D1 of Cycles 1-6, the following 2 central laboratory kits must be completed: assessment kit and disease evaluation kit											
Local laboratory	Pregnancy test (Women of childbearing potential only)	Serum β-hCG pregnancy tests: within 10-14 days before and again within 24 hours before first dose of C1D1; weekly during Cycle 1, then monthly in subsequent cycles in women with regular menstrual cycles, or every 2 weeks in women with irregular menstrual cycles. A serum (β-hCG) or urine pregnancy test is also required at the EOT visit. Testing must continue as per standard of care in follow-up phase for subjects remaining on lenalidomide.									

		Screening Phase Within 28 days before randomization	Induction/Consolidation Phase					EOT[f] (30 days [±7 days] after last dose)	FU[g,h] Phase	
			Induction[a] (Cycles 1-4)		ASCT[b]	Consolidation (Cycles 5-6)[a,c] (start 60-100 days post-ASCT)	Post-ASCT Consolidation Disease Evaluation[d] (+7 day window after C6D21)		Pre-PD	Post-PD
			D1 (Cycles 1-4)	D21 (C4 only)		D1				
	Hematology[r,s]	X	D 1, D8, D15			X	X	D1 of each cycle when daratumumab is administered	X		
	Serum chemistry[r,t]	X	X			X	X	D1 of each cycle when daratumumab is administered	X		
Send to central laboratory	Daratumumab PK (D-RVd/D-R group only)		C1, C4 only[u]			X[u]			Posttreatment Weeks 4 and 8	
	Anti-daratumumab antibodies (Immunogenicity) (D-RVd/D-R group only)[v]		No additional sample required; taken from PK sample (see Section 9.3.4)							
			C1, C4 predose			C5 predose			Posttreatment Weeks 4 and 8	
	HCV viral load[w]	X	Every 3 months during induction and consolidation					Every 4 months during maintenance		
Study Drug Administration										
Randomization[x]			X							
Study drug dosing			See Study Drug Dosing Schedule							
PRO Assessments and MRU (The initial set up of the ePRO device and administration of the first questionnaire for each subject are to be completed on C1D1 (and subsequent D1 visits) before any study-specific procedures are performed.) PRO assessments and MRU data collection will not be performed at any time during the study for subjects enrolled in safety run-in phase.										
EORTC QLQ-C30			C1-C3 only	X		C5 only	X	6, 12, 18, and 24 months after start of maintenance	X	X	
EORTC QLQ-MY20			C1-C3 only	X		C5 only	X		X	X	
EQ-5D-5L			C1-C3 only	X		C5 only	X		X	X	
MRU			X			X	X	D1 of each cycle when daratumumab is administered[e]	X		

		Screening Phase Within 28 days before randomization	Induction/Consolidation Phase					Maintenance Phase[a] (Cycles 7[e]-32)	EOT[f] (30 days [±7 days] after last dose)	FU[g,h] Phase	
			Induction[a] (Cycles 1-4)		ASCT[b]	Consolidation (Cycles 5-6)[a,c] (start 60-100 days post-ASCT)	Post-ASCT Consolidation Disease Evaluation[d] (+7 day window after C6D21)			Pre-PD	Post-PD
			D1 (Cycles 1-4)	D21 (C4 only)		D1					
Disease Evaluations: To be performed on Day 1 of each cycle during induction, consolidation and every 8 weeks during maintenance phase. Note that an additional disease evaluation occurs on Day 21 of Cycle 4 and the day after Day 21 of Cycle 6 (with a 7-day window) to assess end of Cycle 4 and end of Cycle 6 response, respectively. Refer to Section 9.2 for details on efficacy evaluations.											
Send to central laboratory	β_2-microglobulin, LDH	X									
Blood and 24-hour urine samples: **In addition to the time points below, samples will also be collected whenever CR or sCR is suspected.** Only 1 blood and 1 24-hour urine sample are required to perform the following tests:											
Send to central laboratory	SPEP[y]	X	X	X		X	X	D1 of odd cycles (7, 9, 11, etc)[e]	X	Q12 wks	
	UPEP	X	X	X		X	X		X		
	Serum QIg[z]	X	X	X		X	X		X		
	Serum IFE[y]	X	X	X		X	X	Performed whenever CR or sCR is suspected or maintained for all subjects.	X		
	Urine IFE	X	X	X		X	X		X		
	Serum FLC assay	X	X	X		X	X	Performed whenever CR or sCR is suspected or maintained for all subjects For subjects without measurable disease in serum or urine, also performed on D1 of each odd cycle	X		
Bone marrow aspirate/biopsy sample and blood samples (additional details are provided in Table 10).											
Local laboratory	Cytogenetics-FISH (aspirate)[aa]	X[bb]									
Send to central laboratory[cc]	MRD (aspirate)	X[bb]	• at first evidence of suspected CR or sCR (including subjects with VGPR or better and suspected daratumumab interference) • after induction / before stem cell collection • at post-ASCT consolidation disease evaluation • at 12 and 24 months (±3 weeks) during maintenance								

		Screening Phase Within 28 days before randomization	Induction/Consolidation Phase					Maintenance Phase[a] (Cycles 7[e]-32)	EOT[f] (30 days [±7 days] after last dose)	FU[g,h] Phase	
			Induction[a] (Cycles 1-4)		ASCT[b]	Consolidation (Cycles 5-6)[a,c] (start 60-100 days post-ASCT)	Post-ASCT Consolidation Disease Evaluation[d] (+7 day window after C6D21)			Pre-PD	Post-PD
			D1 (Cycles 1-4)	D21 (C4 only)		D1					
	Biomarker (CyTOF, PBMC, and plasma) (blood)[dd]		X	X			X		X		
	Immunophenotyping (blood)[dd]		X	X			X		X		
Send to local laboratory	PC clonality assay (immunohistochemistry, immunofluorescence or flow cytometry)	X[bb]	• At first evidence of suspected CR or sCR (including subjects with VGPR or better and suspected daratumumab interference) • after induction / before stem cell collection • at post-ASCT consolidation disease evaluation • at 12 and 24 months (±3 weeks) during maintenance								
	Morphology (aspirate and biopsy)[ee]	X[bb]									
Assessment of lytic bone disease		X[k]	As clinically indicated to document response or progression; see Section 9.2.7 for details.						X		
Extramedullary plasmacytomas (subjects with history; physical or radiologic examination, as applicable)		X[k]		X		C5 only	X	6, 12, and 24 months (±3 weeks) after start of maintenance (within 14 days before scheduled visit)	X		
Follow-up After EOT											
Other malignancy										Q12 wks	Q12 wks
Next-line therapy and start/stop date											
Survival											
Date of PD on next-line therapy											
Ongoing Subject Review											
Adverse events		Continuous from the time of signing of ICF until 30 days after last dose of any component of the study treatment in the maintenance phase with the exception of adverse events related to mobilization and ASCT procedures; see Section 12 for detailed instructions.									
Concomitant medications		Continuous from the time of signing of ICF until 30 days after last dose of any component of the study treatment; see Section 8 for detailed instructions. During the mobilization and stem cell transplantation procedures, concomitant medications related to the planned procedures do not need to be reported in the eCRF. However, concomitant medications related to the mobilization and transplantation procedures should be documented by providing a copy of the medication order set.									

ASCT = autologous stem cell transplantation; β-hCG = β-human chorionic gonadotropin; BUN = blood urea nitrogen; C = cycle; CR = complete response; D = day; D-R = daratumumab and lenalidomide; D-RVd = daratumumab, lenalidomide, bortezomib, and dexamethasone; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; FEV1 = Forced Expiratory Volume (in 1 second); FISH = fluorescence in situ hybridization; FLC = free light chain; FU = follow-up; HCV = hepatitis C virus; HDT = high-dose chemotherapy; ICF = informed consent form; IFE = immunofixation; Ig = immunoglobulin; LDH = lactic acid dehydrogenase; M-protein = monoclonal paraprotein; MRD = minimal residual disease; MRU = medical resource utilization; PBMC = peripheral blood mononuclear cell; PC = plasma cell; PD = progressive disease; PK = pharmacokinetic; PRO = patient-reported outcome; Q12wks = every 12 weeks; QIg = quantitative immunoglobulin; RVd = lenalidomide, bortezomib, and dexamethasone; sCR = stringent complete response; SPEP = serum M-protein quantitation by electrophoresis; UPEP = urine M-protein quantitation by electrophoresis; VGPR = very good partial response.

NOTE: Subjects who are enrolled in the safety run-in phase will have all procedures performed except PRO assessments and MRU data collection.

a) Induction and consolidation cycles are 21 days in duration; there will be a maximum of 4 induction cycles and 2 consolidation cycles. Maintenance therapy cycles are 28 days in duration. The start of each cycle may occur within ±3 days during induction, ±14 days during consolidation, and ±14 days during maintenance of the scheduled day to accommodate the schedule of the site or subject. Every effort should be made to keep a subject on schedule with dosing; however, in exceptional circumstances, dose delay may be considered.
For C4D21 procedures, a window of +7 days will be allowed; must be performed before ASCT. For C5D1 procedures, a window of -7 days will be allowed.
If a D-RVd subject opts to remain on the every 8-week daratumumab maintenance dosing schedule, it is not necessary for that subject to return for office visits for D1 procedures during cycles when they are not receiving a daratumumab infusion. These subjects will continue to come to the clinic for D1 of daratumumab dosing cycles only.
For those D-RVd subjects consenting to every 4-week daratumumab dosing, central laboratory disease evaluation samples (SPEP, UPEP, etc.) will continue to be collected every other cycle during maintenance (D1 of odd cycles). All other necessary evaluations (vital signs, ECOG etc.) are to be conducted monthly on D1 of every cycle during maintenance or as otherwise specified in the protocol.
b) Stem cell mobilization, HDT, and ASCT will be performed according to institutional standards. Subjects who do not undergo HDT and ASCT will not receive consolidation or maintenance treatment on protocol; however, they will have EOT assessments then enter the long-term follow-up phase.
c) Consolidation therapy may commence when engraftment is complete and when in the opinion of the investigator the subject is fit enough to tolerate subsequent systemic therapy and should start in the 60 to 100 days post-ASCT.
d) The post-ASCT consolidation disease evaluation (primary endpoint) should be performed the day after completion of C6D21 (+7 day window; 100 to 150 days post-ASCT).
e) If C7D1 is started within the 14 days following the post-ASCT consolidation disease evaluation, C7D1 collection of MRU data and disease evaluations do not need to be repeated.
f) Subjects will receive study treatment through completion of the 24-month maintenance phase, or until confirmed disease progression, discontinuation of study treatment due to an unacceptable drug toxicity, or other reasons. Unless a subject withdraws consent for study participation, or is lost to follow-up, an EOT visit is to be scheduled 30 days after the last dose of all components of the study treatment have been discontinued, or as soon as possible before the start of next-line therapy. Lenalidomide will be continued as per local standard of care at the end of the maintenance phase, the EOT visit should be performed 30 days after all other study treatment is permanently discontinued or as soon as possible before the start of next-line therapy.
g) Before disease progression, subjects will return to the site for assessments until confirmed disease progression, death, the start of a new treatment for multiple myeloma, withdrawal of consent for study participation, or the end of study, whichever occurs first. Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation. Clinical judgment should prevail; however, repeat assessments after 1 to 3 weeks can be used as a general guideline. After confirmed disease progression or the start of a new treatment for multiple myeloma, subjects will return to the site or be contacted by telephone for follow-up assessments until death, withdrawal of consent for study participation, or the end of study, whichever occurs first. Following disease progression on the next-line therapy, subjects will only be followed for survival.
h) Subjects will be followed in the long-term follow-up phase for at least 1 year after last dose of study treatment and will continue until death, withdrawal of consent for study participation, or the end of study definition is met. The end of study is defined as when all subjects have completed at least 1 year of long-term follow up, or until death or withdrawal of consent for study participation, whichever occurs first.
i) Must be signed before any study-related procedures are performed.
j) Medical history including surgery or procedures planned prior to entry into the study.
k) Acceptable for screening if performed as part of standard of care within 42 days before randomization.
l) Pulmonary function testing (spirometry) is required only for subjects with chronic obstructive pulmonary disease or asthma. FEV1 should be measured for subjects with chronic obstructive pulmonary disease or asthma.
m) General neurological exam focused on sensory peripheral neuropathy.
n) Each subject's dose will be calculated based on the subject's weight at Cycle 1 Day 1 rounded to the nearest kilogram. If a subject's weight changes by more than 10% from C1D1 or the most recent weight used for dose calculation, the dose of all study treatments should be re-calculated. Weight to be recorded on all daratumumab dosing days.
o) Temperature, pulse/heart rate, respiratory rate, and blood pressure. Measured in sitting position. For all infusions except C1D1 (see note below), measured immediately before the start of and at the end of daratumumab infusion. Day 15 vital signs are required only for subjects in D-RVd arm.
p) For C1D1 only: immediately before the start of daratumumab infusion; at 0.5, 1, 1.5, 2, and 3.5 hours after the start of the infusion and then every 2 hours through duration of infusion; at end of infusion; and 0.5 and 1 hour after the end of the infusion.
q) To be performed once randomization to D-RVd is known, prior to dosing with daratumumab. A wallet card with the subject's blood type will be provided to subjects randomly assigned to D-RVd group.
r) For C1D1, there is no need to repeat the tests if they have been performed within the past 3 days. Laboratory evaluations may be performed up to 2 days before other infusion days. Perform at additional time points, as clinically indicated.

s) On-site or accredited local laboratory must be used for hematology laboratory assessments. Results of local hematology tests must be evaluated before each study drug administration to guide treatment decisions. Hematology panel: hemoglobin, white blood count with absolute neutrophils and lymphocytes, red blood cell count, and platelet count.
t) Serum chemistry panel: sodium, potassium, creatinine and creatinine clearance (must be calculated per protocol, see Section 9.8), glucose, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, BUN, calcium and albumin-adjusted calcium, and albumin.
u) If the sampling falls on a dosing day, 1 sample is to be collected before the start of (window -2 hours) the daratumumab infusion and 1 sample is to be collected immediately after the end of (window +2 hours) the daratumumab infusion.
v) In addition, any time an infusion-related reaction is observed during the study, an unscheduled blood sample should be drawn as soon as possible after the reaction for potential determination of anti-daratumumab antibodies.
w) Subjects who completed treatment for hepatitis C at least 6 months prior to screening and have no detectable circulating hepatitis C virus (HCV) at screening, may participate in the study. Such subjects will be required to undergo regular assessment for HCV reactivation, as shown and will be withdrawn from the study if they test positive at any time during the study.
x) Randomization will be performed up to 72 hours before the first dose of study treatment on C1D1.
y) If daratumumab interference is suspected based on SPEP and IFE results, additional reflex IFE testing will be performed by the central laboratory.
z) All subject's samples will be tested for IgG, IgA, and IgM. Subjects with IgE or IgD myeloma will have samples tested for IgE or IgD.
aa) FISH testing to include del(1p), gain of 1q, del(17p), t(4;14), t(14;16), and t(14;20).
bb) Acceptable for screening if performed as part of standard of care within 28 days before randomization.
cc) A fresh aspirate and biopsy are preferred at screening; if not available, obtain non-decalcified clot sections (block or slides) or aspirate smear slides.
At all visits, during the bone marrow aspirate procedure, the first aspirate sample that is drawn will be sent to the central laboratory to determine MRD. All bone marrow aspirates to be sent to the central laboratory should be at least 2 mL. Additional bone marrow aspirate samples may be taken and used for local laboratory testing.
dd) An additional blood sample for biomarker and immunophenotyping analyses will be collected at the time of disease progression.
ee) Bone marrow biopsy and aspirate are required at screening and aspirate will be requested at time of disease progression, if feasible. For all other assessments, only bone marrow aspirates are required.

TIME AND EVENTS SCHEDULE - RVD

	Screening Phase Within 28 days before randomization	**Induction/Consolidation Phase**					**Maintenance Phase[a] (Cycles 7[e]-32)**	**EOT[f]** (30 days [±7 days] after last dose)	**FU[g,h] Phase**	
		Induction[a] (Cycles 1-4)		**ASCT[b]**	**Consolidation (Cycles 5-6)[a,c]** (start 60-100 days post-ASCT)	**Post-ASCT Consolidation Disease Evaluation[d]** (+7 day window after C6D21)			**Pre-PD**	**Post-PD**
		D1 (Cycles 1-4)	**D21 (C4 only)**		**D1**					
Procedures										
Informed consent[l]	X									
Eligibility criteria	X									
Demographics/Medical History[j]	X									
Height	X									
Chest x-ray	X[k]									
Spirometry (FEV1)	X[k,l]									
ECOG performance status	X	X			X	X	Day 1 of odd cycles (7, 9, 11, etc)	X		
12-lead ECG	X[k]				C5 only		As clinically indicated			
Physical examination	X	X			X		Day 1 of odd cycles (7, 9, 11, etc)			

Neurological examination[m]		X	X			X		As clinically indicated			
Weight[n]		X	X			X	X	Day 1 of odd cycles (7, 9, 11, etc)			
Vital signs[o]		X	D1, D8			X		Day 1 of odd cycles (7, 9, 11, etc)			
Laboratory Assessments **For D1 of Cycles 1-6, the following 2 central laboratory kits must be completed: assessment kit and disease evaluation kit**											
Local laboratory	Pregnancy test (Women of childbearing potential only)	Serum β-hCG pregnancy tests: within 10-14 days before and again within 24 hours before first dose of C1D1; weekly during Cycle 1, then monthly in subsequent cycles in women with regular menstrual cycles, or every 2 weeks in women with irregular menstrual cycles. A serum (β-hCG) or urine pregnancy test is also required at the EOT visit. Testing must continue as per standard of care in follow-up phase for subjects remaining on lenalidomide.									
	Hematology[r,s]	X	D1, D8, D15			X	X	Day 1 of odd cycles (7, 9, 11, etc)	X		
	Serum chemistry[r,t]	X	X			X	X	Day 1 of odd cycles (7, 9, 11, etc)	X		
	HCV viral load[w]	X	Every 3 months during induction and consolidation					Every 4 months during maintenance			
Study Drug Administration											
Randomization[x]			X								
Study drug dosing			See Study Drug Dosing								

	Screening Phase Within 28 days before randomization	**Induction/Consolidation Phase**					**Maintenance Phase[a] (Cycles 7[e]-32)**	**EOT[f]** (30 days [±7 days] after last dose)	**FU[g,h] Phase**	
		Induction[a] (Cycles 1-4)		**ASCT[b]**	**Consolidation (Cycles 5-6)[a,c]** (start 60-100 days post-ASCT)	**Post-ASCT Consolidation Disease Evaluation[d]** (+7 day window after C6D21)			**Pre-PD**	**Post-PD**
		D1 (Cycles 1-4)	**D21 (C4 only)**		**D1**					
PRO Assessments and MRU (The initial set up of the ePRO device and administration of the first questionnaire for each subject are to be completed on C1D1 (and subsequent D1 visits) before any study specific procedures are performed.) PRO assessments and MRU data collection will not be performed at any time during the study for subjects enrolled in safety run-in phase.										
EORTC QLQ-C30		C1-C3 only	X		C5 only	X	6, 12, 18, and 24 months after start of maintenance	X	X	
EORTC QLQ-MY20		C1-C3 only	X		C5 only	X		X	X	
EQ-5D-5L		C1-C3 only	X		C5 only	X		X	X	
MRU		X			X	X	D1 of odd cycles (7, 9, 11, etc)[e]	X		

Disease Evaluations: To be performed on Day 1 of each cycle during induction, consolidation and every 8 weeks during maintenance phase. Note that an additional disease evaluation occurs on Day 21 of Cycle 4 and the day after Day 21 of Cycle 6 (with a 7-day window) to assess end of Cycle 4 and end of Cycle 6 response, respectively. Refer to Section 9.2 for details on efficacy evaluations.											
Send to central laboratory	β_2-microglobulin, LDH	X									
Blood and 24-hour urine samples: **In addition to the time points below, samples will also be collected whenever CR or sCR is suspected.** Only 1 blood and 1 24-hour urine sample are required to perform the following tests:											
Send to central laboratory	SPEP[y]	X	X	X		X	X	D1 of odd cycles (7, 9, 11, etc)[e]	X	Q12 wks	
	UPEP	X	X	X		X	X		X		
	Serum QIg[z]	X	X	X		X	X		X		
	Serum IFE[y]	X	X	X		X	X	Performed whenever CR or sCR is suspected or maintained for all subjects.	X		
	Urine IFE	X	X	X		X	X		X		

			Induction/Consolidation Phase							**FU[g,h] Phase**	
		Screening Phase Within 28 days before randomization	**Induction[a] (Cycles 1-4)**		**ASCT[b]**	**Consolidation (Cycles 5-6)[a,c]** (start 60-100 days post-ASCT)	**Post-ASCT Consolidation Disease Evaluation[d]** (+7 day window after C6D21)	**Maintenance Phase[a] (Cycles 7[e]-32)**	**EOT[f]** (30 days [±7 days] after last dose)	**Pre-PD**	**Post-PD**
			D1 (Cycles 1-4)	**D21 (C4 only)**		**D1**					
	Serum FLC assay	X	X	X		X	X	Performed whenever CR or sCR is suspected or maintained for all subjects For subjects without measurable disease in serum or urine, also performed on D1 of odd cycles (7, 9, 11, etc)[e]	X		
Bone marrow aspirate/biopsy sample and blood samples (additional details are provided in Table 10).											
Local laboratory	Cytogenetics-FISH (aspirate)[aa]	X[bb]									

Send to central laboratory[cc]	MRD (aspirate)	X[bb]	• at first evidence of suspected CR or sCR • after induction / before stem cell collection • at post-ASCT consolidation disease evaluation • at 12 and 24 months (±3 weeks) during maintenance								
	Biomarker (CyTOF, PBMC, and plasma) (blood)[dd]		X	X			X		X		
	Immunophenotyping (blood)[dd]		X	X			X		X		
Send to local laboratory	PC clonality assay (immunohistochemistry, immunofluorescence or flow cytometry)	X[bb]	• At first evidence of suspected CR or sCR) • after induction / before stem cell collection • at post-ASCT consolidation disease evaluation • at 12 and 24 months (±3 weeks) during maintenance								
	Morphology (aspirate and biopsy)[ee]	X[bb]									
Assessment of lytic bone disease		X[k]	As clinically indicated to document response or progression; see Section 9.2.7 for details.						X		
Extramedullary plasmacytomas (subjects with history; physical or radiologic examination, as applicable)		X[k]		X		C5 only	X	6, 12, and 24 months (±3 weeks) after start of maintenance (within 14 days before scheduled visit)	X		
Follow-up After EOT											
Other malignancy										Q12 wks	Q12 wks
Next-line therapy and start/stop date											
Survival											
Date of PD on next-line therapy											

	Screening Phase Within 28 days before randomization	**Induction/Consolidation Phase**					**Maintenance Phase[a] (Cycles 7[e]-32)**	**EOT[f]** (30 days [±7 days] after last dose)	**FU[g,h] Phase**	
		Induction[a] (Cycles 1-4)		**ASCT[b]**	**Consolidation (Cycles 5-6)[a,c]** (start 60-100 days post-ASCT)	**Post-ASCT Consolidation Disease Evaluation[d]** (+7 day window after C6D21)			**Pre-PD**	**Post-PD**
		D1 (Cycles 1-4)	**D21 (C4 only)**		**D1**					
Ongoing Subject Review										
Adverse events	Continuous from the time of signing of ICF until 30 days after last dose of any component of the study treatment in the maintenance phase with the exception of adverse events related to mobilization and ASCT procedures; see Section 12 for detailed instructions.									

Concomitant medications	Continuous from the time of signing of ICF until 30 days after last dose of any component of the study treatment; see Section 8 for detailed instructions. During the mobilization and stem cell transplantation procedures, concomitant medications related to the planned procedures do not need to be reported in the eCRF. However, concomitant medications related to the mobilization and transplantation procedures should be documented by providing a copy of the medication order set.		

ASCT = autologous stem cell transplantation; β-hCG = β-human chorionic gonadotropin; C = cycle; CR = complete response; D = day; D-R = daratumumab and lenalidomide; D-RVd = daratumumab, lenalidomide, bortezomib, and dexamethasone; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; FEV1 = Forced Expiratory Volume (in 1 second); FISH = fluorescence in situ hybridization; FLC = free light chain; FU = follow-up; HDT = high-dose chemotherapy; ICF = informed consent form; IFE = immunofixation; Ig = immunoglobulin; LDH = lactic acid dehydrogenase; M-protein = monoclonal paraprotein; MRD = minimal residual disease; MRU = medical resource utilization; PBMC = peripheral blood mononuclear cell; PC = plasma cell; PD = progressive disease; PK = pharmacokinetic; PRO = patient-reported outcome; Q12wks = every 12 weeks; QIg = quantitative immunoglobulin; RVd = lenalidomide, bortezomib, and dexamethasone; SPEP = serum M-protein quantitation by electrophoresis; UPEP = urine M-protein quantitation by electrophoresis; VGPR = very good partial response.

NOTE: Subjects who are enrolled in the safety run-in phase will have all procedures performed except PRO assessments and MRU data collection.

a) Induction and consolidation cycles are 21 days in duration; there will be a maximum of 4 induction cycles and 2 consolidation cycles. Maintenance therapy cycles are 28 days in duration. The start of each cycle may occur within ±3 days during induction, ±14 days during consolidation, and ±14 days during maintenance of the scheduled day to accommodate the schedule of the site or subject. Every effort should be made to keep a subject on schedule with dosing; however, in exceptional circumstances, dose delay may be considered. For C4D21 procedures, a window of +7 days will be allowed; must be performed before ASCT. For C5D1 procedures, a window of -7 days will be allowed.
b) Stem cell mobilization, HDT, and ASCT will be performed according to institutional standards. Subjects who do not undergo HDT and ASCT will not receive consolidation or maintenance treatment on protocol; however, they will have EOT assessments then enter the long-term follow-up phase.
c) Consolidation therapy may commence when engraftment is complete and when in the opinion of the investigator the subject is fit enough to tolerate subsequent systemic therapy and should start in the 60 to 100 days post-ASCT.
d) The post-ASCT consolidation disease evaluation (primary endpoint) should be performed the day after completion of C6D21 (+7 day window; 100 to 150 days post-ASCT).
e) If C7D1 is started within the 14 days following the post-ASCT consolidation disease evaluation, C7D1 collection of MRU data and disease evaluations do not need to be repeated.
f) Subjects will receive study treatment through completion of the 24-month maintenance phase, or until confirmed disease progression, discontinuation of study treatment due to an unacceptable drug toxicity, or other reasons. Unless a subject withdraws consent for study participation, or is lost to follow-up, an EOT visit is to be scheduled 30 days after the last dose of all components of the study treatment have been discontinued, or as soon as possible before the start of next-line therapy. Lenalidomide will be continued as per local standard of care at the end of the maintenance phase, the EOT visit should be performed 30 days after all other study treatment is permanently discontinued or as soon as possible before the start of next-line therapy.
g) Before disease progression, subjects will return to the site for assessments until confirmed disease progression, death, the start of a new treatment for multiple myeloma, withdrawal of consent for study participation, or the end of study, whichever occurs first. Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation. Clinical judgment should prevail; however, repeat assessments after 1 to 3 weeks can be used as a general guideline. After confirmed disease progression or the start of a new treatment for multiple myeloma, subjects will return to the site or be contacted by telephone for follow-up assessments until death, withdrawal of consent for study participation, or the end of study, whichever occurs first. Following disease progression on the next-line therapy, subjects will only be followed for survival.
h) Subjects will be followed in the long-term follow-up phase for at least 1 year after last dose of study treatment and will continue until death, withdrawal of consent for study participation, or the end of study definition is met. The end of study is defined as when all subjects have completed at least 1 year of long-term follow up, or until death or withdrawal of consent for study participation, whichever occurs first.
i) Must be signed before any study-related procedures are performed.
j) Medical history including surgery or procedures planned prior to entry into the study.
k) Acceptable for screening if performed as part of standard of care within 42 days before randomization.
l) Pulmonary function testing (spirometry) is required only for subjects with chronic obstructive pulmonary disease or asthma. FEV1 should be measured for subjects with chronic obstructive pulmonary disease or asthma.
m) General neurological exam focused on sensory peripheral neuropathy
n) Each subject's dose will be calculated based on the subject's weight at Cycle 1 Day 1 rounded to the nearest kilogram. If a subject's weight changes by more than 10% from C1D1

or the most recent weight used for dose calculation, the dose of all study treatments should be re-calculated.

o) Temperature, pulse/heart rate, respiratory rate, and blood pressure. Measured in sitting position. For all infusions except C1D1 (see note below), measured immediately before the start of and at the end of daratumumab infusion.
p) Left blank for consistency across Time and Event Schedules.
q) Left blank for consistency across Time and Event Schedules.
r) For C1D1, there is no need to repeat the tests if they have been performed within the past 3 days. Laboratory evaluations may be performed up to 2 days before other infusion days. Perform at additional time points, as clinically indicated.
s) On-site or accredited local laboratory must be used for hematology laboratory assessments. Results of local hematology tests must be evaluated before each study drug administration to guide treatment decisions. Hematology panel: hemoglobin, white blood count with absolute neutrophils and lymphocytes, red blood cell count, and platelet count.
t) Serum chemistry panel: sodium, potassium, creatinine and creatinine clearance (must be calculated per protocol, see Section 9.8), glucose, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase, BUN, calcium and albumin-adjusted calcium, and albumin.
u) Left blank for consistency across Time and Event Schedules.
v) Left blank for consistency across Time and Event Schedules.
w) Subjects who completed treatment for hepatitis C at least 6 months prior to screening and have no detectable circulating hepatitis C virus (HCV) at screening, may participate in the study. Such subjects will be required to undergo regular assessment for HCV reactivation, as shown and will be withdrawn from the study if they test positive at any time during the study.
x) Randomization will be performed up to 72 hours before the first dose of study treatment on C1D1.
z) All subject's samples will be tested for IgG, IgA, and IgM. Subjects with IgE or IgD myeloma will have samples tested for IgE or IgD.
aa) FISH testing to include del(1p), gain of 1q, del(17p), t(4;14), t(14;16), and t(14;20).
bb) Acceptable for screening if performed as part of standard of care within 28 days before randomization.
cc) A fresh aspirate and biopsy are preferred at screening; if not available, obtain non-decalcified clot sections (block or slides) or aspirate smear slides.
At all visits, during the bone marrow aspirate procedure, the first aspirate sample that is drawn will be sent to the central laboratory to determine MRD. All bone marrow aspirates to be sent to the central laboratory should be at least 2 mL. Additional bone marrow aspirate samples may be taken and used for local laboratory testing.
dd) An additional blood sample for biomarker and immunophenotyping analyses will be collected at the time of disease progression.
ee) Bone marrow biopsy and aspirate are required at screening and aspirate will be requested at time of disease progression, if feasible. For all other assessments, only bone marrow aspirates are required.

STUDY DRUG DOSING SCHEDULE

	Notes	Induction			Consolidation	Maintenance	EOT
		Cycle 1-4 (21-day cycles)			Cycle 5-6[a] (21-day cycles)	Cycle 7-32 (28-day cycles)	
		D1	D8	D15	D1	D1	
Refer to the TIME AND EVENTS SCHEDULE for important information regarding hematology, serum chemistry, weight, and vital signs assessments related to dosing.							
Ongoing Review							
Diary review	Accountability/exposure check	X	X	X	X	Day 1 of odd cycles when daratumumab is administered	X
Preinfusion Medications: Only for the Daratumumab group (D-RVd [induction/consolidation phase]/D-R [maintenance phase]); administer approximately 1 hour prior to daratumumab infusion; oral preinfusion medications may be administered within 3 hours prior to daratumumab infusion. For subjects with a higher risk of respiratory complications, see Section 6.1.3.2 for postinfusion medications.							
Dexamethasone	Dexamethasone 20 mg PO or IV (only if oral is not available). Substitutions for dexamethasone allowed, see Attachment 1.	X	X	X	X	D1 of each cycle when daratumumab is administered	
Antihistamine	Diphenhydramine 25-50 mg or equivalent, PO or IV.	X	X	X	X	D1 of each cycle only for D-R group when daratumumab is administered	
Acetaminophen	Acetaminophen 650-1,000 mg PO or IV equivalent	X	X	X	X	D1 of each cycle only for D-R group when daratumumab is administered	
Montelukast	Montelukast 10 mg PO, at C1D1 approximately 1 hour or less before the daratumumab infusion. An additional 10 mg PO can be given the day before infusion at the discretion of the investigator. May be omitted for any daratumumab dose after the second infusion if the subject has no respiratory symptoms.	X	X	As clinically indicated			
Study Treatment Administration, D-RVd group and RVd group in induction/consolidation phase and D-R group and lenalidomide group in maintenance phase							
Daratumumab (D-RVd/D-R group, only)	Refer to Section 6.1.2 and the SIPPM for recommendations on daratumumab infusion rate. Note: Subject's weight will be recorded on all daratumumab dosing days. D-RVd treatment group: Beginning at Cycle 7 Day 1 and onward, if clinically feasible, subjects will be given the option to receive an accelerated 90-minute infusion of daratumumab.	16 mg/kg IV Days 1, 8, 15 of Cycles 1-4 Day 1 of Cycles 5-6				16 mg/kg IV every 4 or 8 weeks[b] (Day 1 of **each applicable cycle)**	
Lenalidomide[c]	Dispense on Day 1 for self-administration.	25 mg PO daily[a,d] Day 1-14 of Cycles 1-6				10 mg PO daily[e] Days 1-21. Beginning at Cycle 10, the dose will be increased to 15 mg unless there is a tolerability concern	

Bortezomib	Administer by SC injection. Dose may be delayed up to 48 hours. Doses that need to be withheld are skipped and will not be made up later in the cycle. For subjects who experience SC injection-site reactions, IV injection allowed. Note: Each subject's dose will be calculated based on the subject's weight at Cycle 1 Day 1 rounded to the nearest kilogram. Dose should be readjusted if weight changes >10% from value on C1D1.	1.3 mg/m^2 SC[a] Days 1, 4, 8, and 11 during Cycles 1-6	-	
Dexamethasone	Dispense on Day 1 for self-administration. Substitutions for dexamethasone allowed, see Attachment 1.	20 mg PO[a] Days 1, 2, 8, 9, 15, and 16 during Cycles 1-6. Not required in D-RVd group on daratumumab infusion days, since the subject will receive PO dexamethasone as a pre-medication prior to daratumumab infusion.	D-R group: pre-infusion medication (see above).	

CrCl = creatinine clearance; D = day; D-R = daratumumab and lenalidomide; D-RVd = daratumumab, lenalidomide, bortezomib, and dexamethasone; EOT = end-of-treatment; ICF = informed consent form; IV = intravenous; PO = oral; REMS = Risk Evaluation and Mitigation Strategy; RVd = lenalidomide, bortezomib, and dexamethasone; SC = subcutaneous; SIPPM = study site investigational product and procedures manual.

[a] The doses of RVd that were tolerated by a subject at the end of induction should be used at the start of the consolidation phase.

[b] Subjects who signed the original ICF stating that daratumumab maintenance was to be administered every other month and who do not agree to the revised daratumumab maintenance administration every month will be permitted to receive daratumumab every other month. However, every effort should be taken to ensure that the subject understands the benefit of the monthly daratumumab maintenance schedule.

[c] Due to the potential of birth defects or embryo-fetal death associated with the use of lenalidomide, investigators and subjects must adhere to the lenalidomide REMS program that can be accessed at http://www.revlimidrems.com/.

[d] Lenalidomide dose adjustment should be instituted for subjects with a CrCl ≤50 mL/min: CrCl 30-50 mL/min, 10 mg every 24 hours (escalate the dose to 15 mg after 2 cycles if the subject tolerates the 10 mg dose without dose-limiting toxicity); CrCl <30 mL/min (not requiring dialysis), 15 mg every 48 hours; CrCl <30 mL/min (requiring dialysis), 5 mg once daily (on dialysis days, administer the dose after dialysis).

[e] Following completion of the maintenance phase, subjects may continue lenalidomide as per local standard of care.

1. INTRODUCTION

Daratumumab (JNJ-54767414) is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that binds CD38 expressed on the cell surface in a variety of hematological malignancies, including myeloma, lymphomas, and leukemias, as well as on other cell types and tissues with various expression levels.[3] The mechanisms of action of daratumumab comprise immune-mediated effects, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and apoptosis by means of cross-linking. Moreover, daratumumab also induces immunomodulatory effects via several different pathways that contribute to killing CD38+ immune cells that modulate T cell activity, namely myeloid-derived suppressor cells (MDSC) and regulatory T (TReg), and B (BReg) cells (Krejcik 2016).[13] Daratumumab's converging mechanisms of actions are hypothesized to lead synergistically to the deep responses observed in patients with multiple myeloma.

Daratumumab by intravenous (IV) injection is approved in the United States (US), European Union, and other countries for the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who are double-refractory to a PI and an IMiD. On 21 November 2016, the US Food and Drug Administration (FDA) approved daratumumab 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 June 2017, the US FDA approved daratumumab 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.

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

1.1. Background

1.1.1. Multiple Myeloma

Multiple myeloma, a malignant disorder of the plasma cells, is characterized by uncontrolled and progressive proliferation of a plasma cell clone. Patients with multiple myeloma produce a monoclonal protein, also known as paraprotein (comprising monoclonal protein [M-protein] and free light chain [FLC]), which is an immunoglobulin (Ig) or a fragment of one that has lost its function.[14,21] The proliferation of myeloma cells causes displacement of the normal bone marrow. Normal Ig levels are compromised, leading to susceptibility to infections. Hypercalcemia, renal insufficiency or failure, and neurological complications are frequently reported side effects of the disease.[21]

Treatment choices for multiple myeloma vary with age, performance status, comorbidity, aggressiveness of the disease, and related prognostic factors.[21] Current treatments include combination chemotherapy, proteasome inhibitors (bortezomib [and carfilzomib in the United States (US)]), immunomodulatory drugs (thalidomide, lenalidomide, and pomalidomide), and high-dose chemotherapy (HDT) with melphalan supported by autologous stem cell transplantation (ASCT). Newly diagnosed patients with multiple myeloma are typically categorized into 2 subpopulations usually defined by their age and suitability for the subsequent approach to treatment. Younger patients will typically receive an induction regimen followed by consolidation treatment with HDT and ASCT. For those not considered suitable for HDT and ASCT, treatment is longer and consists of multi-agent combinations including alkylating agents (melphalan and cyclophosphamide), anthracyclines (doxorubicin), vincristine, glucocorticoids, or combinations of these agents.

Although treatments for multiple myeloma have improved significantly over the last 10 years, the vast majority of patients have multiple relapses and ultimately succumb to complications of the disease.

1.1.2. Daratumumab

1.1.2.1. Nonclinical Studies

In mouse xenograft models, daratumumab reduced tumor growth in both preventive and therapeutic settings. Daratumumab had no effect on proliferation of human peripheral blood mononuclear cells (PBMCs), and cytokine release was similar to other marketed therapeutic antibodies. Hence, daratumumab can recruit multiple effector mechanisms to facilitate the lysis of malignant cells in vitro and in vivo. In-vitro studies, using bone marrow mononuclear cells from patients with multiple myeloma (MM), demonstrated increased killing of tumor cells when daratumumab was combined with lenalidomide or bortezomib as well as with both lenalidomide and bortezomib. Additionally, the upregulation of CD38 by pomalidomide or lenalidomide can enhance the activity of anti-CD38 antibodies including daratumumab. These observations suggest a strong potential for the treatment of CD38-expressing malignancies using daratumumab as monotherapy and in combinations.

The potential toxicity of daratumumab was evaluated in a repeat dose study in chimpanzees. The primary toxicities identified in chimpanzees were infusion-related reactions during the first, but not subsequent, daratumumab infusions and thrombocytopenia. The binding affinity of daratumumab is ≥15-fold higher for chimpanzee platelets than for human platelets, suggesting that thrombocytopenia may be less pronounced in humans. Depletion of specific lymphocyte phenotypic cell populations, as expected, based on the intended pharmacological effect of daratumumab, was observed in chimpanzees. No genotoxicity, chronic toxicity, carcinogenicity, or reproductive toxicity testing has been conducted.

1.1.2.2. Clinical Studies

As of 30 June 2017, daratumumab is being evaluated in 21 ongoing and completed company-sponsored clinical studies in subjects across the multiple myeloma disease continuum, ie, smoldering multiple myeloma, previously untreated multiple myeloma, relapsed/refractory multiple myeloma, and other diseases including myelodysplastic syndrome (MDS), lung cancer, natural killer (NK)/T-cell lymphoma and non-Hodgkin lymphoma. Approximately 2,700 subjects have been treated with daratumumab monotherapy or combination therapy in 14 clinical studies that contribute study-specific safety summaries to the current daratumumab Investigator Brochure (IB; version 14, dated 5 October 2017). Of these subjects, daratumumab has been administered to approximately 1,160 subjects as monotherapy in Studies GEN501, MMY1002, and MMY2002, SMM2001, LYM2001, MMY1004 (SC) and MMY3010. Daratumumab as combination therapy has been administered to approximately 1,533 subjects in Studies GEN503, MMY1001, MMY1005, MMY3003, MMY3004, MMY3007, and MMY3008.

- Monotherapy studies in subjects with relapsed/refractory multiple myeloma are:
  - GEN501, MMY1002, MMY1004, MMY2002, SMM2001, MMY3010
- Combination therapy studies are:
  - Subjects with previously untreated and relapsed/refractory multiple myeloma:
    - MMY1001: daratumumab in combination with bortezomib-dexamethasone (Vd), bortezomib-thalidomide-dexamethasone (VTd), bortezomib-melphalan-prednisone (VMP), carfilzomib-lenalidomide-dexamethasone [KRd] in subjects with previously untreated multiple myeloma and pomalidomide dexamethasone [Pom-dex] and carfilzomib-dexamethasone [Kd])
  - Subjects with relapsed/refractory multiple myeloma:
    - GEN503: daratumumab in combination with lenalidomide-dexamethasone (Rd)
    - MMY1005: daratumumab in combination with Vd (in Japan)
    - MMY3003: daratumumab in combination with Rd
    - MMY3004: daratumumab in combination with Vd
  - Subjects with previously untreated multiple myeloma:
    - MMY3007: daratumumab in combination with VMP
    - MMY3008: daratumumab in combination with Rd
- Monotherapy Non-Hodgkin's Lymphoma
  - LYM2001

Limited safety data are available for ongoing clinical studies in untreated multiple myeloma (Studies MMY3007, MMY3008), smoldering multiple myeloma (Study SMM2001), and for an early-access study (Study MMY3010).

In addition, there are 7 other ongoing clinical studies in subjects with multiple myeloma, natural killer/T cell lymphoma, MDS, and lung cancer; however, data from those studies are preliminary and not included in the current daratumumab IB.

Daratumumab IV Monotherapy Studies

- MMY1003: Subjects with relapsed/refractory multiple myeloma
- NKT2001: Subjects with relapsed/refractory natural killer/Tcell lymphoma
- MDS2002: Daratumumab or talacotuzumab in Subjects with MDS

Daratumumab IV Combination Therapy

- MMY1006: daratumumab in combination with Rd in newly diagnosed MM
- MMY2004: daratumumab in combination with RVd in newly diagnosed MM
- MMY2012: daratumumab in combination with CyBorD in relapsed/refractory and newly diagnosed MM
- LUC2001: daratumumab in combination with atezolizumab in NSCLC

As of 30 June 2017, the final analysis had occurred for Studies MMY2002, GEN501, MMY1002 and MMY1005. The primary analysis had occurred for Studies GEN503, MMY1001, MMY3003, and MMY3004. The following studies are ongoing: SMM2001, MMY3010, GEN503, MMY3007, MMY3008 and LYM2001.

1.1.2.2.1. Pharmacokinetics

Daratumumab Intravenous (IV) Administration

Over the dose range from 1 to 24 mg/kg as monotherapy or 1 to 16 mg/kg in combination with other treatments, increases in area under the curve (AUC) were more than dose-proportional. Clearance was rapid at low doses and slower at higher doses; clearance also decreased with multiple doses. This PK profile was consistent with target-mediated disposition indicating target saturation at higher doses. The PK of daratumumab was similar following monotherapy and combination therapies in multiple myeloma. The mean ± SD estimated terminal half-life of daratumumab associated with linear clearance was 18 ± 9 days when administered as monotherapy and 23 ± 12 days when administered as combination therapy.

1.1.2.2.2. Efficacy

A total of 148 subjects relapsed /refractory multiple myeloma treated with 16 mg/kg monotherapy daratumumab were included in the combined analysis of Study GEN501 and Study MMY2002. The overall response rate (ORR) for the combined data set was 31% after a median duration of follow-up of 20.7 months, the Kaplan-Meier based median OS was 20.1 months.

Daratumumab IV Combination Therapy

Clinical benefit in relapsed/refractory multiple myeloma with daratumumab IV in combination with Rd and Vd was demonstrated by a significant improvement in progression free survival

(PFS) which corresponds to clinically meaningful reductions in the risk of disease progression or death. Clinical benefit in relapsed/refractory multiple myeloma with daratumumab IV in combination Pd in heavily pretreated subjects resulted in deep and durable responses, as exemplified by a high ORR, complete response or better rate, and minimal residual disease (MRD) negativity rates.

Primary efficacy analysis data for Studies GEN501, MMY2002, GEN501+MMY2002 (pooled monotherapy efficacy analysis), GEN503, MMY1002, MMY3003, MMY3004, MMY1001, MMY1005, and LYM2001 are provided in the Investigator Brochure.

Efficacy results for Study MMY2002 and Study GEN501 Part 2 (Part 1 was the dose-escalation phase of this first-in-human study), single-arm, open-label studies in which subjects with relapsed and refractory multiple myeloma were administered 16 mg/kg of daratumumab by intravenous (IV) route as monotherapy weekly for 8 weeks, every 2 weeks for an additional 16 weeks, and every 4 weeks thereafter until disease progression or unacceptable toxicity. Response and progressive disease assessment in both studies were evaluated based on the International Myeloma Working Group (IMWG) criteria. Efficacy results from the primary analysis of 148 subjects receiving daratumumab 16 mg/kg in Study MMY2002 (n = 106) and Study GEN501 Part 2 (n = 42) were integrated. After a median duration of follow-up of 20.7 months, the median overall survival (OS) was 20.1 months and an overall response rate (ORR) of 31%. Within the individual studies, the ORR was 36% in Study GEN501 and 29% in Study MMY2002.

In Study GEN503, a Phase 1/2, open-label, dose-escalation study of DRd in subjects with relapsed/refractory MM, efficacy results from the primary analysis of 13 subjects (Part 1) and 32 subjects (Part 2) receiving daratumumab 16 mg/kg showed an ORR of 88% and very good partial response of 53% after a median follow up of 7.8 months. Efficacy results from the final analysis showed ORR of 81% and very good partial response (VGPR) or better of 69% after median follow-up of 32.5 months. Median PFS has not been established in this study.

In Study MMY1002, a Phase 1 open-label, single-arm study in 9 Japanese subjects with relapsed/refractory MM who received daratumumab at a dose of 16 mg/kg, efficacy results from the primary analysis showed ORR of 60% after median follow-up of 9.9 months. The median PFS was 9.5 months and median duration of response was 7.7 months. In Study MMY3003, daratumumab in combination with lenalidomide and dexamethasone (DRd) in relapsed/refractory MM, the primary analysis showed a significant improvement in PFS and ORR for subjects in the DRd group, compared with the lenalidomide/dexamethasone (Rd) group. This represents a 63% reduction in the risk of disease progression or death for the DRd group compared with the Rd group. The ORR for the DRd group was 91% and 75%% for the Rd group. In Study MMY3004, daratumumab in combination with bortezomib and dexamethasone (DVd) in subjects with relapsed/refractory MM, the primary analysis showed a significant improvement in PFS for subjects in the DVd group, compared with the bortezomib/dexamethasone (Vd) group. This represents a 61% reduction in the risk of disease progression or death for the DVd group compared with the Vd group. The ORR was significant for the DVd group (79%) compared with the Vd group (60%).

In Study MMY1001, daratumumab in combination with various background treatment regimens for multiple myeloma in either newly diagnosed subjects or those who received prior therapies, the primary analysis showed ORR of 59% (median follow up time 9.8 months).

In Study MMY1005, nonrandomized study to evaluate the safety and tolerability of DVd in 8 Japanese subjects with relapsed/refractory multiple myeloma, primary analysis showed ORR of 100% (median follow up duration 5.5 months), VGPR or better 50% and clinical benefit (including overall response plus MR) of 100%. Median time to response was 0.9 months and median duration of response was 4.1 months.

In Study LYM2001, efficacy and safety of daratumumab in subjects with relapsed/refractory MCL, DLBCL or FL. Primary analysis after median duration of treatment of 35 days (DLBCL), 70 days (FL) and 36 days (MCL) showed overall best response rated: DLBCL:7%; FL 12.5% MCL: 0.

1.1.2.2.3. Safety

The safety results from all ongoing studies of daratumumab are summarized (through June 2017) in Table 1, below.

Table 1: Available Safety Findings in Ongoing Daratumumab Clinical Trials Through 30 June 2017	
Study Number (N exposed to dara)	**Safety Results**
Daratumumab Monotherapy Trials	
MMY2002, GEN501, and MMY1002 (Relapsed/Refractory MM, 156) Integrated analysis	• **Most common TEAEs**: fatigue (40%), nausea and anemia (28% each), back pain (26%), cough (24%), neutropenia (23%), pyrexia (22%), upper respiratory tract infection (22%), and thrombocytopenia (21%). • **Grade 3/4 TEAEs** in 57% of subjects; most common were anemia (17%), thrombocytopenia (14%), neutropenia (12%), lymphopenia and pneumonia (6%), leukopenia and hypertension (5% each), hypercalcemia (3%). • **TEAEs leading to DC of study treatment** in 4% of subjects; none considered drug related. • **SAEs** in 34% of subjects; most common were pneumonia (6%) and pyrexia, general physical health deterioration, and hypercalcemia (3% each). • **Deaths** due to progressive disease (7%), and 3 (2%) due to TEAEs (cardiorespiratory arrest in the setting of H1N1 influenza, general physical health deterioration secondary to aspiration pneumonia, and pneumonia). None of the fatal TEAEs were considered related to daratumumab.
SMM2001 (smoldering MM, 122)	• SAEs were reported for 15 subjects (24% in the long intense, 2% in intermediate, and 10% in short intense treatment groups). No **IRRs** or **deaths**.
MMY1004 - Relapsed/Refractory MM (subcutaneous administration, 53)	• A total of 8 subjects received dara-MD 1200 mg and 45 subjects received dara-MD 1800 mg. • **Most common TEAEs** (≥20% of all subjects): upper respiratory tract infection (1200 mg: 38%; 1800 mg: 22%), insomnia (1200 mg: 38%; 1800 mg: 11%), decreased appetite (1200 mg: 38%; 1800 mg: 7%), thrombocytopenia (1200 mg: 38%; 1800 mg: 18%), viral upper respiratory tract infection (1200 mg: 25%; 1800 mg: 13%), vomiting (1200 mg: 25%; 1800 mg: 13%), hyperuricaemia (1200 mg: 25%; 1800 mg: 2%), hypokalaemia (1200 mg: 25%; 1800 mg: 4%), blood creatinine increased (1200 mg: 25%; 1800 mg: 4%), anemia (1200 mg: 25%; 1800 mg: 33%), fatigue (1200 mg: 25%; 1800 mg: 20%), pyrexia (1200 mg: 25%; 1800 mg: 27%), diarrhea (1200 mg: 25%; 1800 mg: 22%), headache (1200 mg: 25%; 1800 mg: 18%), cough (1200 mg: 25%; 1800 mg: 13%), epistaxis (1200 mg: 25%; 1800 mg: 4%), hypertension (1200 mg: 25%; 1800 mg: 7%), rhinitis allergic (1200 mg: 25%; 1800 mg: 2%), nasal congestion (1200 mg: 25%; 1800 mg: 2%), rectal hemorrhage (1200 mg: 25%; 1800 mg: 0%), and asthenia (1200 mg: 13%; 1800 mg: 20%), • **Grade 3/4 TEAEs**: in 63% and 49% of subjects in the 1200 mg and 1800 mg cohorts, respectively. The most frequently reported Grade 3 or 4 TEAEs were in the Blood and Lymphatic System Disorders System Organ Class (SOC), reported in 38% and 31% of subjects in the 1200 mg and 1800 mg cohorts, respectively. Two of 8 (25%) subjects in the 1200 mg cohort and 4% in the 1800 mg cohort had Grade 3 or 4 hypertension. • **SAEs:** SAEs were reported in 26% of all subjects: 50% and 31% of subjects in the 1200 mg and 1800 mg cohorts, respectively. The most frequently reported serious TEAEs were in the Infections and Infestations SOC (1200 mg: 38%, 1800 mg: 16%), the Nervous System Disorders SOC (1200 mg: 13%, 1800 mg: 4%), and the Respiratory, thoracic and mediastinal disorders (1200 mg: 13%, 1800 mg: 2%). • **No TEAEs leading to DC of study treatment**. One subject in the dara-MD 1800 SC cohort died within 30 days of the last dose of study drug from progressive disease.
MMY3010 (Relapsed/Refractory MM, 687)	• **SAEs** in 38% of subjects; most common were pneumonia (4%), hypercalcemia (3%), pyrexia (3%), dyspnea (2%), thrombocytopenia (2%), acute kidney injury (2%), and back pain (2%). • **Deaths:** Forty-eight subjects (7%) reported TEAEs with an outcome of death.

Table 1: Available Safety Findings in Ongoing Daratumumab Clinical Trials Through 30 June 2017	
Study Number (N exposed to dara)	**Safety Results**
LYM2001 (non-Hodgkin's lymphoma, 36)	• All subjects had at least 1 or more TEAE. Most common TEAEs were reported from SOC of respiratory, thoracic and mediastinal disorders; cough (DLBCL cohort: 47%; FL cohort: 38%; MCL cohort: 80%); SOC of gastrointestinal disorders: abdominal pain (DLBCL cohort: 13%; FL cohort: 31%; MCL cohort: 20%), and nausea (DLBCL cohort: 33%; FL cohort: 6%; MCL cohort: 40%), and SOC of general disorders and administration site conditions; fatigue (DLBCL cohort: 27%; FL cohort: 19%; MCL cohort: 20%), and pyrexia (DLBCL cohort: 13%; FL cohort: 25%; MCL cohort: 40%) • **SAEs** in 15 subjects. All SAEs were reported in 1 subject each, except for febrile neutropenia, pneumonia, general physical health deterioration, and pyrexia (2 subjects each). • **Deaths** in 4 subjects: 2 due to progressive disease and 2 due to an adverse event (chronic kidney disease and pneumonia). • **IRRs** – none.
Daratumumab Combination Trials	
GEN503 and MMY3003 (integrated; dara in combination with lenalidomide and dexamethasone (318)	• **Most common TEAEs** (DRd treatment group**)**: neutropenia (64%), diarrhea (53%), upper respiratory tract infection (37%), fatigue (37%), anemia (36%), cough (34%), muscle spasms (31%), constipation (31%), thrombocytopenia (29%), viral upper respiratory tract infection (29%), nausea (28%), and pyrexia (25%). • **Grade 3/4 TEAEs** (DRd treatment group**)**: 89%; most common, neutropenia (58%), anemia (16%), and thrombocytopenia (14%). • **TEAEs leading to DC of treatment** in 13% of subjects in the DRd treatment group; most common were pneumonia (4 subjects, 1.3%), general physical health deterioration (3 subjects, 0.9%), and septic shock (2 subjects, 0.6%). • **SAEs** (DRd treatment group**)** in 63% of subjects; most common were pneumonia (13%), influenza, febrile neutropenia (4%) and pyrexia (4% each), and bronchitis, pulmonary embolism, lower respiratory tract infection, diarrhea (3% each). • **Deaths (**DRd treatment group**)**:7% of subjects died within 30 days of the last dose of study drug: 21 due to TEAEs and 1 due to disease progression.
MMY1001 (dara in combination with pomalidomide and dexamethasone, 240)	• **Most common TEAEs**: neutropenia (81%), anemia (55%), fatigue (52%), diarrhea (50%), thrombocytopenia (43%), cough (41%), leukopenia (39%), constipation (36%), nausea (34%), dyspnea (33%), pyrexia (33%), upper respiratory tract infection (32%), muscle spasms (29%), vomiting (28%), arthralgia (26%). • **Grade 3 or 4 TEAEs** in 99% of subjects; most common were neutropenia (79%), anemia (28%), leukopenia (24%), thrombocytopenia (19%), lymphopenia (14%), and pneumonia and fatigue (13% each). • **TEAEs leading to DC of treatment** in 16% of subjects (no single AE reported in >1 subject). • **SAEs** in 57% of subjects; most common were pneumonia (12%), sepsis (7%), febrile neutropenia (5%), fall (4%), anemia, dyspnea, small intestinal obstruction, and urinary tract infection (3% each). • **Deaths:** 9% of subjects died during study treatment or within 30 days after the last dose of study drug; 7 due to AEs and 2 deaths due to disease progression.
MMY1001 (Dara plus bortezomib and dexamethasone, 30)	• **SAEs** were reported for 3 subjects in the DVd arm (Hyperglycemia [1 subject], soft tissue infection, pneumonia, prerenal failure, diarrhea, respiratory failure [1 subject], laboratory test interference [1 subject]. In DVMP arm, SAEs were reported in 1 subject (cardiac failure). No subjects in the D-VTd arm were reported to have SAEs. • No **deaths** reported.

Table 1: Available Safety Findings in Ongoing Daratumumab Clinical Trials Through 30 June 2017	
Study Number (N exposed to dara)	**Safety Results**
MMY1001 (Dara in combination with carfilzomib/dexamethasone +/- lenalidomide DKd = 20, DKRd = 20)	• **AEs of Interest** – Cardiac Events: In the DKd arm, cardiac disorder TEAEs of interest were reported in 15% of subjects; 4 (5%) subjects had a Grade 3 or Grade 4 event. No cardiac disorder TEAEs of Grade 5 was reported. In the DKRd arm, cardiac disorder TEAEs of interest were reported in 41% of subjects, with 1 subject (5%) having a Grade 3 or Grade 4 event (congestive heart failure) that was also an SAE. No Grade 5 events were reported. • **SAEs** reported in 32% of subjects in the DKd arm (n=85); most common was pneumonia (7%). SAEs were reported in 46% of subjects in the DKRd arm (n=22). The most frequently reported SAEs were pulmonary embolism (n=3; 14%) and influenza and pyrexia (n=2; 9% each). All other SAEs were reported in 1 subject each. • One **death** in the DKd arm due to progressive disease.
MMY1005 (Dara in combination with bortezomib and dexamethasone; Japan, 8)	• **SAEs** in 3 subject each (herpes zoster, prostate cancer, nasopharyngitis). • No **IRRs.** • No **deaths.**
MMY3004 (Dara in combination with bortezomib and dexamethasone, 243)	• **Most common TEAEs** were thrombocytopenia (60%), peripheral sensory neuropathy (50%), diarrhea (35%), upper respiratory tract infection (33%), anemia (28%), and cough (28%). • **Grade 3/4 AEs** were reported in 81% of subjects; most common were thrombocytopenia (46%), anemia (15%), and neutropenia (14%). • **TEAEs leading to DC of treatment** were reported for 10% of subjects; most common were pneumonia (4 subjects; 2%), and cardiac failure congestive (2 subjects; 0.8%). • **SAEs** in 50% of subjects; most common were pneumonia (10%), and anemia, bronchitis, thrombocytopenia, atrial fibrillation, upper respiratory tract infection, and pyrexia (3% each). • **Deaths**:15 subjects died within 30 days of the last dose of study drug; 13 deaths were due to TEAEs and 2 were due to disease progression.
MMY3007 (Dara in combination with bortezomib, melphalan and prednisone, 700)	• **Most common TEAEs** were thrombocytopenia (51%), neutropenia (51%), anemia (33%), peripheral sensory neuropathy (31%), diarrhea (24%), pyrexia (22%), nausea (21%), upper respiratory tract infection (20%) and constipation (18%). • **Grade 3/4 TEAEs** were reported in 74% of subjects, with neutropenia (39%) and thrombocytopenia (36%) being the most frequently reported. • **SAEs** were reported in 37% of subjects, with pneumonia being the most frequent (7%). • **Deaths**: Thirty-eight (5%) subjects had a Grade 5 TEAE.
MMY3008 (Dara in combination with lenalidomide and dexamethasone, 729)	• **Most common TEAEs** were neutropenia (39%), diarrhea (34%), constipation (33%), fatigue (28%), anemia (25%), nausea and edema peripheral (24% each), insomnia (22%), muscle spasms (21%), and asthenia (20%). • **Grade 3/4 TEAEs** were reported in 70% of subjects, with neutropenia being the most frequently reported (32%). • **SAEs** were reported in 50% of subjects; most common were pneumonia (6%), pyrexia and pulmonary embolism (3% each). • **Deaths** Thirty-four subjects (5%) had a Grade 5 TEAE. .

TEAE = treatment emergent adverse event; dara = daratumumab; DC = discontinuation; DKd = daratumumab+carfilzomib+dexamethasone; DKRd = daratumumab+carfilzomib+lenalidomide+dexamethasone; IRR = infusion-related reaction; MM = multiple myeloma; N = number of subjects; SAE = serious adverse event.

1.1.3. Lenalidomide

Lenalidomide is an immunomodulatory drug 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.[12] Importantly, it has also been shown that lenalidomide causes upregulation of natural killer (NK) cells in myeloma[12] and enhances the effector cells of antibody-dependent cell-mediated cytotoxicity, which is one mechanism of action of daratumumab shown in preclinical studies.[29,30]

Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Lenalidomide can cause significant neutropenia and thrombocytopenia. There is a significantly increased risk of deep vein thrombosis and pulmonary embolism, as well as risk of myocardial infarction and stroke in patients with multiple myeloma who receive lenalidomide with dexamethasone. Higher incidences of secondary primary malignancies were observed in controlled trials of subjects with multiple myeloma receiving lenalidomide. Additionally, administration of lenalidomide has been associated with hepatotoxicity (hepatic failure including fatalities); allergic reactions, including fatalities (hypersensitivity, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis); tumor lysis syndrome including fatalities; and impaired stem cell mobilization (a decrease in the number of CD34+ cells collected after treatment [>4 cycles]). Most common adverse reactions (≥20%) include diarrhea, fatigue, anemia, constipation, neutropenia, peripheral edema, insomnia, muscle cramp/spasms, back pain, nausea, asthenia, pyrexia, upper respiratory tract infection, cough, rash, dyspnea, dizziness, decreased appetite, thrombocytopenia, and tremor.[25]

1.1.4. Bortezomib

Bortezomib is a proteasome inhibitor. It is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types in vitro. Bortezomib causes a delay in tumor growth in vivo in nonclinical tumor models, including multiple myeloma. In addition, bortezomib-based treatment regimens have demonstrated significant improvements in response, progression-free survival (PFS), and OS compared with non-bortezomib-based therapy for multiple myeloma, both in newly diagnosed transplant ineligible patients and those suitable for induction and transplant.[8,28] Administration of bortezomib has been associated with peripheral neuropathy, hypotension, cardiac toxicity (worsening of and development of cardiac failure), pulmonary toxicity (acute respiratory syndromes), posterior reversible encephalopathy syndrome, gastrointestinal toxicity (nausea, diarrhea, constipation, and vomiting), thrombocytopenia, neutropenia, tumor lysis syndrome, hepatic toxicity, and embryo-fetal risk. Most commonly reported adverse reactions (incidence ≥20%) in clinical studies include nausea, diarrhea, thrombocytopenia, neutropenia,

peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia.[35]

1.1.5. Dexamethasone

Dexamethasone is a corticosteroid used to decrease the nausea and vomiting associated with chemotherapy.[2] Common adverse reactions include hyperglycemia, increased appetite and weight gain, irritability, insomnia, impaired wound healing, and cataracts and osteoporosis with long-term use.

For further information regarding lenalidomide, bortezomib, and dexamethasone, refer to the individual prescribing information.[7,25,35]

1.1.6. Combination Therapy: Lenalidomide-Bortezomib-Dexamethasone

In an important proof of concept study, Richardson and colleagues[26] published a Phase 1/2 study assessing the combination of lenalidomide, bortezomib, and dexamethasone (RVd) for newly diagnosed subjects with multiple myeloma, regardless of eligibility for HDT and ASCT. Sixty-six subjects were treated on this single-arm study. A partial response (PR) or better was achieved by 100% of subjects (N=66), with favorable tolerability. Complete response (CR) was achieved in 19 subjects (29%) with an additional 7 subjects (11%) in near CR. Importantly, this study showed that RVd was a feasible induction regimen prior to ASCT. Twenty-eight subjects (42%) proceeded to undergo ASCT. Stem cell harvesting and engraftment were not adversely impacted by the 3-drug induction regimen.

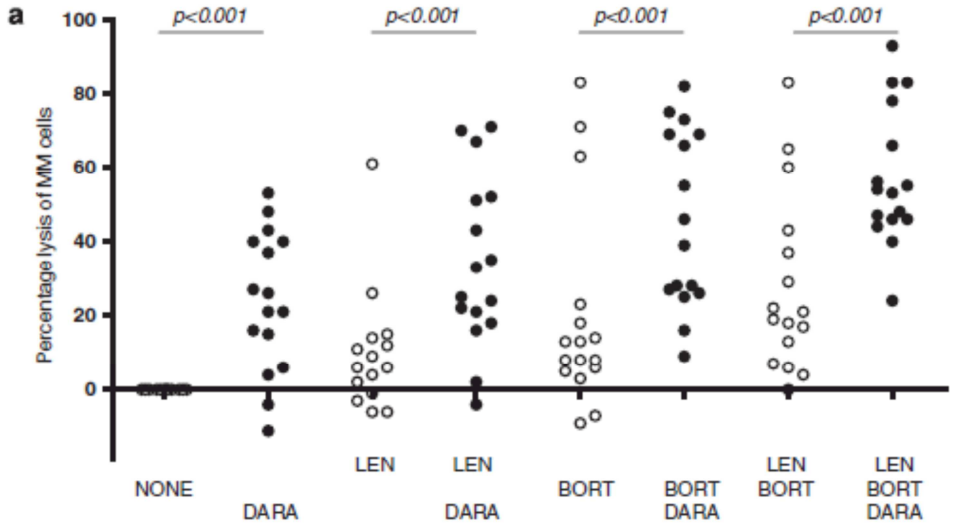
More recently, the Intergroupe Francophone du Myélome conducted a Phase 2 study of RVd in newly diagnosed subjects with multiple myeloma who were eligible for ASCT.[27] In this study, 31 subjects received 3 cycles of RVd followed by stem cell harvest and transplantation, followed by an additional 2 consolidation cycles of RVd, and lastly an additional year of lenalidomide maintenance therapy. The overall response after 3 cycles of induction therapy was 94% with 3 subjects achieving sCR (10%) and an additional 4 subjects in CR (13%). Interestingly, 4 out of 25 tested were minimal residual disease (MRD) negative by flow cytometry. The best response at any time during the study was sCR in 15 (48%) subjects, CR in 3 (10%) subjects, and 21 out of 31 (68%) subjects achieved MRD negative status by flow cytometry.

Although RVd is a commonly given front-line regimen in the United States, the sCR rate demonstrated was approximately 10% to 15%. In a recent publication by Kapoor and colleagues,[11] the authors correlate the achievement of sCR to long-term outcomes including time to progression (TTP) and OS. Specifically, median TTP of subjects achieving sCR was significantly longer (50 months) than TTP of subjects achieving CR or near CR (20 months and 19 months, respectively). Furthermore, subjects attaining sCR were found to have a 5-year OS rate of 80% compared with subjects at CR (53%) or near CR (47%).

1.1.7. Combination Therapy: Daratumumab-Lenalidomide-Bortezomib-Dexamethasone

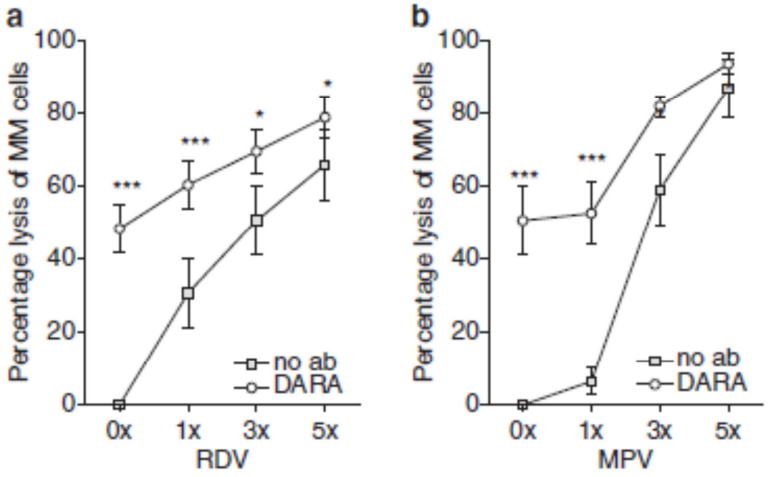
The potential benefit of combining daratumumab with multi-drug chemotherapy regimens was evaluated in fresh tumor cells from subjects with multiple myeloma (data on file-study GMB3003-070). Lysis of primary tumor cells was measured directly in bone marrow mononuclear cell (BM-MNC) isolates obtained from subjects with multiple myeloma. Synergistic tumor cell lysis was demonstrated when daratumumab was combined with lenalidomide and/or bortezomib, even in samples from subjects that were refractory to lenalidomide and bortezomib treatment. Treatment of BM-MNC with lenalidomide or bortezomib resulted in 10% and 18% lysis, respectively. A combination of lenalidomide and bortezomib resulted in 25% lysis of BM-MNC. When daratumumab was added to either lenalidomide or bortezomib, a 2-fold increase in lysis was observed compared with lenalidomide or bortezomib alone. When daratumumab was added to combinations of dexamethasone, lenalidomide, and bortezomib or to bortezomib, prednisone, and dexamethasone, the cell lysis was significantly increased ($p<0.001$) compared with the triple combination alone (no daratumumab).[34] Refer to Figure 1 and Figure 2.

Figure 1: Daratumumab-Enhanced Multiple Myeloma Cell Killing by Key Multiple Myeloma Chemotherapeutic Agents



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

Figure 2: Dose-dependent Lysis of Multiple Myeloma Cells in Triple Chemotherapy Treatments



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

Thus, in this ex vivo clinical setting, daratumumab-mediated multiple myeloma tumor cell killing was demonstrated to be significantly augmented by stimulating effector cells. Preclinical data, both the literature and the sponsor's own ex vivo studies, support the combination of daratumumab with lenalidomide and bortezomib in the treatment of multiple myeloma.

1.2. Overall Rationale for the Study

To date, targeting multiple myeloma cells by a combination-therapy approach has demonstrated superior clinical response as compared with that of single agents.[5] In theory, targeting both the tumor cells and the surrounding stromal compartment upon which the tumor is dependent should lead to higher efficacy. Targeted immunotherapy based on monoclonal antibodies against relevant tumor antigens has shown to be not only feasible, but also an effective approach in treating hematological malignancies when combined with chemotherapy agents. The future of successful multiple myeloma treatment lies in both the development of novel agents targeting the multiple myeloma cells or the bone marrow microenvironment, and the development of rationally-based combination therapies. The addition of daratumumab to RVd induction therapy (D-RVd) could potentially improve initial disease control and long-term outcomes. Based upon the pre-clinical synergism observed, and promising clinical data in the relapsed/refractory setting, the D-RVd combination will be investigated in this study in newly diagnosed, transplant-eligible patients.

Based on the current safety data from ongoing daratumumab studies, and the safety information in the label for lenalidomide and for bortezomib, the expected safety profile of daratumumab in this combination therapy study is considered manageable. See the daratumumab Investigator's Brochure for additional data. The safety profile of daratumumab in combination with other

agents is consistent with the known safety profiles of the backbone therapies (bortezomib, lenalidomide, pomalidomide, dexamethasone, melphalan, prednisone, thalidomide). With the exception of IRRs, the addition of daratumumab to standard multiple myeloma treatment regimens did not seem to add toxicity to the safety profiles previously reported with these backbone regimens.

2. OBJECTIVES, Endpoints, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

The primary objective is to determine if the addition of daratumumab to RVd will increase the proportion of subjects achieving sCR, as defined by the IMWG criteria, by the time of completion of post-ASCT consolidation treatment, compared with RVd alone.

Secondary Objectives

The secondary objectives are:

- To evaluate CR and sCR rate following induction, ASCT, post-ASCT consolidation, and maintenance treatment
- To evaluate overall response rate (ORR) and rate of VGPR or better following induction, ASCT, post-ASCT consolidation, and maintenance treatment
- To evaluate duration of and time to sCR and time to CR
- To evaluate time to VGPR or better
- To evaluate time to PR or better
- To assess negative MRD rate following induction, post-ASCT consolidation, and maintenance treatment
- To evaluate clinical outcomes including:
  - Time to progression
  - Progression-free survival
  - Overall survival
  - Duration of response
- To assess the safety and tolerability of D-RVd
- To assess the pharmacokinetics of daratumumab
- To assess the immunogenicity of daratumumab

- To evaluate patient-reported outcomes (PROs)
- To evaluate stem cell yield after mobilization
- To assess time to absolute neutrophil count (ANC) recovery, defined as the date from transplant to the first of 3 consecutive laboratory values (obtained on different days) where the ANC is > 0.5 x 10^9/L.
- To assess time to platelet count recovery, defined as the date from transplant to the first of 3 consecutive laboratory values (obtained on different days) where the platelet count is > 20 x 10^9/L and at least 7 days after the most recent prior platelet transfusion
- To evaluate the tolerability of daratumumab when administered as a rapid infusion during maintenance treatment (ie, an accelerated infusion rate whereby 20% of the daratumumab dose is administered over 30 minutes and the remaining 80% is administered over 60 minutes for a total dose administration time of 90 minutes)

Exploratory Objectives

The exploratory objectives are:

- To evaluate PFS on next-line therapy
- To evaluate the clinical efficacy of D-RVd in high-risk cytogenetic subgroups: del(17p), t(4;14), and t(14;16),
- To explore immune modulatory effects of D-RVd as compared with RVd through immune profiling (NK, T, and B cells) and T-cell receptor sequencing
- To collect medical resource utilization (MRU) data that may be used in future economic modeling (the construction and reporting of the economic model will be conducted separately from this study)
- To evaluate serum concentrations and potential immunogenicity of daratumumab with respect to IRRs in the setting of rapid infusion during maintenance.

2.1.2. Endpoints

Primary Endpoint

The primary endpoint is the sCR rate by the end of post-ASCT consolidation treatment, defined as the proportion of subjects who have achieved sCR, according to the IMWG criteria, by the end of post-ASCT consolidation treatment.

Secondary Endpoints

M-protein levels need to meet the definition of disease progression (see Table 9: International Uniform Response Criteria Consensus Recommendations) for subjects to have disease progression. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed.

The secondary efficacy endpoints include:

- Following induction treatment (prior to HDT/ASCT), ASCT (prior to start of consolidation treatment), post-ASCT consolidation (after Cycle 6), and maintenance treatment:
  - Overall CR and sCR rate is defined as the proportion of subjects who achieve CR (or sCR), according to the IMWG criteria, by the respective time point.
  - ORR is defined as the proportion of subjects who achieve PR or better, according to the IMWG criteria, by the respective time point.
  - VGPR or better rate is defined as the proportion of subjects achieving VGPR or better, according to the IMWG criteria, by the respective time point.
  - MRD negative rate is defined as the proportion of subjects who achieve MRD negative status by the respective time point.

    Note: A subject not tested for MRD will be considered as MRD positive.
- Duration of CR (and sCR) is the duration from the date of initial documentation of a CR (or sCR) response, according to the IMWG criteria, to the date of first documented evidence of progressive disease, or relapse from CR. For subjects who have not progressed or relapsed, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.
- Time to CR (and sCR) is the duration from the date of randomization to the date of initial documentation of CR (or sCR), which was confirmed by a repeated measurement as required by the IMWG criteria. For subjects who have not achieved CR (or sCR), data will be censored at the date of progressive disease or the last disease evaluation before the start of any subsequent anti-myeloma therapy, whichever comes first.
- Time to VGPR or better is the duration from the date of randomization to the date of initial documentation of VGPR or better, which was confirmed by a repeated measurement as required by the IMWG criteria. For subjects who have not achieved VGPR or better, data will be censored at the date of progressive disease or the last disease evaluation before the start of any subsequent anti-myeloma therapy, whichever comes first.
- Time to PR or better is the duration from the date of randomization to the date of initial documentation of PR or better, which was confirmed by a repeated measurement as required by the IMWG criteria. For subjects who have not achieved PR or better, data will be censored at the date of progressive disease or the last disease evaluation before the start of any subsequent anti-myeloma therapy, whichever comes first.
- Time to progression is defined as the duration from the date of randomization to the date of first documented evidence of progressive disease according to the IMWG criteria. Subjects who have not progressed will be censored at the last date of the disease evaluation before the start of any subsequent anti-myeloma therapy.
- Progression-free survival is defined as the duration from the date of randomization to the date of first documented evidence of progressive disease or death, whichever comes first. First documented evidence of progressive disease must have been confirmed by a repeat measurement as required by the IMWG criteria. Subjects who have not progressed nor died

by the data cutoff will be censored at the last date of the disease evaluation before the start of any subsequent anti-myeloma therapy.

- Overall survival is measured from the date of randomization to the date of the subject's death. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive.
- Duration of response is defined as the duration from the date of initial documentation of a response (PR or better) according to the IMWG criteria to the date of first documented evidence of progressive disease according to the IMWG criteria. For subjects who have not progressed, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.

Exploratory Endpoint

- Progression-free survival after next-line therapy will be measured from randomization to the date of the progressive disease on the next line of treatment or death, whichever comes first. Subjects who are still alive and have not yet progressed on the next line of treatment will be censored on the last date of follow-up.

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

2.2. Hypothesis

The primary hypothesis of this study is that D-RVd will improve the sCR rate by the end of post-ASCT consolidation treatment compared with RVd alone.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a multicenter, randomized, open-label, active-controlled, Phase 2 study in subjects with newly diagnosed multiple myeloma eligible for HDT and ASCT. Initially, there will be a safety run-in phase in up-to-16 subjects to assess potential dose-limiting toxicities (DLTs) that may be associated with the addition of daratumumab to the RVd regimen. The main study consists of 4 phases: a 28-day screening phase; an induction/consolidation phase (which is inclusive of four 21-day induction treatment cycles followed by stem cell mobilization, HDT, and ASCT, followed by two 21-day consolidation treatment cycles); a 24-month maintenance phase that starts after the post-ASCT consolidation disease evaluation; and a long-term follow-up phase. All subjects will be followed in the long-term follow-up phase for at least 1 year after last dose of study treatment and will continue until death, withdrawal of consent for study participation, or the end of study definition is met. The end of study is defined as when all subjects have completed at least 1 year of long-term follow up, or until death or withdrawal of consent for study participation, whichever occurs first.

Initially, a safety run-in phase will be performed at selected study sites. In this safety run-in phase, a total of 8 to 16 subjects will be enrolled and assigned to receive D-RVd to assess potential DLTs during Cycle 1 of treatment. Subjects who are enrolled in the safety run-in phase will have all procedures indicated in the TIME AND EVENTS SCHEDULE performed except PRO assessments and MRU data collection.

Dose-limiting toxicities are defined as:

- Grade 4 neutropenia lasting more than 7 days.
- Grade 4 thrombocytopenia lasting more than 7 days despite transfusion support.
- Grade 3 or higher nonhematological toxicity except:
  - Grade 3 nausea, vomiting, or diarrhea that can be controlled within 48 hours with maximal supportive care.
  - Grade 3 hyperglycemia that can be controlled within 48 hours with appropriate supportive care.
  - Asymptomatic Grade 3 or higher electrolyte disturbances that can be controlled with repletion within 24 hours.
  - Grade 3 maculopapular rash attributable to lenalidomide.
- Infusion-related reactions:
  - Any Grade 4 IRR occurring within 48 hours of the infusion of daratumumab.
  - Any Grade 3 IRR occurring within 48 hours of the infusion of daratumumab that does not resolve with a reduced infusion rate or temporarily stopping the infusion, as well as administration of supportive care and symptomatic therapy such as a steroid and an antihistamine.

Alopecia, lymphopenia, and anemia will not be part of DLT determination.

Up-to 16 subjects (minimum 8) will be enrolled in the safety run-in phase. Subjects will be monitored according to stopping boundaries specified in Section 11.10, Safety Analyses. Subjects who experience a DLT during the safety run-in will be withdrawn from the study (based on investigator's judgment and best clinical practice). If the stopping boundaries are crossed after 8, 12, or 16 subjects, all subjects will be withdrawn from the study, and the study will be stopped. Unless the study is stopped due to DLTs, subjects enrolled in the safety run-in phase will continue in the study and follow the visit schedule and procedures described for the main study (except PRO assessments and MRU data collection).

Following successful completion of the safety run-in phase, approximately 200 subjects will be randomly assigned to 1 of 2 treatment groups (100 per treatment group) in the main study:

- D-RVd group: RVd with daratumumab 16 mg/kg IV weekly during induction treatment (Days 1, 8, and 15 of Cycles 1 through 4) and every 3 weeks during consolidation treatment (Day 1 of Cycles 5 and 6), followed by every 4 or 8 weeks during maintenance treatment. Subjects will receive pre- and postinfusion medications for each dose of daratumumab as described in Sections 6.1.3.1 and 6.1.3.2, respectively.
- RVd group: RVd alone as induction and consolidation treatment (Cycles 1 through 6: lenalidomide 25 mg orally on Days 1 through 14, bortezomib 1.3 mg/m^2 subcutaneously on Days 1, 4, 8, and 11, and oral dexamethasone 40 mg weekly [20 mg on Days 1, 2,8, 9, 15, and 16]) followed by maintenance treatment with oral lenalidomide 10 mg daily on Days 1-

21 throughout each 28-day cycle on Cycles 7 through 9. Beginning at Cycle 10, the lenalidomide dose will be increased to 15 mg unless there is a tolerability concern.

Subjects will be stratified at randomization by International Staging System Stage I, II, or III disease (β-2 microglobulin and albumin) and creatinine clearance (CrCl [30-50 mL/min and >50 mL/min]).

Additional details for daratumumab and RVd administration are provided in Section 6, Dosage and Administration and in the Study Drug Dosing. After 4 cycles of induction study treatment, subjects will undergo stem cell mobilization and then proceed to HDT and ASCT, which will be performed according to institutional standards (see Section 9.1.3 Induction/Consolidation Phase for additional details). If the decision is made by the investigator not to pursue HDT and ASCT, subjects will be discontinued from study treatment and enter the long-term follow-up phase; subjects who do not undergo HDT and ASCT will not receive consolidation or maintenance treatment on protocol.

Consolidation treatment may commence when engraftment is complete and when in the opinion of the investigator the subject is fit enough to tolerate subsequent systemic therapy (60-100 days post-ASCT). At the start of consolidation treatment, both groups will receive the same dosages of lenalidomide, bortezomib, and oral dexamethasone that were tolerated at the end of induction treatment. Subjects will be evaluated for the primary endpoint (post-ASCT consolidation sCR). MRD will be assessed by next-generation sequencing, regardless of treatment group, as detailed in the TIME AND EVENTS SCHEDULE. After the post-ASCT consolidation disease evaluation, subjects will enter the 24-month maintenance phase of the study. Following completion of the last cycle of the maintenance phase, subjects may continue lenalidomide as per local standard of care.

Subjects will receive study treatment through completion of the 24-month maintenance phase, or until confirmed disease progression, discontinue study treatment due to an unacceptable drug toxicity, or other reasons. Unless a subject withdraws consent for study participation, or is lost to follow-up, an EOT visit is to be scheduled 30 days after the last dose of all components of the study treatment have been discontinued, or as soon as possible before the start of next-line therapy. After completion of the EOT visit, subjects will enter the long-term follow-up phase of the study. Subjects who enter the long-term follow-up phase before disease progression will return to the site every 12 weeks for disease evaluation, PRO assessments, and other follow-up assessments (ie, other malignancies, start of next-line therapy, and survival), until confirmed disease progression, death, the start of a new treatment for multiple myeloma, withdrawal of consent for study participation, or the end of study, whichever occurs first (see TIME AND EVENTS SCHEDULE). After confirmed disease progression or the start of a new treatment for multiple myeloma, subjects will return to the site or be contacted by telephone every 12 weeks for follow-up assessments (ie, other malignancies, next-line therapy, progressive disease (PD) on next-line therapy, and survival, as applicable). Following disease progression on the next-line therapy, subjects will only be followed for survival.

No daratumumab dose modification (increase or decrease) will be permitted. Protocol-specified dose delays for daratumumab have been included in this protocol (refer to Section 6.1.4, Dose Modification and Dose Delays) and will be implemented as necessary. Subjects will be evaluated for toxicity before each dose of daratumumab is administered. Investigators will focus on hematologic toxicity and the occurrence of IRRs (refer to Section 6.1.3, Guidelines for Prevention and Management of Infusion Reactions and Section 6.1.4, Dose Modification and Dose Delays). Doses may be held based on the severity of and recovery from a previous toxicity. Dose adjustments and delays of lenalidomide, bortezomib, and dexamethasone will be permitted (refer to Sections 6.2.1, 6.3.1, and 6.4, respectively).

Disease response and progression will be based on assessments according to the IMWG guidelines. Efficacy evaluations include: M-protein measurements (serum and urine), immunofixation (IFE) (serum and urine), serum FLC, serum calcium corrected for albumin, examination of bone marrow aspirate or biopsy, skeletal survey (assessment of lytic bone disease), and documentation of extramedullary plasmacytomas. Minimal residual disease in the bone marrow aspirate will also be assessed.

Throughout the study, subjects will be monitored closely for adverse events, laboratory abnormalities, and clinical response, as specified in the TIME AND EVENTS SCHEDULE. The National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE Version 4.03) will be used to grade toxicity throughout the study.

Blood samples for biomarker studies will be collected from all subjects. Blood samples for pharmacokinetic and immunogenicity assessments will only be collected from subjects in the D-RVd/D-R group.

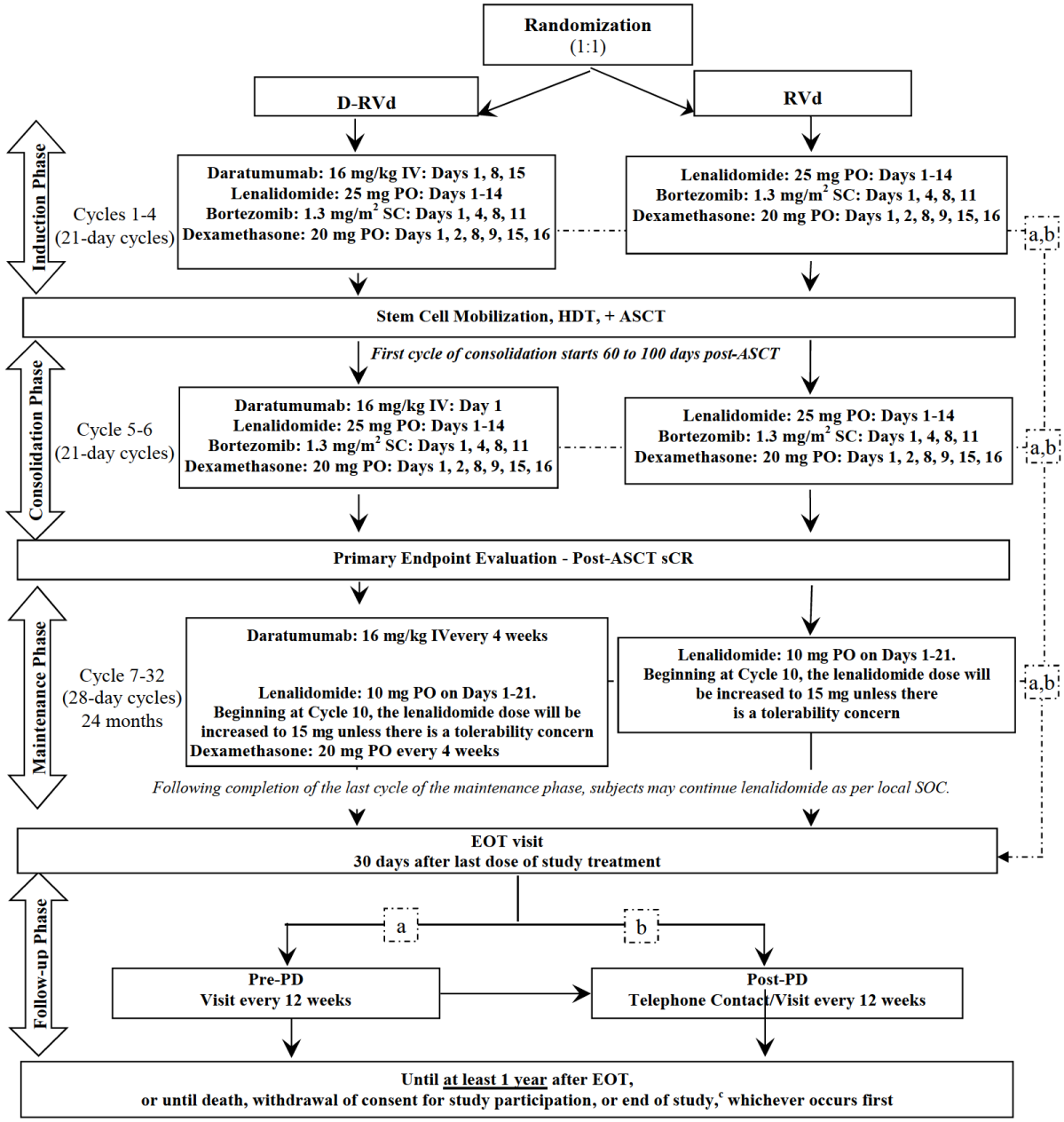
To measure functional status, well-being, and symptoms, the EORTC QLQ-C30, EORTC QLQ-MY20, and the EQ-5D-5L instruments will be completed by subjects throughout the study. Medical resource utilization data will also be collected.

A Data Review Committee will review safety data after 8, 12, and 16 subjects in the safety run-in phase complete Cycle 1 (or discontinue before the end of Cycle 1) and will use stopping boundaries described in Section 11.10, Safety Analyses. Refer to Section 11.13, for details. If the study is not stopped due to DLTs in the safety run-in phase, one interim safety analysis is planned for the safety run-in cohort after all subjects are treated for at least 4 cycles or discontinue study participation.

An independent Data Monitoring Committee (DMC) will meet periodically to review interim safety data during the main study. One planned interim safety analysis will occur after at least 50 subjects are treated for at least 4 cycles and undergo stem cell mobilization (or are evaluated for mobilization feasibility) in the main study or have discontinued before completing 4 cycles/stem cell mobilization/feasibility. Refer to Section 11.12, Independent Data Monitoring Committee for details.

A diagram of the study design is provided in Figure 3.

Figure 3: Schematic Overview of the Study



[a] For subjects who discontinue study treatment before disease progression, an EOT visit will be performed, and then subjects will enter the Pre-PD follow-up phase and have visit procedures performed every 12 weeks until confirmed disease progression, death, the start of a new treatment for multiple myeloma, withdrawal of consent for study participation, or the end of study, whichever occurs first.

[b] After confirmed disease progression or the start of a new treatment for multiple myeloma, an EOT visit will be performed, and then subjects will enter the Post-PD follow-up phase and have visit procedures performed every 12 weeks until death, withdrawal of consent for study participation, or the end of study, whichever occurs first. Following disease progression on the next-line therapy, subjects will only be followed for survival.

[c] The end of study is defined as when all subjects have completed at least 1 year of long-term follow up, or until death or withdrawal of consent for study participation, whichever occurs first.

Abbreviations: d = dexamethasone; D = daratumumab; EOT = end-of-treatment; HDT = high-dose chemotherapy; IV = intravenous; PD = progressive disease; PO = oral; R = lenalidomide; SOC = standard of care; V = bortezomib.

Note: In the above figure it states that daratumumab is to be administered every 4 weeks during the maintenance phase. While this is the preferred treatment schedule, for those who do not elect to receive daratumumab every 4 weeks, daratumumab will be administered every 8 weeks during maintenance as originally planned.

3.2. Study Design Rationale

3.2.1. Study Phase/Periods, Treatment Groups

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Additionally, randomization will be stratified by International Staging System Stage I, II, or III disease and by CrCl (30-50 mL/min and >50 mL/min) to ensure that these prognostic factors are balanced across the treatment groups.

3.2.2. Rationale for Daratumumab Dose Selection, Infusion Rate, and Backbone Chemotherapy Regimen

The dose of daratumumab in this study was based on the GEN501 and MMY2002 studies, which demonstrated that a dose of 16 mg/kg was more clinically active, with no significant increase in toxicity, than 8 mg/kg when given as a single agent. Preliminary evidence from ongoing studies combining daratumumab with other agents has demonstrated that 16 mg/kg of daratumumab can be safely given in conjunction with other anti-myeloma agents. Furthermore, extensive experience with monoclonal anti-CD20 antibodies such as rituximab in B-cell lymphoproliferative malignancies such as chronic lymphocytic leukemia, follicular lymphoma, and diffuse large cell lymphoma showed that combining full dose monoclonal antibodies with chemotherapy can greatly improve anti-tumor activity in hematologic malignancies with an acceptable toxicity profile.

All subjects will receive RVd treatment during Cycles 1 through 6 in the study; the rationale for selection of this backbone regimen is provided in Section 1.1.6, Combination Therapy: Daratumumab-Lenalidomide-Bortezomib-Dexamethasone. Lenalidomide will be administered on Days 1 through 14 in the induction and consolidation cycles. A duration of 14 days, rather than 21 days as per the prescribing information, was chosen based on the co-administration with bortezomib; this schedule of lenalidomide with bortezomib and dexamethasone has been shown to be tolerable, safe, and effective in the treatment of patients with previously untreated multiple myeloma who are transplant eligible. Therefore, this study will utilize this dosing schedule for lenalidomide.

The daratumumab infusion rate initially chosen for this study was based on historic data obtained from the sponsor in clinical trials of daratumumab. Since then, the efficacy, safety, and tolerability of an accelerated infusion rate of daratumumab was evaluated in a study by Barr et al.[1] In this single-center study, 28 subjects were treated with daratumumab utilizing an accelerated infusion rate after at least 2 prior doses of daratumumab administered as per standard prescribing information. The accelerated infusion was calculated to deliver 20% of the dose over the first 30 minutes followed by the remaining 80% over 60 minutes, resulting in an estimated 90-minute infusion. Subjects who tolerated the infusion were allowed to continue dosing at the accelerated rate. Premedication regimens were allowed to be altered based on previous tolerability. Out of all 28 subjects treated, only 1 adverse reaction (grade 2 hypertension in a subject who received 10 prior infusions at standard rates) was observed. The infusion was

paused, and a diuretic was administered. After symptom resolution, the infusion was restarted, and the infusion rate was subsequently increased to the accelerated rate without further incidence. There were no grade 3 or greater IRRs. At the 4-week follow-up, all subjects remaining on daratumumab treatment continued at the accelerated infusion rate.

The protocol has been amended (Protocol Amendment 3) to allow subjects the option to receive daratumumab via accelerated infusion., This change will impact dosing from Cycle 7 onward. Subjects who elect to receive the rapid infusion must sign a new informed consent form (ICF) prior to dosing. No changes are permitted to the protocol requirements with respect to pre- and post-infusion daratumumab medications.

3.2.3. Rationale for Pharmacokinetics, Immunogenicity, and Biomarker Evaluations

Data obtained from the current study will provide information about the pharmacokinetics of daratumumab by IV delivery in subjects with multiple myeloma.

Immunogenicity to daratumumab is possible. Therefore, samples to determine the presence of anti-daratumumab antibodies (immunogenicity) will be collected from all subjects who receive daratumumab.

Biomarkers collected in this study will potentially provide information about the mechanism of action of daratumumab in newly diagnosed multiple myeloma, as well as information on potential markers of clinical response. Depth of clinical response will be measured by MRD using next-generation sequencing of immunoglobulin genes in bone marrow. Immunophenotyping may include analysis of NK cells (including activated NK cells), T cells (cytotoxic, regulatory, memory T cells subsets) B cells, MDSC, macrophages, and dendritic cells, as these cells are involved in immune-mediated tumor lysis. Samples may be used to evaluate specific subsets of immune cells such as cytotoxic T cells, regulatory T cells, myeloid-derived suppressor cells, and activated NK cells. Refer to Section 9.5, Biomarkers for details of the biomarker analyses.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 28 days before randomization.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

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

1. 18 to 70 years of age, inclusive at study entry.

2. considered by the investigator to be eligible for HDT and ASCT according to the institution's criteria based on age, medical history, cardiac and pulmonary status, overall health and condition, co-morbid condition(s), physical examination, and laboratory studies.

3. have documented multiple myeloma as defined by the IMWG 2014 criteria[22] including: Clonal bone marrow plasma cells ≥10%*. In addition, the subject must meet one of the criteria in 3a or 3b:

   a. Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically (one or more of the following):

      i. Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal (ULN) or >2.75 mmol/L (>11 mg/dL)

      ii. Renal insufficiency: CrCl <40 mL/min (measured or estimated by validated equations, Attachment 2) or serum creatinine >177 µmol/L (>2 mg/dL)

      iii. Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L

      iv. Bone lesions: 1 or more osteolytic lesions on skeletal radiography, computed tomography (CT), or magnetic resonance imaging (MRI)**.

   b. Any one or more of the following:

      i. Clonal bone marrow plasma cell percentage** ≥60%

      ii. Involved:uninvolved serum FLC ratio*** >100

      iii. >1 focal lesions on MRI studies; Each focal lesion must be 5 mm or more in size.

   * If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

   ** Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

   *** These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved FLC must be ≥100 mg/L.

4. Measurable disease as defined by any of the following:

   i. Serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours. Note: All attempts should be made to determine eligibility of the subject based on the central laboratory results of screening blood and urine M-protein measurements. In exceptional circumstances, the local laboratory results for 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; or

   ii. IgA, IgD, IgE, or IgM multiple myeloma: serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or

   iii. Light chain multiple myeloma without measurable disease in the urine: serum Ig FLC ≥10 mg/dL and abnormal serum Ig kappa/lambda FLC ratio.

5. has not had prior systemic therapy for multiple myeloma. An emergency course of steroids (defined as no greater than 40 mg of dexamethasone, or equivalent per day for a maximum of 4 days (ie, a total of 160 mg) is permitted. In addition, radiation therapy is permitted prior to study entry, during screening, and during Cycles 1-2 of study treatment as needed for lytic bone disease.

6. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 (refer to Attachment 3).[20]

7. woman of childbearing potential must have 2 negative highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) during screening, the first one within 10 to 14 days prior to the first dose of any component of study treatment and the second within 24 hours prior to the first dose of any component of study treatment.

8. before randomization, a woman must be either:

   a. Not of childbearing potential defined as:

      - postmenopausal
        A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level (>40 IU/L or mIU/mL in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.
      - permanently sterile
        Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

b. Of childbearing potential and

- practicing 2 highly effective user-independent methods of contraception (failure rate of <1% per year when used consistently and correctly

  Examples of highly effective user-independent methods of contraception include:

  implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (sexual abstinence is considered a highly effective method **only** if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)

  Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.
  Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method.

- agrees to remain on a highly effective method for 4 weeks before the first dose of any component of study treatment, throughout the study (including during dose interruptions), and for 4 weeks following discontinuation of lenalidomide, and if receiving daratumumab, for 3 months after the last dose.

Note: If 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.

9. a woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study (including during dose interruptions), and for 4 weeks following discontinuation of lenalidomide, and if receiving daratumumab, for 3 months after the last dose.

10. due to the teratogenicity of lenalidomide and the lack of adequate reproductive toxicity data for daratumumab, in addition to the user independent highly effective method of contraception, a male or female condom with or without spermicide, diaphragm, or cervical cap is required. Male condom and female condom should not be used together (due to risk of failure with friction).

11. during the study (including during dose interruptions), and for 4 weeks following discontinuation of lenalidomide, and if receiving daratumumab, for 3 months after the last dose, in addition to the user independent highly effective method of contraception (even if he has undergone a successful vasectomy), a man

    - who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (ie, latex or synthetic condom with spermicidal foam/gel/film/cream/suppository)
    - who is sexually active with a woman who is pregnant must use a latex or synthetic condom.
    - must agree not to donate sperm

12. willing and able to adhere to the prohibitions and restrictions specified in this protocol and referenced in the ICF.

13. must sign an ICF (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

    Note: Subjects who elect to receive daratumumab every 4 weeks instead of every 8 weeks during the maintenance phase and/or those who elect to receive the rapid infusion of daratumumab during the maintenance phase must sign (or their legally acceptable representative must sign) a new ICF, consenting to the new daratumumab dosing administration(s).

4.2. Exclusion Criteria

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

1. diagnosed or treated for malignancy other than multiple myeloma, except:

    - Malignancy treated with curative intent and with no known active disease present for ≥3 years before randomization.
    - Adequately treated non-melanoma skin cancer, lentigo maligna or in situ malignancies (including but not limited to, cervical, breast) with no evidence of disease.

2. exhibiting clinical signs of or has a known history of meningeal or central nervous system involvement by multiple myeloma.

3. known to be seropositive for human immunodeficiency virus, known to have hepatitis B surface antigen positivity, or known to have a history of hepatitis C. Subjects who completed treatment for hepatitis C at least 6 months prior to screening and have no detectable circulating hepatitis C virus (HCV) at screening, may participate in the study. Such subjects will be required to undergo regular assessment for HCV

reactivation during their participation in the study. Subjects who test positive for HCV at any time during these assessments will be withdrawn from the study.

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

   Note: FEV1 testing is required for subjects suspected of having chronic obstructive pulmonary disease and asthma. Subjects must be excluded if FEV1 <50% of predicted normal.

5. known moderate or severe persistent asthma within the past 2 years (see Attachment 4), or currently has uncontrolled asthma of any classification.

   Note: Subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study. FEV1 testing is required for subjects suspected of having asthma.

6. concurrent medical condition or disease (eg, active systemic infection) that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study. Specifically, any potential subject who is unsuitable for ASCT would be excluded from the study.

7. clinically significant cardiac disease, including:

   a. Myocardial infarction within 6 months before Cycle 1, Day 1, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV).

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

   c. Screening 12-lead ECG showing a baseline corrected QT interval (QTc) >470 msec.

8. any of the following laboratory test results during the screening phase:

   a. Absolute neutrophil count $<1.0 \times 10^9$/L; no granulocyte colony stimulating factor (G-CSF) treatment in the past 7 days are allowed.

   b. Hemoglobin level ≤7.5 g/dL (≤5 mmol/L); blood transfusions to maintain hemoglobin >7.5 g/dL are acceptable.

   c. Platelet count $<75 \times 10^9$/L for subjects in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count $<50 \times 10^9$/L; no platelet transfusions in the past 7 days are allowed.

   d. Alanine aminotransferase (ALT) level ≥2.5 × ULN

   e. Aspartate aminotransferase (AST) level ≥2.5 × ULN

f. Total bilirubin level ≥1.5 × ULN, (except for Gilbert Syndrome: direct bilirubin ≥2 × ULN)

g. Creatinine clearance <30 mL/min (lenalidomide dose adjustment for subjects with CrCl ≤50 mL/min; see Section 6.2.1, Renal Impairment); please note that the CrCl can be either measured by 24-hour urine study, or estimated using a validated equation, such as a the Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-epi), or Cockcroft-Gault (Attachment 2).

h. Corrected serum calcium >14.0 mg/dL (>3.5 mmol/L) or free ionized calcium >6.5 mg/dL (>1.6 mmol/L); see Attachment 5.[4]

9. known allergies, hypersensitivity, or intolerance to monoclonal antibodies or human proteins, daratumumab or its excipients (refer to Investigator's Brochure), or known sensitivity to mammalian-derived products.

10. plasma cell leukemia (>2.0 × 10^9/L circulating plasma cells by standard differential), Waldenström's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and/or skin changes), or light-chain amyloidosis.

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

12. contraindications to the use of lenalidomide, bortezomib, or dexamethasone per local prescribing information.[7,25,35]

13. taken any disallowed therapies as noted in Section 8, Pre-study and Concomitant Therapy before the planned first dose of study drug.

14. participated in an interventional clinical trial(s) and received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before Cycle 1, Day 1.

15. pregnant or breast-feeding or planning to become pregnant while enrolled in this study or within 4 weeks following discontinuation of lenalidomide, and if receiving daratumumab, within 3 months after the last dose.

16. plans to father a child while enrolled in this study or within 4 weeks following discontinuation of lenalidomide, and if receiving daratumumab, within 3 months after the last dose.

17. had major surgery within 2 weeks before Cycle 1, Day 1, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study drug administration.

    Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate. Kyphoplasty is not considered a major surgery.

18. has had a plasmapheresis within 28 days before randomization

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before Cycle 1 Day 1 such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

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

1. agree to follow the contraceptive requirements as noted in the inclusion criteria.

2. agree to required serum pregnancy tests 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 serum or urine pregnancy test is also required at the EOT visit. Additional pregnancy tests may be required, as specified in the lenalidomide REMS program that can be accessed at http://www.revlimidrems.com/.

3. because of the embryo-fetal risk of lenalidomide, all subjects must adhere to the lenalidomide REMS program that can be accessed at http://www.revlimidrems.com/.

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

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

6. refer to Section 8, Prestudy and Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by International Staging System Stage I, II, or III (β-2 microglobulin and albumin) and by CrCL (30-50 mL/min and >50 mL/min). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant subject details to uniquely identify the subject.

Blinding

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

6. DOSAGE AND ADMINISTRATION

In this protocol, the term "study drug" refers to daratumumab only, and "study treatment" refers to D-RVd or RVd. Daratumumab is to be administered as described in the Study Drug Dosing.

Induction and consolidation cycles are 21 days in duration; there will be a maximum of 4 induction cycles and 2 consolidation cycles. All subjects will receive RVd with or without daratumumab, based on random assignment, during induction and consolidation cycles. The D-RVd group will receive daratumumab weekly during induction and every 3 weeks during consolidation. At the start of the consolidation phase, both groups will receive the same dosages of lenalidomide, bortezomib, and oral dexamethasone that were tolerated at the end of induction treatment. Maintenance treatment cycles are 28 days in duration with lenalidomide given on Days 1-21; the D-RVd group will receive daratumumab every 4 or 8 weeks. Maintenance treatment will continue until disease progression or up to a maximum of 2 years. The start of a cycle will be the day of the first full dose of lenalidomide, depending on the treatment group and study phase.

At a minimum, subjects must have an absolute neutrophil count of 1 x 10^9/L and a platelet count of 50 x 10^9/L to begin a new cycle. Delays of up to 14 days for the start of the subsequent cycle are acceptable. Any delays more than 14 days of the scheduled day will need to be discussed with the sponsor.

Every effort should be made to keep subjects on the planned dosing schedule. The start of each cycle may occur within ±3 days during induction, ±14 days (consolidation), or ±14 days (maintenance) of the scheduled day to accommodate the schedule of the site or subject. Every effort should be made to keep a subject on schedule with dosing; however, in exceptional circumstances dose delay may be considered.

Subjects who need to temporarily interrupt treatment due to toxicity or discontinue treatment with any one component of study treatment (lenalidomide, bortezomib, dexamethasone, or daratumumab, as applicable depending on the study phase) may continue to receive treatment with the other component(s) of study treatment, as assigned.

6.1. Daratumumab

6.1.1. Preparation

Infusion solution will be prepared as a 1,000-mL (first dose) or 500-mL (second and subsequent doses) dilution of daratumumab in sterile, pyrogen-free 0.9% NaCl. Preparation of infusion bags should be done on the day of the planned infusion. Daratumumab must be administered as an IV infusion given through a well-functioning IV catheter by using an infusion pump. The study drug must be filtered by using an inline filter (0.2 μM) during the infusion. Manuals with detailed descriptions for preparation and administration of daratumumab will be supplied to each pharmacy and site.

6.1.2. Treatment Schedule and Administration

Daratumumab (16 mg/kg) will be administered as an IV infusion. Each subject's dose will be calculated based on the subject's weight at Cycle 1 Day 1 rounded to the nearest kilogram. The dose of daratumumab will remain constant throughout the study unless the subject's weight changes more than 10% from Cycle 1 Day 1 or the most recent weight used for dose calculation. Subject's weight will be recorded on all daratumumab dosing days. All infusions will be planned as outpatient visits. Subjects will receive preinfusion medications and postinfusion medications as detailed in the protocol (Sections 6.1.3.1 and 6.1.3.2, respectively).

Daratumumab will be administered weekly during induction treatment in Cycles 1 to 4 (Days 1, 8, and 15), every 3 weeks during consolidation treatment in Cycles 5 and 6 (Day 1), and every 4 or 8 weeks during maintenance treatment in Cycle 7 and beyond for 24 months, at which time all study treatment will be discontinued. Subjects who signed the original ICF stating that daratumumab maintenance was to be administered every other month and who do not agree to the revised daratumumab maintenance administration every month will be permitted to receive daratumumab every other month. However, every effort should be taken to ensure that the subject understands the benefit of the monthly daratumumab maintenance schedule. The dilution volumes, initial infusion rates, and increment for the first, second, and subsequent doses are provided in Table 2. The first infusion, with a volume of 1,000 mL, takes approximately 8 hours; the second and subsequent infusions, with volumes of 500 mL, take approximately 4 hours. The maximum infusion rate for all infusions is 200 mL/hour. The sponsor may modify the infusion rates or the preinfusion medications prospectively based upon the information collected to date from this and other studies. Additional details for administration times and rates, as well as preinfusion medications, will be provided in the administration guidelines (study site investigational product and procedures manual).

Beginning at Cycle 7 Day 1 and onward, all subjects in the D-RVd arm, if clinically feasible, will be given the option to receive an accelerated 90-minute infusion of daratumumab.

Table 2: Daratumumab Infusion Rates

	Dilution Volume	Initial Infusion Rate (first hour)	Increments of Infusion Rate	Maximum Infusion Rate
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[a]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[b] **(C1D15 through C6D1)**	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour
Accelerated infusion (beginning C7D1)	**Dilution Volume**	**Initial Infusion Rate (first 30 minutes)**	**Subsequent Infusion Rate (last 60 minutes)**	**Maximum Infusion Rate**
	500 mL	200 mL/hour	400 mL/hour	400 mL/hour

[a] Modified rates should only be used if the first infusion of daratumumab was well-tolerated as defined by an absence of > Grade 1 infusion-related reactions during the first 3 hours.

[b] Modified rates should only be used if the first 2 infusions of daratumumab were well-tolerated as defined by an absence of > Grade 1 infusion-related reactions during a final infusion rate of ≥100 mL/hr.

As noted in the TIME AND EVENTS SCHEDULE, vital signs should be monitored extensively on Cycle 1 Day 1 before, during, and after the first infusion of daratumumab. For all other infusions, vital signs should be measured before the start of the infusion and at the end of the infusion. If a subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event.

6.1.3. Guidelines for Prevention and Management of Infusion-Related Reactions

6.1.3.1. Preinfusion Medication

The following preinfusion medications are administered, as described in the Study Drug Dosing, approximately 1 hour before each daratumumab infusion:

Dexamethasone 20 mg oral or IV (only if oral is not available) (an equivalent of long-acting corticosteroid may be substituted [see Attachment 1 for conversion table]).

> **Note:** During Cycles 1 to 6, when dexamethasone is taken at a total 40 mg weekly dose (ie, 20 mg orally on Days 1, 2, 8, 9, 15, and 16), the dexamethasone 20 mg oral dose administered as a preinfusion medication on daratumumab infusion days (Days 1, 8, and 15) replaces the oral dexamethasone 20 mg dose for that day for subjects in the D-RVd group.

- Acetaminophen 650 to 1,000 mg oral or IV equivalent
- Diphenhydramine 25 to 50 mg, or equivalent dose of another antihistamine, either given oral or IV

- Montelukast 10 mg PO, at Cycle 1 Day 1 approximately 1 hour or less before the daratumumab infusion. An additional 10 mg PO can be given the day before infusion at the discretion of the investigator. Montelukast may be omitted for any daratumumab dose after the second infusion if the subject has no respiratory symptoms.

If necessary, oral preinfusion medications may be administered outside of the clinic on the day of the infusion, provided they are given within 3 hours prior to the infusion.

6.1.3.2. Postinfusion Medication

For subjects with a higher risk of respiratory complications (eg, subjects who have mild asthma, or subjects with chronic obstructive pulmonary disease who have an FEV1 <80%), the following postinfusion medications should be considered:

- Antihistamine (diphenhydramine or equivalent) on the first and second days after all infusions
- Short-acting β2-adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2-adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with chronic obstructive pulmonary disease)

If an at-risk subject experiences no major IRRs, these post-infusion measures may be stopped after 4 full doses of daratumumab at the investigator's discretion.

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after an infusion. If subjects are hospitalized, then their FEV1 should be measured before discharge. If these subjects are not hospitalized, then a follow up telephone call should be made to monitor their condition within 48 hours after all infusions. If no IRR has occurred, the follow-up telephone call 48 hours after the infusion is not required. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic.

6.1.3.3. Management of Infusion-Related Reactions

Subjects should be carefully observed during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions occurring, 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 bedside. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

If an IRR develops, then the infusion should be temporarily interrupted. Subjects who experience adverse events during the infusion must be treated according to the investigator's judgment and best clinical practice. The following guidelines apply:

- Subjects should be treated with acetaminophen, antihistamine, or corticosteroids as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, and/or bronchodilators. For hypotension, subjects may require vasopressors.
- In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject. Aggressive symptomatic treatment should be applied. Cases of severe reaction should be discussed with the sponsor's medical monitor.

If an infusion is paused or the infusion rate is decreased, then a longer-than-anticipated infusion time may occur. Overnight stays at the hospital because of slow infusion times should not be reported as a serious adverse event. However, if the underlying cause of the delayed infusion time is an adverse event or serious adverse event, then that should be reported as such.

6.1.3.3.1. Infusion-Related Reactions of Grade 1 or Grade 2

If the investigator assesses an adverse event to be related to the daratumumab infusion, then the infusion should be paused. When the subject's condition is stable, the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.

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

6.1.3.3.2. Infusion-Related Reactions of Grade 3 or Higher

For infusion-related adverse events that are Grade 4, the infusion should be stopped and treatment with daratumumab will be discontinued for that subject.

For infusion-related adverse events that are Grade 3, the daratumumab infusion must be stopped, and the subject must be observed carefully until the resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion. If the intensity of the adverse event returns to Grade 3 after restart of the infusion, then the procedure described in this section may be repeated at the investigator's discretion. Should the intensity of the adverse event increase to Grade 3 for a third time, then treatment with daratumumab will be discontinued for that subject.

6.1.4. Dose Modification and Dose Delays

6.1.4.1. Dose Modification

No daratumumab dose modification (increase or decrease) will be permitted unless the subject's weight changes more than 10% from Cycle 1 Day 1 or the most recent weight used for dose calculation. Subject's weight will be recorded on all daratumumab dosing days.

6.1.4.2. Toxicity Management

ONLY if any of the following criteria are met and the event cannot be ascribed to lenalidomide, bortezomib, dexamethasone, or underlying multiple myeloma, the daratumumab infusion must be held to allow for recovery from toxicity. The criteria for a dose delay are:

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

If daratumumab administration does not commence within the prespecified window (Table 3) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date. See Section 6.1.4.3, Interruption or Missed Doses for additional information.

Table 3: Daratumumab-Related Toxicity Management

Cycles	Frequency	Missed Dose	Dosing Resumption
1-4	Weekly (every 1 week)	>3 days	Next planned weekly dosing date
5-6	Every cycle (every 3 weeks)	>14 days	Next planned every 3 week dosing date
7 and beyond	Every 4 or 8 weeks	>14 days	Next planned every 4 or 8 week dosing date

A missed dose will not be made up. 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. If a dose delay occurs, then pharmacokinetic blood samples should be collected on the actual day of study drug administration, not on the original scheduled administration day.

6.1.4.3. Interruption or Missed Doses

A daratumumab dose held for more than 3 days during induction, 14 days during consolidation, or 14 days during maintenance from the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the sponsor at the earliest possible time. Subjects who miss ≥3 consecutive planned doses of daratumumab for reasons other than toxicity will be withdrawn from treatment, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

6.2. Lenalidomide

In Cycles 1 through 6, lenalidomide will be self-administered at a dose of 25 mg orally each day on Days 1 through 14 of each 21-day cycle for subjects with CrCl >50 mL/min; or at the start of consolidation (Cycle 5 Day 1), at the same dose that was tolerated at the end of induction treatment. During maintenance treatment in Cycle 7 and beyond, lenalidomide 10 mg will be administered daily on Days 1-21 throughout each 28-day cycle. Beginning at Cycle 10, the lenalidomide dose will be increased to 15 mg unless there is a tolerability concern. Following completion of the last cycle of the 24-month maintenance phase, subjects may continue lenalidomide as per local standard of care. See Section 6.2.5, Renal Impairment for lenalidomide dose adjustments in subjects with renal impairment.

6.2.1. Dose Adjustments of Lenalidomide

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

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

Dose adjustments should be based on the highest grade of toxicity that is ascribed to lenalidomide.

6.2.2. Deep Vein Thrombosis and Pulmonary Embolism

Lenalidomide has been associated with increased incidence of deep vein thrombosis and pulmonary embolism. Therefore, all subjects should be prophylactically treated with baby aspirin (162 mg, at a minimum) by mouth daily. Subjects at increased risk of thromboembolic events (based on their medical history) should be treated with enoxaparin at a dose of 40 mg subcutaneously daily (or other low molecular heparin with equivalent dose and frequency for prophylaxis indication). The injection should be handled according to local practice. Vitamin K antagonists, or direct thrombin inhibitors are another option for deep vein thrombosis/pulmonary embolism prophylaxis and treatment and may be used at the discretion of the treating physician.

6.2.3. Thrombocytopenia

If the subject's platelet count decreases, dose adjustments should be made according to the recommendations in Table 4.

Table 4: Lenalidomide Dose Adjustment for Thrombocytopenia

Platelet Count	Recommended Course of Action
• When count first falls to $<30 \times 10^9$/L	• Interrupt lenalidomide treatment, follow complete blood count weekly
• When count returns to $\geq 30 \times 10^9$/L	• Resume lenalidomide at dose level -1 (or at 5 mg per day if the subject is on maintenance therapy)
• For each subsequent drop in count to $<30 \times 10^9$/L	• Interrupt lenalidomide treatment
• When count returns to $\geq 30 \times 10^9$/L	• Resume lenalidomide at the next lower dose level once daily. Do not decrease dose below 5 mg once daily

6.2.4. Neutropenia

If the subject experiences neutropenia, the investigator should consider the use of growth factors in the subject's management. If the subject's neutrophil count decreases further despite growth factor utilization, dose adjustments should be made according to the recommendations in Table 5.

Table 5: Lenalidomide Dose Adjustment for Neutropenia

Neutrophil Count	Recommended Course of Action
• When count first falls to $<1.0 \times 10^9$/L	• Interrupt lenalidomide treatment, start G-CSF treatment, follow complete blood count weekly
• When count returns to $\geq 1.0 \times 10^9$/L and neutropenia is the only observed toxicity	• Resume lenalidomide at 25 mg once daily if during induction phase of the study. Resume lenalidomide at 10 mg once daily on Days 1-21 if during maintenance phase of the study.
• When count returns to $\geq 1.0 \times 10^9$/L and other hematologic toxicity attributable to lenalidomide is observed	• During induction therapy, resume lenalidomide at 20 mg once daily • If the subject is on maintenance therapy, continue 10 mg of daily lenalidomide every 21 days to allow for a 7-day rest period at the end of each cycle.
• For each subsequent drop in count to $<1.0 \times 10^9$/L	• Interrupt lenalidomide treatment
• When count returns to $\geq 1.0 \times 10^9$/L	• Resume lenalidomide at the next lower dose level once daily. Do not decrease dose below 5 mg once daily.

G-CSF = granulocyte colony stimulating factor

6.2.5. Renal Impairment

Because lenalidomide is primarily excreted unchanged by the kidney, adjustments to the dose of lenalidomide are recommended to provide appropriate drug exposure in subjects with moderate or severe renal impairment. Lenalidomide dose adjustment should be instituted for subjects with a CrCl $\leq$50 mL/min. The recommended doses for subjects with multiple myeloma and renal impairment are shown in Table 6. To be enrolled in the study, subjects must have

CrCl ≥30 mL/min. If during treatment a subject's renal status changes, the dose should be adjusted as shown in Table 6.

Table 6: Lenalidomide Dose Adjustment for Renal Impairment

Category	Renal Function[a]	Dose
Moderate renal impairment[b]	CrCl 30-50 mL/min	10 mg every 24 hours
Severe renal impairment	CrCl <30 mL/min (not requiring dialysis)	15 mg every 48 hours
End-stage renal disease	CrCl <30 mL/min (requiring dialysis)	5 mg once daily. On dialysis days, administer the dose after dialysis

CrCl = creatinine clearance.
[a] Estimated by creatinine clearance as calculated by the Cockcroft-Gault equation (Attachment 2).
[b] For subjects with moderate renal impairment, escalate the dose to 15 mg after 2 cycles if the subject tolerates the 10 mg dose without dose-limiting toxicity.

6.2.6. Other Grade 3 or 4 Adverse Events

For other Grade 3 or 4 toxicities judged by the investigator to be related to lenalidomide alone, treatment with lenalidomide should be interrupted and restarted at the next lower dose level once the toxicity has resolved to Grade 2 or less. If a Grade 3 toxicity can be controlled (eg, a Grade 3 electrolyte disturbance that can be controlled with repletion within 24 hours), the investigator should discuss the toxicity with the sponsor's medical monitor before interrupting or lowering the lenalidomide dose. Treatment with daratumumab, bortezomib, and dexamethasone may continue, as applicable depending on the study phase.

6.3. Bortezomib

The amount (in mg) of bortezomib to be administered will be determined by body surface area, calculated according to a standard nomogram (Attachment 6). Each subject's dose will be calculated based on the subject's weight at Cycle 1 Day 1 rounded to the nearest kilogram. The dose should be readjusted if weight changes >10% from the value on C1D1.The total calculated dose of bortezomib may be rounded to the nearest decimal point (eg, a calculated dose of 2.47 mg can be rounded to 2.5 mg). Subjects will receive 1.3 mg/m^2 bortezomib as a subcutaneous injection twice weekly (Days 1, 4, 8, and 11) during the 21-day induction and consolidation cycles (Cycles 1-6); or at the start of consolidation [Cycle 5 Day 1], at the same dose that was tolerated at the end of induction treatment. For subjects who experience injection-site reactions at the subcutaneous administration site, bortezomib may be administered by IV injection (see study site investigational product and procedures manual and bortezomib US prescribing information). On daratumumab infusion days, bortezomib will be administered at the end of the daratumumab infusion. Neither group will receive bortezomib after the first 6 cycles of D-RVd or RVd.

6.3.1. Dose Adjustments of Bortezomib

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

Table 7. Once the symptoms of the toxicity have resolved, bortezomib therapy may be reinitiated at a 25% reduced dose per approved labelling, as follows:

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

A dose of bortezomib may be delayed up to 48 hours. Doses that need to be withheld are skipped and will not be made up later in the cycle.

6.3.2. Neurologic Toxicity

If the subject experiences peripheral neuropathy, then dose adjustments should be made according to the recommendations in Table 7.

Table 7: Recommended Dose Modification for Bortezomib-related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms[a]	Recommended Modification of Dose and Regimen
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental ADL[b])	Reduce bortezomib to 1 mg/m^2 or Change bortezomib treatment schedule to 1.3 mg/m^2 once per week (ie, Day 1 and Day 8).
Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL[c])	Withhold bortezomib treatment until symptoms of toxicity have resolved. When toxicity resolves, reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 once per week (ie, Day 1 and Day 8).
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue bortezomib.

ADL = activities of daily living

[a] Grading based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.

[b] Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc.

[c] Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

6.4. Dexamethasone

Dexamethasone (or equivalent in accordance with local standards; see Attachment 1 for conversion table) will be self-administered orally at a total dose of 40 mg weekly (ie, 20 mg on Days 1, 2, 8, 9, 15, and 16) during induction and consolidation cycles (Cycles 1-6); or at the start of consolidation [Cycle 5 Day 1], at the same dose that was tolerated at the end of induction treatment. For subjects in the D-RVd group, the dexamethasone 20 mg oral or IV (only if oral is not available) dose administered as a preinfusion medication on daratumumab infusion days (Days 1, 8, and 15) replaces the oral dexamethasone dose for that day. Dexamethasone will be

administered until the subject experiences disease progression or unacceptable toxicity during the induction/consolidation phase.

In the maintenance phase, dexamethasone, 20 mg orally (or IV), will be administered to subjects in the D-R group as a preinfusion medication prior to daratumumab.

After Cycle 4, the dose of dexamethasone may be reduced at the investigator's discretion. The 20-mg oral dose of dexamethasone given before the infusion on the day of daratumumab infusions must not be decreased. When dexamethasone is reduced to 20 mg/week and is given as preinfusion medication, subjects may receive low-dose methylprednisolone (≤20 mg) orally (or equivalent in accordance with local standards) for the prevention of delayed IRRs as clinically indicated.

Dexamethasone Toxicity

For management of dexamethasone toxicity see Table 8. If dexamethasone is permanently discontinued due to toxicity, pre- and post-infusion doses administered on the day of daratumumab dosing for subjects in the D-RVd group may be given at the investigators discretion. This table represents suggested dose modifications of dexamethasone, but physician discretion and clinical judgment should prevail.

Table 8: Dexamethasone Dose Modification Based on Toxicity

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

NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

7. TREATMENT COMPLIANCE

Study drug (daratumumab) will be administered as an IV infusion by qualified staff and the details of each administration will be recorded in the case report form (CRF). Additional details are provided in the study site investigational product and procedures manual. Subjects will be provided with a diary to record intake of lenalidomide and dexamethasone; sites will use information to complete exposure information in the CRF.

8. PRESTUDY AND CONCOMITANT THERAPY

The following prestudy therapies given at any time before first dose of study treatment must be recorded at screening: steroids of any dose or duration given for multiple myeloma, or radiation therapy for multiple myeloma.

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 8.3, Prohibited Therapies. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Systemic use of the following concomitant medications will be collected in the CRF and recorded in the source documents beginning with signing of the ICF to 30 days after the last dose of the last study treatment or until the start of next-line anticancer treatment, if earlier: growth factors, transfusions, anti-infective medications (antibacterials, antivirals, and antimycotics), steroids, anti-arrhythmic medications and other cardiac supportive therapy, anti-epileptic medications, centrally acting psychiatric medications, anti-histamines and other medications targeting post-infusion systemic reactions, and any anticancer therapy (including radiation).

During the mobilization and stem cell transplantation procedures, concomitant medications related to the planned procedures do not need to be reported in the eCRF. However, concomitant medications related to the mobilization and transplantation procedures should be documented by providing a copy of the medication order set.

8.1. Recommended Therapies

8.1.1. Bisphosphonate Therapy

For subjects who have not previously received bisphosphonates, bisphosphonates are recommended for all subjects with evidence of lytic destruction of bone or with osteopenia. Bisphosphonate therapy is recommended to be continued per treatment guidelines.[17,19] Commercially available IV bisphosphonates (pamidronate and zoledronic acid) are preferred when available, and should be used according to the manufacturer's recommendations, as described in the prescribing information, for subjects with osteolytic or osteopenic myelomatous bone disease. Oral bisphosphonates may be used as alternatives if IV bisphosphonates are not available at the study site. Investigators should use the same route of bisphosphonate therapy for all subjects at their sites. Subjects who are currently using bisphosphonate therapy when they enter the study should continue the same treatment. Subjects who are not using a bisphosphonate at the time of randomization should start a bisphosphonate as soon as possible. In addition, denosumab use is also permitted in this study.

8.1.2. Therapy for Tumor Lysis Syndrome

Subjects should be monitored for symptoms of tumor lysis syndrome. Subjects who develop signs or symptoms of tumor lysis syndrome, including dehydration and abnormal laboratory test results such as hyperkalemia, hyperuricemia, and hypocalcemia, should be managed appropriately according to institutional guidelines and the investigator's medical judgment. It is recommended that high-risk subjects (ie, those with a high tumor burden, or high lactate dehydrogenase and/or high uric acid level before the start of treatment) be treated prophylactically in accordance with local standards (eg, rehydration; diuretics; allopurinol 300 mg daily and medication to increase urate excretion). Subjects are to be provided

prophylactic therapy to manage infusion reactions during the induction, consolidation, and maintenance treatment as described in Section 6.1.3.1, Preinfusion Medication.

8.1.3. Prophylaxis for Bacterial Infection

Prophylaxis for bacterial infections should be considered per institutional guidelines, especially for subjects with a history of recurrent bacterial infections or severe hypogammaglobulinemia.

8.1.4. Prophylaxis for Herpes Zoster Reactivation

Prophylaxis for herpes zoster reactivation should be given unless contraindicated. 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 orally, twice a day or per institutional standards), or valacyclovir (eg, 500 mg given orally, twice a day or per institutional standards), initiated within 1 week after the start of study treatment and continued at least through Cycle 6.

8.1.5. Prophylaxis for Pneumonia

Prophylaxis for pneumonia is recommended during the first 2 cycles of study treatment. Antibacterial therapy with quinolones (or alternative if contraindicated) should be administered as per institutional guidelines.

8.1.6. Therapy for Pneumocystis Carinii

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

8.1.7. Prevention of Steroid Induced Gastritis

Dexamethasone and other steroids 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).

8.2. Permitted Therapies

In addition, subjects are to receive full supportive care. The following medications and supportive therapies are examples of support therapies that may be used at any time during the study:

- Antiviral medications should be considered per institutional guidelines.
- Colony stimulating factors, erythropoietin, and transfusion of platelets and RBCs. If erythropoietin is given, then this should be given according to the US prescribing information for lenalidomide and epoetin alfa, as there is an increased risk of thrombosis with lenalidomide.
- It is important to prevent constipation (eg, adequate hydration, high-fiber diet, and stool softeners if needed).
- Adequate hydration is recommended for prevention of myeloma-related kidney disease.

- Intravenous immunoglobulin (IVIG) may be considered for subjects with recurrent infection related to hypogammaglobulinemia.
- Prophylactic antiemetics, with the exception of corticosteroids
- Loperamide is recommended for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose and regimen is according to institutional guidelines. Prophylactic loperamide is not recommended.

8.3. Prohibited Therapies

Concomitant administration of any other antineoplastic therapy for the intention of treating multiple myeloma is prohibited, including medications that target CD38, as well as medications used for other indications that have anti-myeloma properties (for example, interferon). Continuation of study drug and components of the RVd regimen during or after emergency orthopedic surgery or radiotherapy because of subject benefit may only occur in the absence of disease progression and after consultation with and approval by the sponsor. Such emergency radiotherapy may consist of localized radiotherapy for pain control or for stabilization of an extensive bone lesion at high risk of pathologic fracture or damage to surrounding tissues in a subject in whom delay of systemic therapy is not appropriate. Such radiotherapy is to occur within the first 2 cycles of treatment and the absence of evidence of disease progression is to be reviewed and approved by the sponsor.

During Cycle 1 of the safety run-in, the prophylactic use of hematopoietic growth factors is prohibited.

Concomitant participation in an interventional clinical trial(s) or use of investigational agent(s) as well as medical devices is prohibited. Administration of commercially available agents with activity against or under investigation for multiple myeloma, including systemic corticosteroids (>10 mg prednisone per day or equivalent) (other than those given for IRRs as described in Section 6.1.3.3, Management of Infusion-Related Reactions) should be avoided. Nonsteroidal anti-inflammatory agents should be avoided to prevent myeloma-related kidney disease.

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

Concomitant administration of the strong cytochrome P450 (CYP) 3A4 inhibitors (eg, ketoconazole, ritonavir) and inducers should be avoided and is not recommended with the use of bortezomib. If a strong CYP3A4 inhibitor must be given in combination with bortezomib, monitor subjects for signs of bortezomib toxicity and consider a bortezomib dose reduction. For an ongoing list of CYP3A inhibitors and inducers, see http://medicine.iupui.edu/clinpharm/ddis/main-table/.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of study procedures and assessments applicable to this study.

Study assessments will be performed only after written informed consent is obtained. At each visit, study assessments should be completed before the administration of any treatment. All PRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing subject perceptions.

Throughout the study, subjects will be closely monitored for adverse events, laboratory abnormalities, and clinical response. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated.

Due to the potential of birth defects or embryo-fetal death associated with the use of lenalidomide, investigators and subjects must adhere to the lenalidomide REMS program throughout the study; details are available at http://www.revlimidrems.com/.

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

Medical resource utilization data will be collected. Refer to Section 9.7, Medical Resource Utilization for details.

The total blood volume for the study is approximately 700 mL. This includes laboratory assessments for safety, efficacy, pharmacokinetics/immunogenicity, and biomarkers. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

The signed ICF must be obtained before any study-specific procedures are performed. Subjects who elect to receive daratumumab every 4 weeks during maintenance and/or the rapid infusion of daratumumab must sign an additional ICF prior to dosing.

The screening phase begins when the ICF is signed. During the screening phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed. Screening procedures will be performed within 28 days before randomization; however, results of tests such as skeletal survey, radiologic tests (eg, MRI) to document baseline size of known or suspected extramedullary plasmacytomas; or chest X-rays) performed up to 6 weeks (42 days) before randomization may be used if these tests have been performed as part of routine follow-up for the subject's disease.

A negative highly sensitive serum (β-hCG) pregnancy test for women of childbearing potential must be documented within 10 to 14 days before the first dose and again within 24 hours before the first dose for Cycle 1 Day 1.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including 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 subject should be excluded from participation in the study. Section 4, describes the required documentation to support meeting the enrollment criteria. Subjects who fail to meet the inclusion and exclusion criteria (ie, screen failures) may be rescreened once if their condition changes. Rescreening must be discussed with and approved by the sponsor on a case-by-case basis. Subjects who are determined to be eligible for rescreening must sign a new ICF and will then be assigned a new screening number.

9.1.3. Induction/Consolidation Phase

Induction Treatment

Subjects who meet the entry criteria will be randomly assigned within 72 hours before the first dose on Cycle 1 Day 1 to receive either D-RVd or RVd alone. Subjects will receive four 21-day treatment cycles of induction treatment as detailed in Section 6, Dosage and Administration.

Subjects who have confirmed disease progression will discontinue study treatment, have an EOT visit, and enter the long-term follow-up phase. Subjects may also discontinue study treatment due to occurrence of unacceptable toxicity or other reasons outlined in Section 10.2, Discontinuation of Study Treatment/Withdrawal From the Study.

Stem Cell Mobilization, High-Dose Chemotherapy, and Autologous Stem Cell Transplantation

After completion of Cycle 4 of induction treatment, subjects will undergo stem cell mobilization with G-CSF, with or without plerixafor. G-CSF and plerixafor should be administered according to institutional standards of dose and schedule. Use of cyclophosphamide is only allowed if G-CSF with or without plerixafor is not successful. Stem cell collection should be performed and stem cells frozen according to institutional standards. Subjects will then proceed to HDT and ASCT.

Melphalan 200 mg/m^2 should be used as the conditioning regimen which can either be given on a single day or divided into 2 days depending on local practice. A dose adjustment of melphalan (for renal failure or other co-morbidity) can also be considered per investigator discretion. Treatment with prophylactic antibiotics, G-CSF, and other supportive care, and laboratory testing during and in the post-ASCT phase should be per institutional standards.

An assessment of the efficiency of harvesting will be recorded in the CRF (see Section 9.8, Safety Evaluations). During the mobilization and stem cell transplantation procedures, adverse events related to the planned procedures do not need to be reported, however any toxicity related

to daratumumab, lenalidomide, bortezomib, or dexamethasone exposure should continue to be reported.

If the decision is made by the investigator not to pursue HDT and ASCT, subjects will be discontinued from study treatment, have an EOT visit, and then enter the long-term follow-up phase. Subjects who do not undergo HDT and ASCT will not receive consolidation or maintenance treatment on protocol.

Consolidation Treatment

Based upon initial randomization and as detailed in Section 6, Dosage and Administration an additional two 21-day cycles of either D-RVd or RVd will be given as consolidation treatment starting approximately 60 to 100 days after ASCT, when the subject has recovered sufficiently and engraftment is complete.

Subjects will be evaluated for the primary endpoint (post-ASCT consolidation sCR). MRD will be assessed by next-generation sequencing, regardless of treatment group, as detailed in the TIME AND EVENTS SCHEDULE. The post-ASCT consolidation disease evaluation should be performed the day after completion of C6D21 (+7-day window).

After the post-ASCT consolidation disease evaluation for the primary endpoint, subjects will enter the maintenance phase of the study based upon initial randomization.

Subjects who have confirmed disease progression will discontinue study treatment, have an EOT visit, and enter the long-term follow-up phase. Subjects may also discontinue study treatment due to occurrence of unacceptable toxicity or other reasons outlined in Section 10.2, Discontinuation of Study Treatment/Withdrawal From the Study.

9.1.4. Maintenance Phase

The 24-month maintenance phase starts after assessment of the primary endpoint (post-ASCT consolidation disease evaluation for sCR). The timing of start of maintenance is at the discretion of the investigator, however, it should start within the 14 days following post-ASCT consolidation disease evaluation.

If Cycle 7 Day 1 is started within the 14 days following the post-ASCT consolidation disease evaluation, Cycle 7 Day 1 collection of MRU data and disease evaluations do not need to be repeated; other procedures will be performed as indicated in the TIME AND EVENTS SCHEDULE. Subjects will have study visits every 4 to 8 weeks in the D-R group dependent on when daratumumab is administered and every 8 weeks in the lenalidomide group. Subjects who signed the original ICF stating that daratumumab maintenance was to be administered every other month and who do not agree to the revised daratumumab maintenance administration every month will be permitted to receive daratumumab every other month. However, every effort should be taken to ensure that the subject understands the benefit of the monthly daratumumab maintenance schedule. Treatment will continue until disease progression, occurrence of unacceptable toxicity, or other reasons outlined in Section 10.2, Discontinuation of Study Treatment/Withdrawal From the Study. At the end of the maintenance phase or at the time of

treatment discontinuation, all subjects will have an EOT visit and then enter the long-term follow-up phase.

Following completion of the last cycle of the maintenance phase, subjects may continue lenalidomide as per local standard of care. The day of the EOT visit will be based on the last dose of study treatment in the maintenance phase.

9.1.5. End-of-Treatment

Subjects will receive study treatment through completion of the 24-month maintenance phase, or until confirmed disease progression, discontinuation of study treatment due to an unacceptable drug toxicity, or other reasons outlined in Section 10.2, Discontinuation of Study Treatment/Withdrawal From the Study. Unless a subject withdraws consent for study participation, or is lost to follow-up, an EOT visit is to be scheduled 30 days (±7 days) after the last dose of all components of the study treatment have been discontinued, or as soon as possible before the start of next-line therapy. After completion of the EOT visit, subjects will enter the long-term follow up phase of the study.

9.1.6. Long-Term Follow-Up Phase

All subjects will be followed in the long-term follow-up phase until at least 1 year after last dose of study treatment and will continue until death, withdrawal of consent for study participation, or the end of study definition is met. The end of study is defined as when all subjects have completed at least 1 year of long-term follow-up, or until death or withdrawal of consent for study participation, whichever occurs first.

Subjects who enter the long-term follow-up phase before disease progression will return to the site every 12 weeks for disease evaluation, PRO assessments, and other follow-up assessments (ie, other malignancies, start of next-line therapy, and survival) until confirmed disease progression, death, the start of a new treatment for multiple myeloma, withdrawal of consent for study participation, or the end of study, whichever occurs first (see TIME AND EVENTS SCHEDULE). After confirmed disease progression or the start of a new treatment for multiple myeloma, subjects will return to the site or be contacted by telephone every 12 weeks for follow-up assessments (ie, other malignancies, next-line therapy, PD on next-line therapy, and survival, as applicable) until death, withdrawal of consent for study participation, or the end of study, whichever occurs first. Following disease progression on the next-line therapy, subjects will only be followed for survival.

If the information on other malignancies, next-line therapy, PD on next-line therapy, and survival is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and documented on the CRF.

Investigators may recontact the subject to obtain long-term follow-up information regarding the subject's safety or survival status as noted in the ICF (refer to Section 16.2.3, Informed Consent).

Subjects will be instructed that study drug (ie, daratumumab) will not be made available to them after they have completed/discontinued study drug and that they should return to their primary physician to determine standard of care.

9.2. Efficacy Evaluations

Disease response and progression will be based on assessments according to the IMWG Guidelines[23] as defined in Section 9.2.1, Response Categories. Daratumumab detection on serum IFE has been demonstrated in subjects treated with 16 mg/kg and may interfere with the traditional IMWG criteria of negative serum IFE for CR or sCR. To mitigate this interference, the sponsor has developed a reflex assay that utilizes anti-idiotype antibody to bind daratumumab and confirm its interference on IFE (see laboratory manual). For all subjects in the D-RVd/D-R group with VGPR, a positive serum IFE, and a negative M-protein by SPEP, reflex IFE testing will be performed to confirm the presence of daratumumab on IFE. In addition, subjects who have an SPEP of ≤0.2 g/dL and IgG kappa myeloma, reflex testing will also be performed to determine whether the para-protein identified on SPEP/IFE is monoclonal daratumumab or the subject's endogenous myeloma protein.

9.2.1. Response Categories

Disease evaluations must be performed during the induction, consolidation phase and every 8 weeks during the maintenance phase according to the TIME AND EVENTS SCHEDULE. Note that an additional disease evaluation occurs on Day 21 of Cycle 4 and the day after Day 21 of Cycle 6 (with a 7-day window) to assess end of Cycle 4 and end of Cycle 6 response, respectively.

Disease evaluations will be performed by central and local laboratories (unless otherwise specified) according to the TIME AND EVENTS SCHEDULE until disease progression. This study will use the IMWG consensus recommendations for multiple myeloma treatment response criteria presented in Table 9.[14,22] For quantitative Ig, M-protein, and IFE measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory. Subjects with positive serum IFE and confirmed daratumumab IFE interference, that meet all other clinical criteria for CR or sCR, will be considered CR/sCR.

Table 9: International Uniform Response Criteria Consensus Recommendations

Response	Response Criteria
Stringent complete response (sCR)	• CR as defined below, *plus* • Normal FLC ratio, *and* • Absence of clonal PCs by immunohistochemistry, immunofluorescence[a] or flow cytometry
Complete response (CR)[b]	• Negative immunofixation on the serum and urine, *and* • Disappearance of any soft tissue plasmacytomas, *and* • <5% PCs in bone marrow
Very good partial response (VGPR)[b]	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or* • ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours
Partial response (PR)	≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours If the serum and urine M-protein are not measurable, a decrease of ≥50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum FLC assay is also not measurable, ≥50% reduction in bone marrow PCs is required in place of M-protein, provided baseline bone marrow PC percentage was ≥30%. In addition to the above criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, or PD
Progressive disease (PD)[c]	Increase of 25% from lowest response value in any one of the following: Serum M-component (absolute increase must be ≥0.5 g/dL) Urine M-component (absolute increase must be ≥200 mg/24 hours) Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥10%) Bone marrow PC percentage: the absolute percentage must be >10% Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L) that can be attributed solely to the PC proliferative disorder
Relapse from CR	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis. Development of ≥5% plasma cells in the bone marrow. Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

FLC = free light chain; IMWG = International Myeloma Working Group; M-protein = monoclonal paraprotein; PC = plasma cell.

All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require documentation of no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL. Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation. Clinical judgment should prevail; however, repeat assessments after 1 to 3 weeks can be used as a general guideline.

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

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

Table 9: International Uniform Response Criteria Consensus Recommendations

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

Clinical Relapse

Clinical relapse is defined using the definition of clinical relapse in the IMWG criteria[15,22] In the IMWG criteria, clinical relapse is defined as requiring one or more of the following direct indicators of increasing disease or end-organ dysfunction that are considered related to the underlying plasma cell proliferative disorder:

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

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

Disease progression must be consistently documented across clinical study sites using the criteria in Table 9. Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation. Clinical judgment should prevail; however, repeat assessments after 1 to 3 weeks can be used as a general guideline.

It is important that instances of disease progression be reported to the sponsor as soon as possible. Diagnosis and documentation of disease progression will be faxed within 24 hours to the sponsor (see Contact Information provided in the Investigator File). The medical monitor will review the form to confirm that the IMWG criteria for disease progression have been met. If the medical monitor agrees that disease progression has occurred, then a confirmation fax or email will be returned to the investigator, and the subject will be withdrawn from study treatment. If the medical monitor considers that the IMWG criteria for disease progression have not been met, then the medical monitor will contact the investigator to discuss the subject.

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

Serum FLC assay test results will be analyzed by the central laboratory for the assessment of sCR, according to the most recently published IMWG criteria.[14] Additionally, the absence of clonal plasma cells by immunohistochemistry, immunofluorescence or flow cytometry will be analyzed at the local laboratory as required for sCR. Morphology (aspirate and biopsy) will also be assessed at the local laboratory for clinical staging. For subjects who discontinue study treatment before disease progression, disease evaluations should continue to be performed as described in the TIME AND EVENTS SCHEDULE, until confirmed disease progression, death, the start of a new treatment for multiple myeloma, withdrawal of consent for study participation, or the end of study, whichever occurs first. Disease evaluations scheduled for treatment days should be collected before any study treatment is administered.

9.2.2. Myeloma Protein Measurements in Serum and Urine

Blood and 24-hour urine samples will be collected for serum quantitative Igs, serum and urine M-protein measurements, serum and urine IFE measurements, and serum FLC assay on Day 1 (24-hour urine samples can be completed or started on Day 1 and returned at the next visit), of Cycles 1 to 6, Day 21 of Cycle 4, post-ASCT consolidation disease evaluation, and EOT visit. During the maintenance phase, blood and 24-hour urine samples will be collected from all subjects for serum quantitative Igs and serum and urine M-protein measurements according to the TIME AND EVENTS SCHEDULE and for serum and urine IFE measurements and serum FLC assay whenever CR or sCR is suspected or maintained. For FLC-only subjects, without measurable disease in the serum or urine, blood and 24-hour urine samples for serum and urine IFE measurements and serum FLC assay will be collected according to the TIME AND EVENTS SCHEDULE. All samples will be sent to and analyzed by a central laboratory. Only 1 serum and one 24-hour urine sample per time point as specified in the TIME AND EVENTS SCHEDULE are required by the central laboratory to perform the following tests:

- Serum quantitative Igs
  - All subjects: IgG, IgA, IgM
  - For subjects with IgE or IgD myeloma: IgE or IgD
- Serum M-protein quantitation by electrophoresis and serum IFE
  - If daratumumab interference is suspected based on SPEP and IFE results, additional reflex IFE testing will be performed
- Serum FLC assay
- 24-hour urine M-protein quantitation by electrophoresis (UPEP)
- Urine IFE

Blood and 24-hour urine samples will be collected until the development of confirmed disease progression. Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation. Clinical judgment should prevail; however, repeat assessments after 1 to 3 weeks can be used as a general guideline. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed.

For subjects in the D-RVd/D-R group with VGPR and suspected daratumumab interference (see Section 9.2, Efficacy Evaluations), reflex serum IFE using the anti-idiotype monoclonal antibody will be used to confirm daratumumab migration on the IFE. Subjects that meet all other IMWG criteria for CR, and whose positive IFE is confirmed to be daratumumab, will be considered complete responders.

9.2.3. Serum Calcium Corrected for Albumin

Blood samples for calculating serum calcium corrected for albumin will be collected and analyzed by the local laboratory until the development of confirmed disease progression. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L) can indicate disease progression or relapse if it is not attributable to any other cause (see disease

response criteria in Table 9). Calcium binds to albumin and only the unbound (free) calcium is biologically active; therefore, the serum calcium level must be adjusted for abnormal albumin levels ("corrected serum calcium"). The formula for adjustment is presented in Attachment 5.

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

9.2.4. β2-microglobulin

A blood sample for β2-microglobulin will be collected at screening and will be analyzed by the central laboratory to determine the International Staging System stage.

9.2.5. Bone Marrow Examination

Clinical staging of the bone marrow aspirate or biopsy will be performed and a portion of the bone marrow aspirate will be used to assess MRD and plasma clonality at the time points described in Table 10.

During the bone marrow aspirate procedure, the first aspirate sample that is drawn will be sent to the central laboratory to determine MRD. The second aspirate sample will be sent to the local laboratory to determine plasma cell clonality. Additional bone marrow aspirate samples may be taken and used for local laboratory testing. Refer to the TIME AND EVENTS SCHEDULE for the time points of bone marrow aspirate collection.

9.2.6. Minimal Residual Disease Assessment

At the time the original protocol was written, MRD assessment was a relatively new tool in the assessment of subjects with multiple myeloma. Some investigators have shown that MRD assessment is predictive of overall outcome in patients with myeloma.[18,24] and several studies have demonstrated that MRD status is correlated with PFS and OS.[16] In the present study, MRD will be assessed in bone marrow aspirate whenever a bone marrow sample is obtained as described below and in the TIME AND EVENTS SCHEDULE.

Table 10: Bone Marrow Testing Requirements

Study Time Point	Sample to be Collected	Local Laboratory Testing	Central Laboratory Testing
Screening	**Bone marrow biopsy and aspirate**	**Cytogenetics** (FISH)[a] **PC clonality assay** (immunohistochemistry or immunofluorescence, or flow cytometry) **Morphology** (aspirate and biopsy)	**MRD aspirate**[b]
At the following times: • At first evidence of suspected CR or sCR (including subjects with VGPR or better) • After induction and before stem cell collection • Post-ASCT consolidation disease evaluation (+7-day window after Cycle 6 Day 21) • At 12 and 24 months (+/-3 weeks) during maintenance phase	**Bone marrow aspirate** (The collection of an additional biopsy specimen is optional based on the site's preference for PC clonality testing)	**PC clonality assay** **Morphology** (aspirate)	**MRD aspirate**

ASCT = autologous stem cell transplantation; CR = complete response; FISH = fluorescence in situ hybridization; MRD = minimal residual disease; PC = plasma cell; sCR = stringent complete response; and VGPR = very good partial response.

a: FISH testing to include del(1p), gain of 1q, del(17p), t(4;14), t(14;16), and t(14;20).

b: May also be used to investigate markers of response, resistance and progression: a portion of the bone marrow aspirates (at least 2 mL) collected at screening will be sent to a central laboratory. If a fresh bone marrow aspirate will not be performed at screening because a sample is available within 28 days prior to randomization, then diagnostic tissue such as non-decalcified bone marrow clot sections or bone marrow aspirate smears can be utilized for MRD assessment (characterization of MRD clone).

9.2.7. Assessment of Lytic Bone Disease

A complete skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease) is to be performed and evaluated by the local laboratory by roentgenography during the screening phase. During the induction/consolidation and maintenance treatment phases and before disease progression is confirmed, x-rays should be performed whenever clinically indicated based on symptoms, to document response or progression. Magnetic resonance imaging and/or low dose CT-scan studies are acceptable methods for evaluation of bone disease and may be included at the discretion of the investigator; (see the disease response criteria in Table 9: International Uniform Response Criteria Consensus Recommendations). If an alternative imaging modality (MRI, CT) was used at screening in addition to the complete skeletal survey, then both methods must be used to document disease status. These tests must be performed at the same time.

Sometimes subjects present with disease progression manifested by symptoms of pain due to bone changes. Therefore, disease progression may be documented, in these cases, by skeletal survey or other imaging studies, depending on the symptoms that the subject experiences. If the diagnosis of disease progression is obvious by radiographic investigations, then no repeat confirmatory x-rays are necessary. In instances where changes may be more subtle, a repeat x-ray may be needed in 1 to 3 weeks.

9.2.8. Documentation of Extramedullary Plasmacytomas

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

Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas, or if clinically indicated at screening, by clinical examination or radiologic imaging. Assessment of measurable sites of extramedullary disease will be performed and evaluated locally for subjects with a history of plasmacytomas or as clinically indicated during treatment until development of confirmed CR or confirmed disease progression. If assessment can only be performed radiologically, then evaluation of extramedullary plasmacytomas must be performed according to the TIME AND EVENTS SCHEDULE. For every subject, the methodology used for evaluation of each disease site should be consistent across all visits. Irradiated or excised lesions will be considered not measurable and will be monitored only for disease progression.

To qualify for PR, the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have decreased by at least 50%, and new plasmacytomas must not have developed (see the disease response criteria in Table 9: International Uniform Response Criteria Consensus Recommendations). To qualify for disease progression, either the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have increased by at least 50% or a new plasmacytoma must have developed. In the cases where not all existing extramedullary plasmacytomas are reported, but the sum of products of the perpendicular diameters of the reported plasmacytomas have increased by at least 50%, this will also qualify as disease progression.

9.3. Pharmacokinetics and Immunogenicity

9.3.1. Evaluations

For all subjects who receive daratumumab (D-RVd during induction/consolidation and/or D-R during maintenance), blood samples will be collected according to the TIME AND EVENTS SCHEDULE to determine serum concentration of daratumumab as well as immunogenicity (anti-daratumumab antibodies). Venous blood samples (5 mL per sample) will be collected and the serum will be divided into 3 aliquots (1 aliquot for pharmacokinetic analysis, 1 aliquot for anti-daratumumab antibodies analysis [when appropriate], and 1 aliquot as a backup). Samples collected for determining serum concentrations of daratumumab and anti-daratumumab antibodies in this study may be retained to address questions about drug characteristics that may arise at a later time point. Genetic analyses will not be performed on these samples, and subject confidentiality will be maintained.

The exact dates and times of blood sampling must be recorded. Refer to the Laboratory Manual or equivalent document for sample collection requirements. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the laboratory manual.

9.3.2. Analytical Procedures

Serum samples will be analyzed to determine concentrations of daratumumab or generation of anti-daratumumab antibodies using validated immunoassay methods by or under the supervision of the sponsor's bioanalytical facility.

9.3.3. Pharmacokinetic Parameters

Pharmacokinetic samples to determine serum concentration of daratumumab will be obtained from all subjects in the D-RVd and D-R groups. Pharmacokinetic endpoints include:

- Minimum observed concentration (C_{min})
- Maximum observed concentration (C_{max})

If sufficient data are available, then other pharmacokinetic parameters may be calculated.

9.3.4. Immunogenicity Assessments

Venous blood samples drawn from all subjects who receive daratumumab (D-RVd during induction/consolidation and/or D-R during maintenance) will be assessed for the generation of anti-daratumumab antibodies (immunogenicity), according to the TIME AND EVENTS SCHEDULE. Subjects who discontinue treatment will also be asked to return for immunogenicity evaluation during the long-term follow-up phase.

All samples collected for immunogenicity analysis will also be evaluated for daratumumab serum concentration to ensure appropriate interpretation of immunogenicity data. At each time point, immunogenicity and serum daratumumab concentration analyses will be performed on aliquots from the same blood draw and no additional sampling is required. Procedures for sample collection, preparation, identification, storage, and shipment will be provided in the Laboratory Manual or equivalent document.

Serum samples will be screened for antibodies binding to daratumumab and serum titer will also be determined from confirmed positive samples using validated assay methods by or under the supervision of the sponsor. Other immunogenicity analyses (eg, assessment of neutralizing capabilities) may be performed to further characterize the immune responses that are generated.

A blood sample should be drawn, if possible, for determination of anti-daratumumab antibodies, at any time an infusion reaction is observed or reported during the study. Daratumumab serum concentration will also be determined from the same infusion reaction sample for the purpose of interpreting immunogenicity data. These samples will be stored and evaluated if deemed necessary. If the infusion reaction results in treatment discontinuation, then subjects should undergo all scheduled safety and efficacy evaluations. Samples collected for the analysis of daratumumab immunogenicity/serum concentration may additionally be used to evaluate safety

or efficacy aspects that address concerns arising during or after the study period or for the evaluation of relevant biomarkers by the sponsor or sponsor's designee.

9.4. Pharmacokinetic/Pharmacodynamic Evaluations

If sufficient data are available, then other pharmacokinetic/pharmacodynamic modeling may be performed.

9.5. Biomarkers

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and may be deferred or not performed if during or at the end of the study it becomes clear that the analysis will have no scientific value, or if there are not enough samples or not enough responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data. Samples for biomarker evaluations will be collected as specified in TIME AND EVENTS SCHEDULE.

Biomarker evaluations will focus on the assessment of MRD. Minimal residual disease negativity is being evaluated in the field as a potential surrogate for PFS and OS. Minimal residual disease will be evaluated in subjects who achieve CR or sCR (including subjects with VGPR or better and suspected daratumumab interference) using next-generation sequencing which utilizes multiple myeloma cell DNA from bone marrow aspirates.[9] If this methodology is unavailable, or determined to be scientifically inferior, then alternative methods for MRD assessment may be utilized. Baseline bone marrow aspirates will be used to define myeloma clones and samples collected as specified in the TIME AND EVENTS SCHEDULE will evaluate the depth of MRD. Baseline bone marrow aspirate samples will be subjected to DNA and RNA sequencing to establish the myeloma clone for MRD monitoring. In cases where daratumumab is suspected of interfering with IFE and preventing clinical CR calls, subjects with VGPR may also be evaluated for MRD.

In addition to evaluating MRD, a whole blood sample will be collected from subjects, as outlined in the TIME AND EVENTS SCHEDULE, for processing to plasma and PBMCs and monitoring changes in immune cell subpopulations. The immune system-related parameters (immunophenotyping) to be analyzed may include the determination of the frequency and activity of immune effector cells including T cells (cytotoxic, regulatory, memory T cells subsets), B cells, NK cells (including activated NK cells), myeloid derived suppressor cells, macrophages, and dendritic cells, as these cells are involved in immune-mediated tumor lysis. The initial values of all these parameters and the relative changes during therapy will be correlated with the quality and the duration of CR. For these immune monitoring studies, flow cytometry and/or CyTOF may be performed. These immune profiles will be analyzed for associations with clinical data (quality of response, MRD status and depth, PFS, OS) as well as with multiple myeloma sequencing data. In addition to immunophenotyping, gene expression profiling of peripheral blood mononuclear cells for immune specific signatures, and T-cell receptor sequencing to examine clonal T-cell expansion may be examined to determine whether a specific immune signature or T-cell response may be associated with D-RVd response.

9.6. Patient-Reported Outcomes

It is anticipated that the addition of daratumumab will provide benefits in terms of symptom reduction, improved functioning, and improved utilities. To measure functional status, well-being, and symptoms, the EORTC QLQ-C30, EORTC QLQ-MY20, and the EQ-5D-5L instruments will be used. These questionnaires will be completed at the time points outlined in the TIME AND EVENTS SCHEDULE before any other study procedures scheduled for the same day.

The EORTC QLQ-C30 includes 30 items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status 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 (the past week). The EORTC QLQ-C30 has been widely used among cancer patients. Scores are transformed to a 0 to 100 scale. Administration time is approximately 11 minutes. Reliability, validity, and clinically meaningful change have been demonstrated in multiple myeloma patients.[36,37] The focus of the PRO assessment will be the global health scale which is designated as a secondary endpoint. The remaining domains are included as exploratory endpoints.

The EORTC QLQ-MY20 is a disease-specific validated instrument, which measures the symptom burden of multiple myeloma. The module contains 20 questions that measures 4 myeloma-specific PRO domains: disease symptoms, side effects of treatment, future perspective, and body image. Three of the QLQ-MY20 domains are multi-item scales (disease symptoms, side effects of treatment, future perspective), while the body image scale contains a single-item that addresses physical attractiveness. Similar to the QLQ-C30, QLQ-MY20 domain scores are transformed to a 0 to 100 scale. A higher score on the disease symptoms and side effects of treatment scales represents a high level of symptom burden, and, in contrast, a higher score for future perspective and body image represents a more positive outcome.

An example of the EORTC QLQ-C30 and EORTC QLQ-MY20 is provided in Attachment 7.

The EQ-5D-5L is a standardized instrument for use as a measure of health status. For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost effective analyses. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale rating “health today” with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).[10] 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. An example of the EQ-5D-5L is provided in Attachment 8.

9.7. Medical Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all subjects throughout the study at each time point as indicated in the TIME AND EVENTS SCHEDULE. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

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

9.8. Safety Evaluations

Safety will be measured by adverse events, laboratory test results, pregnancy tests, ECGs, vital sign measurements, physical examination findings, and ECOG performance status. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF. During the mobilization and stem cell transplantation procedures, adverse events related to the planned procedures do not need to be reported, however any toxicity related to daratumumab, lenalidomide, bortezomib, or dexamethasone exposure should continue to be reported. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

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

Details regarding the independent DMC are provided in Section 11.12, Independent Data Monitoring Committee. Details regarding the Safety Run-in Data Review Committee are provided in Section 11.13.

The study will include the following evaluations of safety and tolerability according to the time points provided in the TIME AND EVENTS SCHEDULE.

9.8.1. Adverse Events

Adverse events (with the exception of progression of multiple myeloma) will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study (ie, from the time a signed and dated informed

consent if obtained until 30 days following the last dose of study treatment). Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

9.8.2. Clinical Laboratory Tests

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

At a minimum the following tests will be performed by the local laboratory, unless otherwise noted:

- Hematology Panel

  -hemoglobin
  -white blood cell (WBC) count with absolute counts for neutrophils and lymphocytes
  -RBC count
  -platelet count

- Serum Chemistry Panel

  -sodium
  -potassium
  -creatinine and CrCl[a]
  -glucose
  -aspartate aminotransferase (AST)
  -alanine aminotransferase (ALT)
  -total bilirubin
  -alkaline phosphatase
  - BUN
  -calcium and albumin-adjusted calcium[b]
  - albumin

  -lactic acid dehydrogenase (screening only; sample to be sent to central laboratory)

  [a] Creatinine clearance can be either measured by 24-hour urine study, or estimated using a validated equation, such as the Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-epi), or Cockcroft-Gault (Attachment 2).
  [b] These parameters will be part of the efficacy evaluations as specified in Section 9.2.3, Serum Calcium Corrected for Albumin.

- Pregnancy testing
- Cytogenetics (FISH)
- PC Clonality (immunohistochemistry, immunofluorescence or flow cytometry)
- Morphology of bone marrow aspirate or biopsy

9.8.3. Pregnancy Testing (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, throughout the study, and at the EOT visit as specified in the TIME AND EVENTS SCHEDULE. Highly sensitive serum (β-hCG) pregnancy tests are required during screening and throughout the study; either a serum (β-hCG) or urine pregnancy test may be performed at the

EOT visit. All pregnancy testing will be performed locally. Subjects (women of childbearing potential and men who are sexually active with a woman of childbearing potential) must adhere to the lenalidomide REMS program that can be accessed at http://www.revlimidrems.com/.

9.8.4. Daratumumab Interference With Indirect Antiglobulin Test Results

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

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

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

a) Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping prior to daratumumab administration) 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.

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 Investigator's Brochure for daratumumab.

9.8.5. Stem Cell Harvest

The following information will be recorded for each subject: target CD34 dose prior to collection, agents used for mobilization, total number of CD34+ cells collected, number of days required to collect stem cells, and hematopoietic engraftment information. During the mobilization and stem cell transplantation procedures, adverse events related to the planned procedures do not need to be reported, however any toxicity related to daratumumab, lenalidomide, bortezomib, or dexamethasone exposure should continue to be reported.

Stem cell mobilization will be performed with G-CSF, with or without plerixafor. G-CSF and plerixafor should be administered according to institutional standards of dose and schedule. Use of cyclophosphamide is only allowed if G-CSF with or without plerixafor is not successful. Stem cell collection should be performed and stem cells frozen according to institutional standards. Subjects will then proceed to HDT and ASCT.

9.8.6. FEV1 Test

Subjects with known or suspected chronic obstructive pulmonary disease and asthma must have an FEV1 test during screening. Refer to Section 6.1.3.2, Postinfusion Medication for details on subjects with higher risk of respiratory complications.

9.8.7. Electrocardiogram and Vital Signs

Electrocardiograms will be performed as specified in the TIME AND EVENTS SCHEDULE. During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Vital Signs (temperature, pulse/heart rate, respiratory rate, blood pressure) will be measured in the sitting position and recorded as specified in the TIME AND EVENTS SCHEDULE. It is recommended that blood pressure and pulse/heart rate measurements be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

9.8.8. Physical Examination and ECOG Performance Status

Physical examinations will be performed on the day of the study treatment and ECOG performance status will be assessed as specified in the TIME AND EVENTS SCHEDULE. ECOG performance status (Attachment 3) will be used to evaluate the impact of the disease status on the activities of daily living.

9.9. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken.

Refer to the TIME AND EVENTS SCHEDULE for the timing and frequency of all sample collections.

Further instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

10. SUBJECT COMPLETION, DISCONTINUATION OF STUDY TREATMENT, AND WITHDRAWAL FROMTHE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she has died before the end of the study, has not been lost to follow up, or has not withdrawn consent for study participation before the end of the study.

10.2. Discontinuation of Study Treatment/Withdrawal From the Study

Discontinuation of Study Treatment

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

A subject's study treatment must be discontinued if:

- The investigator believes that for safety or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- The subject (or the subject's legally acceptable representative) withdraws consent for administration of study treatment
- The subject initiates treatment with a prohibited medication.
- The subject received concurrent (non-protocol) treatment for multiple myeloma
- Subjects with a history of HCV who completed treatment at least 6 months prior to screening, but who do not agree to undergo regular assessment for HCV reactivation during their participation in the study.
- The subject experiences unacceptable toxicity, including IRRs as described in Section 6.1.3.3, Management of Infusion-Related Reactions. For subjects whose daratumumab treatment is discontinued because of a daratumumab-related infusion reaction, they may continue to receive lenalidomide, bortezomib, and dexamethasone (as applicable depending on study phase). For subjects whose lenalidomide is discontinued because of a lenalidomide-related toxicity (eg, deep vein thrombosis), bortezomib and daratumumab treatment may be continued (as applicable depending on study phase). For subjects whose bortezomib is discontinued because of a bortezomib-related toxicity (eg, peripheral neuropathy), lenalidomide and daratumumab treatment may be continued.

- The subject's daratumumab dose is held for more than 28 days or if ≥3 consecutive planned doses are missed for reasons other than toxicity
- The subject experiences disease progression. Relapse from CR is not considered as disease progression.

If a subject discontinues study treatment for any reason before the end of the induction/consolidation phase or maintenance phase, EOT assessments should be obtained and posttreatment long-term follow-up scheduled assessments should be continued.

The primary reason for discontinuation of study treatment is to be recorded in the CRF. For subjects who discontinue study treatment due to disease progression, sites will complete a disease progression form and fax the form to the sponsor's medical monitor. If study treatment is discontinued for a reason other than disease progression, then disease evaluations will continue to be performed as specified in the TIME AND EVENTS SCHEDULE.

Withdrawal from the Study

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

- Lost to follow-up
- Withdrawal of consent
- Death
- Sponsor terminates the study
- Subjects with a history of HCV who completed treatment at least 6 months prior to screening but who test positive for HCV at any time during the regular assessments
- The study investigator, for any reason, stops the subject's participation in the study

If a subject withdraws from the study before the end of the induction/consolidation phase or maintenance phase, EOT assessments should be obtained.

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

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

10.3. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

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

11. STATISTICAL METHODS

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

The primary analysis will be performed after all randomized subjects have completed the post-ASCT consolidation disease evaluation or have been discontinued from study treatment by this time point. A second analysis will be performed after all randomized subjects complete the maintenance phase or have been discontinued from study treatment by this time point. A final data cutoff and analysis, to update secondary endpoints and safety, will occur at the end of study when all subjects have completed at least 1 year of long-term follow up, or until death or withdrawal of consent for study participation, whichever occurs first.

All data, including efficacy and safety, from subjects enrolled in the safety run-in phase during the study will be summarized and presented separately from the randomized portion of the study (main study) using similar methods.

11.1. Subject Information

Analysis of primary and secondary efficacy variables will be based on the response-evaluable population, which includes all randomized subjects who have measurable disease, receive at least 1 dose of study treatment, and have at least 1 efficacy evaluation assessment.

All safety analyses will be based on the safety analysis set, which includes all randomized subjects who receive at least 1 dose of study treatment.

11.2. Sample Size Determination

Historical data suggest that the post-consolidation sCR rate is approximately 35% for RVd therapy. To detect an absolute 15% increase in post-consolidation sCR rate with 80% power using a 1-sided likelihood ratio test at the 10% significance level, 200 subjects need to be randomized with a 1:1 randomization ratio, assuming a 5% non-evaluable rate.

11.3. Efficacy Analyses

Response to study treatment and progressive disease will be evaluated by a validated computer algorithm to calculate IMWG response. Rate of sCR achieved after post-ASCT consolidation will be tabulated. Treatment comparison will be made using the Cochran-Mantel-Haenszel test. The difference in post-ASCT consolidation sCR rate and its 2-sided 95% confidence interval will be provided. Other binary endpoints, including overall CR, sCR, ORR, VGPR, or better rate following induction, ASCT, post-ASCT consolidation, maintenance, and MRD-negative rate after consolidation, will be analyzed similarly.

Time-to-event efficacy endpoints, such as duration of CR, sCR, TTP, PFS, OS, and time to next-line anti-myeloma treatment, will be descriptively summarized using the Kaplan-Meier method. Except for duration of CR and sCR, treatment comparisons will be made via a log-rank test, and

treatment effects, measured by hazard ratios, will be estimated via a Cox regression model with treatment as the sole explanatory variable in the model.

11.4. Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed on the pharmacokinetic-evaluable population, defined as subjects who have received at least 1 dose of daratumumab and have at least 1 postinfusion sample. All serum concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the study report.

Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point and pharmacokinetic parameters of daratumumab such as C_{min} and C_{max}. C_{min} is defined as the concentration observed immediately before infusion and C_{max} is defined as the concentration observed at the end of infusion, as presented in the summary of serum concentration by sampling time point.

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

11.5. Immunogenicity Analyses

The incidence of anti-daratumumab antibodies (immunogenicity) will be summarized for all subjects who receive a dose of daratumumab and have appropriate samples for detection of anti-daratumumab antibodies. In addition, subjects who are positive for antibodies to daratumumab will be listed.

11.6. Pharmacokinetic/Pharmacodynamic Analyses

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

11.7. Biomarker Analyses

Biomarker studies are designed to identify markers predictive of response (or resistance) to daratumumab and to monitor subjects for MRD. Analyses will be stratified by clinical covariates using the appropriate statistical methods (eg, parametric or non-parametric, univariate or multivariate, analysis of variance [ANOVA], or survival analysis, depending on the endpoint). Correlation of baseline expression levels or changes in expression levels with response or time-to-event endpoints will identify responsive (or resistant) subgroups following treatment with daratumumab.

Any biomarker measurements will be listed, tabulated, and where appropriate, plotted. As this is an open-label study with an active control treatment, statistical analyses will be done to aid in the understanding of the results.

Results of biomarker and pharmacodynamic analyses may be presented in a separate report. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information.

11.8. Medical Resource Utilization Analyses

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

11.9. Patient-Reported Outcomes

EORTC QLQ-C30 and QLQ-MY20 domain scores and EQ-5D-5L scores will be descriptively summarized by treatment group at each time point as indicated in the TIME AND EVENTS SCHEDULE.

11.10. Safety Analyses

During the safety run-in phase for D-RVd, DLTs in Cycle 1 will be monitored in cohorts of 4 subjects, after first 8 subjects have completed Cycle 1 or discontinued due to DLT, using the Bayesian approach of Thall, Simon, Estey[31,32] as extended by Thall and Sung.[33] The prior probability of DLT in Cycle 1 for the D-RVd regimen is modeled by beta distribution (*Beta*(0.25, 0.75)). This distribution has the same *mean* as the maximum acceptable DLT in Cycle 1 of 0.25, and an Effective Sample Size of 1. The decision criteria applied will be to stop if Prob{p(DLT) >0.25| data}>0.95; ie, the posterior probability of the unknown DLT rate being >0.25 given the observed data is more than 0.95.

Subjects will be monitored according to the following stopping boundaries for DLT.

	Stop the study if there are this many toxicities total:
Number of Subjects (in complete cohorts of 4)	Number of Toxicities
8	≥5
12	≥6
16	≥8

Adverse Events

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

treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

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

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). Worst toxicity grade during treatment will be presented, according to NCI-CTCAE (version 4.03). A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Stem Cell Harvest

Descriptive statistics of the number of planned ASCTs, agents used for mobilization, total number of CD34+ cells collected, number of days required to collect stem cells, and hematopoietic engraftment information will be summarized by treatment group.

Vital Signs

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

Electrocardiogram data will be summarized by vital signs parameters (temperature, pulse/heart rate and blood pressure (systolic and diastolic). Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

11.11. Interim Analysis

If the study is not stopped due to DLTs in the safety run-in phase, one interim safety analysis is planned for the safety run-in cohort after all subjects are treated for at least 4 cycles or discontinue study participation.

One interim safety analysis is planned for the main study. The interim safety analysis will occur after at least 50 subjects are treated for at least 4 cycles and undergo stem cell mobilization (or are evaluated for mobilization feasibility) in the main study.

An independent Data Monitoring Committee (DMC) as described in Section 11.12, Independent DMC will be established to review the interim results in the main study.

11.12. Independent Data Monitoring Committee

An independent DMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in the main study. The committee will meet periodically during the main study to review interim safety data and will also perform the predetermined interim safety analysis in the main study as detailed in Section 11.11, Interim Analysis. After the review, the DMC will make recommendations regarding the continuation of the main study. The details will be provided in a separate DMC charter.

The DMC will consist of at least 2 medical experts in the relevant therapeutic area and at least 1 statistician. The DMC responsibilities, authorities, and procedures will be documented in its charter.

11.13. Safety Run-in Data Review Committee

A Safety Run-in Data Review Committee will be established to review safety data after 8, 12, and 16 subjects in the safety run-in phase complete Cycle 1 (or discontinue before the end of Cycle 1) and will use stopping boundaries described in Section 11.10, Safety Analyses. The Safety Run-in Data Review Committee will consist of the sponsor's medical monitor, a sponsor physician who is not involved in the study, a sponsor statistician who is not involved in the study, and a medical safety representative.

12. ADVERSE EVENT REPORTING

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

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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

Serious Adverse Event

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

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

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

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For daratumumab, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For lenalidomide, bortezomib, and dexamethasone with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the respective prescribing information.[7,25,35]

Adverse Event Associated With the Use of the Drug

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

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

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

Probable

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

Very Likely

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

12.1.3. Severity Criteria

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

Grade 1 (Mild): Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Grade 2 (Moderate): Sufficient discomfort is present to cause interference with normal activity.

Grade 3 (Severe): Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

Grade 4: Life-threatening of disabling adverse event

Grade 5: Death related to the adverse event

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

12.2. Special Reporting Situations

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

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

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

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of any component of the study treatment, until the subject withdraws consent for study participation or is lost to follow-up, or until the subject starts next-line anticancer therapy, whichever occurs first. The only exceptions are for subjects who have withdrawn informed consent for study participation or for subjects who have received additional treatment with therapeutic intent for multiple myeloma within 30 days after the last administration of any component of the study treatment. For subjects who have received additional treatment with therapeutic intent for multiple myeloma during the adverse event reporting period, only adverse events that are considered to be possibly, probably, or definitely related to any component of the study treatment must be reported (unless the subject has been withdrawn from the study). Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of any component of the study treatment and those that are considered related to daratumumab within the long-term follow-up phase, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

During the mobilization and stem cell transplantation procedures, adverse events related to the planned procedures do not need to be reported, however any toxicity related to daratumumab, lenalidomide, bortezomib, or dexamethasone exposure should continue to be reported.

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, Adverse Event Definitions and Classifications).

Death should not be recorded as an adverse event or serious adverse event, but as the outcome of an adverse event. The adverse 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.

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

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

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

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

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, which must be completed and signed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

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

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

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

- If the subject has not experienced a significant medical event but is hospitalized overnight only for observation following infusion 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 CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment. The subject should be referred to a physician experienced in teratology for evaluation and advice. Investigators should follow the local label for guidance on subject education and ensure that all subjects adhere to the lenalidomide REMS program that can be accessed at http://www.revlimidrems.com/.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug

The daratumumab supplied for this study is a colorless to yellow liquid and sterile concentrate of 20 mg/mL as a liquid vial. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

14.2. Packaging

Daratumumab is supplied in glass vials containing daratumumab at a concentration of 20 mg/mL.

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

Daratumumab product must be stored in the original carton in a refrigerator at controlled temperatures ranging from 2°C to 8°C. Daratumumab must not be utilized after the expiry date printed on the label. The daratumumab 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 study site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

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

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

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

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

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure for daratumumab
- Study site investigational product and procedures manual
- Laboratory manual
- NCI-CTCAE Version 4.03
- PRO questionnaires (electronic or paper, as appropriate)
- Electronic Data Capture (eDC) Manual
- Sample ICF
- Subject diaries

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Based on the potential IRRs associated with administration of daratumumab, guidelines for prevention and management of IRRs are provided (see Section 6.1.3). Based on the mode of action of daratumumab, a potential risk could be infection; therefore, the protocol requires the review of hematological laboratory results prior to daratumumab infusion. CD38 is distributed in erythrocytes and platelets. A significant reduction of platelets was reported in an animal study. In a human clinical study (Study GEN501), thrombocytopenia was also reported. However, safety laboratory monitoring did not show 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.

All subjects will be receiving RVd for multiple myeloma in this study. Refer to Section 1.1.6, Combination Therapy: Daratumumab-Lenalidomide-Bortezomib-Dexamethasone regarding the use of daratumumab in combination with RVd in newly diagnosed patients with multiple myeloma who are eligible for ASCT.

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

The total blood volume to be collected is considered to be acceptable for subjects participating in a cancer clinical study and reasonable (eg, less than the standard blood donation [500 mL over 60 days][3]) 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 subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

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

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

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

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects

- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

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

16.2.3. Informed Consent

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

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed

that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations and subsequent disease-related treatments, if needed.

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

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

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

Note that per Protocol Amendments 2 and 3, subjects who elect to receive daratumumab every 4 weeks instead of every 8 weeks during the maintenance phase and/or who elect to receive the rapid infusion of daratumumab, must sign a new ICF prior to the change in daratumumab administration.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

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

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

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

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

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

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

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate

document). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

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

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

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)

- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

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

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

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

17.4. Source Documentation

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

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

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

Subject-completed scales and assessments designated by the sponsor (EORTC QLQ-C30, EORTC QLQ-MY20, and EQ-5D-5L) will be recorded directly into an electronic device and will be considered source data.

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

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

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

17.5. Case Report Form Completion

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

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

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

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

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done 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 and electronic PRO data from the vendor into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

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

17.7. Record Retention

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

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

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

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

17.8. Monitoring

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

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

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

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed once all subjects have completed at least 1 year of long-term follow up, or until death or withdrawal of consent for study participation, whichever occurs first. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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

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

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

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

17.10. On-Site Audits

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

available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

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

17.11. Use of Information and Publication

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

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

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain 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. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor

will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

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

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ATTACHMENTS

Attachment 1: Conversion Table for Glucocorticoid Dose

Generic Name	Oral or Intravenous Dose (mg)
Dexamethasone	0.75
Hydrocortisone	20
Methylprednisolone	4
Prednisolone	5
Prednisone	5

Attachment 2: Calculated Creatinine Clearance

To calculate the subject'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 International System of Units (SI) (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).

Modification of Diet in Renal Disease (MDRD)

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)

Alternatively, creatinine clearance may be calculated or measured according to the MDRD (Levey 2006) or the CKD-EPI (Levey 2009).

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

References:

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

Reference: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655.

Attachment 4: Guideline for Asthma Eligibility Criteria

Components of Severity		Classification of Asthma Severity											
		Intermittent			Persistent								
					Mild			Moderate			Severe		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
Impairment	Symptoms	≤ 2 days/week			> 2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤ 2x/month		1-2x/ month	3-4x/month		3-4x/ month	> 1x/week but not nightly		> 1x/ month	Often 7x/week	
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			≤ 2 days/week but not daily		>2 days/ week but not daily, and not more than 1x	Daily			Several time per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
Normal FEV_1/FVC : 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	Lung function FEV_1 FEV_1/FVC	N/A	Normal FEV_1 between exacerbations > 80% > 85%	Normal FEV_1 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
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	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.											

Attachment 5: Serum Calcium Corrected for Albumin

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

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

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

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

Source: Burtis CA, Ashwood ER. Tietz textbook of clinical chemistry, 3rd ed. Philadelphia; WB Saunders, 1998.

Attachment 6: Standard Nomogram for Calculation of Body Surface Area

The body surface area (BSA) should be calculated using the standard calculation given below. However, the DuBois Formula can be used as an alternative to calculate BSA.

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

OR

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

Attachment 7: EORTC QLQ-C30 and EORTC QLQ-MY20

EORTC QLQ-C30 (version 3)

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

Today's date (Day, Month, Year): 31

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

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

EORTC Multiple Myeloma Module (QLQ-MY20)

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

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

Please turn to next page

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

Attachment 8: EQ-5D-5L

(English version for the UK)

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

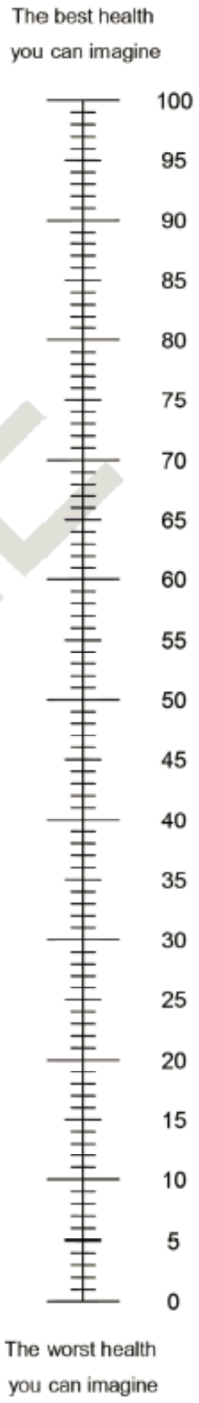
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐



Attachment 9: Protocol Amendments 1 and 2

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	4 April 2016
Amendment 1	24 May 2017
Amendment 2	5 Feb 2018

Amendment 2 (5 Feb 2018)

The major reasons for this amendment are to revise the daratumumab dosing schedule during the Maintenance Phase (based on new information), to update background information, and to revise the instructions for various study procedures as needed, for clarity or improved patient safety.

Edits and additions to original text are noted in bold, and deletions are noted in strikeout.

Applicable Section(s)	Description of Change(s)
Rationale: Daratumumab administration is being changed from every 8 weeks to every 4 weeks during the Maintenance phase based on pharmacokinetic results from Study SMM2001 in smoldering multiple myeloma showing that dosing every 8 weeks is insufficient to maintain target daratumumab saturation. To align with this new finding and to improve clarity, the Time and Events Schedule was revised to have separate schedules for each treatment group (Daratumumab-RVd/D-R and RVd/lenalidomide). Changes to the Time and Events Schedule for D-RVd (eg, in response and disease evaluations, laboratory tests, etc) reflect the new dosing regimen during the Maintenance Phase. The RVd/lenalidomide Time and Events Schedule has all of the relevant changes that the D-RVd/D-R Time and Events Schedule has; for consistency, the footnote identifiers were kept the same in both Schedules, resulting in some being left blank in the RVd Time and Events Schedule.	
D-RVd Time and Events Schedule, Study Drug Dosing Schedule, and throughout protocol as appropriate	To reflect every 4 week (q4w) dosing for the D-R group during the Maintenance Phase, ECOG performance status, physical examinations, weight and vital signs, hematology and serum chemistry tests, and MRU evaluations now to be done on Day 1 of each cycle. Medications to be given prior to daratumumab infusions during the Maintenance phase are also reflected in the Study Drug Dosing Schedule.
Rationale: Text regarding daratumumab informed consent for the new maintenance dosing schedule was added.	
Study Drug Dosing Schedule; Section 6.1.2 Treatment Schedule and Administration; 2nd paragraph; Section 9.1.4 Maintenance Phase; 2nd paragraph	**Subjects who signed the original ICF stating that daratumumab maintenance was to be administered every other month and who do not agree to the revised daratumumab maintenance administration every month will be permitted to receive daratumumab every other month. However, every effort should be taken to ensure that the subject understands the benefit of the monthly daratumumab maintenance schedule.**

Applicable Section(s)	Description of Change(s)
Rationale: In order for subjects to receive the correct, weight-based daratumumab dose, a requirement to check subject weight on all daratumumab dosing days was added. Similarly, a requirement to check and adjust weight was made for bortezomib dosing.	
Section 6.1.2 Treatment Schedule and Administration, 1st paragraph, new 3rd sentence (and Time and Events Schedule)	… The dose of daratumumab will remain constant throughout the study unless the subject's weight changes more than 10% from Cycle 1 Day 1…. **Subject's weight will be recorded on all daratumumab dosing days…**
Section 6.3, Bortezomib (and Time and Events Schedule)	The amount (in mg) of bortezomib to be administered will be determined by body surface area, calculated according to a standard nomogram (Attachment 6). **Each subject's dose will be calculated based on the subject's weight at Cycle 1 Day 1 rounded to the nearest kilogram. The dose should be readjusted if weight changes >10% from value on C1D1.**The total calculated dose…
Rationale: For both groups, the window for the start of each cycle during consolidation was changed from 7 days to 14 days to be consistent with dose delays during the consolidation phase specified in Table 3 (Daratumumab-Related Toxicity Management).	
Throughout protocol as appropriate	The start of each cycle may occur within… ±~~7~~**14** days (consolidation)…
Rationale: Several clarifications were made to both groups' Time and Events Schedules (for laboratory assessments and PROs), as listed below.	
(Both) Time and Events Schedules:	
Laboratory assessments	**For D1 of Cycles 1-6, the following 2 central laboratory kits must be completed: assessment kit and disease evaluation kit.**
PRO Assessments and MRU	~~The PRO assessments should be performed before any other study procedures scheduled for the same day.~~ **The initial set up of the PRO device and administration of the first questionnaire for each subject are to be completed on C1D1 (and subsequent D1 visits) before any study-specific procedures are performed.** (Under Cycles 5-6) C5 **only** (added for PROs)
Rationale: In both Time and Events Schedules, clarification was made for the extramedullary plasmacytoma row.	
Under Consolidation (Cycles 5-6)	C5 **only**
Rationale: Additional instructions for Montelukast dosing were added.	
Study Drug Dosing Schedule, Daratumumab; Section 6.1.3.1 Preinfusion Medication	~~Montelukast 10 mg/day PO, day before and the day of infusion; may be omitted after the second infusion if the subject has no respiratory symptoms.~~ **Montelukast 10 mg/day PO, at C1D1 approximately 1 hour or less before the daratumumab infusion. An additional 10 mg PO can be given the day before infusion at the discretion of the investigator. May be omitted for any daratumumab dose after the second infusion if the subject has no respiratory symptoms.**

Applicable Section(s)	Description of Change(s)
Rationale: In Section 1 (Introduction), the background information for daratumumab was brought up to date.	
Paragraph 1, revised from 2nd sentence through the end of the paragraph and corresponding update to reference list	~~Daratumumab can induce complement dependent cytotoxicity, antibody dependent cell mediated cytotoxicity, antibody dependent cellular phagocytosis, direct apoptosis after cross linking, and can modulate CD38 enzymatic activity. CD38 is highly expressed on myeloma cells, but is expressed at relatively low levels on normal lymphoid and myeloid cells and in some tissues of non hematopoietic origin, making it a relevant target for the treatment of multiple myeloma.~~ **The mechanisms of action of daratumumab comprise immune-mediated effects, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and apoptosis by means of cross-linking. Moreover, daratumumab also induces immunomodulatory effects via several different pathways that contribute to killing CD38+ immune cells that modulate T cell activity, namely myeloid-derived suppressor cells (MDSC) and regulatory T (TReg), and B (BReg) cells (Krejcik 2016).[12] Daratumumab's converging mechanisms of actions are hypothesized to lead synergistically to the deep responses observed in patients with multiple myeloma.**
Paragraph 2, last sentence added	**In June 2017, the US FDA approved daratumumab 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.**
	12. Krejcik J, Casneuf, Nijhof IS, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. BLOOD. 2016;128:384-394.
Section 1.1.2, text for nonclinical, and clinical efficacy and pharmacokinetic results and Table 1 (safety information) were updated to reflect the most recent data.	*(Refer to current body of the protocol for the most up to date information)*
Rationale: Since RVd is no longer the standard of care for multiple myeloma, text was revised accordingly.	
General change made throughout the protocol as appropriate	RVd ~~(standard of care)~~
Rationale: The language pertaining to lenalidomide use after the maintenance phase was clarified.	
General change made throughout the protocol as appropriate	Following completion of the last cycle of the maintenance phase, subjects ~~will~~ **may** continue lenalidomide as per local standard of care.

Applicable Section(s)	Description of Change(s)
Rationale: Clarifications were made to text summarizing the study design.	
Section 3.1 (Overview of Study Design) 5th paragraph, 2nd sentence	Subjects who experience a DLT during the safety run-in will be withdrawn from the study **(based on investigator's judgment and best clinical practice)**.
4th to last paragraph, last sentence	Secondary endpoints include overall CR and sCR rate, ORR, **VGPR**, duration of response, **negative MRD rate**, time to response, TTP, PFS, OS, safety and tolerability, PROs, stem cell yield after mobilization, and time to engraftment after ASCT.
2nd to last paragraph, 2nd sentence *(Note, a similar change was made in the synopsis)*	…One planned interim safety analysis will occur after at least 50 subjects are treated for at least 4 cycles and undergo stem cell mobilization (or are evaluated for mobilization feasibility) in the main study **or have discontinued before completing 4 cycles / stem cell mobilization / feasibility.** Refer to Section 11.12, Independent Data Monitoring Committee for details.
Figure 3 was revised for clarity, and to show the new q4Wk daratumumab dosing during the Maintenance Phase. The increased dose of lenalidomide beginning at Cycle 10 applies to **both** treatment groups.	Daratumumab: 16 mg/kg IV **every 4 weeks**~~every 8 weeks (on day 1 of odd cycles (ie, 7, 9, 11, etc))~~ Lenalidomide: 10 mg PO on Days 1-21. **Beginning at Cycle 10, the lenalidomide dose will be increased to 15 mg unless there is a tolerability concern**
Rationale: Text for concomitant medications to be recorded during mobilization and stem cell transplantation were clarified.	
Time and Events Schedules (both), row for Concomitant Medications; Section 8, Prestudy and Concomitant Therapy, 4th paragraph	**During the mobilization and stem cell transplantation procedures, concomitant medications related to the planned procedures do not need to be reported in the eCRF. However, concomitant medications related to the mobilization and transplantation procedures should be documented by providing a copy of the medication order set.**
Rationale: Text regarding dexamethasone administration for the lenalidomide group was deleted to align with evolving standard of care for maintenance therapy.	
Synopsis, Dosage and Administration; Section 3.1, Overview of Study Design; and Section 6.4, Dexamethasone	~~To prevent administration of dexamethasone from being a confounding factor, subjects in the lenalidomide group will also have dexamethasone 20 mg administered orally on Day 1 of odd cycles.~~

Applicable Section(s)	Description of Change(s)
Rationale: Text describing the analysis of immune cells was clarified.	
Section 3.2.3 (Rationale for Pharmacokinetics, Immunogenicity, and Biomarker Evaluations) 3rd paragraph, 3rd sentence	Immunophenotyping may include analysis of NK cells **(including activated NK cells),** T cells **(cytotoxic, regulatory, memory T cells subsets),** B cells, **MDSC, macrophages, and dendritic cells, as these cells are involved in immune-mediated tumor lysis.** Samples may be used to evaluate specific subsets of immune cells….
Rationale: Several entry criteria were clarified in Sections 4.1 (Inclusion Criteria) and 4.2 (Exclusion Criteria, as well as the Time and Events Schedule).	
Inclusion criterion No. 1	1. 18 to 70 years of age, inclusive **at study entry.**
Exclusion criterion No. 1 2nd bullet	1. diagnosed or treated for malignancy other than multiple myeloma, except: • Malignancy treated with curative intent and with no known active disease present for ≥3 years before randomization. • Adequately treated non-melanoma skin cancer, lentigo maligna or in situ malignancies **(including but not limited to** cervical, breast) with no evidence of disease.
Exclusion criterion No. 4, under the "Note:". A similar clarification regarding asthma was made in Section 9.8.6 FEV1 Testing	4. Note: FEV1 testing is required for subjects suspected of having chronic obstructive pulmonary disease **and asthma. S**ubjects must be excluded if FEV1 <50% of predicted normal.
Exclusion criterion No. 5, under the "Note:"	5. Note: Subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study. **FEV1 testing is required for subjects suspected of having asthma.**
Rationale: A requirement to increase the lenalidomide dose as of Cycle 10 was added, as it was not clearly stated previously.	
Section 6.2 Lenalidomide, new 2nd sentence; Figure 3; and Study Drug Dosing Schedule	During maintenance treatment in Cycle 7 and beyond, lenalidomide 10 mg will be administered daily on Days 1-21 throughout each 28-day cycle. **Beginning at Cycle 10, the lenalidomide dose will be increased to 15 mg unless there is a tolerability concern.** Following completion …
Rationale: The instructions for prophylactic treatment with aspirin were clarified.	
Section 6.2.2 Deep Vein Thrombosis and Pulmonary Edema, 2nd sentence revised	Therefore, all subjects should be prophylactically treated with baby aspirin (162 mg**, at a minimum**) by mouth daily.

Applicable Section(s)	Description of Change(s)
Rationale: Text regarding participation in another interventional clinical trial was clarified.	
Section 8.3 Prohibited Therapies, 3rd paragraph, 1st sentence revised	~~Concomitant administration of investigational agents is prohibited.~~ **Concomitant participation in an interventional clinical trial(s) or use of investigational agent(s) as well as medical devices is prohibited.**
Rationale: Text for disease evaluations was updated.	
Section 9.2.1 Response Categories, 1st paragraph revised; and Time and Events Schedule	~~Disease evaluations must be performed every 21 days during the induction (±3 days)/ consolidation (±7 days) phase and every 8 weeks (±14 days) during the maintenance phase.~~ **Disease evaluations must be performed according to the TIME AND EVENTS SCHEDULE. Note that an additional disease evaluation occurs on Day 21 of Cycle 4 and the day after Day 21 of Cycle 6 (with a 7-day window) to assess end of Cycle 4 and end of Cycle 6 response, respectively.**
Rationale: Details describing assessment of response were clarified.	
Section 9.2.1, Response Categories: Table 9, 1st paragraph under abbreviation definitions; and text following Table 9	All response categories … require **documentation of** no known evidence of progressive or new bone lesions if radiographic studies were performed. Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation. **Clinical judgment should prevail; however, repeat assessments after 1 to 3 weeks can be used as a general guideline.**
1st paragraph under Table 9, new 2nd sentence	Disease progression must be consistently documented across clinical study sites using the criteria in Table 9. **Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation. Clinical judgment should prevail; however, repeat assessments after 1 to 3 weeks can be used as a general guideline.**
3rd paragraph under Table 9, revised 1st sentence	For continuation of treatment, the IMWG response will be determined **and recorded** on an ongoing basis by the investigator.
Rationale: Text describing the timing of screening procedures was corrected.	
Section 9.1.2 Screening Phase, 1st paragraph 3rd sentence	Screening procedures will be performed within 28 days before ~~Cycle 1 Day 1~~ **randomization**; however, results of tests such as skeletal survey, radiologic tests (eg, MRI) to document baseline size of known or suspected extramedullary plasmacytomas; or chest X-rays) performed up to 6 weeks (42 days) before ~~Cycle 1 Day 1~~**randomization** may be used….
Rationale: Timing for the post-ASCT consolidation disease evaluation was clarified.	
Section 9.1.3, Induction/Consolidation Phase; Consolidation Treatment, sentence added to 2nd paragraph	**The post-ASCT consolidation disease evaluation should be performed the day after completion of C6D21 (+7-day window).**

Applicable Section(s)	Description of Change(s)
Rationale: Timing for the start of the maintenance phase was clarified.	
Section 9.1.4, Maintenance Phase; sentence added to 1st paragraph	**The timing of start of maintenance is at the discretion of the investigator, however, it should start within the 14 days following post-ASCT consolidation disease evaluation.**
Rationale: Table 10 (Section 9.2.6, Minimal Residual Disease Assessment) was reformatted and revised for clarity, with corresponding changes to the TIME AND EVENTS SCHEDULE.	
Table 10 Bone Marrow Testing Requirements, Text for when to collect samples for local or central laboratory testing.	**At the following times:** • **At first evidence of suspected CR or sCR (including subjects with VGPR or better)** • **After induction and before stem cell collection** • **Post-ASCT consolidation disease evaluation (+7-day window after Cycle 6 Day 21)** • **At 12 and 24 months (+/-3 weeks) during maintenance phase**
Rationale: Additional detail was provided for the description of biomarkers to be evaluated.	
Section 9.5 Biomarkers, 2nd paragraph, new 2nd to last sentence	…will evaluate the depth of MRD. **Baseline bone marrow aspirate samples will be subjected to DNA and RNA sequencing to establish the myeloma clone for MRD monitoring.** In cases where daratumumab is suspected of interfering with IFE and preventing clinical CR calls, subjects with VGPR may also be evaluated for MRD.
Section 9.5 Biomarkers, 3rd paragraph, revised 1st sentence	In addition to evaluating MRD, **a whole blood sample will be collected from subjects, as outlined in the TIME AND EVENTS SCHEDULE, for processing to plasma and PBMCs and monitoring changes in immune cell subpopulations.**
Rationale: Text was clarified for neutrophil counts; text pertaining to local laboratory testing was corrected or clarified.	
Section 9.8.2 Clinical Laboratory Tests Hematology panel Text under serum chemistry panel	• White blood cell (WBC) count with absolute **counts for** neutrophils and… • ~~Hepatitis C viral load testing – for reactivation of HCV for any subjects who had prior, treated hepatitis C and no detectable circulating HCV at study entry~~ • **Pregnancy testing** • **Cytogenetics (FISH)** • PC Clonality (immunohistochemistry, immunofluorescence or flow cytometry) • Morphology of bone marrow aspirate or biopsy

Applicable Section(s)	Description of Change(s)
Rationale: Instructions for stem call harvest and mobilization were added as they were not mentioned in the previous version of the protocol.	
Section 9.8.5 Stem Cell Harvest, 1st paragraph revised and new 2nd paragraph	The following information will be recorded for each subject: target CD34 dose prior to collection, agents used for mobilization, total number of CD34+ cells collected, number of days required to collect stem cells, and hematopoietic engraftment information. **During the mobilization and stem cell transplantation procedures, adverse events related to the planned procedures do not need to be reported, however any toxicity related to daratumumab, lenalidomide, bortezomib, or dexamethasone exposure should continue to be reported.** **Stem cell mobilization will be performed with G-CSF, with or without plerixafor. G-CSF and plerixafor should be administered according to institutional standards of dose and schedule. Use of cyclophosphamide is only allowed if G-CSF with or without plerixafor is not successful. Stem cell collection should be performed and stem cells frozen according to institutional standards. Subjects will then proceed to HDT and ASCT.**
Rationale: Text for the timing of physical examinations was added for clarity.	
Section 9.8.8 Physical Examination…, 1st paragraph	Physical examinations will be performed **on the day of the study treatment** and ECOG performance status will…
Rationale: Text pertaining to a daratumumab dose delay was clarified.	
Section 10.2, Discontinuation of Study Treatment/Withdrawal from the Study, 8th bullet	The subject's daratumumab dose is held for more than 28 days ~~during induction or consolidation cycles~~ or if ≥3 consecutive planned doses are missed for reasons other than toxicity;
Rationale: The ECG assessment was clarified to show is only needed at C5 (not C5 and C6).	
(Both) Time and Events Schedules	(Under Cycles 5-6) ~~X~~ **C5 only**
Rationale: The diary review at Day 15 in Cycles 5 and 6 was deleted as its prior inclusion was a typographical error.	
Study Drug Dosing Schedule	~~D15~~ (under Cycle5-6)
Rationale: Clarification was made regarding vital signs.	
Footnote o of the D-RVd Time and Events Schedule.	**Day 15 vital signs are required only for subjects in D-RVd arm.**
Rationale: The requirement for the local laboratories to be used for hematology testing was added.	
Footnote s of (both) Time and Events Schedules	**On-site or accredited local laboratory must be used for hematology laboratory assessments.**

Applicable Section(s)	Description of Change(s)
Rationale: The timing for randomization was clarified.	
Footnote x, (both) Time and Events Schedules	Randomization ~~may~~ **will** be performed up to 72 hours before the first dose of study treatment on C1D1.
Rationale: The instructions for aspirate and biopsy samples were clarified and the bone marrow aspirate amount required was decreased.	
Footnote cc, (both) Time and Events Schedules; and Table 10 footnote b.	A fresh aspirate and biopsy are preferred at screening; if not available, obtain non-decalcified **clot sections (block or slides) or** aspirate smear ~~or clot~~ slides. At all visits, during the bone marrow aspirate procedure, the first aspirate sample that is drawn will be sent to the central laboratory to determine MRD. All bone marrow aspirates to be sent to the central laboratory should be at least ~~5~~ **2** mL.

Amendment Int-1 (24 May 2017)

This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reasons for the amendment are to revise lenalidomide dosing, to update background information, and to clarify several instructions for study procedures or entry criteria.

Edits and additions to original text are noted in bold, and deletions are noted in strikeout.

Applicable Section(s)	Description of Change(s)
Rationale: Lenalidomide dosing was changed to be on days 1-21 of each 28-day cycle (in both treatment groups); and to allow the dose to be increased at Cycle 10. Since both continuous and non-continuous dosing has been found to be efficacious in recent Phase 3 maintenance studies, the non-continuous dosing is being called for as it may be better tolerated, may lessen the risk of neutropenia in the daratumumab arm, and may lessen the risk of secondary malignancies.	
Synopsis, Overview of Study Design; Dosage and Administration; Time and Events Schedule - Study Drug Dosing 3.1, Overview of Study Design; 6, Dosage and Administration; 6.2, Lenalidomide	….maintenance treatment with daratumumab every 8 weeks plus oral lenalidomide … **on days 1-21** throughout each 28-day cycle. **Beginning at Cycle 10, the lenalidomide dose will be increased to 15 mg unless there is a tolerability concern.**

Rationale: An interim analysis was added to review the data for subjects who participate in the safety run-in phase.	
Synopsis, Overview of Study Design; 3.1, Overview of Study Design; 11.11. Interim Analysis	**If the study is not stopped due to DLTs in the safety run-in phase, one interim safety analysis is planned for the safety run-in cohort after all subjects are treated for at least 4 cycles or discontinue study participation.**
Rationale: A correction was made to the Synopsis text describing the patients.	
Synopsis, Subject Population	Potential subjects will not be eligible if they have been diagnosed or treated for malignancy other than multiple myeloma (with exception of malignancies treated with curative intent and no known disease for ≥~~5~~**3** years….
Rationale: A detail regarding timing of bortezomib dosing was removed for the bortezomib dosing as it is not required.	
Time and Events Schedule – Study Drug Dosing; 6.3.1, Dose Adjustments of Bortezomib	Dose may be delayed up to 48 hours~~; however, subsequent doses must be adjusted as all bortezomib doses must be at least 72 hours apart~~.
Rationale: Clarifications were made to the Time and Events Schedule.	
Time and Events Schedule	(C4 only) was added to the column heading for Day 21 (for Induction Cycles 1-4). Medical history was clarified by adding footnote j: **Including Surgery or procedure planned prior to entry into the study** The neurological examination was clarified by adding footnote m: **General neurological exam focused on sensory peripheral neuropathy** ~~Pulmonary function test~~ changed to **Spirometry (FEV1)** and footnote l was edited as below: **Pulmonary function testing (spirometry) is required only for subjects with chronic obstructive pulmonary disease or asthma. FEV1 should be measured.** ~~Only subjects with known or suspected chronic obstructive pulmonary disease must have FEV1 measured.~~ PK sampling for daratumumab recipients was clarified in footnote u: **If the sampling falls on a dosing day,** ~~On a daratumumab dosing day~~

Rationale: Brief text regarding approval dates for daratumumab was added to the Introduction (Section 1), for information.	
Rationale: The background information for ongoing trials with daratumumab (Section 1.1.2.2.3) was updated with data through 30 June 2016. Text was updated based on the last version of the IB; safety data is summarized in a table rather than in text (Table 1: Safety Findings in Ongoing Daratumumab Clinical Trials Through 30 June 2016).	
Rationale: The timing of the primary endpoint was clarified.	
Synopsis and 3.1, Overview of Study Design; 9.1.3, Induction/Consolidation Phase; 9.1.4, Maintenance Phase	Subjects will be evaluated for the primary endpoint **(post-ASCT consolidation sCR)**. **MRD will be assessed by next-generation sequencing**~~, regardless of treatment group, as detailed in the sCR (+7 day window after Cycle 6, Day 21; primary endpoint, approximately 100 to 150 days post-ASCT and MRD by next-generation sequencing,~~ regardless of treatment group, as detailed in the TIME AND EVENTS SCHEDULE.
Rationale: The inclusion criterion (#3) for diagnosis of multiple myeloma was edited to match the 2015 IMWG criteria, in order to have the most current criteria, and one error was corrected (see below). For clarity, inclusion criterion #3 was edited and split into 2 separate criteria (#3 and #4), resulting in renumbering of the inclusion criteria.	
4.1, Inclusion criterion 3a.iii	Anemia: hemoglobin value of >20~~0~~ g/L below the lower limit of normal, or a hemoglobin value <100~~0~~ g/L
Rationale: The exclusion criterion regarding malignancy was clarified.	
4.2, Exclusion criterion #1; Synopsis, Subject Population	• Adequately treated non-melanoma skin cancer, lentigo maligna **or in situ malignancies (eg, cervical, breast) with no evidence of disease.** • ~~Adequately treated carcinoma in situ (eg, cervical, breast) with no evidence of disease~~
Rationale: The exclusion criterion related to QT interval on electrocardiogram was clarified.	
4.2, Exclusion criterion #7c	Screening 12-lead ECG showing a baseline **corrected** QT interval ~~as corrected by Fridericia's formula~~ (QTc~~F~~) >470 msec.

Rationale:	The exclusion criterion for human immunodeficiency virus and hepatitis was clarified, and assessments for hepatitis C reactivation were added.
4.2, Exclusion Criteria, #3;	Known to be seropositive for human immunodeficiency virus, known to have hepatitis B surface antigen positivity, or known to have a history of hepatitis C. **Subjects who completed treatment for hepatitis C at least 6 months prior to screening and have no detectable circulating hepatitis C virus (HCV) at screening, may participate in the study. Such subjects will be required to undergo regular assessment for HCV reactivation during their participation in the study. Subjects who test positive for HCV at any time during these assessments will be withdrawn from the study.**
Treatment and Events Schedule, new row for HCV viral load; and footnote w	**[To be checked every 3 months through 6 months after last daratumumab administration and every 4 months during Maintenance Phase]** **Subjects who completed treatment for hepatitis C at least 6 months prior to screening and have no detectable circulating hepatitis C virus (HCV) at screening, may participate in the study. Such subjects will be required to undergo regular assessment for HCV reactivation, as shown and will be withdrawn from the study if they test positive at any time during the study.**
9.8.2, Clinical Laboratory Tests	**Hepatitis C viral load testing – for reactivation of HCV for any subjects who had prior, treated hepatitis C and no detectable circulating HCV at study entry**
10.2, Discontinuation of Study Treatment	**Subjects with a history of HCV who completed treatment at least 6 months prior to screening, but who do not agree to undergo regular assessment for HCV reactivation during their participation in the study.**
10.2, Withdrawal from the Study	**Subjects with a history of HCV who completed treatment at least 6 months prior to screening but who test positive for HCV at any time during the regular assessments.**
Rationale: For patient safety, instructions were added for minimum neutrophil and platelet counts considered acceptable for a new cycle to be administered.	
6, Dosage and Administration	**At a minimum, subjects must have an absolute neutrophil count of 1 x 10^9/L and a platelet count of 50 x 10^9/L to begin a new cycle. Delays of up to 14 days for the start of the subsequent cycle are acceptable. Any delays more than 14 days of the scheduled day will need to be discussed with the sponsor.**
Rationale: For patient safety, instructions were added for prophylaxis for deep vein thrombosis or pulmonary embolism while taking lenalidomide.	
6.2.2, Deep Vein Thrombosis and Pulmonary Embolism	**Therefore, all subjects should be prophylactically treated with baby aspirin (162 mg) by mouth daily.**

Rationale: Positron emission tomography (PET)/computed tomography (CT) fusion studies were removed for assessing lytic bone disease and extramedullary plasmacytomas since this method is unlikely to be used.	
9.2.7, Assessment of Lytic Bone Disease 9.2.8, Documentation of Extramedullary Plasmacytomas	Magnetic resonance imaging and/or low dose CT-scan~~, and/or PET/CT fusion~~ studies are acceptable methods for evaluation of bone disease…. If an alternative imaging modality (MRI, CT~~, or PET/CT~~) was used at screening…. Positron emission tomography scan or ultrasound tests are not acceptable to document the size of extramedullary plasmacytomas. ~~However, PET/CT fusion studies are acceptable.~~
Rationale: A clarification was added for safety run-in dosing.	
8.3, Prohibited Therapies	During Cycle 1 **of the safety run-in**, the prophylactic use of hematopoietic growth factors is prohibited.
Rationale: A correction was made regarding timing of the start of the screening phase.	
9.1.2, Screening Phase	The screening phase begins when the ~~first screening assessment is conducted~~**ICF is signed**.
Rationale: The timing of Day 1 sample for myeloma protein was clarified.	
9.2.2, Myeloma Protein Measurement in Serum and Urine	Blood and 24-hour urine samples will be collected for serum quantitative Igs, serum and urine M-protein measurements, serum and urine IFE measurements, and serum FLC assay on Day 1 (the **24-hour urine samples can be completed or started on Day 1 and returned at the next visit)**….
Rationale: Prophylaxis for pneumonia language was softened as it may not be necessary for all patients.	
8.1.5, Prophylaxis for Pneumonia	Prophylaxis for pneumonia is ~~required~~ **recommended** during the first 2 cycles of study treatment.
Rationale: Minimal residual disease (MRD) will no longer be assessed from whole blood samples. It will only be assessed from bone marrow biopsies. Whole blood assessment has been determined not to be comparable to assessment from aspirate, and is not a substitute for aspirate in MRD testing via NGS (the intended platform for all of our trials).	
Synopsis, Efficacy Evaluations and Biomarker Evaluations; Time and Events Schedule; 3.1, Overview of Study Design; 3.2, Study Design Rationale; 9.2.5, Bone Marrow Examination; 9.2.6, Minimal Residual Disease Assessment; 9.5, Biomarkers	Only bone marrow aspirates are now mentioned for measurement of Minimal Residual Disease; mention of samples from whole blood have been deleted.

Rationale: The details for assessing minimal residual disease were clarified.	
9.2.6, Minimal residual disease assessment, Table 10	Bone marrow aspirate **for CR:** • For response confirmation, additional bone marrow aspirates (or both) will be performed locally ~~to confirm CR or sCR~~for **all subjects with suspected or maintained CR or sCR (including subjects with VGPR or better and suspected daratumumab interference):** o **After induction and before stem cell collection** o **Post-ASCT consolidation disease evaluation (+7 day window after Cycle 6 Day 21)** o At 12 and 24 months (±3 weeks) during maintenance phase Bone marrow aspirate **for MRD**: ~~After induction and before stem cell collection: subjects with CR or sCR (including subjects with VGPR or better and suspected daratumumab interference)~~**To confirm CR or sCR at any time (including subjects with VGPR or better and suspected daratumumab interference)**
Rationale: Membership on the planned Safety Run-in Data Review Committee was corrected and the Data Safety Monitoring Board is now referred to as the Data Monitoring Committee, per Sponsor conventions.	
Synopsis and 3.1, Overview of Study Design; 9.8, Safety Evaluations; 11.11, Interim Analysis; 11.12, Independent Data Monitoring Committee; 11.13, Safety Run-in Data Review Committee	The Safety Run-in Data Review Committee will consist of the sponsor's medical monitor, ~~the principal investigators,~~ a sponsor physician who is not involved in the study, a sponsor statistician who is not involved in the study, **and a medical safety representative**.
Rationale: Minor updates to the required laboratory tests were made.	
Time and Events, Serum chemistry footnote t; 9.8.2, Clinical Laboratory Tests	**At a minimum** the following tests will be performed by the local laboratory, unless otherwise noted:…. Uric acid changed to **BUN**, and Phosphate deleted
Rationale: Dosing for acetaminophen was clarified.	
Time and Events – Drug Dosing; 6.1.3.1, Preinfusion Medication	Acetaminophen 650 to 1,000 mg oral or IV **equivalent**
Rationale: No IWRS manual is being provided to investigators and this was corrected.	
Section 15, Study-specific Materials	• ~~IWRS Manual~~
Rationale: The classifications of asthma severity in Attachment 4 have been corrected.	
Rationale: The DuBois formula for body surface area (BSA) calculation is an acceptable alternative to the Mostellar formula and language was added to allow use of both formulas.	
Attachment 6	The body surface area (BSA) should be calculated using the standard calculation given below. **However, the DuBois Formula can be used as an alternative to calculate BSA.**

INVESTIGATOR AGREEMENT

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JNJ-54767414 (daratumumab)
Clinical Protocol 54767414MMY2004 Amendment 3

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Daniela Hoehn, MD, PhD

Institution: Janssen Research & Development

Signature: [redacted] Date: 1/10/2019
(Day Month Year)

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

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Approved, Date: 10 January 2019