Protocol

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STUDY MAIA (MMY3008)

Janssen Research & Development *

Clinical Protocol

A Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High Dose Therapy

Protocol 54767414MMY3008; Phase 3

JNJ-54767414 Daratumumab

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SYNOPSIS

A Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High Dose Therapy

Daratumumab is a human IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38, such as plasma cells from patients with multiple myeloma. This target is distinct from those of other approved agents for multiple myeloma therapy.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective is to compare the efficacy of daratumumab when combined with lenalidomide and dexamethasone (DRd) to that of lenalidomide and dexamethasone (Rd), in terms of progression-free survival (PFS) in subjects with newly diagnosed myeloma who are not candidates for high dose chemotherapy and autologous stem cell transplant.

Secondary Objectives

The secondary objectives are:

- To evaluate clinical outcomes including:
  - Time to disease progression (TTP)
  - Stringent CR (sCR) rate
  - CR rate
  - PFS2 (defined as time from randomization to progression on the next line of therapy or death, whichever comes first)
  - Time to next treatment
  - Overall response rate (CR + partial response [PR] rate)
  - Proportion of subjects who achieve very good partial response (VGPR) or better
  - Duration of response
  - Overall survival
- To assess the safety and tolerability of daratumumab when administered in combination with Rd.
- To assess the pharmacokinetics of daratumumab in combination with Rd.
- To assess the immunogenicity of daratumumab.
- To evaluate treatment effects on patient reported outcomes and heath economic/resource utilization
- To determine the ability of daratumumab to reduce minimal residual disease (MRD)
- To evaluate the clinical efficacy of daratumumab combination with Rd in high-risk molecular subgroups

Exploratory Objectives

- To explore biomarkers predictive of response and resistance to therapy

Hypothesis

The primary hypothesis of this study is that daratumumab in combination with Rd will prolong PFS as compared with Rd alone in subjects with newly diagnosed multiple myeloma who are ineligible for high dose chemotherapy and autologous stem cell transplant.

OVERVIEW OF STUDY DESIGN

This is a randomized, open-label, active controlled, parallel-group, multicenter study in subjects at least 18 years of age with newly diagnosed multiple myeloma who are not candidates for high dose chemotherapy and ASCT. Approximately 730 subjects will be enrolled in this study with 365 subjects planned per treatment arm.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 21 days before Cycle 1, Day 1. The Treatment Phase will extend from Day 1 of Cycle 1 until discontinuation of all study treatment. For subjects assigned to DRd, daratumumab will be administered weekly for the first 2 cycles of treatment and then every other week for 16 weeks, then monthly. This will equate to 9 consecutive weeks of dosing at the start of the study and a total of 23 doses in the first year. Lenalidomide will be administered at a dose of 25 mg orally (PO) on Days 1 through 21 of each 28-day cycle, and dexamethasone will be administered at a dose of 40 mg once a week for both treatment groups. Subjects in the DRd arm will receive lenalidomide for a maximum of two years; those in the Rd arm will continue lenalidomide until progression of disease. Subjects will continue on daratumumab until progression of disease. Randomization will be stratified by International Scoring System (I vs II vs III), region (North America vs Other), and age (<75 vs ≥75), using an equal allocation ratio of 1:1.

Measures to prevent cytokine release syndrome will include preinfusion medication with dexamethasone, paracetamol, and an antihistamine before each daratumumab infusion.

The Follow-up Phase will begin once a subject discontinues all study treatments. Subjects who discontinue for reasons other than disease progression must continue to have disease evaluations according to the Time and Events Schedule. The Follow-up Phase will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first. After the clinical cut-off (see below for definition), data collection will be reduced as per Section 9.1.4.

Two interim analyses are planned. The first interim analysis, with a purpose to evaluate safety, will be performed after a total of approximately 100 subjects have been treated for at least 8 weeks or discontinued the study treatment. The second interim analysis will be performed when 234 PFS events, which is 60% of the total planned events, have been accumulated. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. The significance level at this interim analysis to establish the superiority of DRd over Rd with regard to PFS will be determined based on the observed number of PFS events at the interim analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. If the experimental arm (DRd) is numerically worse than the control arm in terms of PFS (observed hazard ratio > 1 favoring the control arm), then the study may be terminated for futility.

The primary PFS analysis will occur when approximately 390 PFS events have been observed. The date established for the primary PFS analysis will serve as the clinical cut-off date, after which data collection in the study will be reduced as per Section 9.1.4. Investigators will be informed when each interim analysis is to occur.

The end of the study will occur when 330 subjects have died, or 5 years after the last subject is randomized, whichever comes first. The sponsor will ensure that subjects benefiting from treatment with daratumumab will be able to continue treatment after the end of the study.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study to review efficacy and safety results at the planned interim analyses. After the interim review, they will make recommendations regarding the continuation of the study. In addition, the IDMC may also review cumulative safety data every 6 months besides the two interim analyses.

Assessment of tumor response and disease progression will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria. An assessment of MRD will be conducted on whole blood and bone marrow samples. Safety evaluations will include AE monitoring, physical examinations, electrocardiogram (ECG) monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status. Blood samples will be drawn for assessment of pharmacokinetic parameters.

SUBJECT POPULATION

Key eligibility criteria include the following: subjects who are ≥18 years of age, have a confirmed diagnosis of symptomatic multiple myeloma and measurable secretory disease, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2, must be newly diagnosed and not considered candidates for high-dose chemotherapy with stem cell transplantation (SCT).

DOSAGE AND ADMINISTRATION

Daratumumab (16 mg/kg) will be administered by IV infusion to subjects in Arm B initially once every week for 8 weeks; then once every other week for 16 weeks; thereafter once every 4 weeks until documented progression, unacceptable toxicity, or study end.

Lenalidomide will be self-administered at a dose of 25 mg PO each day on Days 1 through 21 of each 28 day cycle.

Dexamethasone (or equivalent in accordance with local standards; see Attachment 6 for conversion table) will be administered at a total dose of 40 mg weekly.

EFFICACY EVALUATIONS/ENDPOINTS

Disease evaluations must be performed every 28 days for the first 2 years and then every 8 weeks until disease progression (or other reasons as per Section 10). A window of ±7 days is allowed. If treatment has been delayed for any reason, the disease evaluations must be performed according to schedule, regardless of any changes to the dosing regimen.

The primary endpoint is PFS, which is defined as the duration from the date of randomization to either progressive disease, or death, whichever occurs first. Disease progression will be determined according to the IMWG criteria.

The secondary efficacy endpoints include:

- Time to disease progression (TTP) is defined as the time from the date of randomization to the date of first documented evidence of PD, as defined in the IMWG criteria. For subjects who have not progressed, data will be censored at the date of the disease evaluation before the start of any subsequent anti-myeloma therapy.
- sCR rate, defined as the percentage of subjects achieving CR in addition to having a normal FLC ratio and an absence of clonal cells in bone marrow by immunohistochemistry, immunofluorescence, 2-4 color flow cytometry
- CR rate, defined as the percentage of subjects achieving CR, as defined:
  - Negative immunofixation of serum and urine, and

  - Disappearance of any soft tissue plasmacytomas, and
  - <5% PCs in bone marrow
  - For those subjects with negative SPEP and suspected daratumumab interference on immunofixation, a reflex assay using anti-idiotype antibody will be utilized to confirm daratumumab interference and rule out false positive immunofixation. Patients who have confirmed daratumumab interference, but meet all other clinical criteria for CR or sCR, will be considered CR/sCR.

- Progression-free Survival on Next line of Therapy (PFS2), defined as the time from randomization to progression on the next line of treatment or death, whichever comes first. Disease progression will be based on investigator judgment. For those subjects who are still alive and not yet progressed on the next line of treatment, they will be censored on the last date of follow-up.
- Minimal residual disease (MRD) status and depth, as measured in subjects who achieve CR/sCR, at 6 and 12 months after confirmed CR
- Time to next treatment, defined as the time from randomization to the start of the next-line treatment.
- Overall response rate (ORR), defined as the proportion of subjects who achieve CR or PR, according to the IMWG criteria, during or after the study treatment.
- Proportion of subjects who achieve VGPR or better, defined as the proportion of subjects achieving VGPR and CR (including sCR) according to the IMWG criteria during or after the study treatment at the time of data cutoff.
- Duration of response, calculated from the date of initial documentation of a response (CR or PR) to the date of first documented evidence of progressive disease, as defined in 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.
- OS, 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.
- To evaluate clinical efficacy of DRd in high risk molecular subgroups compared to Rd alone.
- To evaluate the impact of DRd compared to Rd on patient-reported perception of global health.

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

For all subjects in Arm B, pharmacokinetic samples to determine serum concentration of daratumumab will be obtained according to the Time and Events Schedule. Venous blood samples (5 mL per sample) will be collected to determine serum concentration of daratumumab and the serum will be divided into 3 aliquots (1 aliquot for pharmacokinetic analysis, 1 aliquot for antibodies to daratumumab analysis [when appropriate], and 1 aliquot as a backup).

BIOMARKER EVALUATIONS

Bone marrow aspirates will be collected at screening and following treatment as outlined in the Time and Events Schedule. Baseline bone marrow aspirate samples will be subjected to DNA and RNA sequencing in order to classify subjects into high-risk molecular subgroups and to establish the myeloma clone for MRD monitoring.

In addition to planned bone marrow aspirate assessments, a whole blood sample will be collected from subjects as outlined in the Time and Events Schedule for assessment of MRD and for processing to plasma and PBMCs.

SAFETY EVALUATIONS

Safety will be measured by adverse events, laboratory test results, ECGs, vital sign measurements, physical examination findings, and assessment of ECOG performance status score.

STATISTICAL METHODS

The sample size calculation is performed on the basis of the following assumption. Based on the published data, the median PFS for Rd arm is assumed to be approximately 26 months. Assuming that DRd can reduce the risk of the disease progression or death by 25%, ie, assuming the hazard ratio (DRd vs. Rd) of 0.724, a total of 390 PFS events is needed to achieve a power of 85% to detect this hazard ratio with a log-rank test (two-sided alpha is 0.05). With a 21-month accrual period and an additional 24-month follow-up, the total sample size needed for the study is approximately 730 (365/arm) subjects. The sample size calculation has taken into consideration an annual dropout rate of 5%.

Long-term survival follow-up will continue until 330 deaths have been observed or 5 years after the last subject is randomized. Therefore, this study will achieve approximately 80% power to detect a 27% reduction in the risk of death (hazard ratio = 0.73) with a log-rank test (two-sided alpha = 0.05).

Response to study treatment and progressive disease will be evaluated by a computer algorithm. For the primary endpoint of PFS, the primary analysis will consist of a stratified log rank test for the comparison of the PFS distribution between the 2 treatment arms. The Kaplan-Meier method will be used to estimate the distribution of overall PFS for each treatment. The treatment effect (hazard ratio) and its two-sided 95% confidence intervals are to be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

TIME AND EVENTS SCHEDULE OVERVIEW

	Notes	Screening Phase	Treatment Phase	EOT	Follow-up Phase	
		within 21 days before randomization	Day 1 of each cycle (28-day cycles)	within 30 days of last dose	Prior to PD	After PD (Q16wks)
Study treatment should be initiated within 72 hours after randomization. Each study visit may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. After EOT, subjects in both treatment arms prior to PD will continue to return for disease evaluations. After PD is documented, subjects will be followed for survival, PFS2; second primary malignancies, and subsequent anticancer therapy. After the clinical cut-off date, disease evaluations are no longer required and data collection will be reduced as per Section 9.1.4.						
Procedures						
Informed consent	ICF must be signed before any study-related procedures					
Eligibility criteria		X				
Demography/ Medical History		X				
Height		X				
Chest X-ray	Acceptable for screening if performed as part of SOC within 42 days before randomization	X				
PFT	Subjects with COPD or asthma, FEV1 should be measured	X				
ECOG		X	Q3mo in year 1, thereafter Q6mo until PD, post PD Wk8, Wk16			
12-lead ECG	Acceptable for screening if performed as part of SOC within 42 days before randomization	X	C3D1, C6D1	X		
Physical exam	including neurological exam	X	symptom and disease directed exam as clinically indicated			
Vital signs, weight		X	Please see following table for details.			
Blood type	A wallet card with the subject's blood type will be provided to subjects randomized to Arm B.		C1D1 predose, Arm B only			
Laboratory Assessments						
Pregnancy test	For women of childbearing potential only. During screening, within 10-14 days prior to first dose and again within 24 hrs prior to first dose. Minimum testing requirements during study: weekly during Cycle 1 and then monthly in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Please refer to Section 9.8 for details.			X		
Hematology		X	Please see following table for details.	X		
Serum chemistry		X	Please see following table for details.	X		
Daratumumab PK	Arm B only. On dara infusion days, 1 sample to be collected before (window -2 hrs) and 1 sample after (window +2 hrs) infusion. Samples to be sent to central laboratory.		C1D1, C6D1, C12D1	Arm B only	8 wks after last dara dose	

Abbreviations at end of table

	Notes	Screening Phase	Treatment Phase	EOT	Follow-up Phase	
		within 21 days before randomization	Day 1 of each cycle (28-day cycles)	within 30 days of last dose	Prior to PD	After PD (Q16wks)
Daratumumab immunogenicity	Arm B only. No additional sample needed; will be taken from PK sample. If an infusion reaction occurs, obtain unscheduled blood sample as soon as possible.		predose C1D1 only	Arm B only	8 wks after last dara dose	
Whole blood	Plasma or PBMC biomarker assessments		predose C1D1 only	X		
Disease Evaluations: Every effort should be made to conduct disease evaluations as per schedule (window ± 7 days). Refer to Section 9.2 for details on efficacy evaluations						
Serum disease evaluations (SPEP)	Sample to be sent to central laboratory. IFE and FLC when CR is suspected or maintained. FLC every cycle for subjects with light chain only myeloma.	X	X (for first 2 years and then every 8 wks until PD)			
Urine disease evaluations (UPEP)	Sample to be sent to central laboratory. IFE when CR is suspected or maintained.	X	X (for first 2 years and then every 8 wks until PD)			
Calcium, albumin, β2-microglobulin	Sample to be sent to central laboratory	X	calcium/albumin every cycle for first 2 years and then every 8wks until PD			
Bone marrow aspirate/biopsy	For screening (up to 42 days before randomization) fresh aspirate/biopsy preferred. If not available, obtain non-decalcified slides or FFPE block. Fresh biopsy and aspirate required to confirm CR/sCR. Samples for biomarker anaylsis to be sent to central laboratory	X	To confirm CR/sCR and at PD (if feasible). For subjects who maintain CR, aspirate will also be obtained at 6 and 12 months +/- 1 month after confirmed CR. A portion of all bone marrow aspirates may be used for other biomarker assessments			
Blood sample for MRD	Whole blood sample to be sent to central laboratory	X	To confirm CR/sCR. For subjects who maintain CR, whole blood sample will also be obtained at 6 and 12 months after confirmed CR.			
Quantitative Ig	See Section 9.2.1.2	X	every 3 months	X		
Assessment of lytic disease	Acceptable for screening if performed within 42 days before randomization	X	As clinically indicated, using the same methodology as used at screening			
Extramedullary plasmacytomas	Subjects with history of plasmacytoma; acceptable for screening if performed within 42 days before randomization	X	If applicable, by physical exam every 4 wks, by radiologic exam (if required) every 12 wks using same methodology as used at screening			
PRO	EORTC-QLQ-30, EQ-5D-5L		Q3mo in year 1, thereafter Q6mo until PD, post PD Wk8, Wk16			
Follow-up						
Survival, PFS2, second primary malignancy, subsequent anticancer therapy						Q16wk
Ongoing Subject Review						
Adverse Events	See Section 12 for detailed instructions.	continuous from the time of signing of ICF until 30 days after last dose of last study drug				
Concomitant Medications	See Section 8 for detailed instructions.	continuous from the time of signing of ICF until 30 days after last dose of last study drug				

Abbreviations at end of table

Abbreviations to Time and Events Tables:
AE=adverse event; C=cycle; COPD=chronic obstructive pulmonary disease; CR=complete response; ECOG=Eastern Cooperative Oncology Group; D=day; Dara=daratumumab; ECG=electrocardiogram; EOT= End-of-Treatment; FEV1= Forced Expiratory Volume (in 1 second); FFPE=formalin-fixed paraffin embedded; FLC=free light chain; ICF=informed consent form; IFE=immunofixation; Ig=immunoglobulin; MRD=minimal residual disease; MRI=magnetic resonance imaging; PBMC= peripheral blood mononuclear cell ; PFT=pulmonary function test; PFS2= time from randomization to progression on the next line of therapy or death, whichever comes first; PK=pharmacokinetics; PD= disease progression; PRO=patient reported outcomes; Q(3)(6)mo=every (3)(6) months; Q16wk=every 16 weeks; SAE=serious adverse event; sCR=stringent complete response; SIPPM= Site Investigational Product Procedures Manual (or equivalent document); SPEP=serum M-protein quantitation by electrophoresis; UPEP=urine M-protein quantitation by electrophoresis; Wk=week

TIME AND EVENTS SCHEDULE, DOSE ADMINISTRATION

	Notes	Cycle 1 and Cycle 2				Cycle 3 to Cycle 6		Cycle 7 and after	EOT
		D1	D8	D15	D22	D1	D15	D1	
The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. The start of each cycle should be scheduled relative to Cycle 1 Day 1 and should not change if visits have shifted within the allowed window.									
Hematology	For Cycle 1 Day 1, no need to repeat tests if they have been performed within the past 5 days. Testing may be performed up to 2 days before other infusion days. Results of hematology tests must be evaluated before each study drug administration. Perform at additional timepoints, as clinically indicated. To be done by local lab.	X	X	X	X	X	X	X	X
Clinical Chemistry		X				X		X	X
Weight	If a subject's weight changes by more than 10% from baseline, the dose of all study treatments will be re-calculated	X				X		X	
Vital Signs	Vital signs (blood pressure, temperature, pulse) measured in sitting position. On Cycle 1 Day 1: immediately before the start of dara infusion; at 0.5, 1, 1.5, 2, 3.5 hrs after the start of the infusion; at end of infusion; and 0.5, 1, 2 hr after end of infusion. For all other infusions, vital signs will be measured immediately before infusion start and at end of dara infusion.	X	X	X	X	X	X	X	
Diary review	Accountability/exposure check	X	X	X	X	X	X	X	X
Pre-infusion Medications, Arm B only									
Dexamethasone	Administer 1 hour before dara infusion. Dexamethasone 40 mg. Substitutions for dexamethasone allowed, see Attachment 6. Paracetamol or acetaminophen 650-1000 mg. Diphenhydramine 25-50 mg or equivalent; on C1D1 administer 12 hours before infusion and again 1 hr before infusion.	X	X	X	X	X	X	X	
Antihistamine		X	X	X	X	X	X	X	
Paracetamol		X	X	X	X	X	X	X	
Study Drug Administration, Arm A and Arm B									
Lenalidomide	Dispense on Day 1 for self-administration.	25 mg daily, Day 1-21 of each cycle (until PD in Arm A, maximum of 2 yrs in Arm B)							
Dexamethasone	Dispense on Day 1 for self-administration.	40mg PO Day 1, 8, 15, 22 of each cycle. Not required in Arm B on daratumumab infusion days.							
Study Drug Administration, Arm B Only									
Daratumumab	Refer to SIPPM for recommendations on daratumumab infusion rate. For windows see Table 3.	X	X	X	X	X	X	X	

ABBREVIATIONS

ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
ALT	alanine aminotransferase
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
CDC	complement-dependent cytotoxicity
CL	total systemic clearance
Cmax	maximum observed concentration
Cmin	minimum observed concentration
COPD	chronic obstructive pulmonary disease
CR	complete response
sCR	stringent complete response
CrCl	creatinine clearance
CT	computed tomography
D_{LCO}	diffusing capacity of the lung for carbon monoxide
DLT	dose limiting toxicity
DRd	daratumumab with lenalidomide plus low-dose dexamethasone
eCRF	electronic case report form
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDC	electronic data capture
EOT	end of treatment
EU	European Union
FEV	forced expiratory volume
FFPE	formalin fixed paraffin embedded
FLC	free light chain
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
HIV	human immunodeficiency virus
HR	hazard ratio
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFE	immunofixation
Ig	immunoglobuin
IHC	immunohistochemistry
IMiD	immunomodulatory agent
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MP	melphalan-prednisone
MPT	melphalan-prednisone-thalidomide
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
NK	natural killer
OR	overall response

ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PC	plasma cell
PD	disease progression
PFS	progression free survival
PFS2	time from randomization to progression on the next line of therapy or death, whichever comes first
PI	proteasome inhibitor
PK	pharmacokinetics
PO	per oral
PQC	Product Quality Complaint
PR	partial response
PRO	patient-reported outcome(s)
QD	once daily
QIg	quantitative immunoglobulins
RBC	red blood cell
Rd	lenalidomide plus low-dose dexamethasone
REMS	Risk Evaluation and Mitigation Strategy
SAE	serious adverse event
SCT	stem cell transplantation
SIPPM	Site Investigational Product Procedures Manual (or equivalent document)
SPEP	serum M-protein quantitation by electrophoresis
TTP	time to progression
ULN	upper limit of normal
UPEP	urine M-protein quantitation by electrophoresis
US	United States
V	volume of distribution
Vd	VELCADE-dexamethasone
VGPR	very good partial response
VMP	VELCADE-melphalan-prednisone
VMPT	VELCADE-melphalan-prednisone-thalidomide
VP	VELCADE-prednisone
VTP	VELCADE-thalidomide-prednisone
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

1.1.1. Multiple Myeloma

Multiple myeloma is a malignant disorder of the plasma cells, characterized by uncontrolled and progressive proliferation of a plasma cell clone. The disease leads to progressive morbidity and eventual mortality by lowering resistance to infection and causing significant skeletal destruction (with bone pain, pathological fractures, and hypercalcemia), anemia, renal failure, neurological complications and hyperviscosity syndrome.

The majority of patients with multiple myeloma produce a monoclonal protein, also called paraprotein, M-protein or M-component, which is an immunoglobulin (Ig) or a fragment of one that has lost its function (Kyle 2009, Palumbo 2011).[13,23] Normal immunoglobulin levels are compromised, leading to susceptibility of infections. The proliferating multiple myeloma cells displace the normal bone marrow leading to dysfunction in normal hematopoietic tissue and destruction of the normal bone marrow architecture, which is reflected by clinical findings such as anemia, paraprotein in serum or urine, and bone resorption seen as diffuse osteoporosis or lytic lesions shown in radiographs (Kyle 2003).[12] Furthermore, hypercalcemia, renal insufficiency or failure, and neurological complications are frequently seen (Palumbo 2011).[21] A small minority of patients with multiple myeloma are non-secretory.

At the time of diagnosis, multiple myeloma is a heterogeneous disease, with a course that varies on the basis of both disease- and host-related factors (eg, age, renal function, stage, chromosomal abnormalities). Multiple myeloma causes significant morbidity and mortality. It accounts for approximately 1% of all malignancies and 13% of hematologic cancers. Approximately 50,000 patients per year are diagnosed with multiple myeloma in the EU and US, and 30,000 patients per year die due to multiple myeloma (ACS 2013, Ferlay 2010).[1,6]

1.1.2. Treatment Options for Multiple Myeloma

Treatment choices for multiple myeloma vary with age, performance status, comorbidity, the aggressiveness of the disease, and related prognostic factors (Palumbo 2011).[21] 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 high-dose chemotherapy and autologous stem cell transplantation (ASCT). For those not considered suitable for high-dose chemotherapy and ASCT, longer-term treatment with multi-agent combinations including alkylators, high-dose steroids, and novel agents are currently considered as standards of care.

The availability of different efficacious multi-agent regimens has provided clinicians with the opportunity of tailoring treatment for each patient. Selection is based on patients' comorbidities and biologic age, while at the same time, taking into account the expected toxicity profiles of each treatment regimen (Gay 2011).[7]

1.1.3. Transplant-ineligible Population

In general, patients over the age of 65 or with significant comorbidities are usually not considered eligible for more intensive forms of first line therapy, and as a result the treatment approach often favors longer, less-intensive/toxic treatments (Gay 2011).[7] Treatment traditionally consists of systemic chemotherapy, with adjunctive use of radiation or surgery in selected cases associated with extramedullary disease (NCCN 2013, Palumbo 2009, Smith 2005).[18,23,26] For many years, the oral combination melphalan-prednisone (MP) was considered the standard of care for patients with multiple myeloma who were not eligible for ASCT (Gay 2011).[7] The advent of immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs) has led to a multiplicity of new treatment options for newly diagnosed patients not considered suitable for transplant based therapy.

Most recently, the results of the MM-20/IFM 07-01 trial were presented at the American Society of Hematology Meeting in December 2013 (Facon, 2013).[5] In this Phase 3 protocol, non-transplant eligible patients with newly diagnosed myeloma were randomized to either melphalan-prednisone-thalidomide (MPT) or lenalidomide + low-dose dexamethasone (Rd). Patients who received Rd until disease progression had an improved outcomes compared to those randomized to MPT, with a 28% reduction in the risk of progressive disease or death (median: 25.5 months, HR=0.72; p=0.00006). Secondary endpoints including duration of response and overall response were superior in the Rd cohorts. The safety profile of Rd was manageable, with reduced hematologic second primary malignancies compared with MPT. In the oral presentation at ASH 2013, the authors indicated that overall survival for patients who received Rd until disease progression was 59.4%, based on landmark analysis at 4 years.

1.2. Daratumumab

Daratumumab is a human IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38, such as plasma cells from patients with multiple myeloma. This target is distinct from those of other approved agents for multiple myeloma therapy.

For the most comprehensive nonclinical and clinical information as well as Reference Safety Information regarding daratumumab, refer to the latest version of the Investigator's Brochure (Daratumumab IB).[10]

1.2.1. Nonclinical Studies

Based on preclinical data, daratumumab may utilize multiple effector cell functions, resulting in immune mediated killing of tumor cells. In ex vivo experiments utilizing human bone marrow stromal cells co-cultured with primary multiple myeloma cells, complement-dependent cytotoxicity (CDC) occurs rapidly and demonstrates maximal myeloma cell killing by daratumumab within 1 hour of antibody-mediated activation of the complement proteins (de Weers 2011).[3] Daratumumab-induced antibody-dependent cell-mediated cytotoxicity (ADCC) is slower in its action, with maximal ADCC by daratumumab observed at 4 hours in vitro (de Weers 2011).[3] Daratumumab has also been shown to induce antibody-dependent cellular

phagocytosis (ADCP) in the presence of macrophages within 4 hours in vitro (Overdijk 2013).[20] The precise role of some or all of these effector functions in reducing tumor burden in patients is unknown.

In toxicology studies in cynomolgus monkeys and chimpanzees, the major observed toxicities were cytokine release syndrome and thrombocytopenia. A minor decrease in red blood parameters was also observed. Cytokine release was seen only following the first dose and was markedly reduced following implementation of a 10-mg predose of daratumumab. The effect on platelets and red blood cells was reversible.

1.2.2. Clinical Studies

1.2.2.1. Single-Agent Daratumumab Studies (GEN501 and MMY2002)

Two single-agent studies with daratumumab are ongoing (Studies GEN501 and MMY2002), as described in Table 1.

Table 1: Daratumumab Single-Agent Studies GEN501 and MMY2002

<table>
<tr><th>Study Number</th><th>Study Design</th><th colspan="2">Number of subjects Treated/
Treatment Regimen</th></tr>
<tr><td rowspan="4">GEN501</td><td rowspan="4">Open-label, Phase 1/2, first-in-human, single-agent study in subjects with multiple myeloma whose disease is relapsed or refractory to at least 2 prior lines of therapies

Population was heavily treated with prior treatment, including ASCT, chemotherapy based regimens, IMiDs, and PIs</td><td colspan="2"><u>Part 1</u>
n=32 total treated with daratumumab weekly

0.005-1 mg/kg (n=17)
2 mg/kg (n=3)
4 mg/kg (n=3)
8 mg/kg (n=3)
16 mg/kg (n=3)
24 mg/kg (n=3)</td></tr>
<tr><td colspan="2"><u>Part 2</u>
n=51 total treated</td></tr>
<tr><td>8 mg/kg (n=30)

Weekly for 8 weeks, followed by q2w for an additional 16 weeks, and monthly thereafter</td><td>16 mg/kg (n=21)

First dose, followed by a 3-week resting period, followed by weekly doses for 7 weeks, then q2w for an additional 14 weeks, and monthly thereafter</td></tr>
<tr><td></td><td></td></tr>
<tr><td rowspan="2">MMY2002</td><td rowspan="2">Open-label, multicenter, 2-stage, Phase 2 study of daratumumab for the treatment of subjects with multiple myeloma who have received at least 3 prior lines of therapy including a PI and an IMiD or whose disease is double refractory to both a PI and an IMiD</td><td colspan="2">n=34 total treated in Stage 1</td></tr>
<tr><td>8 mg/kg (n=18)
q4w</td><td>16 mg/kg (n=16)
qw for 8 weeks, then q2w for another 16 weeks, and then q4w thereafter</td></tr>
<tr><td colspan="3">ASCT= autologous stem cell transplantation; ImiD=immunomodulatory agent; PI=proteasome inhibitor; q2w=every 2 weeks; q4w=every 4 weeks</td></tr>
</table>

Among the 32 subjects treated in Part 1 of Study GEN501, the maximum tolerated dose (MTD) was not reached following intravenous (IV) infusions up to 24 mg/kg. Two subjects experienced dose-limiting toxicities (DLTs) in the lower dose cohorts (a subject in the 0.1-mg/kg group had Grade 3 anemia and Grade 4 thrombocytopenia, and a subject in the 1.0-mg/kg group had Grade 3 aspartate aminotransferase increased).

Among the 51 subjects treated in Part 2 of Study GEN501, serious adverse events (SAEs) were reported in 37% of subjects (43% of subjects in the 8-mg/kg group and 29% of subjects in the 16 mg/kg-group). The most frequently reported SAEs were pneumonia (6% subjects), and pyrexia (4% of subjects).

Among the 34 subjects treated in Stage 1 of Study MMY2002, SAEs were reported in 27% of subjects (33% of subjects in the 8 mg/kg group, and 19% of subjects in the 16 mg/kg group). The most frequently reported SAE was renal failure acute (6% of subjects).

1.2.2.2. Combination Daratumumab Studies

One study of daratumumab in combination with lenalidomide and dexamethasone (Study GEN503), and one study of daratumumab in combination with various backbone treatment regimens (Study MMY1001) are ongoing (Table 2).

Table 2: Daratumumab Combination Studies GEN503 and MMY1001

Study Number	Study Design	Treatment Regimen	Status/Estimated Start Date Number of subjects Treated/Planned
GEN503	Open-label, Phase 1/2 multicenter, dose-escalating study investigating the safety of daratumumab in combination with lenalidomide and dexamethasone in subjects with relapsed or refractory multiple myeloma	Phase 1: 2-16 mg/kg daratumumab, in combination with lenalidomide (25 mg daily Days 1-21 of 28 days) and dexamethasone (40 mg weekly)	Part 1: Ongoing (n=13 subjects treated) 2 mg/kg (n=3) 4 mg/kg (n=3) 8 mg/kg (n=4) 16 mg/kg (n=3)
		Phase 2: 16 mg/kg daratumumab, in combination with lenalidomide (25 mg daily Days 1-21 of 28 days) and dexamethasone (40 mg weekly)	Part 2: n=18 subjects treated approximately 30 subjects planned
MMY1001	Open-label, non-randomized, multicenter, Phase 1b study to evaluate the safety, tolerability, and dose regimen of daratumumab in combination with various backbone treatment regimens for multiple myeloma in either newly diagnosed or those who have received at least 2 prior therapies, depending on backbone treatment regimen	Daratumumab 16 mg/kg (initially, with possibility to de-escalate, if necessary) The backbone regimens to be combined with daratumumab include VELCADE-dexamethasone (VD), VMP, VTD, and Pom-dex	n=18 subjects treated[1] VTD (n=6) VMP (n=5) Vd (n=1) Pom-dex (n=6) approximately 80 subjects planned

1. As of 21May2014

Pom-dex=pomalidomide-dexamethasone; VMP-VELCADE-melphalan-prednisone; VTD=VELCADE-thalidomide-dexamethasone

Based on preliminary efficacy data, 15 of 20 efficacy evaluable subjects in Study GEN503 have achieved a PR or better following treatment with daratumumab in combination with lenalidomide and dexamethasone.

The safety profile observed in Study GEN503 is consistent with historical safety data for lenalidomide and dexamethasone. Doses ranged from 2 mg/kg to 16 mg/kg daratumumab, in combination with the approved doses of lenalidomide (25 mg daily Days 1-21 of 28 days) and dexamethasone (40 mg weekly). No dose-limiting toxicity (DLT) drug-related safety signals have been observed in this heavily pre-treated population of subjects with advanced multiple myeloma. The Part 2 daratumumab dose was determined to be 16 mg/kg. Across all dose cohorts in Part 1 and in the 16 mg/kg expansion cohort for Part 2, the most frequently reported Grade 3 or higher AE was neutropenia (6 subjects), which is a known toxicity of lenalidomide. Eight serious adverse events (SAEs) have been reported. All SAEs were assessed by the investigator as not related to daratumumab. Four subjects experienced infusion-related reactions during the first infusion of daratumumab. These events were determined by the investigator to be related to daratumumab. In all instances, daratumumab was interrupted temporarily and restarted without complication or further incident.

Planned Phase 3 combination studies include a Phase 3 study (MMY3003) comparing daratumumab, lenalidomide, and dexamethasone with Rd and a Phase 3 study (MMY3004) comparing daratumumab, VELCADE, and dexamethasone with Vd. Both studies are in patients with relapsed or refractory multiple myeloma and are planned to start in the second half of 2014.

1.3. Lenalidomide

Lenalidomide is an immunomodulatory (IMiD) agent that is thought to mediate antimyeloma activity by 3 main mechanisms: 1) direct antitumor effect; 2) inhibition of the microenvironment support for tumor cells; and 3) an immunomodulatory role (Kotla, 2009).[11] Direct tumor effect is described both as growth inhibition of myeloma cell lines and induction of apoptosis. The microenvironment support is affected by downregulation of cell adhesion molecules (eg, intercellular adhesion molecule), thus inhibiting stromal cell interaction with tumor cells, and inhibition of growth factors (eg, insulin growth factor 1 and vascular endothelial growth factor) induced by myeloma cell adhesion. Finally, lenalidomide exhibits immunomodulatory activity including inhibition of proinflammatory signaling molecules (cytokines) such as tumor necrosis factor α, IL-1β, and IL-6, the latter of which is a known growth factor for myeloma cells (Vallet, 2008).[29]

Importantly, it has also been shown that lenalidomide causes upregulation of natural killer (NK) cells in myeloma (Kotla, 2009)[11] and enhances the effector cells of ADCC (Tai 2005, Tai 2008).[28,27]

Lenalidomide is currently approved in the US and EU for the treatment for relapsed/refractory myeloma. However, there is accumulating evidence that lenalidomide is an effective treatment strategy for new diagnosed patients as well. The Eastern Cooperative Oncology Group (ECOG) published a trial in which patients with newly diagnosed myeloma were randomized to either

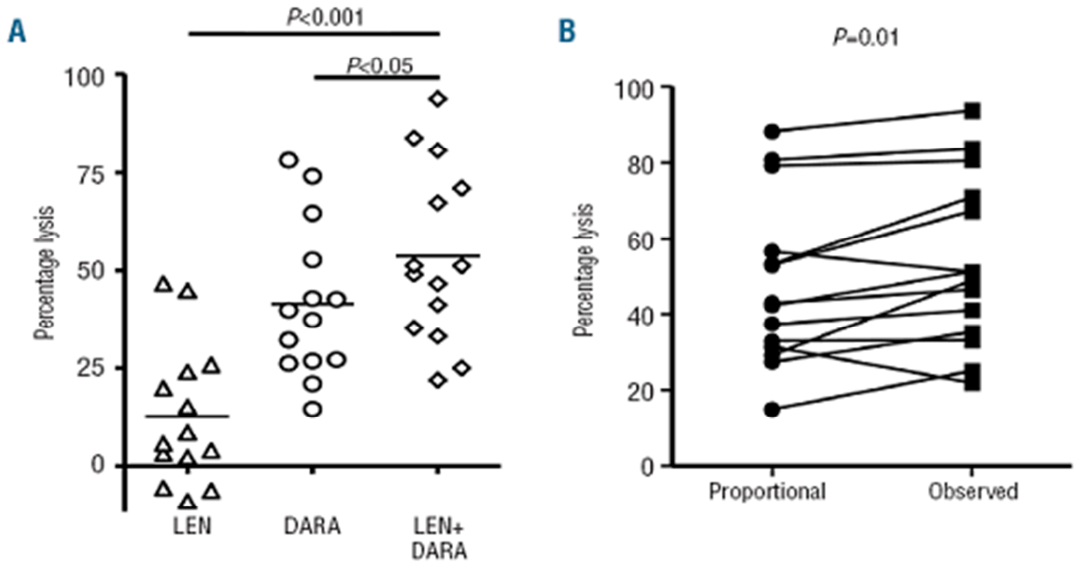
high-dose (160 mg/week) or low-dose (40 mg/week) dexamethasone in combination with lenalidomide (Rajukumar, 2010).[24] Patients randomized to the low-dose dexamethasone treatment arm had an improved overall survival at one year (96% vs 87%). In terms of response rates, patients in the low-dose cohort had an overall response rate (≥PR) of 68.3%. Median time to progression was 26.1 months in the low dose group.

A large, randomized Phase 3 study (MM-020/IFM 07-01) compared lenalidomide and low-dose dexamethasone (Rd) given until disease progression (Arm A) or for eighteen 28-day cycles (Arm B) with melphalan-prednisone-thalidomide (MPT, Arm C) in subjects newly diagnosed with multiple myeloma (Facon 2013).[5] Continuous treatment with Rd (Arm A) significantly improved the primary endpoint of PFS compared with MPT (Arm C). Secondary endpoints (overall response rate [ORR], defined as PR or better, DOR, and PFS2) consistently showed improvement in favor of Arm A over Arm C. The safety profile of Rd was manageable, with reduced hematologic second primary malignancies compared with MPT.

1.4. Lenalidomide and Daratumumab

Preclinically, using bone marrow mononuclear cells from patients with multiple myeloma, increased killing of tumor cells was demonstrated when daratumumab was combined with lenalidomide as compared with that of either agent alone as shown in (Figure 1A) (van der Veer, 2011a).[30] Notably, daratumumab and lenalidomide acted in a synergistic fashion to generate an extra effect (Figure 1B).

Figure 1: Improvement of Daratumumab-induced Antibody-dependent Cell-mediated Cytotoxicity by Lenalidomide in Bone Marrow Mononuclear Cells from Patients with Multiple Myeloma



Key: DARA = daratumumab; LEN = lenalidomide; MM = multiple myeloma.
(A) Bone marrow mononuclear cells of 14 patients with multiple myeloma were incubated for 47 hours with the control antibody, with lenalidomide (3 μM), and/or daratumumab (0.1 μg/mL). Surviving multiple myeloma cells were enumerated by Fluorescence-activated Cell Sorting analysis of CD138+ cells. The percentages of lysis of multiple myeloma cells treated with lenalidomide, daratumumab, and lenalidomide + daratumumab were calculated by the Tukey's post hoc analysis of repeated measures analysis of variance.
(B) The observed effect (% lysis) of the combination treatment was compared with the expected additive effect (proportional) of the combined treatments. Mixed model analysis supported the conclusion that the combination treatment was synergistic.

Finally, it was demonstrated that peripheral blood mononuclear cells isolated from patients during or just after lenalidomide treatment showed a significantly increased capacity to mediate daratumumab-dependent ADCC against multiple myeloma cells alone (van der Veer, 2011a).[30]

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

1.5. Overall Rationale for the Study

Multiple myeloma remains incurable with standard chemotherapy, despite the availability of multi agent therapy. Strategies directed at improving and maintaining response for longer periods of time and new treatment options directed at alternative mechanisms are also urgently needed for patients with multiple myeloma.

Recent studies have indicated that multiple drug combinations are superior over single- or double-agent combinations in treating multiple myeloma (van der Veer 2011b).[31] The addition of new drugs to available regimens can mediate their clinical benefit because of the induction of a higher rate of initial CRs, which then improves relapse-free and overall survival. Contingent on the premise that the combined agents have non-overlapping and synergistic MoAs, the immediate and effective targeting of the tumors with multiple agents appears to be a successful strategy in improving the clinical outcome of multiple myeloma therapy. Such a strategy is in agreement with the emerging concept that the genetic signature of multiple myeloma, and consequently the patient's susceptibility to a specific agent, will be highly heterogeneous, which may lead to drug resistance. Nevertheless, the CR rate of the best chemotherapeutic combinations is currently <50%, and all current combination therapies eventually induce drug resistance.

Based on data from ongoing studies with and the safety information in the label for lenalidomide, the expected safety profile of daratumumab in this combination therapy study is considered manageable. To date, 31 subjects have been treated in Study GEN503, an open-label, Phase 1/2 multicenter, dose-escalating study investigating the safety of daratumumab in combination with lenalidomide and dexamethasone in subjects with relapsed or refractory multiple myeloma. No DLTs have been reported, and the safety profile is consistent with what has been previously reported for lenalidomide monotherapy. Data from several clinical studies support the choice of 16mg/kg as the daratumumab dose to be administered in this study. Based upon the pre-clinical synergism observed, and the promising clinical data in the relapsed/refractory setting, this is a rational combination to investigate in newly diagnosed patients.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective is to compare the efficacy of daratumumab when combined with lenalidomide and dexamethasone (DRd) to that of lenalidomide and dexamethasone (Rd), in terms of progression-free survival (PFS) in subjects with newly diagnosed myeloma who are not candidates for high dose chemotherapy and autologous stem cell transplant.

Secondary Objectives

The secondary objectives are:

- To evaluate clinical outcomes including:
  - Time to disease progression (TTP)
  - Stringent CR (sCR) rate
  - CR rate
  - PFS2 (defined as time from randomization to progression on the next line of therapy or death, whichever comes first)

  - Time to next treatment
  - Overall response rate (CR + partial response [PR] rate)
  - Proportion of subjects who achieve very good partial response (VGPR) or better
  - Duration of response
  - Overall survival
- To assess the safety and tolerability of daratumumab when administered in combination with Rd.
- To assess the pharmacokinetics of daratumumab in combination with Rd.
- To assess the immunogenicity of daratumumab.
- To evaluate treatment effects on patient reported outcomes and heath economic/resource utilization
- To determine the ability of daratumumab to reduce minimal residual disease (MRD)
- To evaluate the clinical efficacy of daratumumab combination with Rd in high-risk molecular subgroups

Exploratory Objective

- To explore biomarkers predictive of response and resistance to therapy

2.2. Hypothesis

The primary hypothesis of this study is that daratumumab in combination with Rd will prolong PFS as compared with Rd alone in subjects with newly diagnosed multiple myeloma who are ineligible for high dose chemotherapy and autologous stem cell transplant.

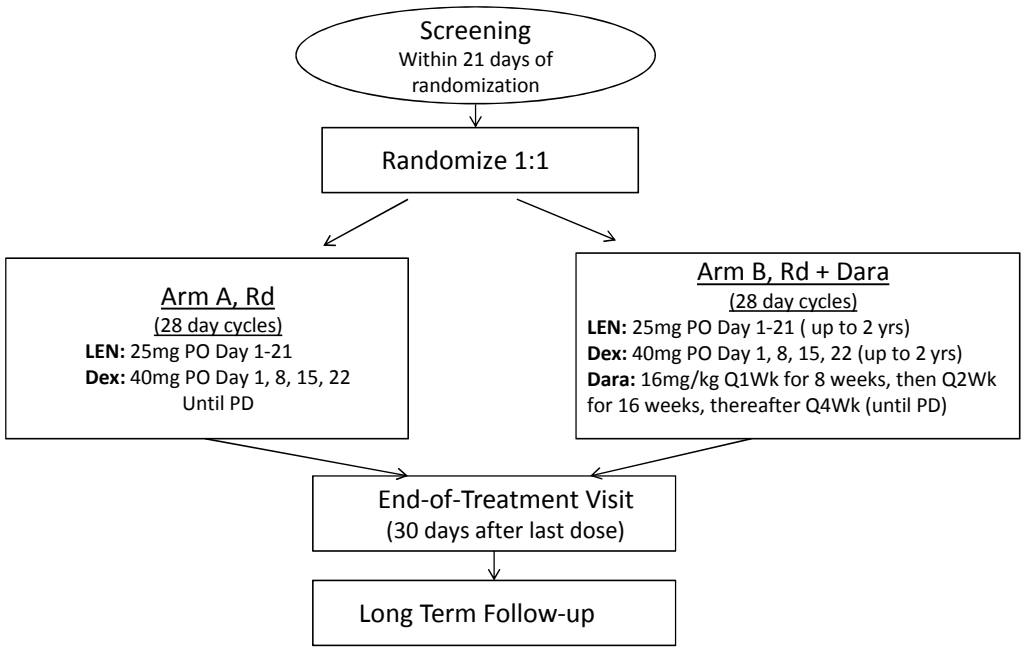
3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, open-label, active controlled, parallel-group, multicenter study in subjects at least 18 years of age with newly diagnosed multiple myeloma who are not candidates for high dose chemotherapy and ASCT. Approximately 730 subjects will be enrolled in this study with 365 subjects planned per treatment arm.

A diagram of the study design is provided in Figure 2.

Figure 2: Schematic Overview of the Study



Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 21 days before Cycle 1, Day 1. The Treatment Phase will extend from Day 1 of Cycle 1 until discontinuation of all study treatment. For subjects assigned to DRd, daratumumab will be administered weekly for the first 2 cycles of treatment and then every other week for 16 weeks, then monthly. This will equate to 9 consecutive weeks of dosing at the start of the study and a total of 23 doses in the first year. Lenalidomide will be administered at a dose of 25 mg orally (PO) on Days 1 through 21 of each 28-day cycle, and dexamethasone will be administered at a dose of 40 mg once a week for both treatment groups. Subjects in the DRd arm will receive lenalidomide/dexamethasone for a maximum of two years; those in the Rd arm will continue lenalidomide/dexamethasone until progression of disease. In the DRd arm, subjects will continue on daratumumab until progression of disease. Randomization will be stratified by International Scoring System (I vs II vs III), region (North America vs Other), and age (<75 vs ≥75), using an equal allocation ratio of 1:1.

Measures to prevent cytokine release syndrome will include preinfusion medication with dexamethasone, paracetamol, and an antihistamine before each daratumumab infusion.

The Follow-up Phase will begin once a subject discontinues all study treatments. Subjects who discontinue for reasons other than disease progression must continue to have disease evaluations according to the Time and Events Schedule. The Follow-up Phase will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first. After the clinical cut-off (see below for definition), data collection will be reduced as per Section 9.1.4.

Two interim analyses are planned. The first interim analysis, with a purpose to evaluate safety, will be performed after a total of approximately 100 subjects have been treated for at least 8 weeks or discontinued the study treatment. The second interim analysis will be performed when 234 PFS events, which is 60% of the total planned events, have been accumulated. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. The significance level at this interim analysis to establish the superiority of DRd over Rd with regard to PFS will be determined based on the observed number of PFS events at the interim analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. If the experimental arm (DRd) is numerically worse than the control arm in terms of PFS (observed hazard ratio > 1 favoring the control arm), then the study may be terminated for futility.

The primary PFS analysis will occur when approximately 390 PFS events have been observed. The date established for the primary PFS analysis will serve as the clinical cut-off date, after which data collection in the study will be reduced as per Section 9.1.4. Investigators will be informed when each interim analysis is to occur.

The end of the study will occur when 330 subjects have died, or 5 years after the last subject is randomized, whichever comes first. The sponsor will ensure that subjects benefiting from treatment with daratumumab will be able to continue treatment after the end of the study.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study to review efficacy and safety results at the planned interim analyses. After the interim review, they will make recommendations regarding the continuation of the study. In addition, the IDMC may also review cumulative safety data every 6 months besides the two interim analyses.

Assessment of tumor response and disease progression will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria. An assessment of MRD will be conducted on whole blood and bone marrow samples. Safety evaluations will include AE monitoring, physical examinations, electrocardiogram (ECG) monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status. Blood samples will be drawn for assessment of pharmacokinetic parameters.

3.2. Study Design Rationale

Rationale for Duration of Lenalidomide Administration

Lenalidomide and dexamethasone are commonly given in the front-line setting in the US. Based upon the MM-020 study (Facon, 2013),[5] the front-line treatment paradigm in the EU will likely evolve to include Rd in the future. The Facon study showed that treatment until progression conferred clinical benefit over treatment for a fixed duration of time. A retrospective analysis of two Phase 3 trials, one administering a lenalidomide based regimen and one administering a VELCADE based regimen, also showed that PFS1, PFS2, and OS were all significantly longer following continuous treatment to progression (Palumbo, 2014).[22] This was observed regardless

of the particular chemotherapy backbone. Taken together, these data support the principle of treatment until progression.

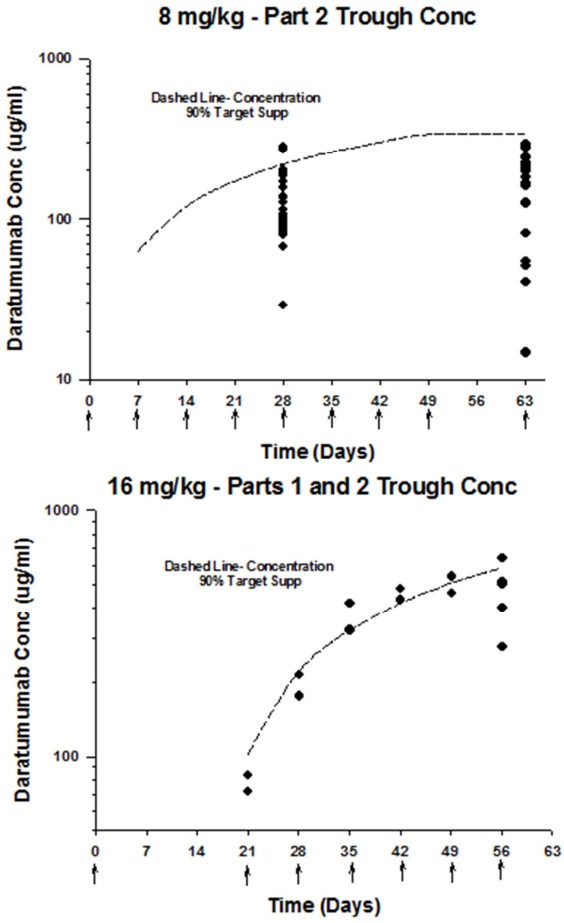
In the current study, treatment with Rd will continue until disease progression in the control arm (Arm A). This treatment duration is consistent with best current clinical practice based on the above published results.

In the experimental arm (Arm B), treatment with daratumumab will continue until disease progression, in keeping with the principle of treatment until progression, while discontinuing Rd after 24 months. This strategy isolates the efficacy and safety of daratumumab from continued exposure to Rd. Treatment with Rd for 2 years in the experimental arm approximates the reported median PFS of 25 months (Rajkumar, 2010; Facon, 2013)[24,5] and should ensure comparable lenalidomide exposure in both arms. In the Facon study, 13% of subjects had discontinued Rd at 18 months due to toxicity, and only 39% of subjects were still on treatment at 24 months, illustrating the challenge of balancing continued treatment with developing toxicity. The 2 year treatment period is expected to minimize potential long-term side effects of chemotherapy and will make it possible to attribute additional benefit in the experimental arm to daratumumab.

Rationale for Daratumumab Dose

CD38, the target for daratumumab, is expressed on NK cells and clinical data has shown NK cell suppression to be a marker of on target drug activity. Clinical pharmacokinetic data have shown the 16 mg/kg dose to be the lowest dose that results in complete target suppression at all timepoints. This dose and schedule continuously suppressed NK cells throughout dosing. Daratumumab maximal target suppression is presented in Figure 3.

Figure 3: Daratumumab Maximal Target Suppression



8mg/kg: Observed trough concentration values below predicted 90% suppression throughout dosing

16mg/kg: Observed trough concentration values at 90% suppression throughout dosing

The ORR appeared higher for the 16mg/kg dose compared with the 8 mg/kg dose, based on early preliminary data from Part 2 of Study GEN501 and from Study MMY2002 (both ongoing studies) as of a cutoff date of 24 January 2014. In Study GEN501, the ORRs (ie, PR or greater) were 11% and 40% for the 8 mg/kg (n=28) and 16 mg/kg (n=15) dose regimens, respectively. For Study MMY2002, the unconfirmed ORRs for the 8 mg/kg and 16 mg/kg dose regimens were similar to those observed in GEN501. In addition, VGPRs were observed for 7 of 30 subjects treated with the 16 mg/kg dose in the 2 studies. VGPR had not been observed at lower dose levels. These preliminary data support that full target saturation at the 16 mg/kg dose is needed to achieve higher and deeper response rates.

Rationale for DNA and Biomarker Collection

Biomarker samples will be collected to evaluate the depth of clinical response to daratumumab through evaluation of MRD, using DNA sequencing of immunoglobulin genes, and to determine response rates in specific molecular subgroups of multiple myeloma, using DNA/RNA sequencing of MM cells to allow for assessment of high–risk genomics such as deletion 17p, t(4;14), t(14;20), t(14;16), deletion13, GEP signatures such as UAMS-70, and mutations in p53, BRAF, FGFR, IGH, PI3K, or other molecular subtypes associated with disease progression.

Other biomarker goals include evaluation of potential mechanisms of resistance, inter-individual variability in clinical outcomes or identification of population subgroups that respond differently to treatment.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 21 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. Subject must be at least 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place).

2. Subject must have documented multiple myeloma satisfying the CRAB criteria (see Attachment 1) and measurable disease defined as:

   - Monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma
   - Measurable disease as defined by any of the following:
     - IgG myeloma: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
     - IgA, IgM, IgD, or IgE multiple myeloma: serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or
     - Light chain multiple myeloma: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.

3. Newly diagnosed and not considered candidate for high-dose chemotherapy with SCT due to:

   - Being age ≥65 years, OR
   - In subjects <65 years: presence of important comorbid condition(s) likely to have a negative impact on tolerability of high dose chemotherapy with stem cell transplantation. Sponsor review and approval of subjects under 65 years of age is required before randomization.

4. Subject must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 (refer to Attachment 2)

5. Subject must have pretreatment clinical laboratory values meeting the following criteria during the Screening Phase:

   a) hemoglobin ≥7.5 g/dL (≥5 mmol/L; prior red blood cell [RBC] transfusion or recombinant human erythropoietin use is permitted);

   b) absolute neutrophil count (ANC) ≥1.0 x 10^9/L (GCSF use is permitted);

   c) platelet count ≥70 x 10^9/L for subjects in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count >50 × 10^9/L (transfusions are not permitted to achieve this minimum platelet count).

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

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

   f) total bilirubin ≤1.5 x ULN, except in subjects with congenital bilirubinemia, such as Gilbert syndrome;

   g) measured creatinine clearance >30 mL/min/1.73 mm^2 (please refer to Attachment 3)

   h) corrected serum calcium <14 mg/dL (<3.5 mmol/L); or free ionized calcium <6.5 mg/dL (<1.6 mmol/L) (Attachment 4)

6. Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously. This includes one highly effective form of contraception (tubal ligation, intrauterine device [IUD], hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy

7. A man who is sexually active with a woman of childbearing potential must agree to use a latex or synthetic condom, even if they had a successful vasectomy. All men must also not donate sperm during the study, for 4 weeks after the last dose of lenalidomide, and for 4 months after the last dose of daratumumab.

8. A woman of childbearing potential must have 2 negative serum or urine pregnancy tests at Screening, first within 10 to 14 days prior to dosing and the second within 24 hours prior to dosing. For requirements during the Treatment Phase, please see Section 4.3.

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

4.2. Exclusion Criteria

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

1. Subject has a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma. Monoclonal gammopathy of undetermined significance is defined by presence of serum M-protein <3 g/dL; absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the M-protein; and (if determined) proportion of plasma cells in the bone marrow of 10% or less (Kyle 2003).[12] Smoldering multiple myeloma is defined as asymptomatic multiple myeloma with absence of related organ or tissue impairment end organ damage (Kyle 2003, Kyle 2007).[12,14]

2. Subject has a diagnosis of Waldenström's disease, or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions.

3. Subject has prior or current systemic therapy or SCT for multiple myeloma, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for a maximum 4 days) of corticosteroids before treatment.

4. Subject has a history of malignancy (other than multiple myeloma) within 5 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 5 years).

5. Subject has had radiation therapy within 14 days of randomization.

6. Subject has had plasmapheresis within 28 days of randomization.

7. Subject is exhibiting clinical signs of meningeal involvement of multiple myeloma.

8. Subject has known chronic obstructive pulmonary disease (COPD) (defined as a forced expiratory volume [FEV] in 1 second <60% of predicted normal), persistent asthma, or a history of asthma within the last 2 years (intermittent asthma is allowed). Subjects with known or suspected COPD or asthma must have a FEV1 test during screening.

9. Subject is known to be seropositive for history of human immunodeficiency virus (HIV) or known to have active hepatitis B or hepatitis C.

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

11. Subject has clinically significant cardiac disease, including:

    - myocardial infarction within 1 year before randomization, or an unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV
    - cardiac arrhythmia (NCI CTCAE Version 4 Grade ≥2) or clinically significant ECG abnormalities
    - screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >470 msec

12. Subject has known allergies, hypersensitivity, or intolerance to lenalidomide, corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to respective package inserts or Investigator's Brochure), or known sensitivity to mammalian-derived products.

13. Subject has plasma cell leukemia (according to WHO criterion: ≥20% of cells in the peripheral blood with an absolute plasma cell count of more than 2×10^9/L) or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

14. Subject is known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder). Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. Subject is taking any prohibited medications as per Section 8.3

15. Subject is a woman who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study, within 4 weeks after the last dose of lenalidomide, or within 4 months after the last dose of daratumumab. Or, subject is a man who plans to father a child while enrolled in this study, within 4 weeks after the last dose of lenalidomide, or within 4 months after the last dose of daratumumab.

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

17. Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before randomization or is currently enrolled in an interventional investigational study.

18. Subject has contraindications to required prophylaxis for deep vein thrombosis and pulmonary embolism.

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

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 17.4, 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.

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. For restrictions related to concomitant medications, please refer to Section 8.3.

1. For women of childbearing potential, adequate contraception as specified in Section 4.1 must continue during the Treatment Phase, during any dose interruptions, for 4 weeks after the last dose of lenalidomide, and for 4 months after the last dose of daratumumab. All women must not donate ova during the study, for 4 weeks after the last dose of lenalidomide, and for 4 months after the last dose of daratumumab.

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

3. A man who is sexually active with a woman of childbearing potential must always use a latex or synthetic condom during the study, for 4 weeks after discontinuing lenalidomide, and for 4 months after discontinuing daratumumab (even if they have undergone a successful vasectomy). All men must not donate sperm during the study, for 4 weeks after the last dose of lenalidomide, and for 4 months after the last dose of daratumumab.

4. Because of the embryo-fetal risk of lenalidomide, all subjects must adhere to the local lenalidomide REMS program (when lenalidomide is supplied locally), or the lenalidomide Global Pregnancy Prevention Plan provided in Attachment 5 (when lenalidomide is supplied centrally and no local lenalidomide REMS program exists).

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

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

7. **Blood Typing**: CD38 is expressed on erythrocytes to a minor extent. Hemolysis could occur following the infusion of daratumumab, which would confound a blood type assessment. To guard against this risk, in case of an urgent need for blood transfusion, the subject's blood type, including minor group, must be assessed before the first infusion of daratumumab. Subjects in Arm B must agree to carry a card at all times indicating their blood type.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Eligible subjects will be stratified by International Scoring System (I vs II vs III), region (North America vs Other), and age (<75 vs ≥75) and then randomized to treatment in a 1:1 ratio to either Treatment Arm A (Rd alone) or Treatment Arm B (daratumumab+Rd [DRd]). The method of randomization is randomly permuted blocks. An interactive web based randomization system (IWRS) will be used. Each subject will be assigned a unique subject number.

Blinding

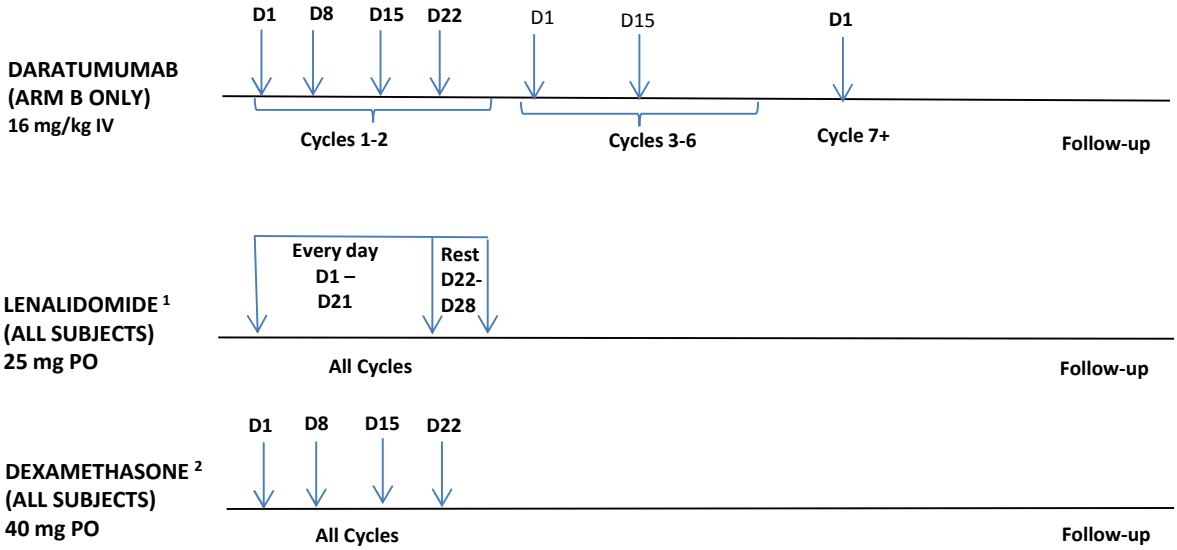
As this is an open study, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

In this protocol, the term "study drug" refers to daratumumab only, and "study treatment" refers to daratumumab, lenalidomide, and dexamethasone. Daratumumab is to be administered as described in the Time and Events Schedule. Each cycle is 28 days. The first visit of a cycle should be 4 weeks after the start of the previous cycle. The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. The start of each cycle should be scheduled relative to Cycle 1 Day 1 and should not change if visits have shifted within the allowed window. Subjects in the DRd arm will continue to receive daratumumab according to the Time and Events Schedule until disease progression, unacceptable toxicity, or other reasons as listed in Section 10.2.

A schematic of study treatment administration is provided in Figure 4.

Figure 4: Schematic Overview Study Treatment Administration



1. In Arm A, subjects will continue on lenalidomide/dexamethasone until progression of disease. In Arm B, lenalidomide /dexamethasone will be administered for a maximum of 2 years.
2. On days when daratumumab is administered, dexamethasone will be administered to subjects in Arm B in the clinic and will serve as the treatment dose of steroid as well as the required pre-medication prior to daratumumab infusion.

6.1. Daratumumab (Arm B Only)

6.1.1. Daratumumab Preparation

The infusion solution will be prepared on the day of the planned infusion. Detailed instructions for preparation and administration of daratumumab will be supplied in the SIPPM or equivalent document.

6.1.2. Daratumumab Administration

Daratumumab (16 mg/kg) will be administered by IV infusion to subjects in Arm B initially once every week for 8 weeks; then once every other week for 16 weeks; thereafter once every 4 weeks until documented progression, unacceptable toxicity, or study end. After the end of the study, the sponsor will ensure that subjects benefiting from treatment with daratumumab will be able to continue treatment.

Each subject's dose will be calculated based on the subject's weight rounded to the nearest kilogram. There is no cap on the absolute dose allowed, as long as the dose does not exceed 16 mg/kg. If a subject's weight changes by more than 10% from baseline, the dose of daratumumab will be re-calculated. For recommendations on daratumumab infusion rate, please refer to the SIPPM. All infusions will be performed as outpatient visits. Subjects will receive preinfusion medications and postinfusion medications as outlined in Section 6.1.3.

Every effort should be made to keep subjects on the planned dosing schedule. Time windows for daratumumab administration are outlined in Table 3.

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 immediately before the start of 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.

6.1.3. Guidelines for Prevention of Infusion Reactions

6.1.3.1. Preinfusion Medication

Preinfusion medications for subjects receiving daratumumab will be administered as described in the Time and Events Schedules. On daratumumab infusion days, subjects will receive the following medications prior to infusion:

- Paracetamol (acetaminophen) 650-1000 mg IV or orally (PO) 1 hour or less prior to daratumumab infusion
- An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent) approximately 12 hours prior and again approximately 1 hour prior to infusion on Cycle 1 Day 1, for all subsequent infusions approximately 1 hour prior
- Dexamethasone 40 mg IV or PO, 1 hour or less prior to daratumumab infusion. Dexamethasone 20 mg may be administered as appropriate [see Section 6.3]. An equivalent long-acting corticosteroid may substitute [see Attachment 6 for conversion table]. On days when subjects receive this dose of dexamethasone in the clinic, dexamethasone will not be self-administered at home.

6.1.3.2. Postinfusion Medication

For subjects with higher risk of respiratory complications (ie, subjects who have a FEV1 <80%), the following postinfusion medications should be considered:

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

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 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. If an

at-risk subject experiences no major infusion-related reactions, then these postinfusion medications may be waived after 4 full doses at the investigator's discretion.

6.1.4. Management of Infusion-related Reactions

Subjects in Arm B 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 the bedside. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

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

- Subjects should be treated with acetaminophen, antihistamine, or corticosteroids. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors.
- In the event of a life-threatening infusion-related reaction (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.

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.

6.1.4.1. Infusion-Related Events 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 the onset, then the subject must be withdrawn from treatment.

6.1.4.2. 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.

6.2. Lenalidomide (Arm A and Arm B)

Lenalidomide will be self-administered at a dose of 25 mg PO each day on Days 1 through 21 of each 28 day cycle for subjects with creatinine clearance >60 mL/min. If creatinine clearance is between 30 and 60 mL/min, the dose of lenalidomide will be 10 mg every 24 hours. Once the creatinine clearance is >60 mL/min during the course of the treatment, lenalidomide can be increased to 25 mg. In the DRd arm, lenalidomide will be administered for a maximum of 2 years or until the subject experiences disease progression or unacceptable toxicity, whichever comes first. In the Rd arm, subjects will continue on lenalidomide until progression of disease.

6.3. Dexamethasone (Arm A and Arm B)

Dexamethasone (or equivalent in accordance with local standards; see Attachment 6 for conversion table) will be administered at a total dose of 40 mg weekly. For subjects older than 75 years or underweight (body mass index [BMI] <18.5), the dexamethasone dose may be administered at a dose of 20 mg weekly. Dexamethasone will be administered until the subject experiences disease progression or unacceptable toxicity.

On days when subjects in Arm B receive an infusion of daratumumab, dexamethasone will not be self-administered but instead will be administered in the clinic. In this setting, dexamethasone will be utilized as the treatment dose of steroid for that particular day, as well as the required pre-medication prior to daratumumab infusion.

6.4. Dose Delays and Dose Modification

Subjects who need to discontinue treatment with any one component of study treatment (lenalidomide, dexamethasone, or daratumumab) may continue to receive treatment with the other components of study treatment, as assigned.

6.4.1. Daratumumab Dose Modification

Dose modification of daratumumab is not permitted, but dose delay is the primary method for managing daratumumab-related toxicities.

6.4.1.1. Daratumumab-Related Toxicity Management

Refer to Section 6.1.3 for details on management of infusion-related reactions. If any of the following criteria are met and the event cannot be ascribed to lenalidomide, the daratumumab infusion must be held to allow for recovery from toxicity. The criteria for a dose delay are:

- Grade 3 thrombocytopenia with bleeding
- Grade 4 neutropenia, if this is the second occurrence despite growth factor support
- Febrile neutropenia of any grade
- Neutropenia with infection, of any grade
- Grade 3 or higher nonhematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

If a 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.

Table 3: Daratumumab-Related Toxicity Management

Cycles	Frequency	Dose Held	Dosing Re-start
1 and 2	Weekly (q1wk)	>3 days	next planned weekly dosing date
3 to 6	Biweekly (q2wks)`	>1 week	next planned biweekly dosing date
7+	Every 4 weeks (Q4W)	>2 weeks	next planned every 4 weeks dosing date

A missed dose will not be made up. Doses of daratumumab may be delayed up to 4 weeks. If a dose is delayed, then the dates of the subsequent doses must be adjusted. Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 4 weeks will result in permanent discontinuation of daratumumab. If a dose delay occurs, then pharmacokinetic and pharmacodynamic assessments should be performed on the actual administration day of daratumumab, not on the original scheduled administration day.

6.4.1.2. Daratumumab Interruption or Missed Doses

A daratumumab dose that is held for more than the permitted time (Table 3) from the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the Sponsor at the earliest possible time. Subjects whose dose was delayed for more than 4 weeks should have study treatment discontinued, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

6.4.2. Lenalidomide Dose Reductions

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

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

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

6.4.2.1. 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 • When count returns to $\geq 30 \times 10^9$/L	• Interrupt lenalidomide treatment, follow complete blood count weekly • Resume lenalidomide at 15 mg
• For each subsequent drop in count to $< 30 \times 10^9$/L • When count returns to $\geq 30 \times 10^9$/L	• Interrupt lenalidomide treatment • Resume lenalidomide at the next lower dose level (10 mg or 5 mg) once daily. Do not decrease dose below 5 mg once daily

6.4.2.2. 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, 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 < 1.0×10^9/L • When count returns to ≥ 1.0×10^9/L and neutropenia is the only observed toxicity	• Interrupt lenalidomide treatment, start G-CSF treatment, follow complete blood count weekly • Resume lenalidomide at 25 mg once daily
• When count returns to ≥ 1.0×10^9/L and other toxicity is observed	• Resume lenalidomide at 15 mg once daily
• For each subsequent drop in count to < 1.0×10^9/L • When count returns to ≥ 1.0×10^9/L	• Interrupt lenalidomide treatment • Resume lenalidomide at the next lower dose level (15 mg, 10 mg, or 5 mg) once daily. Do not decrease dose below 5 mg once daily

6.4.2.3. 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 creatinine clearance of 60 mL/minute or less. The recommended doses for subjects with multiple myeloma and renal impairment are shown in Table 6.

Table 6: Lenalidomide Dose Adjustment for Renal Impairment

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

Key: CrCl = creatinine clearance.
[a] Estimated by creatinine clearance as calculated by the Cockcroft-Gault equation.

6.4.2.4. Other Grade 3 or 4 Adverse Events

For other Grade 3 or 4 non-hematologic and non-renal 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. Treatment with daratumumab and dexamethasone may continue.

6.4.3. Dexamethasone Dose Modifications

Dexamethasone may be reduced, if necessary, according to Table 7.

Table 7: Recommended Dose Reduction for Dexamethasone

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 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%
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

7. TREATMENT COMPLIANCE

Study drug (daratumumab) will be administered by qualified site staff, and the details of each administration will be recorded in the electronic case report form (eCRF). Subjects will be provided with a treatment diary which will be used to assess compliance with lenalidomide and dexamethasone treatment. Additional details are provided in the SIPPM or equivalent document.

8. CONCOMITANT THERAPY

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

Routine systemic use of the following concomitant medications will be collected in the eCRF and recorded in the source documents beginning with signing of the ICF to 30 days after the last dose of the last study treatment or until the start of subsequent anticancer treatment, if earlier: growth factors, transfusions, anti-infectives (antibacterials, antivirals, and antimycotics), steroids, anti-arrhythmics and other cardiac supportive therapy, anti-epileptics, centrally acting psychiatric medication, anti-histamines and other medications targeting postinfusion systemic reactions, bisphosphonates, and any anticancer therapy (including radiation). Concomitant medications to manage AEs and SAEs will be recorded as per Section 12.3.1.

8.1. Recommended Therapies

8.1.1. Prevention of Deep Vein Thrombosis and Pulmonary Embolism

Lenalidomide has been associated with increased incidence of DVT and PE. Therefore, all subjects should be prophylactically treated with aspirin at a dose of 100 to 150 mg PO 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.

8.1.2. Bisphosphonate Therapy

Bisphosphonate therapy is recommended to be continued per treatment guidelines (NCCN 2013).[18] 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.

Subjects who are currently using bisphosphonate therapy when they enter the study should continue the same treatment. If clinically indicated, subjects may initiate bisphosphonate therapy as soon as possible during Screening and no later than the end of Cycle 1. After Cycle 1, investigators should not prescribe bisphosphonates to subjects who have not received it before, as this would be considered a sign of disease progression.

8.1.3. Therapy for Tumor Lysis Syndrome

Subjects should be monitored for symptoms of tumor lysis syndrome. Management of tumor lysis syndrome, including dehydration and abnormal laboratory test results such as hyperkalemia, hyperuricemia, and hypocalcemia, are highly recommended. It is also recommended that high-risk subjects, ie, those with a high tumor burden, be treated prophylactically in accordance with local standards (eg, rehydration; diuretics; allopurinol 300 mg daily and medication to increase urate excretion).

8.1.4. Prophylaxis for Pneumocystis carinii

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

8.1.5. Prophylaxis for Herpes Zoster Reactivation

Prophylaxis for herpes zoster reactivation may be used at the discretion of the investigator.

8.1.6. 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

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

- Colony stimulating factors, erythropoietin, and transfusion of platelets and red blood cells. If erythropoietin is given, then this should be given according to the local lenalidomide label, 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
- Prophylactic antiemetics, with the exception of corticosteroids

8.3. Prohibited Therapies

Concomitant administration of any other antineoplastic therapy for the intention of treating multiple myeloma not defined in the study protocol is prohibited, including medications that target CD38. Continuation of the study treatment during or after emergency orthopedic surgery or radiotherapy because of the subject's benefit may occur only in the absence of disease progression and after review 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 by the sponsor.

Concomitant administration of investigational agents 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 infusion-related reactions as described in Section 6.1.3.2) should be avoided. Nonsteroidal anti-inflammatory agents should be avoided to prevent myeloma-related kidney disease.

Typically, IV contrast is NOT used in computed tomography (CT) scanning of the 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. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, pharmacokinetic, immunogenicity, biomarker, patient reported outcomes, and safety measurements applicable to this study.

All visit-specific PRO assessments should preferably be conducted/completed before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions. Refer to Section 9.7 for details.

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

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

The blood volume for the study is estimated at approximately 65 mL during screening and 360 mL during the first year (approximately 20-35 mL per cycle for routine testing, plus additional PK and biomarker samples). In the Follow-up Phase, subjects prior to PD will continue to have approximately 20 mL blood drawn per month for serum disease evaluations. This includes laboratory assessments associated with safety, efficacy, and pharmacokinetic evaluations, as well as scientific research samples. 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. The Screening Phase begins when the first screening assessment is conducted (that was not performed as part of the subject’s standard of care). During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in Time and Events Schedule. Screening procedures will be performed within 21 days before randomization; however, results of tests such as skeletal survey, radiologic tests (eg, magnetic resonance imaging [MRI]) to document baseline size of known or suspected extramedullary plasmacytomas; ECG; chest x rays; or bone marrow aspirate/biopsy) performed up to 6 weeks (42 days) before randomization as routine standard of care for the subject’s disease can be used.

Subjects <65 years must have known presence of important comorbid condition(s) likely to have a negative effect on the tolerability of high dose chemotherapy with SCT. Documentation of the condition, for example diagnosis of concomitant infectious disease(s), should be provided. Sponsor review and approval of subjects under 65 years of age is required before randomization.

A negative pregnancy test for women of childbearing potential must be documented twice, once within 10-14 days before the first dose and a second time within 24 hours before the first dose of any component of the treatment regimen.

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

9.1.3. Treatment Phase

Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedule. Subjects should start study treatment within 72 hours after randomization. A window of ±3 days is allowed for visits to the clinic. The start of each cycle should be scheduled relative to Cycle 1 Day 1 and should not change if visits have shifted within the allowed window. 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. If disease progression is diagnosed, then the subject will discontinue study treatment, complete the End-of-Treatment Visit, and enter the Follow-up Phase.

End of Treatment Visits

Unless a subject withdraws consent for study participation or is lost to follow up, an End-of-Treatment Visit is to occur within 4 weeks after the last dose of all study treatments. Every effort should be made to conduct the End-of-Treatment Visit before the subject starts subsequent treatment. If a subject is unable to return to the site for the End-of-Treatment Visit, then the subject should be contacted to collect information on adverse events that occur up to 30 days after the last dose of study treatment. Additional information on reporting of adverse events is presented in Section 12.

9.1.4. Follow-up Phase

The Follow-up Phase will begin once a subject discontinues all study treatments. Subjects who discontinue before disease progression must continue to have disease evaluations according to the Time and Events Schedule until confirmed PD, death, the start of a new anticancer therapy, withdrawal of consent, lost to follow-up, or the end of the study. After disease progression is documented, subsequent anticancer therapy, PFS2 (per investigator judgment), second primary malignancies, and survival status will be obtained at least every 16 weeks.

A clinical cut-off will be established after the primary PFS analysis (390 PFS events). Following the clinical cut-off date, disease assessments will no longer be required and data collection will be limited to the following:

- For subjects still receiving study treatment: study treatment administration, AEs, SAEs, laboratory data associated with SAEs

- For all subjects: all subsequent anticancer treatment, PFS2 (based on investigator judgment), second primary malignancies, and survival follow-up

If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and documented in the eCRF.

The end of the study occurs after 330 subjects have died, or for a maximum of 5 years after the last subject is randomized, whichever occurs first. The sponsor will ensure that subjects benefiting from treatment with daratumumab will be able to continue treatment after the end of the study.

9.2. Efficacy

9.2.1. Evaluations

Disease response and progression will be based on assessments from IMWG Guidelines as defined in Section 9.2.1.1. Previous studies have demonstrated potential interference of therapeutic monoclonal antibodies with detection of endogenous myeloma M-protein on serum IFE (McCudden 2010).[17] Daratumumab detection on serum immunofixation has been demonstrated in subjects treated with 16 mg/kg, and may interfere with the traditional IMWG criteria of negative serum IFE for complete response or stringent complete response. 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 with VGPR, and a negative endogenous M-protein by SPEP, reflex IFE testing will be performed to confirm the presence of daratumumab on IFE.

9.2.1.1. Response Categories

Disease evaluations must be performed every 28 days for the first 2 years and then every 8 weeks until disease progression (or other reasons as per Section 10). A window of ±7 days is allowed. If treatment has been delayed for any reason, the disease evaluations must be performed according to schedule, regardless of any changes to the dosing regimen.

Disease evaluations will be performed by a central laboratory (unless otherwise specified). This study will use the IMWG consensus recommendations for multiple myeloma treatment response criteria (Durie 2006, Rajkumar 2011)[4,25] presented in Table 8. For quantitative immunoglobulin, M-protein, and immunofixation 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 complete response or stringent complete response, will be considered CR/sCR.

Disease progression must be consistently documented across clinical study sites using the criteria in Table 8.

Table 8: International Uniform Response Criteria Consensus Recommendations

Response	Response Criteria
Stringent complete Response (sCR)	• CR as defined below, *plus* • Normal FLC ratio, *and* • Absence of clonal PCs by immunohistochemistry, immunofluorescence[a] or 2- to 4-color flow cytometry
Complete response (CR)*	• Negative immunofixation on the serum and urine, *and* • Disappearance of any soft tissue plasmacytomas, *and* • <5% PCs in bone marrow
Very good partial Response (VGPR)*	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or* • ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours
Partial response (PR)	• ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours • If the serum and urine M-protein are not measurable, a decrease of ≥50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥50% reduction in bone marrow PCs is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% • In addition to the above criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR, or progressive disease
Progressive disease (PD)†	• Increase of 25% from lowest response value in any one of the following: • Serum M-component (absolute increase must be ≥0.5 g/dL), • Urine M-component (absolute increase must be ≥200 mg/24 hours), • Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥10%) • Bone marrow plasma cell percentage: the absolute percentage must be >10% • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the PC proliferative disorder

EBMT = European Group for Blood and Marrow Transplantation; FLC = free light chain; PC = plasma cell

All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither.

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

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

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

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

Clinical Relapse
Clinical relapse is defined using the definition of clinical relapse in the IMWG criteria (Durie 2006, Rajkumar 2011).[4,25] 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; >2.875mM/L)
4. Decrease in hemoglobin of more than 2 g/dL (1.25 mM) or to less than 10 g/dL
5. Rise in serum creatinine by more than or equal to 2 mg/dL (≥177 mM/L)
6. Hyperviscosity

In some 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.

For continuation of treatment, the IMWG response will be determined on an ongoing basis by the investigator. For data analysis and reporting, however, the sponsor will use a validated computer algorithm that has been shown to provide consistent review of the data necessary to determine disease progression and response according to the IMWG criteria. For CR/sCR, the IMWG criteria require subjects to have a negative SPEP and serum IFE. As an immunoglobulin, daratumumab can be picked up by SPEP and serum IFE and may cause false positive SPEP and IFE results. A reflex assay has been developed by the sponsor to confirm daratumumab interference on these assays.

Serum free light chain assay test results will be analyzed by the central laboratory for the assessment of stringent complete response (sCR), according to the most recently published IMWG criteria (Durie 2006).[4] 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 study treatment is administered.

9.2.1.2. Myeloma Protein Measurements in Serum and Urine

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

- Serum quantitative immunoglobulins (QIgs)
  - All subjects will be evaluated for IgG, IgA, IgM, IgE, and IgD at Screening. Every 3 months during treatment and at the EOT visit, subjects with IgD or IgE disease will be evaluated for IgG, IgA, IgM, IgE, and IgD and subjects with IgG, IgA, or IgM disease will be evaluated for IgG, IgA, and IgM.
- Serum M-protein quantitation by electrophoresis (SPEP)
- Serum immunofixation at Screening and thereafter when a CR is suspected or maintained. If daratumumab interference is suspected based on SPEP and IFE results, additional reflex IFE testing may be performed.

- Serum free light chain assay (monthly for subjects with FLC disease, all others per Time and Events Schedule)
- 24-hour urine M-protein quantitation by electrophoresis (UPEP)
- Urine immunofixation at Screening and thereafter when a CR is suspected or maintained.

Blood and 24-hour urine samples will be collected as specified in the Time and Events Schedule until the development of confirmed disease progression. After subjects have completed 24 months of study treatment, the timing of collection for SPEP and UPEP (and the timing of collection of free light chain (FLC) for subjects with light chain multiple myeloma) will change from every 4 weeks to every 8 weeks. Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation performed 1 to 3 weeks later. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed. Serum and urine immunofixation test and serum free light chain assay will be performed at Screening and thereafter when a CR is suspected (when serum or 24-hour urine M-protein electrophoresis [by SPEP or UPEP] are 0 or nonquantifiable) or maintained. However, for subjects with light chain multiple myeloma, serum free light chain assay will be performed routinely. Serum immunofixation (IFE) assay samples will be split into 2 aliquots, with 1 reserved for potential follow-on testing if daratumumab interference with IFE is suspected. As daratumumab is a monoclonal IgG antibody, additional serum samples may be utilized to monitor for potential daratumumab interference with the IFE.

9.2.1.3. Serum Calcium Corrected for Albumin

Blood samples for calculating serum calcium corrected for albumin will be collected and analyzed centrally (as specified in the Time and Events Schedules) 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). 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 4.

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.

9.2.1.4. β2-microglobulin and Albumin

Blood samples for β2 microglobulin and albumin are to be collected at Screening, and will be analyzed by the central laboratory.

9.2.1.5. Bone Marrow Examination

Bone marrow aspirate or biopsy will be performed at Screening for clinical staging (morphology, cytogenetics, and immunohistochemistry [IHC] or immunofluorescence or flow cytometry) to establish baseline multiple myeloma clonality to monitor for MRD, and to perform molecular subtyping to monitor daratumumab activity in high-risk molecular subgroups. Clinical staging

may be performed locally; however, a portion of the bone marrow aspirate/biopsy must be sent to the central lab for analysis of MRD and molecular subtyping. A fresh bone marrow aspirate at screening is required if at all possible, by exception non-decalcified diagnostic tissue (bone marrow aspirate slides or FFPE tissue) may be supplied for MRD assessment instead. Additional bone marrow aspirates will be performed to confirm sCR, CR, or relapse from CR (IHC or immunofluorescence) and to monitor for MRD. Only 1 bone marrow sample is required, with either IHC or immunofluorescence included in the analysis. An additional bone marrow aspirate will be obtained 6 months and 12 months +/- 1 month after the achievement of CR. If feasible, a bone marrow aspirate may be collected from subjects at disease progression to evaluate mechanisms of daratumumab resistance.

9.2.1.6. Minimal Residual Disease Assessment

Minimal Residual Disease (MRD) assessment by next-generation sequencing (NGS) is a relatively new and effective tool in the assessment of patients with multiple myeloma (Ladetto, 2014).[15] Several studies have demonstrated that MRD status is correlated with PFS and OS (Martinez-Lopez, 2014).[16] In the present study, we will assess for MRD in both blood and bone marrow aspirate when a bone marrow sample is obtained at screening, at confirmation of CR and 6 months and 12 months after the achievement of CR.

9.2.1.7. Assessment of Lytic Disease

A complete skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease) is to be performed and evaluated by the local laboratory by roentgenography (or the local standard of care imaging, eg, low-dose CT) during the Screening Phase. Please note that the same methodology used at Screening should be used throughout the study for comparison purposes. During the Treatment Phase and before disease progression is confirmed, imaging should be performed whenever clinically indicated based on symptoms, to document response or progression. Magnetic resonance imaging (MRI) or low-dose CT scan are acceptable methods for evaluation of bone disease, and may be included at the discretion of the investigator (see the disease response criteria in Table 8). If a radionucleotide bone scan was used at Screening in addition to the complete skeletal survey, then both methods must be used to document disease status. These tests must be performed at the same time. However, a radionucleotide bone scan does not replace a complete skeletal survey.

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 radiographs, depending on the symptoms that the subject experiences. If the diagnosis of disease progression is obvious by radiographic investigations, then no repeat confirmatory imaging is necessary. In instances where changes may be more subtle, repeat imaging may be performed in 1 to 3 weeks per investigator discretion

9.2.1.8. Documentation of Extramedullary Plasmacytomas

Sites of known extramedullary plasmacytomas must be documented during the Screening Phase. Clinical examination or MRI may be used to document extramedullary sites of disease.

Computed tomography scan evaluations are an acceptable alternative if there is no contraindication to the use of intravenous 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 every 4 weeks (by physical examination) for subjects with a history of plasmacytomas or as clinically indicated during treatment for other subjects until development of confirmed CR or confirmed disease progression. If assessment can only be performed radiologically, then evaluation of extramedullary plasmacytomas may be done every 12 weeks. 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% or 25%, respectively, and new plasmacytomas must not have developed (see the disease response criteria in Table 8). 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.

9.2.2. Endpoints

Primary Endpoints

The primary endpoint is PFS, which is defined as the duration from the date of randomization to either progressive disease, or death, whichever occurs first. Disease progression will be determined according to the IMWG criteria (Durie 2006, Rajkumar 2011).[4,25] For subjects who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy. Relapse from CR by positive immunofixation or trace amount of M-protein is not considered to be progressive disease and is not included in the PFS calculation.

The primary PFS analysis will occur once the targeted number of PFS events (390) is reached. At that time, for subjects without disease progression, disease assessments are no longer required per protocol but may continue to be performed according to the standard of care.

Secondary Endpoints

The secondary efficacy endpoints include:

- Time to disease progression (TTP) is defined as the time from the date of randomization to the date of first documented evidence of PD, as defined in the IMWG criteria. For subjects

who have not progressed, data will be censored at the date of the disease evaluation before the start of any subsequent anti-myeloma therapy.

- sCR rate, defined as the percentage of subjects achieving CR in addition to having a normal FLC ratio and an absence of clonal cells in bone marrow by immunohistochemistry, immunofluorescence, 2-4 color flow cytometry
- CR rate, defined as the percentage of subjects achieving CR, as defined:
  - Negative immunofixation of serum and urine, and
  - Disappearance of any soft tissue plasmacytomas, and
  - <5% PCs in bone marrow
  - For those subjects with negative SPEP and suspected daratumumab interference on immunofixation, a reflex assay using anti-idiotype antibody will be utilized to confirm daratumumab interference and rule out false positive immunofixation. Subjects who have confirmed daratumumab interference, but meet all other clinical criteria for CR or sCR, will be considered CR/sCR.
- Progression-free Survival on Next line of Therapy (PFS2), defined as the time from randomization to progression on the next line of treatment or death, whichever comes first. Disease progression will be based on investigator judgment. For those subjects who are still alive and not yet progressed on the next line of treatment, they will be censored on the last date of follow-up.
- Minimal residual disease (MRD) status and depth, as measured in subjects who achieve CR/sCR, at 6 and 12 months after confirmed CR
- Time to next treatment, defined as the time from randomization to the start of the next-line treatment.
- Overall response rate (ORR), defined as the proportion of subjects who achieve CR or PR, according to the IMWG criteria, during or after the study treatment.
- Proportion of subjects who achieve VGPR or better, defined as the proportion of subjects achieving VGPR and CR (including sCR) according to the IMWG criteria during or after the study treatment at the time of data cutoff.
- Duration of response, calculated from the date of initial documentation of a response (CR or PR) to the date of first documented evidence of progressive disease, as defined in 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.
- OS, 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.
- To evaluate clinical efficacy of DRd in high risk molecular subgroups compared to Rd alone.
- To evaluate the impact of DRd compared to Rd on patient-reported perception of global health.

Exploratory Endpoints

- Biomarkers predictive of response or resistance to daratumumab

9.3. Pharmacokinetics and Immunogenicity

9.3.1. Evaluations

For all subjects in Arm B, pharmacokinetic samples to determine serum concentration of daratumumab will be obtained according to the Time and Events Schedule. Venous blood samples (5 mL per sample) will be collected to determine serum concentration of daratumumab and the serum will be divided into 3 aliquots (1 aliquot for pharmacokinetic analysis, 1 aliquot for antibodies to daratumumab analysis [when appropriate], and 1 aliquot as a backup). Samples collected for determining serum concentrations of daratumumab in this study may be retained to address questions about drug characteristics that may arise at a later time point.

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 antibodies to daratumumab using validated immunoassay methods by or under the supervision of the sponsor's bioanalytical facility. All samples collected and received up to the time of the primary study endpoint analysis (first bioanalysis) will be analyzed for immunogenicity (when applicable) and serum daratumumab concentration as indicated by the Time and Events Schedule. All data from this first analysis will be considered final and these samples will not be reanalyzed at the end of the study. The final bioanalysis will include all serum daratumumab concentration (pharmacokinetics) and immunogenicity samples that become available after the primary endpoint analysis. If one or more additional rounds of pharmacokinetic or immunogenicity bioanalysis outside of the above planned timings is deemed necessary to facilitate study or program decisions, any data resulting from these additional analyses will also be considered final and samples will not be reanalyzed in conjunction with any other round of bioanalysis.

9.3.3. Pharmacokinetic Parameters

The pharmacokinetic parameters are defined as:

CL	Total systemic clearance of drug after IV administration
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
V	Volume of distribution

Pharmacokinetic samples to determine serum concentration of daratumumab will be obtained from all subjects. Pharmacokinetic endpoints include:

- Minimum observed concentration (Cmin)
- Maximum observed concentration (Cmax)

If sufficient data are available, then other pharmacokinetic parameters may be calculated, including but not limited to total systemic clearance of drug after IV administration (CL) and volume of distribution (V).

9.3.4. Immunogenicity Assessments (Antibodies to daratumumab)

Venous blood samples drawn from all subjects in the DRd group will be assessed for the generation of antibodies to daratumumab (immunogenicity), according to the Time and Events Schedule. Additionally, blood samples to assess immunogenicity should also be collected at the final visit for subjects who discontinue treatment. Subjects who discontinue treatment will also be asked to return for immunogenicity evaluation during the 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 antibodies to daratumumab 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, including exploring the relationship between serum concentrations of daratumumab and endpoints of clinical efficacy. If these analyses are performed, then the details and results will be presented in a separate report.

9.5. Biomarkers

Biomarker assessments will focus on two main objectives including evaluating the ability of daratumumab + Rd to reduce MRD in subjects who achieve a complete response (compared to Rd alone) and to determine the clinical benefit (ORR, PFS, and OS) of daratumumab + Rd in high-risk molecular subtypes (del17p, t(4;14), t(6;14), specific gene signatures, specific mutations). Bone marrow aspirates will be collected at screening and following treatment as outlined in the Time and Events Schedule. Baseline bone marrow aspirate samples will be subjected to DNA and RNA sequencing in order to classify subjects into high-risk molecular subgroups and to establish the myeloma clone for MRD monitoring. A fresh bone marrow aspirate at Screening is required if at all possible, by exception non-decalcified diagnostic tissue (bone marrow aspirate slides or FFPE tissue) may be supplied for MRD assessment instead. For subjects who achieve a CR or sCR, bone marrow aspirates will be utilized for assessment of MRD by next-generation sequencing (NGS) of immunoglobulin heavy and light chains (Vij 2013).[32] If this methodology is unavailable, or determined to be scientifically inferior, then alternative methods for MRD assessment may be utilized. In cases where daratumumab is suspected of interfering with serum IFE and preventing clinical CR response calls, subjects with VGPR will also be evaluated for MRD by NGS.

In addition to planned bone marrow aspirate assessments, a whole blood sample will be collected from subjects as outlined in the Time and Events Schedule for assessment of MRD and for processing to plasma and PBMCs. These samples may be used to evaluate specific subsets of immune cells such as cytotoxic T cells, regulatory T cells, MDSCs, and activated NK cells. Cells may also be used for additional phenotypic and functional profiling. Proteomic analysis may also be used to evaluate changes in cytokines, complement proteins, soluble CD38, soluble CD59, IFNγ, granzyme, perforin, and other proteins associated with ADCC/CDC/ADCP to evaluate potential biomarkers of response and resistance.

Potential mechanisms of tumor resistance, such as changes in antigen (CD38) expression or increased expression in complement inhibitory proteins (CD46, CD55, and CD59) in multiple myeloma cells, may be monitored in subjects if a bone marrow aspirate sample is deemed feasible for collection at progressive disease. In addition, changes in expression patterns of genes associated with ADCC, CDC, or other mechanisms of action of daratumumab may be evaluated.

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 the Time and Events Schedule.

9.6. Medical Resource Utilization

Medical resource utilization (MRU) data, principally number of hospitalizations, will be derived from data collected in the eCRF for all subjects throughout the study.

9.7. 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 and the EQ-5D-5L instruments will be used. Both questionnaires will be completed at the timepoints 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 (Wisloff 1996, Wisloff 1997).[33,34] 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 **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) (Herdman, 2011).[8] 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.

9.8. Safety Evaluations

Safety will be measured by adverse events, laboratory test results, ECGs, vital sign measurements, physical examination findings, and assessment of ECOG performance status score. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

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

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. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

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

The tests below will be performed by the local laboratory unless otherwise noted.

- Hematology Panel

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

- Serum Chemistry Panel

  -blood urea nitrogen (BUN)
  -creatinine
  -glucose
  -aspartate aminotransferase (AST)
  -alanine aminotransferase (ALT)
  -alkaline phosphatase
  -lactic acid dehydrogenase (LDH)
  -uric acid
  -total and direct bilirubin
  -total protein

Serum or urine 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 and throughout the Treatment Phase, as specified in the Time and Events Schedule. Where lenalidomide is supplied locally, subjects must adhere to the local lenalidomide REMS program. Where lenalidomide is supplied centrally and no local lenalidomide REMS program exists, then subjects must adhere to the lenalidomide Global Pregnancy Prevention Plan in Attachment 5.

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

Calcium and albumin adjusted calcium:

These parameters will be part of the efficacy evaluations as specified in Section 9.2.1.3, and will be analyzed by the central laboratory. Measurement of calcium and albumin should follow the schedule for disease assessments. Measurement of free ionized calcium is an acceptable alternative to corrected serum calcium for determining hypercalcemia

Blood type assessment

CD38 is expressed on erythrocytes to a minor extent. Hemolysis could occur following the infusion of daratumumab, which would confound the blood type assessment. To be cautious and in case of urgent need for blood transfusion, the subject's blood type, including minor group, will be assessed before the first infusion of daratumumab. Subjects in Arm B should at all times carry a card with their blood type during the study.

Pulmonary Function Test

Subjects with known or suspected COPD or asthma must have a FEV1 test during screening. Refer to Section 6.1.3.2 for details on subjects with higher risk of respiratory complications

Electrocardiogram (ECG)

ECGs 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, then the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Vital Signs

Vital signs (pulse, temperature, and blood pressure) will be performed as specified in the Time and Events Schedule. It is recommended that blood pressure (sitting) and pulse measurements be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones). Only vital signs associated with an AE will be entered in the eCRF; all measurements will be recorded in the source documents.

Physical Examination and ECOG Performance Status

A complete physical examination (including neurological examination) should be performed during the Screening Phase. Thereafter, only a symptom and disease directed physical examination is required. Height will be measured at screening only; weight will be measured regularly as specified in the Time and Events Schedule. Abnormalities will be recorded in the appropriate sections of the eCRF. ECOG Performance Status (Attachment 2) will be used to evaluate the impact of the disease status on the activities of daily living. When scheduled, ECOG assessments along with PRO questionnaires should be obtained prior to any other study procedures planned for the same day.

9.9. Sample Collection and Handling

If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (or equivalent)/sodium heparin of 10 U/mL and charged with a volume equal to the dead space volume of the lock. If a mandarin (obturator) is used, blood loss due to discard is not expected. Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

For samples collected from the central laboratory, sample dates and times must be recorded on the laboratory requisition form. 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/WITHDRAWAL

10.1. Completion

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

10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, **this will not result in automatic withdrawal of the subject from the study**. After treatment discontinuation, the subject will move into the Follow-up Phase. The End-of-Treatment Visit and Follow-up visit assessments should continue as specified in the Time and Events Schedule. 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.

Subjects who need to discontinue treatment with any one component of study treatment (lenalidomide, dexamethasone, or daratumumab) may continue to receive treatment with the other components of study treatment, as assigned.

A subject's study treatment should be discontinued if:

- The investigator believes that for safety 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

- The subject experiences unacceptable toxicity, including infusion-related reactions described in Section 6.1.4
- The subject's dose of daratumumab is held for more than 4 weeks (unless Sponsor approves continuation)
- The subject experiences disease progression (please see below). Relapse from CR is not considered as disease progression

A subject who experiences a second primary malignancy that cannot be treated by surgery alone must be withdrawn from the study. However, a subject who develops a malignancy that can be cured surgically may continue to receive the assigned study treatment and should continue to be followed for subsequent progression of multiple myeloma.

Before subjects discontinue study treatment due to disease progression, sites will document disease progression (for example by completing a disease progression form or by contacting the IWRS) as soon as possible and within 48 hours. The medical monitor will confirm that treatment should be discontinued. After confirmation from the sponsor, study treatment may be discontinued and the subject entered into Follow-up.

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

10.3. Withdrawal From the Study

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

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

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

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study treatment assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study, assessments outlined in the End-of-Treatment Visit should be obtained.

Withdrawal From the Use of Samples in Future Research

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

11. STATISTICAL METHODS

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

11.1. Subject Information

The primary analysis population will be the intent-to-treat (ITT) population, which will include all randomized subjects. Safety will be evaluated for the population of all treated subjects. The pharmacokinetic analyses will be performed on the pharmacokinetic evaluable population. Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, and range. Categorical variables will be summarized using frequency tables. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries.

11.2. Sample Size Determination

The sample size calculation is performed on the basis of the following assumption. Based on the published data, the median PFS for Rd arm is assumed to be approximately 26 months. Assuming that DRd can reduce the risk of the disease progression or death by 25%, ie, assuming the hazard ratio (DRd vs. Rd) of 0.724, a total of 390 PFS events is needed to achieve a power of 85% to detect this hazard ratio with a log-rank test (two-sided alpha is 0.05). With a 21-month accrual period and an additional 24-month follow-up, the total sample size needed for the study is approximately 730 (365/arm) subjects. The sample size calculation has taken into consideration an annual dropout rate of 5%.

Long-term survival follow-up will continue until 330 deaths have been observed or 5 years after the last subject is randomized. Therefore, this study will achieve approximately 80% power to detect a 27% reduction in the risk of death (hazard ratio = 0.73) with a log-rank test (two-sided alpha = 0.05).

11.3. Efficacy Analyses

Response to study treatment and progressive disease will be evaluated by a computer algorithm. For the primary endpoint of PFS, the primary analysis will consist of a stratified log rank test for the comparison of the PFS distribution between the 2 treatment arms. The Kaplan-Meier method will be used to estimate the distribution of overall PFS for each treatment. The treatment effect (hazard ratio) and its two-sided 95% confidence intervals are to be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

Other time-to-event efficacy endpoints, including TTP, PFS2, OS, and time to subsequent anti myeloma treatment, will be analyzed similarly. For overall survival, the final analysis will occur after 330 deaths have been observed. Earlier analyses, in which overall survival are analyzed, will be considered as interim analyses, and the stopping boundary will be determined using the observed number of deaths at the time of the analyses and a modified linear alpha-spending function per the Lan-DeMets method. At the interim PFS analysis (234 PFS events), a total alpha of 0.0001 (2-sided) will be spent. Cumulative total alpha (2-sided) spent at each subsequent analysis of OS will be the total alpha allocated to OS multiplied by the proportion of the number

of deaths observed at the time of the analysis out of the total planned number of deaths (330). Comparison between the 2 treatment groups of overall response rates, VGPR rate, and other binary endpoints will be conducted using the stratified Cochran Mantel Haenszel test. The Mantel-Haenszel odds ratio will be provided along with its two-sided 95% confidence interval, and will be provided as the measure of treatment effect. Duration of response will be provided descriptively without formal statistical comparison.

Strong control of familywise Type I error rate will be controlled at a two-sided significance level of 0.05 for the following major secondary endpoints: TTP, OS, CR rate, stringent CR rate, MRD negative rate, and time to response. A hierarchical testing procedure will be used. Details about this hierarchical procedure will be specified in the statistical analysis plan for this study prior to any efficacy analysis.

11.4. Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed on the pharmacokinetic-evaluable population, defined as subjects who have received one dose of daratumumab and at least one 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 Cmin and Cmax. If sufficient data are available, then other pharmacokinetic parameters may be calculated, including but not limited to CL and V.

If sufficient data are available, then population pharmacokinetic analysis of serum concentration time data of daratumumab, will be performed using nonlinear mixed-effects modeling. The potential population PK analysis may also include PK 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 antibodies to daratumumab will be summarized for all subjects who receive a dose of daratumumab and have appropriate samples for detection of antibodies to daratumumab.

11.6. Pharmacokinetic/Pharmacodynamic Analyses

If sufficient data are available, then population pharmacokinetic analysis serum concentrations of serum concentration-time data of daratumumab will be performed using nonlinear mixed-effects modeling. If the population pharmacokinetic analysis is conducted, then details will be given in a population pharmacokinetic analysis plan 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. Analyses will be performed and stratified by clinical covariates or molecular subgroups using the appropriate statistical methods (eg, parametric or non-parametric, univariate or multivariate, analysis of variance, 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 in addition to genes and pathways attenuated following treatment with daratumumab. In order to remove any confounding influence of prognostic factors, any predictive biomarker identified in this study could be verified in a prospective clinical study with a control treatment arm.

Any biomarker measures will be listed, tabulated, and where appropriate, plotted. Subjects will be grouped by prescribed dose. Complete responders will be utilized to investigate the prognostic effect of MRD on PFS. MRD analysis will include evaluation of data from other studies to determine if decreased MRD is seen with daratumumab + Rd based chemotherapy regimen compared with the Rd based chemotherapy alone.

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.

In addition, due to the small sample sizes of high-risk subgroups within the multiple myeloma subject population, a meta-analyses may be performed across daratumumab Phase 3 studies to evaluate clinical efficacy of daratumumab with standard of care agents in pre-specified subgroups of multiple myeloma subjects. The meta-analysis protocol will pre-specify the objective of the meta-analysis, the criteria for inclusion and exclusion of studies, the hypotheses and endpoints, and statistical methods including a method for investigation of heterogeneity. This meta-analytic approach, supported by high-quality data from the individual trials, should be able to provide definitive evidence on the effectiveness of daratumumab in the subpopulation of multiple myeloma subjects with high-risk molecular abnormalities. In a similar fashion, a meta-analysis examining MRD negativity in daratumumab treated subjects in frontline, newly diagnosed multiple myeloma (MMY3006, MMY3007, MMY3008) may also be performed.

11.8. Patient Reported Outcomes

EORTC-QLQ-C30 scores will be evaluated for all domains except “financial problems” among subjects with at least one post-baseline assessment and 50% completion of the relevant items for a domain. Descriptive analyses followed by mixed model repeated measures will be used to analyze each domain score. No adjustment for multiple comparisons will be made.

EQ-5D-5L scores will be summarized at each time point.

11.9. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The severity assessment for an adverse event or serious adverse event should be completed using the NCI CTCAE Version 4. All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized 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.

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 post treatment cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. 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.

Parameters with predefined NCI-CTCAE toxicity grades will be summarized. Change from baseline to the worst toxicity grade experienced by the subject during the study will be provided as shift tables. Worst toxicity grade during treatment will be presented, according to NCI-CTCAE (version 4). Clinically relevant changes (i.e. causing a treatment intervention and/or need for concomitant therapy) will be also recorded on the adverse event eCRF. All other lab abnormalities need not be recorded as adverse events.

Electrocardiogram (ECG)

Electrocardiogram data will be summarized and listed.

Vital Signs

Descriptive statistics of temperature and blood pressure (systolic and diastolic) values and changes from baseline will be summarized.

11.10. Interim Analysis

Two interim analyses are planned. The first interim analysis, with a purpose to evaluate safety, will be performed after a total of approximately 100 subjects have been treated for at least 8 weeks or discontinued the study treatment. The second interim analysis will be performed

when 234 PFS events, which is 60% of the total planned events, have been accumulated. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. The significance level at this interim analysis to establish the superiority of DRd over Rd with regard to PFS will be determined based on the observed number of PFS events at the interim analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. If the experimental arm (DRd) is numerically worse than the control arm in terms of PFS (observed hazard ratio >1 favoring the control arm), then the study may be terminated for futility, with a conditional power of less than 20% under the alternative hypothesis given the observed interim data.

11.11. Data Monitoring Committee

An IDMC, consisting of 2 clinicians and 1 statistician who are independent experts not otherwise participating in the study, will be established to review efficacy and safety results at the planned interim analyses. After the interim review, they will make recommendations regarding the continuation of the study. In addition, the IDMC may also review cumulative safety data every 6 months besides the two interim analyses. The details will be provided in a separate IDMC charter.

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 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 within the Reference Safety Information included in the Investigator's Brochure.

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.

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. Any adverse event or serious adverse event not listed in the NCI CTCAE Version 4 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 and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug. No MTD has been reached for daratumumab. However, if the dose exceeds the maximum tested dose of 24 mg/kg, then it will be considered as overdose in this study.
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject exposure to the sponsor study drug, eg, name confusion)

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

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study treatment, unless the subject withdraws consent for study participation, or starts subsequent anticancer therapy. For subjects who have received subsequent 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 daratumumab need to be reported. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study treatment, must be reported using the 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.

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

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

Subjects (or their designees, if appropriate) will 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
- Blood type (as described in Section 9.8 for subjects in Arm B)

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 eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

12.3.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment and promptly be withdrawn from the study. The subject should be referred to a physician experienced in teratology for evaluation and advice. Investigators should follow the local label for guidance on subject education and ensure that all subjects adhere to the local lenalidomide REMS program (when lenalidomide is supplied locally), or the lenalidomide Global Pregnancy Prevention Plan provided in Attachment 5 (when lenalidomide is supplied centrally and no local lenalidomide REMS program exists). Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

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

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 on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on 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 slightly yellow liquid and sterile concentrate of 20 mg/mL in a vial. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

14.2. Packaging

Daratumumab is supplied in glass vials containing daratumumab at a concentration of 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

All study drug vials must be stored in the original carton at controlled temperatures in a refrigerator ranging from 2°C to 8°C and must not be utilized after the expiry date printed on the

label. The product must be protected from direct sunlight and must not be frozen. Daratumumab does not contain preservatives; therefore any unused portion remaining in the vial must be discarded.

If the daratumumab preparation must be stored for longer than 1 hour after it has been diluted in 0.9% NaCl, then it must be kept at 2°C to 8°C. For the subjects' comfort, the solution should be kept at room temperature for approximately 1 hour before the start of the infusion. However, the infusion has to be completed within 24 hours of preparation. Refer to the Site investigational product 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, or used returned study drug for destruction, 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. 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 Brochure for daratumumab
- Site Investigational Product Procedures Manual
- Laboratory manual
- PRO questionnaires and user guidelines
- eCRF completion guidelines

- Sample ICF
- Subject diaries
- Subject wallet card indicating blood type
- Other manuals and guidance documents as needed

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

The primary safety profile of daratumumab is consistent with infusion-related reactions; see Section 6.1.3 for prevention details. 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. Anemia was also reported in Study GEN501. Free hemoglobin was mildly elevated, but other parameters did not support hemolysis. No bleeding events were observed. Routine safety laboratory measurement of RBCs and platelets will be closely monitored in this study.

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

The blood volume for the study is estimated at approximately 65 mL during screening and 360 mL during the first year (approximately 20-35 mL per cycle for routine testing, plus additional PK and biomarker samples). In the Follow-up Phase, subjects prior to PD will continue to have approximately 20 mL blood drawn per month for serum disease evaluations. These blood volumes are not burdensome and fall within the normal range of a single blood donation.

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), 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).

Furthermore, where required, progress reports/written summaries of the trial status will be submitted to the IRB/IEC annually, or more frequently if requested.

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, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the

purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

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

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

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

16.2.4. Privacy of Personal Data

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

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

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

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

Exploratory biomarker/PK/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 Study (Withdrawal From the Use of Samples in Future Research).

16.2.6. Country Selection

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

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and 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 (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

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

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

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

17.3. Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and 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 documentation must be available for the following to confirm data collected in the eCRF: 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 treatment administration information; and date of study completion and reason for early discontinuation of study treatment or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

Subject- and investigator-completed scales and assessments designated by the sponsor (EORTC QLQ-C30 and EQ-5D-5L) will be recorded directly into an electronic device or other tool 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 provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Study site personnel must complete the eCRF 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. The investigator must verify that all data entries in the eCRFs are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the eCRF (if applicable) and complete the query.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- 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).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

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

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRFs 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 eCRFs 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 eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents 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 documentation 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.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed after 330 deaths have occurred or 5 years after the last subject is randomized, whichever is first. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject 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 and comparison with the eCRFs. 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 eCRF data from all study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. 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/or disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENT 1: CRAB CRITERIA FOR MULTIPLE MYELOMA

All 3 required:

1. Monoclonal plasma cells in the bone marrow >10% or presence of a biopsy-proven plasmacytoma

2. M protein in serum or urine

3. Myeloma-related organ dysfunction (1 or more of the following):

a. C = Hypercalcemia (serum calcium 0.25 mmol/L above ULN or >2.75 mmol/L)
b. R = Renal insufficiency attributable to myeloma (creatinine >173 µmol/L or 2 mg/dL)
c. A = Anemia (hemoglobin 2 g/dL below the lower normal limit or hemoglobin <10 g/dL)
d. B = Bone lesions (lytic lesions or osteoporosis with compression fracture)
e. Other: Symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months)

No minimal level of serum M protein or urine M protein was included in the criteria. No minimal level of clonal bone marrow plasma cells was designated. The most critical criterion is the evidence of end organ or tissue impairment.

Reference: IMWG 2003

ATTACHMENT 2: 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 1982[19]

ATTACHMENT 3: MEASURED CREATININE CLEARANCE

$$CrCl = \frac{U_{Cr} * U_{Vol}}{P_{Cr} * T_{min}}$$

$$\text{Corrected CrCl} = CrCl * \frac{1.73}{BSA}$$

ATTACHMENT 4: SERUM CALCIUM CORRECTED FOR ALBUMIN

If calcium is expressed in mg/dL and albumin is expressed in g/dL:
Corrected calcium (mg/dL) =
serum calcium (mg/dL) + 0.8•(4 - serum albumin [g/dL])

If calcium is expressed in mmol/L and albumin is expressed in g/L:
Corrected calcium (mmol/L) =
serum calcium (mmol/L) + 0.02•(40 - serum albumin [g/L])

Source: Burtis 1999

ATTACHMENT 5: LENALIDOMIDE GLOBAL PREGNANCY PREVENTION PLAN

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

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

1.1 Pregnancy Prevention Risk Management Plans

1.1.1 Lenalidomide Pregnancy Prevention Risk Management Plan

1.1.1.1 Lenalidomide Pregnancy Risk Minimisation Plan for Celgene Clinical Trials

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

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

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

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

Risks Associated with Pregnancy

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

Criteria for females of childbearing potential (FCBP)

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

Counseling

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

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

The investigator must ensure that for females of childbearing potential:

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

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

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

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

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential

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

Contraception

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

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

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

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

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

Pregnancy testing

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

Before starting study drug

Female Patients:

FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10 to 14 days prior to the

start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Patients:

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

During study participation and for 28 days following study drug discontinuation

Female Patients:

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

Male Patients:

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

Additional precautions

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of study drug.

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

1.1.1.3 Lenalidomide Education and Counseling Guidance Document

To be completed prior to each dispensing of study drug.

Protocol Number: _____

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

(Check the appropriate box to indicate risk category)

Female: □

If female, check one:

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

Male: □

Do Not Dispense study drug if:

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

FCBP:

1. I verified that the required pregnancy tests performed are negative.
2. I counseled FCBP regarding the following:
   - Potential risk of fetal exposure to lenalidomide: If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. The teratogenic potential of lenalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking lenalidomide.
   - Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to therapy, during therapy, during dose interruption and 28 days after discontinuation of study drug].

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

3. Provide Lenalidomide Information Sheet to the patient.

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

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

MALE:

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

Investigator/Counselor Name (Print): _____

(circle applicable)

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

(circle applicable)

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

1.1.1.4 Lenalidomide Information Sheet

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

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

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

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

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

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

If you are a female not of childbearing potential:

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

If you are a male:

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

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

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

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

ATTACHMENT 6: CONVERSION TABLE FOR GLUCOCORTICOSTEROID DOSE

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

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Tahamtan Ahmadi, MD PhD

Institution: Janssen Research & Development

Signature: [redacted] Date: 14 July, 2014

(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.

LAST PAGE

Janssen Research & Development *

Clinical Protocol

A Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High Dose Therapy

Protocol 54767414MMY3008; Phase 3
AMENDMENT INT-4

JNJ-54767414 Daratumumab

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Sciences Ireland UC; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

EudraCT NUMBER: 2014-002273-11

Status:	Approved
Date:	22 May 2017
Prepared by:	Janssen Research & Development, LLC
EDMS no:	EDMS-ERI-85965381; 6.0

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

TABLE OF CONTENTS

LIST OF ATTACHMENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	14 July 2014
Amendment INT-1	29 October 2014
Amendment INT-2	26 August 2015
Amendment INT-3	2 November 2016
Amendment INT-4	22 May 2017

Amendments below are listed beginning with the most recent amendment.

Amendment INT-4 (22 May 2017)

This amendment is considered to be 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: To allow subjects in Arm B (daratumumab + lenalidomide and dexamethasone [DRd]) to continue treatment with lenalidomide and dexamethasone (Rd) beyond the current protocol-specified 2 years.

Applicable Section(s)	Description of Change(s)
Rationale: Subjects in Arm B will continue treatment with lenalidomide and dexamethasone (Rd) until disease progression or unacceptable toxicity. Based on data from the FIRST study, lenalidomide treatment until disease progression is emerging as the standard of care and is also consistent with the approved lenalidomide package insert.	
Synopsis; Time and Events Schedule, Dose Administration; 3.1. Overview of Study Design; 6.2. Lenalidomide (Arm A and Arm B); 6.3. Dexamethasone (Arm A and Arm B)	Subjects in both treatment arms will continue lenalidomide and dexamethasone (Rd) until disease progression or unacceptable toxicity.
6.2. Lenalidomide (Arm A and Arm B); 6.3. Dexamethasone (Arm A and Arm B)	The following text is added to manage the implementation of this amendment**: Subjects in Arm B who discontinued treatment with Rd at 24 months may re-start treatment with Rd as per Amendment INT-4.**
3.2. Study Design Rationale	Text is added to support the modification of lenalidomide and dexamethasone dosing in Arm B.
Rationale: With the anticipated improved survival for subjects in Arm B (daratumumab, lenalidomide, and dexamethasone [DRd]), who with this amendment will receive continuous lenalidomide and dexamethasone (Rd) regimen, the end of study and long-term survival Follow-up Phase are extended from 5 to 7 years in order to reach 330 deaths as originally planned.	
Synopsis; 3.1. Overview of Study Design; 9.1.4. Follow-up Phase; 11.2. Sample Size Determination; 17.9.1. Study Completion	Text is changed from 5 to 7 years.

Applicable Section(s)	Description of Change(s)
Rationale: Most infusion-related reactions will occur with the first infusion. Because antihistamines have side effects in the elderly population, the benefit-risk ratio of continued prophylaxis with antihistamines during subsequent infusions should be considered.	
6.1.3.1. Preinfusion Medication	The following text is added: After Cycle 6, if a subject has not developed an infusion-related reaction and is intolerant to antihistamines, modifications are acceptable as per investigator discretion.
Rationale: Clarify steroid administration.	
8.3. Prohibited Therapies	Clarify that steroids given for adverse events may exceed >10 mg prednisone if no other treatment options are available.
Rationale: Clarify the permitted treatments for second primary malignancies and follow up requirements.	
10.2. Discontinuation of Study Treatment	The following text regarding second primary malignancies was edited and modified: A subject who experiences a second primary malignancy that can~~not~~ be treated by surgery ~~alone must be withdrawn from the study. However, a subject who develops a malignancy that can be cured surgically~~ may continue to receive the assigned study treatment and **the subject** should continue to be followed for subsequent progression of multiple myeloma. **Subjects who require radiation therapy for treatment of second primary malignancy must have study treatment discontinued unless, upon consultation with the Sponsor and review of data, continuation is agreed upon. Subjects who require systemic treatment of a new malignancy must end study treatment but should continue to be followed for PFS2 and OS.**
Rationale: Update the recommended course of action regarding lenalidomide dose adjustment to treat thrombocytopenia and neutropenia to be more consistent with the current package insert.	
6.4.2.1. Thrombocytopenia (Table 4);	Thrombocytopenia (Table 4): Platelet Count: When count returns to ≥30 x 10^9/L after first fall to <30 x 10^9/L; Recommended Course of Action: Resume lenalidomide at ~~15 mg~~ **the next lower dose** Platelet Count: When count returns to ≥30 x 10^9/L for each subsequent drop in count to <30 x 10^9/L; Recommended Course of Action: Resume lenalidomide at the next lower dose. ~~level (10 mg or 5 mg) once daily. Do not decrease dose below 5 mg once daily.~~
6.4.2.2. Neutropenia (Table 5)	Neutropenia (Table 5): Neutrophil Count: When count first falls to <1.0 x 10^9/L; Recommended Course of Action: Interrupt lenalidomide treatment, ~~start~~ **consider** G-CSF treatment,~~-~~follow complete blood count weekly; Neutrophil Count: When count returns to ≥1.0 x 10^9/L and neutropenia is the only observed toxicity; Recommended Course of Action: Resume lenalidomide at 25 mg ~~once~~ daily **or initial starting dose** Neutrophil Count: When count returns to ≥1.0 x 10^9/L and dose-dependent hematological toxicities other than neutropenia are observed; Recommended Course of Action: Resume lenalidomide at ~~15 mg once daily~~ **the next lower dose** Neutrophil Count: When count returns to ≥1.0 x 10^9/L for each subsequent drop in count to <1.0 x 10^9/L; Recommended Course of Action: Resume lenalidomide at the next lower dose level ~~(15 mg, 10 mg, or 5 mg) once daily. Do not decrease dose below 5 mg once daily.~~
Rationale: Clarify that preinfusion medications are required.	
6.1.3. Prevention of Infusion Reactions	Remove 'guidelines' from Section 6.1.3 header to clarify that preinfusion medications are required.
Rationale: Align text with Amendment INT-3 which removed the whole blood sample for MRD assessment.	

Applicable Section(s)	Description of Change(s)
Synopsis; 3.1. Overview of Study Design; 9.5. Biomarkers	The following text is modified: An assessment of MRD will be conducted on ~~whole blood and~~ bone marrow samples. The following text is modified: In addition to planned bone marrow aspirate assessments, a whole blood sample will be collected from subjects as outlined in the Time and Events Schedule ~~for assessment of MRD and~~ for processing to plasma and PBMCs.
Rationale: Clarify the requirements to meet the primary endpoint of progression-free survival.	
9.1.3. Treatment Phase	Text is added: If disease progression has not occurred at the time of the End-of-Treatment visit, disease evaluations must continue until disease progression is confirmed. Subsequent anti-myeloma treatment will not be started until after disease progression is confirmed by the Sponsor.
Rationale: Clarify MRU procedures.	
Time and Events Schedule Overview; 9.6. Medical Resource Utilization	MRU is added to the Disease Evaluation portion of the Time and Events Schedule Overview. Text is modified: ~~Medical resource utilization (MRU) data, principally number of hospitalizations, will be derived from data collected in the eCRF for all subjects throughout the study.~~ **Medical resource utilization (MRU) data, including primary non-protocol driven hospitalizations, outpatient visits, and emergency room visits, should be collected in the eCRF (Hospitalization/Outpatient Visits CRF) by the Investigator and study-site personnel for all subjects throughout the study. Please see CRF completion guidelines.**
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-3 (2 November 2016)

This amendment is considered to be 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 International Myeloma Working Group (IMWG) has recently defined new categories of minimal residual disease (MRD)–negativity and has clarified several aspects of disease response assessment along with clinical trial endpoints (Kumar, 2016[16]). In order to align with the new categories of MRD-negativity, the timepoints for collection of bone marrow and whole blood for MRD assessment are revised.

Applicable Section(s)	Description of Change(s)
Rationale: Revision of the timepoints for the assessment of MRD-negativity required to align with newly defined IMWG categories	

Applicable Section(s)	Description of Change(s)
Time & Events Schedule (Bone marrow aspirate/biopsy; Blood sample for MRD) 9.2.1.5 Bone Marrow Examination (Table 9); 9.2.1.6 Minimal Residual Disease Assessment; 9.2.2 Endpoints	Text is revised and added to clarify sample timing for MRD assessment: To confirm CR/sCR, assess MRD, and evaluate PD (if feasible). Samples are requested at time of suspected CR/sCR and at 12, 18, 24 and 30 months post C1D1 (+/-1 month). If one of these time points occurs within 1 month of suspected CR, a repeat bone marrow will not be requested. These bone marrow tests will only be required if patient's response is near CR or better by blood and urine evaluations. See Section 9.2.1.5 for additional information including timepoints. The whole blood sample for MRD assessment is removed from the protocol; text is deleted to align with other daratumumab protocols. The following text is modified in Section 9.2.1.5: Additional bone marrow aspirates ~~or biopsies (or both)~~ will be performed to confirm sCR **and** CR~~, or relapse from CR~~ (only one analysis is required, with either IHC or immunofluorescence or 2- to 4- color flow cytometry included in the analysis) and to monitor for MRD **at time points detailed in Table 9**. ~~An additional bone marrow aspirate will be obtained 6, 12, and 18 months +/- 1 month after the achievement of CR to monitor for MRD.~~
Rationale: Secondary objectives modified for consistency with other daratumumab protocols.	
Synopsis; 2. Objectives and Hypothesis; 9.2.2 Endpoints; 11.3 Efficacy Analyses	Time to response is added to objectives and endpoints. This objective is modified: ~~To assess the minimal residual disease (MRD) negative rate after treatment~~ Changed to: **MRD negativity rate** This corresponding endpoint is added: To assess MRD negativity rate, defined as the proportion of subjects assessed as MRD negative, at any timepoint after the date of randomization. Durability of MRD negativity is added to exploratory objectives and endpoints. The order of secondary objectives and efficacy endpoints has been modified for consistency with other daratumumab protocols
Rationale: Criteria modified for the timing of contraception, sperm donation, pregnancy, and fathering a child for consistency across daratumumab protocols.	
4.1 Inclusion Criteria; 4.2 Exclusion Criteria; 4.3 Prohibitions and Restrictions	Inclusion criterion 6: Contraception must continue for **3** months after the last dose of daratumumab. Inclusion criterion 7: Men must not donate sperm for **3** months after the last dose of daratumumab. Excusion criterion 15: Revised pregnancy timing and for men not to father a child for **3** months after last dose of daratumumab. The change to 3 months is also revised in Prohibition and Restriction 1 and 3.
Rationale: Minor clarification regarding use of dexamethasone.	
4.2 Exclusion Criteria	Exclusion criterion 3: the following text is revised: (equivalent of dexamethasone 40 mg/day for ~~a maximum~~ 4 days)
Rationale: Clarifications in the Dosage and Administration section	
6. Dosage and Administration	In Figure 4 Schematic Overview Study Treatment Administration, the parenthetical phrase is deleted for dexamethasone "For 1 yr, 20 mg thereafter" is removed from dexamethasone to align figure with text.

Applicable Section(s)	Description of Change(s)
6.1.3.1 Preinfusion Medication	Text in the third bullet regarding dexamethasone is revised: Dexamethasone 40 mg IV (**preferred**) or PO ~~(only if IV is not available)~~, approximately 1 hour or less prior to daratumumab infusion. For subjects older than 75 years or underweight (body mass index [BMI] <18.5), dexamethasone 20 mg may be administered as appropriate (see Section 6.3). An equivalent intermediate-acting or long-acting corticosteroid may substitute (see Attachment 6 for conversion table). On days when subjects receive this dose of dexamethasone in the clinic, dexamethasone will not be self-administered at home. **If weekly dexamethasone dosing has been reduced below 10 mg due to adverse events during study, a minimum of dexamethasone 10 mg IV should continue to be administered prior to daratumumab infusions.**
6.2 Lenalidomide (Arm A and Arm B)	The following text is modified: On daratumumab infusion days, **it is recommended that lenalidomide should** be administered either prior to or at the same time (preferred) as the premedications. ~~The daratumumab infusion should begin approximately 1 hour after the lenalidomide administration~~.
6.4.1.1 Daratumumab-Related Toxicity Management	The following text is modified: **Other than on Day 1 of a cycle**, if a 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. **Day 1 of a cycle should not be skipped; however**, ~~If~~ Day 1 of a cycle ~~is~~ **may be** delayed, and Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration.
6.4.2 Lenalidomide Dose Reductions	The following text is added: After initiation of lenalidomide, subsequent lenalidomide dose adjustment is based on individual subject treatment tolerance. If the investigator determines that an adverse event may be related to lenalidomide, dose adjustment can be done even if not specified in this protocol.
6.4.2.3 Renal Impairment (Table 6, footnote a); Attachment 3 Calculated and Measured Creatinine Clearance	Text is added to specify that calculation of CrCl should be adjusted for body weight in subjects with a body mass index >30 kg/m^2.
6.4.2.4 Other Grade 3 or 4 Adverse Events	Heading is modified to remove "Grade 3 or 4" and the following text is added: Note that the dose modifications above are suggested, but physician discretion and clinical judgment should prevail.
6.4.3 Dexamethasone Dose Modifications	The following text is added: For other Grade 3 or 4 non-hematologic and non-renal toxicities judged by the investigator to be related to dexamethasone alone, treatment with dexamethasone should be interrupted and restarted at the next lower dose level once the toxicity has resolved to Grade 2 or less. Treatment with daratumumab and lenalidomide may continue. For complete details on dexamethasone, refer to the most current local product prescribing information. If weekly dexamethasone dosing has been reduced below 10 mg due to adverse events during study, a minimum of dexamethasone 10 mg IV should continue to be administered prior to daratumumab infusions.
Rationale: Text is added to clarify timing of urine collection for M-protein analysis.	
9.2.1.2 Myeloma Protein Measurements in Serum and Urine	The following text is added: If the 24-h urine collection (UPEP) began before informed consent was obtained as part of routine patient care, the sample can be used in this study as long as it was sent to the central lab for analysis after the informed consent was obtained.
Rationale: Text is modified to clarify imaging assessments for lytic disease.	

Applicable Section(s)	Description of Change(s)
9.2.1.7 Assessment of Lytic Disease	A complete skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease) is to be performed and evaluated ~~by the~~ locally ~~laboratory~~ by X-ray ~~roentgenography or the local standard of care imaging, eg,~~ or low-dose CT during the Screening Phase. Magnetic resonance imaging (MRI) may be included as an additional assessment at the discretion of the investigator; however, focal lesions identified by MRI alone cannot be counted as lytic disease.
Rationale: A list of anticipated events is added, consistent with other daratumumab studies.	
12.3.1 All Adverse Events; Attachment 10 Anticipated Adverse Events	Standard text on reporting of anticipated adverse events is added. The list of events is added to Attachment 10.
Rationale: Clarifications regarding CRAB criteria eligibility	
Attachment 1 Modified IMWG Diagnostic Criteria for Multiple Myeloma	The following text is added: Note: Subjects only meeting SLiM CRAB are not eligible. c) Hemoglobin measurement performed as part of standard of care within 42 days before randomization is acceptable for screening for CRAB criteria; but must be performed within 21 days before randomization for other eligibility requirements.
Rationale: Additional minor clarifications.	
Time & Events Schedule; 9.1.4 Follow-up Phase	In Follow-up, a window of ±2 weeks is added for after PD (Q16 wks). The following text is added to the first paragraph in 9.1.4: Every 16-week follow-up contacts should be scheduled from the date of confirmed progression. In subjects for whom disease progression will not be documented (eg, received subsequent anticancer treatment or refused disease evaluations, but agreed to follow-up contacts), the every 16-week follow-up should be scheduled from the date of the End of Treatment Visit.
8.1.5 Prophylaxis for Herpes Zoster Reactivation	Standard text for herpes zoster reactivation text is added. The following is revised: Prophylaxis for herpes zoster reactivation **is recommended during the Treatment Phase, as per institutional guidelines** ~~may be used at the discretion of the investigator.~~
9.2.1.1 Response Categories	The following text is added: For patients with measurable disease by SPEP or UPEP at baseline, increases in serum free light chains (FLC) or the FLC ratio alone do not meet criteria for progressive disease
9.8 Safety Evaluations	Minor changes in the serum chemistry panel: -blood urea nitrogen (BUN) **or urea** -total; direct bilirubin **(not required except in case of congenital bilirubinemia, such as Gilbert disease)** *New footnote*: *Sodium and potassium assessment were added in Protocol Amendment 2; however, collection of sodium and potassium results will be done retrospectively from the date of subject consent for the duration of the study, if collected as part of routine care
9.8 Safety Evaluations; 11.9 Safety Analyses; Time & Events Schedule	Text is modified to clarify vital signs: Descriptive statistics of **baseline** temperature, pulse/**heart rate**, and blood pressure (systolic and diastolic) values ~~and changes from baseline~~ will be summarized.
17.5 Case Report Form Completion	Template text is revised based on the current Janssen global protocol template.

Applicable Section(s)	Description of Change(s)
References	New references are added: Chapuy 2016 Kumar 2016
Attachment 7 Asthma Guidelines	Typo corrected for Persistent, Mild: >2 days/week but not daily.
Attachment 8 International Staging System	Typo corrected for Stage III: Serum ß$_2$ microglobulin ≥5.5 mg/L Typo corrected for Note 2: Serum ß$_2$ microglobulin 3.5 – 5.**4** mg/L
Title page	Janssen Sciences Ireland UC is added and Janssen Infectious Diseases BVBA is removed per the protocol template.
Abbreviations	SLiM is defined
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-2 (26 August 2015)

This amendment is considered to be 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: To incorporate Indirect Antiglobulin (Coombs) Testing (IAT) during the Screening Phase due to the risk of daratumumab interference with blood typing, as well as make updates throughout the protocol to align with the other daratumumab Phase 3 protocols and to incorporate regulatory agency feedback.

Applicable Section(s)	Description of Change(s)
Rationale: Due to risk of daratumumab interference with IAT testing, in addition to blood typing, subjects must also have IAT performed at screening.	
Time and Events Schedule Overview;	Blood type assessment **(ABO, Rh) and IAT** must be performed at screening and at C1D1 predose in Arm B only.
4.3 Prohibitions and Restrictions, Criterion #7	Removed the text pertaining to blood typing from here as this information is provided in Section 9.8 Safety Evaluations.
9.8 Safety Evaluations	Updated the requirement for blood typing and IAT results to align with other Phase 3 daratumumab protocols.
Rationale: Updated inclusion and exclusion criteria for clarity, to align with IMWG criteria, and to align with other Phase 3 daratumumab protocols.	

Applicable Section(s)	Description of Change(s)
4.1 Inclusion Criteria Criterion #2, bullet 2.1	**Criterion modified as per Amendment INT-2:** 2.1 Subject must have documented multiple myeloma satisfying the CRAB **(calcium elevation, renal insufficiency, anemia and bone abnormalities)** criteria (see Attachment 1), **monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma,** and measurable disease. • Measurable disease, **as assessed by central laboratory**, defined by any of the following: – IgG myeloma: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or – IgA, IgM, IgD, or IgE multiple myeloma: serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or – Light chain multiple myeloma **without measurable disease in serum or urine:** Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.
Criterion #5, bullet g1	Creatinine clearance ≥30 mL/min (for lenalidomide dose adjustment for subjects with creatinine clearance 30-**50** mL/min, refer to Section 6.2). Creatinine clearance can be calculated using the Cockcroft-Gault formula provided in Attachment 3; **or for subjects with over- or underweight, creatinine clearance may be measured from a 24-hours urine collection using the formula provided in Attachment 3**;--
Criterion #5, bullet h1	corrected serum calcium ≤14 mg/dL (≤3.5 **mM/L**); or free ionized calcium **≤6.5 mg/dL (≤1.6 mM/L)** (Attachment 4)
Criterion #6, bullet 6.1	Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously. This includes one highly effective form of contraception (tubal ligation, **intrauterine device [IUD], hormonal [progesterone-only birth control pills or injections** or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing **and must continue for 4 months after the last dose of daratumumab.** Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy. **(Also see Attachment 5: Lenalidomide Global Pregnancy Prevention Plan).**
4.2 Exclusion Criteria Criterion #8.1a and Criterion #8. 1b	Modified the criteria pertaining to subjects with COPD and severe persistent asthma to align with other Phase 3 daratumumab protocols. **8.1a) Subject has known chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) <50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal.** **8.1b) Subject has had known moderate or severe persistent asthma within the last 2 years (see Attachment 7), or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).** **Attachment 7: Asthma Guidelines was added.**

Applicable Section(s)	Description of Change(s)
Criterion #9.1	Subject is known to be seropositive for human immunodeficiency virus (HIV) or hepatitis B **(defined by a positive test for hepatitis B surface antigen [HBsAg] or antibodies to hepatitis B surface and core antigens [anti-HBs and anti-HBc, respectively])** or hepatitis C (**anti-HCV antibody positive or HCV-RNA quantitation positive).**
Rationale: Clarified that the visit window is not intended for all study visits, only intended for the start of a treatment cycle	
Time and Events Schedule Overview	Modified the second sentence: Study treatment should be initiated within 72 hours after randomization. **Day 1 of each cycle** ~~Each study visit~~ may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject.
Rationale: Clarified that if a full chest CT has been done, it is not necessary to perform an additional chest X-ray	
Time and Events Schedule Overview 9.1.2 Screening	Modified Procedures: Chest X-ray **(or full chest CT scan)**
Rationale: To clarify the timing of daratumumab PK sample collection on infusion days.	
Time and Events Schedule Overview 6.1.2 Daratumumab Administration	Modified Laboratory Assessments for Daratumumab PK sampling: Arm B only. On dara infusion days, 1 sample to be collected before **infusion start** (window -2 hrs) and 1 sample **to be collected** after **end of infusion** (window +2 hrs).~~infusion~~ 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 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.
Rationale: To clarify that vital signs 2 hours post end of infusion are not necessary	
Time and Events Schedule, Dose Administration	Modified Vital Signs Notes: On Cycle 1 Day 1: Immediately before the start of dara infusion; at 0.5, 1, 1.5, 2, 3.5 hrs after the start of the infusion; at end of infusion; and 0.5, **and** 1 hr after end of infusion.
Rationale: To allow for flexibility if preinfusion medications are administered orally.	
6.1.3.1 Time and Events Schedule, Dose Administration, Pre-infusion medications	• **An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent but avoid IV use of promethazine) approximately 1 hour prior to infusion (see Attachment 9 for list of antihistamines that may be used)** Added the sentence: **If necessary, all PO preinfusion medications may be administered outside of the clinic on the day of the infusion, provided they are taken within 3 hours before the infusion.**
Rationale: Removed the requirement that tracheostomy equipment needs to be available in case of infusion-related reactions.	
6.1.4 Management of Infusion Related Reactions	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 the bedside**~~. Attention to staffing should be considered when multiple subjects will be dosed at the same time.
Rationale: To reflect current practice, updated management of infusion-related reactions section to indicate that the infusion will be paused (not interrupted or slowed down) if an infusion-related reaction occurs.	

Applicable Section(s)	Description of Change(s)
6.1.4 Management of Infusion Related Reactions	If an infusion-related reaction develops, then the infusion should be **paused** ~~temporarily interrupted or slowed down~~. If an infusion is **paused** ~~or the infusion rate is decreased~~, then a longer-than-anticipated infusion time may occur.
Rationale: FEV1 measurement is not relevant for asthma assessment.	
Time and Events Schedule Overview; 9.8 Safety Evaluations	For subjects with COPD ~~and/or asthma~~, FEV1 should be measured at baseline.
6.1.3.2 Postinfusion Medications	For subjects with higher risk of respiratory complications (ie, subjects **with mild asthma, or subjects with COPD** who have a FEV1 <80%), the following postinfusion medications should be considered.
Rationale: Updated protocol to align with Revlimid US Package Insert and EU SmPC	
1.3 Lenalidomide	Added: **REVLIMID® (lenalidomide) in combination with dexamethasone was approved by both U.S. Food and Drug Administration and the European Commission for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant, on 18 February 2015 and 20 February 2015, respectively.**
6.2 Lenalidomide (Arm A and Arm B) 6.4.2.3 Renal Impairment	Lenalidomide will be self-administered at a dose of 25 mg PO each day on Days 1 through 21 of each 28 day cycle for subjects with creatinine clearance **>50** mL/min. If creatinine clearance is between 30 and **50** mL/min, the dose of lenalidomide will be 10 mg every 24 hours. Once the creatinine clearance is **>50** mL/min during the course of the treatment, lenalidomide can be increased to 25 mg. Lenalidomide dose adjustment should be instituted for subjects with a creatinine clearance of **50 mL/minute** or less. The recommended doses for subjects with multiple myeloma and renal impairment are shown in Table 6. **Table 6: Lenalidomide Dose Adjustment for Renal Impairment** **Category** / **Renal Function** / **Dose** Moderate renal impairment / 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
Rationale: To provide guidance on management of missed lenalidomide doses	
6.2 Lenalidomide (Arm A and Arm B)	Added the following 3rd paragraph: If a daily lenalidomide dose is missed, it may be taken if <12 hours have elapsed since the time that it should have been taken. If the next dose is scheduled to be taken within 12 hours, the missed lenalidomide dose should be skipped.
Rationale: Aligned language to be consistent with criteria in other Phase 3 protocols.	

Applicable Section(s)	Description of Change(s)
6.4.1.1 Daratumumab-Related Toxicity Management	The criteria for dose delay due to hematologic toxicity have been revised. • Grade 4 **hematologic toxicity** ~~thrombocytopenia or~~ • Grade 3 thrombocytopenia with bleeding • ~~**Grade 4 neutropenia, if this is the second occurrence despite growth factor support**~~ • Febrile neutropenia ~~of any grade~~ ----- ----**A missed dose will not be made up.**--- ---Doses of daratumumab may be delayed up to 4 weeks (Cycle 1 to Cycle 6) or up to 6 weeks **(Cycle 7 and beyond). If Day 1 of a cycle is delayed, Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. However, if a within-cycle dose is delayed, then the dates of the subsequent within-cycle doses should not be adjusted.** Any adverse event deemed to be related to daratumumab **that requires a dose hold of more than 4 weeks (Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond) will result in permanent discontinuation of daratumumab.----**
6.4.1.2 Daratumumab Interruption or Missed Doses	Subjects whose dose was delayed for more than 4 weeks **(Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond)** should have study treatment discontinued, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

Rationale: Changed per Irish Regulatory Authority request (aligned with lenalidomide SmPC and US Package Insert

6.4.2.2. Neutropenia

Modified Table 5 as below:

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

Rationale: Updated recommended therapies to prevent deep vein thrombosis and pulmonary embolism to align with IMWG criteria.

Applicable Section(s)	Description of Change(s)
8.1.1 Prevention of Deep Vein Thrombosis and Pulmonary Embolism	Text in Section 8.1.1 reworded. Lenalidomide has been associated with increased incidence of deep vein thrombosis and pulmonary embolism. **Therefore, prophylaxis of venous thromboembolism (VTE) for all subjects is recommended according to IMWG guidelines as well as at the investigator's discretion (Palumbo 2008). Both individual and myeloma-related risks of VTE should be taken into account in determining the type of thromboprophylaxis. In summary:** • **If no risk factor, or any one risk factor is present, aspirin 81-325 mg once daily is recommended or dose per institutional standards** • **If 2 or more risk factors are present, low molecular weight heparin (LMWH) (equivalent of enoxaparin 40 mg once daily) or full-dose warfarin, international normalized ratio (INR) 2-3, is recommended** • **If any myeloma therapy-related risk factor is present, then LMWH (equivalent of 40 mg enoxaparin once daily) or full-dose warfarin (target INR 2-3) is recommended** ~~all subjects should be prophylactically treated with aspirin at a dose of 100 to 150 mg PO 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.~~
Rationale: Clarification of the use of bisphosphonate after Cycle 1	
8.1.2 Bisphosphonate Therapy	After Cycle 1, investigators should not prescribe bisphosphonates to subjects who have not received it before, **unless it has been discussed with sponsor and there is no** sign of disease progression.
Rationale: Modification of the dexamethasone dose in both treatment arms and provides guidance on management of missed doses.	
Synopsis: Dosage and Administration 6.3 Dexamethasone (Arm A and Arm B)	Added sentence: **If a weekly dexamethasone dose is missed, it may be taken if <4 days have elapsed since the time that it should have been taken. If the next dose is scheduled to be taken within 3 days, the missed dexamethasone dose should be skipped.**
Rationale: Allows for flexibility in scheduling	
6 Dosage and Administration; 9.1.3 Treatment Phase	Inserted following sentence in 1st paragraph: **In Cycles 1 through 6, weekly or bi-weekly daratumumab infusions may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. In all cycles, weekly dexamethasone doses may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. Changes to within-cycle dosing should not impact Day 1 of the next cycle.** Also inserted new **Figure 4: Schematic Overview Study Treatment Administration** in Section 6
Rationale: Clarification of bone marrow examination requirements. Clinical staging must be done locally; no option for this to be done centrally.	

Applicable Section(s)	Description of Change(s)
9.2.1.5 Bone Marrow Examination	Bone marrow aspirate or biopsy will be performed at Screening for clinical **characterization** (morphology, **IHC or immunofluorescence or 2- to 4- color flow cytometry,** and cytogenetics), to establish baseline **multiple myeloma clonality** to monitor for MRD and to perform molecular subtyping to monitor daratumumab activity in high-risk molecular subgroups. Good quality slides are required for morphological examination to determine plasma cell percentage in the bone marrow. Assessment by flow cytometry alone is not sufficient. **Bone marrow examination for disease assessment ~~Clinical staging may~~ will be** performed locally; however, a portion of the bone marrow aspirate must be sent to the central **laboratory** for analysis of MRD and molecular subtyping. A fresh bone marrow aspirate at screening is required if at all possible, by exception non-decalcified diagnostic tissue (bone marrow aspirate slides or FFPE tissue) may be supplied for MRD assessment instead. Additional bone marrow aspirates or biopsies (or both) will be performed to confirm sCR, CR, or relapse from CR **(only one analysis is required, with either** IHC or immunofluorescence **or 2- to 4- color flow cytometry included in the analysis)** and to monitor for **MRD. An** additional bone marrow aspirate will be obtained 6, 12, and 18 months +/- 1 month after the achievement of CR to monitor for MRD. If feasible, a bone marrow aspirate may be collected from subjects at disease progression to evaluate mechanisms of daratumumab resistance. **Inserted Table 9. Bone Marrow Testing**

Applicable Section(s)	Description of Change(s)
Rationale: Description of Daratumumab interference with Indirect Antiglobulin Test (IAT) results.	
9.8 Safety Evaluations	Inserted the following: **Daratumumab Interference with Indirect Antiglobulin Test (IAT) results:** **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 a patient 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. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab IAT interference by treating reagent RBCs with dithiothreitol (DTT) (Chapuy 2015).** Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include: a) Providing ABO/RhD compatible, phenotypically or genotypically matched units b) Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using dithiothreitol (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. ~~Blood type assessment~~ ~~CD38 is expressed on erythrocytes to a minor extent. Hemolysis could occur following the infusion of daratumumab, which would confound the blood type assessment. To be cautious and in case of urgent need for blood transfusion, the subject's blood type, including minor group, will be assessed before the first infusion of daratumumab. Subjects in Arm B should at all times carry a card with their blood type during the study.~~

Applicable Section(s)	Description of Change(s)
Rationale: Inserted information per Irish Regulatory request	
12.1.1 Adverse Event Definitions and Classifications	Inserted: **Suspected Unexpected Serious Adverse Reactions (SUSARs)** **If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between 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). Refer to Section 12.3.3 for SUSAR Reporting Requirements.** ~~If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between 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).~~
12.3.3 Suspected Unexpected Serious Adverse Reactions	Added Section. **The sponsor assumes responsibility for appropriate reporting of all Suspected Unexpected Serious Adverse Reactions (SUSAR) [serious adverse events that are unlisted (unexpected) and associated with the use of the study drug] to the regulatory authorities in accordance with GCP. The sponsor will also report to the investigator (and the head of the investigational institute where required) all serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.**
Rationale: Attachment 1 was updated to be consistent with other Daratumumab protocols	
Attachment 1: Modified IMWG Diagnostic Criteria for Multiple Myeloma	Entire attachment updated to be consistent with other Daratumumab protocols
Rationale: Added for convenience by clinical operations (logistical purposes)	
Time and Events Schedule, Overview: Blood sample for MRD	For subjects who maintain CR, whole blood sample will also be obtained at 6, 12, and 18 months **± 1 month** after confirmed CR.
Rationale: Clarification of disease evaluation testing in Screening Phase	
Time and Events Schedule, Overview:	Added clarification on serum and urine disease evaluation at Screening in the Disease Evaluation section: Serum disease evaluations (SPEP): **X (Repeat on C1D1 if not within 14 days prior to C1D1)** Urine disease evaluations (UPEP): **X (Repeat on C1D1 if not within 14 days prior to C1D1)** Calcium, albumin, β_2-microglobulin: **X (Repeat calcium and albumin on C1D1 if not within 14 days prior to C1D1); don't repeat β_2-microglobulin**

Applicable Section(s)	Description of Change(s)
Rationale: Miscellaneous updates for clarity.	
Time and Events Schedule, Dose Administration	Removed the requirement to measure vital signs 2 hours after the end of infusion.
6.1.3.1 Preinfusion Medication	Change to bullet 3: An equivalent **intermediate-acting or** long-acting corticosteroid may substitute (see Attachment 6 for conversion table).
6.1.3.2 Postinfusion Medication	Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β_2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or ~~salbumatol~~ **salmeterol** ± inhaled corticosteroids for subjects with COPD)
8.3 Prohibited Therapies	Concomitant administration of any other antineoplastic therapy for the intention of treating multiple myeloma **and other cancers** not defined in the study protocol is prohibited. Nonsteroidal anti-inflammatory agents should be **used with caution in order** to prevent myeloma-related kidney disease.
9.2.1.8 Documentation of Extramedullary Plasmacytomas	To qualify for PR, the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have decreased by at least 50% ~~or 25%, respectively~~, and new plasmacytomas must not have developed (see the disease response criteria in Table 8).
9.5 Biomarkers	Biomarker assessments will focus on 2 main objectives including evaluating the ability of daratumumab + Rd to reduce MRD in subjects who achieve a complete response (compared to Rd alone) and to determine the clinical benefit (ORR, PFS, and OS) of daratumumab + Rd in high-risk molecular subtypes (del17p, t(4;14), **t(14;16)**, specific gene signatures, specific mutations).
Attachment 3: Calculated and Measured Creatinine Clearance	Added the formula to measure CrCL to the attachment:
5 Treatment Allocation and Blinding	Eligible subjects will be stratified by **International Staging System (I vs II vs III see Attachment 8),** region (North America vs Other), and age (<75 vs ≥75) and then randomized to treatment in a 1:1 ratio to either Treatment Arm A (Rd alone) or Treatment Arm B (daratumumab+Rd [DRd]). **A new Attachment 8 was added.**
6.1.3.1 Preinfusion Medication	**An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent but avoid IV use of promethazine) approximately 1 hour prior to infusion (see Attachment 9) for list of antihistamines that may be used).** Added Attachment 9.

Applicable Section(s)	Description of Change(s)
9.2.2 Endpoints, Secondary Endpoints	• Endpoints Overall response rate (ORR), defined as the proportion of subjects who achieve **PR or better**, according to the IMWG criteria, during or after the study treatment. • Duration of response, calculated from the date of initial documentation of a response **(PR or better)** to the date of first documented evidence of progressive disease, as defined in 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.
12.3.1 All Adverse Events	Subjects (or their designees, if appropriate) will be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study **and for at least 6 months after treatment ends** indicating the following: ---

Rationale: Hydrocortisone is not an adequate substitute for a glucocorticosteroid as it is a short acting corticosteroid. Per request of Swedish HA, hydrocortisone has been replaced with betamethasone as an acceptable substitute for pre-medication with dexamethasone, due to the short duration of action of hydrocortisone. Attachment 6 is modified accordingly.

Attachment 6: Conversion Table for Glucocorticosteroid Dose

Removed hydrocortisone (20 mg) because it is short-acting and therefore not an adequate substitution.

Generic Name	Oral or Intravenous Dose (mg)
Dexamethasone	0.75
~~Hydrocortisone~~	~~20~~
Methylprednisolone	4
Prednisolone	5
Prednisone	5
Betamethasone	**0.6**

Rationale: Minor errors were noted.

Throughout the protocol

Minor grammatical, formatting, abbreviations or spelling changes were made.

Amendment INT-1 (29 October 2014)

This amendment is considered to be 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: To incorporate investigator feedback into the protocol and to further clarify MRD monitoring.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify that when a subject discontinues lenalidomide/dexamethasone study treatment on Arm B, they would still continue to receive dexamethasone as premedication.	
Synopsis, Overview of Study Design; 3.1 Overview of Study Design; 6.3 Dexamethasone (Arm A and Arm B)	Text was added to indicate that subjects will continue to receive dexamethasone as a premedication for daratumumab administration even after the lenalidomide/dexamethasone treatment is discontinued.
Rationale: To allow for a bone marrow biopsy or aspirate (or both) to confirm CR.	
Time and Events Schedule Overview; 9.2.1.5 Bone Marrow Examination	Additional bone marrow aspirates or biopsies (or both) will be performed to confirm sCR, CR, or relapse from CR (IHC or immunofluorescence) and to monitor for MRD. Only 1 bone marrow sample is required, with either IHC or immunofluorescence included in the analysis. For subjects who maintain CR, fresh aspirate will also be obtained at 6 and 12 months +/- 1 month after confirmed CR to monitor for MRD. A portion of all bone marrow tissues may be used for other biomarker assessments
Rationale: To allow for the possibility of stopping treatment ≥24 months based on MRD status, an additional time point of 18 months was added for collection of fresh aspirate and a whole blood sample after confirmed CR to monitor MRD.	
Synopsis, Efficacy Evaluations/Endpoints; Time and Events Schedule Overview; 9.2.1.5 Bone Marrow Examination; 9.2.1.6 Minimal Residual Disease Assessment; 9.2.2 Endpoints	Text was added to indicate that for subjects with confirmed CR, an additional bone marrow aspirate and whole blood sample will be obtained 6, 12, and **18** months +/- 1 month to monitor for MRD.
Rationale: To indicate that bone marrow aspirate or biopsy performed at Screening for clinical staging will be analyzed for morphology and via cytogenetics, only.	
9.2.1.5 Bone Marrow Examination	Bone marrow aspirate or biopsy will be performed at Screening for clinical staging (morphology and cytogenetics~~, and immunohistochemistry [IHC] or immunofluorescence or flow cytometry~~) to establish baseline multiple myeloma clonality, to monitor for MRD, and to perform molecular subtyping to monitor daratumumab activity in high-risk molecular subgroups.
Rationale: To clarify that good quality slides are required for morphological examination to determine plasma cell percentage in the bone marrow.	
9.2.1.5 Bone Marrow Examination	Good quality slides are required for morphological examination to determine plasma cells percentage in the bone marrow. Assessment by flow cytometry alone is not sufficient

Applicable Section(s)	Description of Change(s)
Rationale: To include clarithromycin as a prohibited therapy because it may have potential anti-multiple myeloma effects when combined with lenalidomide and dexamethasone.	
8.3 Prohibited Therapies	Added clarithromycin as a prohibited therapy.
Rationale: To exclude subjects with uncontrolled cardiac arrhythmias (thereby allowing participation of subjects with controlled cardiac arrhythmias).	
4.2 Exclusion Criteria	Subject has clinically significant cardiac disease, including: • myocardial infarction within 1 year before randomization, or an unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III IV • **uncontrolled** cardiac arrhythmia (NCI CTCAE Version 4 Grade ≥2) or clinically significant ECG abnormalities • screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >470 msec
Rationale: To clarify that the secondary objective and secondary endpoint is to assess the MRD negative rate.	
Synopsis, Secondary Objectives; 2.1 Objectives	To assess the MRD negative rate after treatment
Synopsis, Efficacy Evaluations/Endpoints; 9.2.2 Endpoints	Assess MRD negative rate, as measured in subjects who achieve CR/sCR, at 6 and 12 months after confirmed CR.
Rationale: To align PRO and ECOG performance status evaluations with study visits.	
Time and Events Schedule Overview	Evaluations will be conducted on D1 of Cycle 3, 6, 9, 12 for year 1; every 6th cycle thereafter until EOT (PD). Post-PD evaluations will be collected at Weeks 8 and 16.
Rationale: Added a PRO evaluation at Screening which will allow the PRO assessment conducted during the study to be compared with baseline.	
Time and Events Schedule Overview	Added an assessment during the Screening Phase for the PROs: EORTC-QLQ-30, EQ-5D-5L.
Rationale: To clarify that all PRO measures will be collected via an electronic device (ePRO) and the mode of data transfer.	
Time and Events Schedule Overview; 9.7 Patient Reported Outcomes	All PRO measures will be collected via an electronic device (ePRO).
17.6 Data Quality Assurance/Quality Control	PRO data will be transmitted to the ePRO vendor database and then to the sponsor's database.
Rationale: To clarify the administration schedule of daratumumab, in particular, starting at Cycle 7 and beyond, treatment will be every 4 weeks rather than monthly.	
Synopsis, Overview of Study Design; 3.1 Overview of Study Design	For subjects assigned to DRd, daratumumab will be administered weekly for the first 8 weeks (Cycles 1-2) of treatment and then every other week for 16 weeks (Cycles 3-6), then every 4 weeks (from Cycle 7 and beyond) until disease progression or unacceptable toxicity.

Applicable Section(s)	Description of Change(s)
Rationale: To revise the inclusion criteria to align with the other protocols in the daratumumab program.	
4.1 Inclusion Criteria	total bilirubin ≤**2.0** x ULN, except in subjects with congenital bilirubinemia, such as Gilbert syndrome **(direct bilirubin ≤2.0 x ULN);** corrected serum calcium ≤14 mg/dL (≤3.5 **mM/L**); or free ionized calcium **<6.5 mg/dL (<1.6 mM/L)**
Rationale: To align the creatinine clearance calculation with the other protocols in the daratumumab program.	
4.1 Inclusion Criteria	g) Creatinine clearance ≥30 mL/min (for lenalidomide dose adjustment for subjects with creatinine clearance 30-60 mL/min, refer to Section 6.2). Creatinine clearance may be calculated using the Cockcroft-Gault formula provided in Attachment 3
Attachment 3	Added the Cockcroft-Gault formula for Calculated Creatinine Clearance.
Rationale: To align the criteria for a dose delay with the other protocols in the daratumumab program.	
6.4.1.1 Daratumumab-Related Toxicity Management	Grade 4 thrombocytopenia was added to the criteria for a dose delay.
Rationale: To further clarify procedures not considered to be major surgeries.	
4.2 Exclusion Criteria	Included vertebroplasty as a procedure that is not considered to be a major surgery.
Rationale: To specify the timing of lenalidomide administration and to align with other protocols in the daratumumab program.	
6.2 Lenalidomide (Arm A and Arm B)	On daratumumab infusion days, lenalidomide will be administered at the same time as the premedications. The daratumumab infusion should begin approximately 1 hour after the lenalidomide administration.
Rationale: Fixed typographical errors whereby the sample size remained the same, but the assumptions were corrected.	
Synopsis, Statistical Methods; 11.2 Sample Size Determination	The sample size calculation is performed on the basis of the following assumption. Based on the published data, the median PFS for Rd arm is assumed to be approximately **24** ~~6~~ months. Assuming that DRd can reduce the risk of the disease progression or death by 25%, ie, assuming the hazard ratio (DRd vs Rd) of **0.75** ~~0.724~~, a total of 390 PFS events is needed to achieve a power of **80%** ~~85%~~ to detect this hazard ratio with a log-rank test (two-sided alpha is 0.05). With a 21-month accrual period and an additional 24-month follow-up, the total sample size needed for the study is approximately 730 (365/arm) subjects. The sample size calculation has taken into consideration an annual dropout rate of 5%.
Rationale: Because dexamethasone in IV formulation is not available in some countries, the PO administration of dexamethasone is permitted (only when IV is not available).	
Time and Events Schedule, Dose Administration; 6.1.3.1 Preinfusion Medication	Dexamethasone 40 mg **IV or PO (only if IV is not available)**
Rationale: To make the administration of drug medication more convenient for patients.	
6.2 Lenalidomide (Arm A and Arm B)	On daratumumab infusion days, lenalidomide will be administered **either prior to or** at the same time **(preferred)** as the premedications.

Applicable Section(s)	Description of Change(s)
Rationale: To align with other protocols in the daratumumab program.	
14.4 Preparation, Handling, and Storage	Clarified that daratumumab must be protected from light. Clarified that daratumumab infusion solution prepared for administration does not need to be stored in a refrigerator. Clarified that the daratumumab infusion solution does not need to be kept at room temperature for approximately 1 hour before the start of infusion and that the infusion does not have to be completed within 24 hours of preparation. Added that daratumumab will be diluted in a sterile, pyrogen-free physiological saline solution (0.9%NaCl) prior to IV administration. Included that additional guidance can be found in the Investigational Product Preparation Instructions and Investigational Product Procedures Manual.
6.1.3.1 Preinfusion Medication	Preinfusion medications for subjects receiving daratumumab will be administered as described in the Time and Events Schedules. On daratumumab infusion days, subjects will receive the following medications prior to infusion: • Acetaminophen (paracetamol) 650-1000 mg IV or orally (PO) **approximately** 1 hour or less prior to daratumumab infusion • An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent) approximately ~~12 hours prior and again approximately~~ 1 hour prior to infusion ~~on Cycle 1 Day 1, for all subsequent infusions approximately 1 hour prior~~ • Dexamethasone 40 mg IV or PO, **approximately** 1 hour or less prior to daratumumab infusion. Dexamethasone 20 mg may be administered as appropriate [see Section 6.3]. An equivalent long-acting corticosteroid may substitute [see Attachment 6 for conversion table]. On days when subjects receive this dose of dexamethasone in the clinic, dexamethasone will not be self-administered at home.
Rationale: Miscellaneous grammatical, formatting, or spelling changes were made for consistency and clarification.	
Time and Events Schedule, Dose Administration; 6.1.3.1 Preinfusion Medication	For consistency with other parts of the protocol, added the below bolded text and removed the text in strikeout. Administer **approximately** 1 hour before daratumumab infusion. • Dexamethasone 40 mg IV or PO **(only if IV is not available)**. **For subjects older than 75 years or underweight (BMI <18.5), see Section 6.3**. Substitutions for dexamethasone allowed, see Attachment 6. • An antihistamine (diphenhydramine 25-50 mg **IV or PO**, or equivalent) ~~on C1D1 administer 12 hours before infusion and again 1 hr before infusion~~ • Acetaminophen (paracetamol) 650-1000 mg **IV or PO**
Synopsis, Overview of Study Design; 3.1 Overview of Study Design; 5 Treatment Allocation	Amended the stratification factor wording to "International ~~Scoring~~ **Staging** System" to be consistent with the proper nomenclature.
6.4.1.1 Daratumumab-Related Toxicity Management	To emphasize the criteria when to stop daratumumab, bolded and underlined the following sentence: **ONLY if any of the following criteria are met, and the event cannot be ascribed to lenalidomide, the daratumumab infusion must be held to allow for recovery from toxicity**. Clarified that any adverse event deemed to be related to daratumumab **and unrelated to lenalidomide** that requires a dose hold of more than 4 weeks will result in permanent discontinuation of daratumumab.
Time and Events Schedule Overview	Clarified that both PRO questionnaires and ECOG performance status must be administered and completed prior to any other study procedures or assessments for that study visit. Clarified that β_2-microglobulin will be evaluated at screening only. Clarified that EOT is part of the Treatment Phase of the study.

Applicable Section(s)	Description of Change(s)
4.2 Exclusion Criteria	Removed intolerance to lenalidomide from exclusion criteria 12 because subjects in this study are newly diagnosed multiple myeloma patients and have never been exposed to lenalidomide.
Synopsis, Overview of Study Design; Time and Events Schedule, Dose Administration; 3.1 Overview of Study Design; 6.1.3.1 Preinfusion Medication	Provided the generic name for paracetamol (acetaminophen), as this is a global study
14.2 Physical Description of Study Drug	Clarified that the daratumumab supplied for this study is a colorless to ~~slightly~~ yellow liquid and sterile concentrate of 20 mg/mL in a vial.
1.1.3 Transplant-ineligible Population; 1.3 Lenalidomide; 3.2 Study Design Rationale	Updated the reference to the Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide (FIRST) study (previously referred to in protocol as MM-020 study), with citation to the recently published NEJM publication.
Synopsis, Overview of Study Design; Time and Events Schedule, Dose Administration; 3.1 Overview of Study Design; 3.2 Study Design Rationale; 6.2 6.2 Lenalidomide (Arm A and Arm B); 6.3 Dexamethasone (Arm A and Arm B)	To be consistent throughout the protocol, text was added that treatment would continue until disease progression **or unacceptable toxicity**.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High Dose Therapy

Daratumumab is a human IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38, such as plasma cells from patients with multiple myeloma. This target is distinct from those of other approved agents for multiple myeloma therapy.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective is to compare the efficacy of daratumumab when combined with lenalidomide and dexamethasone (DRd) to that of lenalidomide and dexamethasone (Rd), in terms of progression-free survival (PFS) in subjects with newly diagnosed myeloma who are not candidates for high dose chemotherapy and autologous stem cell transplant.

Secondary Objectives

The secondary objectives are:

- To evaluate clinical outcomes including:
  - Time to disease progression (TTP)
  - CR rate
  - MRD negativity rate
  - PFS2 (defined as time from randomization to progression on the next line of therapy or death, whichever comes first)
  - Overall survival
  - Time to next treatment
  - Stringent CR (sCR) rate
  - Overall response rate (partial response [PR] or better)
  - Proportion of subjects who achieve very good partial response (VGPR) or better
  - Time to response
  - Duration of response
- To assess the safety and tolerability of daratumumab when administered in combination with Rd.
- To assess the pharmacokinetics of daratumumab in combination with Rd.
- To assess the immunogenicity of daratumumab.
- To evaluate treatment effects on patient reported outcomes and heath economic/resource utilization
- To evaluate the clinical efficacy of daratumumab combination with Rd in high-risk molecular subgroups

Exploratory Objectives

- To explore biomarkers predictive of response or resistance to therapy
- To assess durability of MRD negativity

Hypothesis

The primary hypothesis of this study is that daratumumab in combination with Rd will prolong PFS as compared with Rd alone in subjects with newly diagnosed multiple myeloma who are ineligible for high dose chemotherapy and autologous stem cell transplant.

OVERVIEW OF STUDY DESIGN

This is a randomized, open-label, active controlled, parallel-group, multicenter study in subjects at least 18 years of age with newly diagnosed multiple myeloma who are not candidates for high dose chemotherapy and ASCT. Approximately 730 subjects will be enrolled in this study with 365 subjects planned per treatment arm.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 21 days before Cycle 1, Day 1. The Treatment Phase will extend from Day 1 of Cycle 1 until discontinuation of all study treatment. For subjects assigned to DRd, daratumumab will be administered weekly for the first 8 weeks (Cycles 1-2) of treatment and then every other week for 16 weeks (Cycles 3-6), then every 4 weeks (from Cycle 7 and beyond) until disease progression or unacceptable toxicity. This will equate to 9 consecutive weeks of dosing at the start of the study and a total of 23 doses in the first year. Lenalidomide will be administered at a dose of 25 mg orally (PO) on Days 1 through 21 of each 28-day cycle, and dexamethasone will be administered at a dose of 40 mg once a week. Subjects in both treatment arms will continue lenalidomide and dexamethasone until disease progression or unacceptable toxicity. Subjects in the DRd arm will continue on daratumumab until disease progression or unacceptable toxicity. Randomization will be stratified by International Staging System (I vs II vs III), region (North America vs Other), and age (<75 vs ≥75), using an equal allocation ratio of 1:1.

Measures to prevent infusion-related reactions will include preinfusion medication with dexamethasone, acetaminophen (paracetamol), and an antihistamine before each daratumumab infusion.

The Follow-up Phase will begin once a subject discontinues all study treatments. Subjects who discontinue for reasons other than disease progression must continue to have disease evaluations according to the Time and Events Schedule. The Follow-up Phase will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first. After the clinical cut-off (see below for definition), data collection will be reduced as per Section 9.1.4.

Two interim analyses are planned. The first interim analysis, with a purpose to evaluate safety, will be performed after a total of approximately 100 subjects have been treated for at least 8 weeks or discontinued the study treatment. The second interim analysis will be performed when 234 PFS events, which are 60% of the total planned events, have been accumulated. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. The significance level at this interim analysis to establish the superiority of DRd over Rd with regard to PFS will be determined based on the observed number of PFS events at the interim analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. If the experimental arm (DRd) is numerically worse than the control arm in terms of PFS (observed hazard ratio >1 favoring the control arm), then the study may be terminated for futility.

The primary PFS analysis will occur when approximately 390 PFS events have been observed. The date established for the primary PFS analysis will serve as the clinical cut-off date, after which data collection

in the study will be reduced as per Section 9.1.4. Investigators will be informed when each interim analysis is to occur.

The end of the study will occur when 330 subjects have died, or 7 years after the last subject is randomized, whichever comes first. The sponsor will ensure that subjects benefiting from treatment with daratumumab will be able to continue treatment after the end of the study.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study to review efficacy and safety results at the planned interim analyses. After the interim review, they will make recommendations regarding the continuation of the study. In addition, the IDMC may also review cumulative safety data every 6 months besides the 2 interim analyses.

Assessment of tumor response and disease progression will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria. An assessment of MRD will be conducted on bone marrow samples. Safety evaluations will include adverse event monitoring, physical examinations, electrocardiogram (ECG) monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status. Blood samples will be drawn for assessment of pharmacokinetic parameters.

SUBJECT POPULATION

Key eligibility criteria include the following: subjects who are ≥18 years of age, have a confirmed diagnosis of symptomatic multiple myeloma and measurable secretory disease, an ECOG performance status score of 0, 1, or 2, must be newly diagnosed and not considered candidates for high-dose chemotherapy with stem cell transplantation (SCT).

DOSAGE AND ADMINISTRATION

Daratumumab (16 mg/kg) will be administered by IV infusion to subjects in Arm B initially once every week for 8 weeks; then once every other week for 16 weeks; thereafter once every 4 weeks until documented progression, unacceptable toxicity, or study end.

Lenalidomide will be self-administered at a dose of 25 mg PO each day on Days 1 through 21 of each 28 day cycle.

Dexamethasone (or equivalent in accordance with local standards; see Attachment 6 for conversion table) will be administered at a total dose of 40 mg weekly.

EFFICACY EVALUATIONS/ENDPOINTS

Disease evaluations must be performed every 28 days for the first 2 years and then every 8 weeks until disease progression (or other reasons as per Section 10). A window of ±7 days is allowed. If treatment has been delayed for any reason, the disease evaluations must be performed according to schedule, regardless of any changes to the dosing regimen.

The primary endpoint is PFS, which is defined as the duration from the date of randomization to either progressive disease, or death, whichever occurs first. Disease progression will be determined according to the IMWG criteria.

The secondary efficacy endpoints include:

- Time to disease progression (TTP) is defined as the time from the date of randomization to the date of first documented evidence of PD, as defined in the IMWG criteria. For subjects who have not progressed, data will be censored at the date of the disease evaluation before the start of any subsequent anti-myeloma therapy.
- CR rate, defined as the percentage of subjects achieving CR, as defined:

  - Negative immunofixation of serum and urine, and
  - Disappearance of any soft tissue plasmacytomas, and
  - <5% plasma cells (PCs) in bone marrow
  - For those subjects with negative serum M-protein quantitation by electrophoresis (SPEP) and suspected daratumumab interference on immunofixation, a reflex assay using anti-idiotype antibody will be utilized to confirm daratumumab interference and rule out false positive immunofixation. Patients who have confirmed daratumumab interference, but meet all other clinical criteria for CR or sCR, will be considered CR/sCR.

- MRD negativity rate, defined as the proportion of subjects assessed as MRD negative, at any timepoint after the date of randomization.
- Progression-free Survival on Next line of Therapy (PFS2), defined as the time from randomization to progression on the next line of treatment or death, whichever comes first. Disease progression will be based on investigator judgment. For those subjects who are still alive and not yet progressed on the next line of treatment, they will be censored on the last date of follow-up.
- Overall survival (OS), 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.
- Time to next treatment, defined as the time from randomization to the start of the next-line treatment.
- sCR rate, defined as the percentage of subjects achieving CR in addition to having a normal free light chain (FLC) ratio and an absence of clonal cells in bone marrow by immunohistochemistry, immunofluorescence, 2-4 color flow cytometry
- Overall response rate (ORR), defined as the proportion of subjects who achieve PR or better, according to the IMWG criteria, during or after the study treatment.
- Proportion of subjects who achieve VGPR or better, defined as the proportion of subjects achieving VGPR and CR (including sCR) according to the IMWG criteria during or after the study treatment at the time of data cutoff.
- Time to response, defined as the time between the randomization and the first efficacy evaluation that the subject has met all criteria for PR or better. For subjects without response, data will be censored either at the date of progressive disease or, in the absence of progressive disease, at the last disease evaluation before the start of subsequent anti-myeloma therapy.
- Duration of response, calculated from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, as defined in 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.
- To evaluate clinical efficacy of DRd in high risk molecular subgroups compared to Rd alone.
- To evaluate the impact of DRd compared to Rd on patient-reported perception of global health.

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

For all subjects in Arm B, pharmacokinetic samples to determine serum concentration of daratumumab will be obtained according to the Time and Events Schedule. Venous blood samples (5 mL per sample) will be collected to determine serum concentration of daratumumab and the serum will be divided into 3 aliquots (1 aliquot for pharmacokinetic analysis, 1 aliquot for antibodies to daratumumab analysis [when appropriate], and 1 aliquot as a backup).

BIOMARKER EVALUATIONS

Bone marrow aspirates will be collected at screening and following treatment as outlined in the Time and Events Schedule. Baseline bone marrow aspirate samples will be subjected to DNA and RNA sequencing in order to classify subjects into high-risk molecular subgroups and to establish the myeloma clone for MRD monitoring.

In addition to planned bone marrow aspirate assessments, a whole blood sample will be collected from subjects as outlined in the Time and Events Schedule for processing to plasma and PBMCs.

SAFETY EVALUATIONS

Safety will be measured by adverse events, laboratory test results, ECGs, vital sign measurements, physical examination findings, and assessment of ECOG performance status score.

STATISTICAL METHODS

The sample size calculation is performed on the basis of the following assumption. Based on the published data, the median PFS for Rd arm is assumed to be approximately 24 months. Assuming that DRd can reduce the risk of the disease progression or death by 25%, ie, assuming the hazard ratio (DRd vs Rd) of 0.75, a total of 390 PFS events is needed to achieve a power of 80% to detect this hazard ratio with a log-rank test (two-sided alpha is 0.05). With a 21-month accrual period and an additional 24-month follow-up, the total sample size needed for the study is approximately 730 (365/arm) subjects. The sample size calculation has taken into consideration an annual dropout rate of 5%.

Long-term survival follow-up will continue until 330 deaths have been observed or 7 years after the last subject is randomized. Therefore, this study will achieve approximately 80% power to detect a 27% reduction in the risk of death (hazard ratio = 0.73) with a log-rank test (two-sided alpha = 0.05).

Response to study treatment and progressive disease will be evaluated by a computer algorithm. For the primary endpoint of PFS, the primary analysis will consist of a stratified log rank test for the comparison of the PFS distribution between the 2 treatment arms. The Kaplan-Meier method will be used to estimate the distribution of overall PFS for each treatment. The treatment effect (hazard ratio) and its two-sided 95% confidence intervals are to be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

TIME AND EVENTS SCHEDULE OVERVIEW

	Notes	Screening Phase	Treatment Phase		Follow-up Phase	
		within 21 days before randomization	Day 1 of each cycle (28-day cycles)	EOT within 30 days of last dose	Prior to PD	After PD (Q16wks) ±2 wks
Study treatment should be initiated within 72 hours after randomization. Day 1 of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. After EOT, subjects in both treatment arms prior to PD will continue to return for disease evaluations. After PD is documented, subjects will be followed for survival, PFS2; second primary malignancies, and subsequent anticancer therapy. After the clinical cut-off date, disease evaluations are no longer required and data collection will be reduced as per Section 9.1.4.						
Procedures						
Informed consent	ICF must be signed before any study-related procedures					
Eligibility criteria		X				
Demography/ Medical History		X				
Height		X				
Chest X-ray (or full chest CT scan)	Acceptable for screening if performed as part of SOC within 42 days before randomization	X				
PFT	For subjects with COPD, FEV1 should be measured	X				
ECOG	Prior to any other study procedures planned for the same day	X	D1 of Cycle 3, 6, 9, 12 for year 1; every 6th cycle thereafter until EOT (PD). Post-PD collect at Wks 8 and 16.			
12-lead ECG	Acceptable for screening if performed as part of SOC within 42 days before randomization	X	C3D1, C6D1	X		
Physical exam	including neurological exam	X	symptom and disease directed exam as clinically indicated			
Vital signs, weight		X	Please see following table for details.			
Blood type and IAT	ABO, Rh, and IAT. A wallet card with the subject's blood type and IAT will be provided to subjects randomized to Arm B.	X	C1D1 predose, Arm B only			
Laboratory Assessments						
Pregnancy test	For women of childbearing potential only. During screening, within 10-14 days prior to first dose and again within 24 hrs prior to first dose. Minimum testing requirements during study: weekly during Cycle 1 and then monthly in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Please refer to Section 9.8 for details.			X		
Hematology		X	Please see following table for details.	X		
Serum chemistry		X	Please see following table for details.	X		
Daratumumab PK	Arm B only. On dara infusion days, 1 sample to be collected before infusion start (window -2 hrs) and 1 sample to be collected after end of infusion (window +2 hrs). Samples to be sent to central laboratory.		C1D1, C6D1, C12D1	X	8 wks after last dara dose	

	Notes	Screening Phase	Treatment Phase		Follow-up Phase	
		within 21 days before randomization	Day 1 of each cycle (28-day cycles)	EOT within 30 days of last dose	Prior to PD	After PD (Q16wks) ±2 wks
						Abbreviations at end of table
Daratumumab immunogenicity	Arm B only. No additional sample needed; will be taken from PK sample. If an infusion reaction occurs, obtain unscheduled blood sample as soon as possible.		predose C1D1 only	X	8 wks after last dara dose	
Whole blood	Plasma or PBMC biomarker assessments		predose C1D1 only	X		
Disease Evaluations: Every effort should be made to conduct disease evaluations as per schedule (window ± 7 days). Refer to Section 9.2 for details on efficacy evaluations						
Serum disease evaluations (SPEP)	Sample to be sent to central laboratory. IFE and FLC when CR is suspected or maintained. FLC every cycle for subjects with light chain only myeloma.	X (Repeat on C1D1 if not within 14 days prior to C1D1)	X (for first 2 years and then every 8 wks until PD)			
Urine disease evaluations (UPEP)	Sample to be sent to central laboratory. IFE when CR is suspected or maintained.	X (Repeat on C1D1 if not within 14 days prior to C1D1)	X (for first 2 years and then every 8 wks until PD)			
Calcium, albumin, β_2-microglobulin	Sample to be sent to central laboratory. β_2-microglobulin at screening only.	X (Repeat calcium and albumin on C1D1 if not within 14 days prior to C1D1); don't repeat β2-microglobulin	calcium/albumin every cycle for first 2 years and then every 8wks until PD			
Bone marrow aspirate/biopsy	For screening (up to 42 days before randomization) fresh aspirate or biopsy preferred. If not available, obtain non-decalcified tissue according to Section 9.2.1.5 Table 9 and/or FFPE tissue. Fresh biopsy or aspirate (or both) required to confirm CR/sCR. Samples for biomarker analysis to be sent to central laboratory	X	To confirm CR/sCR, assess MRD, and evaluate PD (if feasible). Samples are requested at time of suspected CR/sCR and at 12, 18, 24 and 30 months post C1D1 (+/-1 month). If one of these time points occurs within 1 month of suspected CR, a repeat bone marrow will not be requested. These bone marrow tests will only be required if patient's response is near CR or better by blood and urine evaluations. See Section 9.2.1.5 for additional information including timepoints.			
Quantitative Ig	See Section 9.2.1.2	X	every 3 months	X		
Assessment of lytic disease	Acceptable for screening if performed within 42 days before randomization	X	As clinically indicated, using the same methodology as used at screening			

	Notes	Screening Phase	Treatment Phase		Follow-up Phase	
		within 21 days before randomization	Day 1 of each cycle (28-day cycles)	EOT within 30 days of last dose	Prior to PD	After PD (Q16wks) ±2 wks
Extramedullary plasmacytomas	Subjects with history of plasmacytoma; acceptable for screening if performed within 42 days before randomization	X	If applicable, by physical exam every 4 wks, by radiologic exam (if required) every 12 wks using same methodology as used at screening; for subjects with history of plasmacytoma assessed by physical exam, repeat assessment on C1D1 if not done within 14 days prior to randomization			
PRO	EORTC-QLQ-30, EQ-5D-5L Both questionnaires must be administered and completed prior to any other study procedures or assessments for that study visit. All PRO measures will be collected via an electronic device (ePRO).	X	D1 of Cycle 3, 6, 9, 12 for year 1; every 6th cycle thereafter until EOT (PD). Post-PD collect at Wks 8 and 16.			
MRU			Continuous from C1D1 until End of Treatment (see Section 9.6)			
Follow-up						
Survival, PFS2, second primary malignancy, subsequent anticancer therapy						Q16wk
Ongoing Subject Review						
Adverse Events	See Section 12 for detailed instructions.	continuous from the time of signing of ICF until 30 days after last dose of last study drug				
Concomitant Medications	See Section 8 for detailed instructions.	continuous from the time of signing of ICF until 30 days after last dose of last study drug				

Abbreviations for Time and Events Tables:
AE=adverse event; BMI=body mass index; C=cycle; COPD=chronic obstructive pulmonary disease; CR=complete response; ECOG=Eastern Cooperative Oncology Group; D=day; Dara=daratumumab; ECG=electrocardiogram; EOT= End-of-Treatment; ePRO= electronic patient reported outcomes; FEV1= Forced Expiratory Volume (in 1 second); FFPE=formalin-fixed paraffin embedded; FLC=free light chain; IAT= indirect antiglobulin test; ICF=informed consent form; IFE=immunofixation; Ig=immunoglobulin; IV= intravenous; MRD=minimal residual disease; MRI=magnetic resonance imaging; MRU=medical resource utilization; PBMC= peripheral blood mononuclear cell; PFT=pulmonary function test; PFS2= time from randomization to progression on the next line of therapy or death, whichever comes first; PK=pharmacokinetics; PD= disease progression; PO= per oral; PRO=patient reported outcomes; Q(3)(6)mo=every (3)(6) months; Q16wk=every 16 weeks; SAE=serious adverse event; sCR=stringent complete response; SIPPM= Site Investigational Product Procedures Manual (or equivalent document); SPEP=serum M-protein quantitation by electrophoresis; UPEP=urine M-protein quantitation by electrophoresis; Wk=week

TIME AND EVENTS SCHEDULE, DOSE ADMINISTRATION

	Notes	Cycle 1 and Cycle 2				Cycle 3 to Cycle 6		Cycle 7 and after	EOT
		D1	D8	D15	D22	D1	D15	D1	
The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. The start of each cycle should be scheduled relative to Cycle 1 Day 1 and should not change if visits have shifted within the allowed window.									
Hematology	For Cycle 1 Day 1, no need to repeat tests if they have been performed within the past 5 days. Testing may be performed up to 2 days before other infusion days. Results of hematology tests must be evaluated before each study drug administration. Perform at additional timepoints, as clinically indicated. To be done by local lab.	X	X	X	X	X	X	X	X
Clinical Chemistry		X				X		X	X
Weight	If a subject's weight changes by more than 10% from baseline, the dose of all study treatments will be re-calculated	X				X		X	
Vital Signs	Vital signs (blood pressure, temperature, pulse/heart rate) measured in sitting position. On Cycle 1 Day 1 before the start of dara infusion; at 0.5, 1, 1.5, 2, 3.5 hrs after the start of the infusion; at end of infusion; and 0.5, and 1 hr after end of infusion. For all other infusions, vital signs will be measured before infusion start and at end of dara infusion.	X	X	X	X	X	X	X	
Diary review	Accountability/exposure check	X	X	X	X	X	X	X	X
Pre-infusion Medications, Arm B only									
Dexamethasone	Administer approximately 1 hour before dara infusion. PO preinfusion medications may be administered within 3 hours before the infusion. • Dexamethasone 40 mg weekly IV (preferred) or PO. For subjects older than 75 years or underweight (BMI <18.5), see Section 6.3. Substitutions for dexamethasone allowed, see Attachment 6. • An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent) • Acetaminophen (paracetamol) 650-1000 mg IV or PO	X	X	X	X	X	X	X	
Antihistamine		X	X	X	X	X	X	X	
Acetaminophen (paracetamol)		X	X	X	X	X	X	X	

	Notes	Cycle 1 and Cycle 2				Cycle 3 to Cycle 6		Cycle 7 and after	EOT
		D1	D8	D15	D22	D1	D15	D1	
Study Drug Administration, Arm A and Arm B									
Lenalidomide	Dispense on Day 1 for self-administration. In Arm B, on daratumumab infusion days, lenalidomide will be administered either prior to or at the same time (preferred) as the pre-infusion medications.	25 mg daily, Day 1-21 of each cycle (until PD or unacceptable toxicity)							
Dexamethasone	Dispense on Day 1 for self-administration.	40mg weekly PO; Day 1, 8, 15, 22 of each cycle. (until PD or unacceptable toxicity) Not required in Arm B on daratumumab infusion days.							
Study Drug Administration, Arm B Only									
Daratumumab	Refer to SIPPM for recommendations on daratumumab infusion rate. For windows see Table 3.	X	X	X	X	X	X	X	

ABBREVIATIONS

ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ALT	alanine aminotransferase
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CDC	complement-dependent cytotoxicity
CL	total systemic clearance
Cmax	maximum observed concentration
Cmin	minimum observed concentration
COPD	chronic obstructive pulmonary disease
CR	complete response
CRAB	calcium elevation, renal insufficiency, anemia and bone abnormalities
CrCl	creatinine clearance
CT	computed tomography
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DRd	daratumumab with lenalidomide plus low-dose dexamethasone
DTT	dithiothreitol
EBMT	European Group for Blood and Marrow Transplantation
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EOT	end of treatment
ePRO	electronic patient-reported outcome(s)
EU	European Union
FCBP	females of childbearing potential
FEV	forced expiratory volume
FFPE	formalin fixed paraffin embedded
FISH	fluorescence in situ hybridization
FLC	free light chain
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
HIV	human immunodeficiency virus
HR	hazard ratio
IAT	indirect antiglobulin testing
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFE	immunofixation
Ig	immunoglobulin
IHC	immunohistochemistry
IMiD	immunomodulatory agent
IMWG	International Myeloma Working Group
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous
IWRS	interactive web response system
LDH	lactic acid dehydrogenase
LMWH	low molecular weight heparin
mAb	monoclonal antibody

MedDRA	Medical Dictionary for Regulatory Activities
MP	melphalan-prednisone
MPT	melphalan-prednisone-thalidomide
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
NK	natural killer
OR	overall response
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PC	plasma cell
PCP	pneumocystis carinii pneumonia
PD	disease progression
PFS	progression free survival
PFS2	time from randomization to progression on the next line of therapy or death, whichever comes first
PI	proteasome inhibitor
PK	pharmacokinetics
PO	per oral
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes syndrome
PQC	Product Quality Complaint
PR	partial response
PRO	patient-reported outcome(s)
QD	once daily
QIg	quantitative immunoglobulins
QTcF	QT corrected according to Fridericia's formula
RBC	red blood cell
Rd	lenalidomide plus low-dose dexamethasone
REMS	Risk Evaluation and Mitigation Strategy
SAE	serious adverse event
sCR	stringent complete response
SCT	stem cell transplantation
SIPPM	Site Investigational Product Procedures Manual (or equivalent document)
SLiM	60% Plasmacytosis, Light chains >100, MRI 1 or more focal lesion
SPEP	serum M-protein quantitation by electrophoresis
SUSAR	Suspected Unexpected Serious Adverse Reactions
TTP	time to disease progression
ULN	upper limit of normal
UPEP	urine M-protein quantitation by electrophoresis
US	United States
V	volume of distribution
VD	VELCADE-dexamethasone
VGPR	very good partial response
VMP	VELCADE-melphalan-prednisone
VTD	VELCADE-thalidomide-dexamethasone
VTE	venous thromboembolism
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

1.1.1. Multiple Myeloma

Multiple myeloma is a malignant disorder of the plasma cells, characterized by uncontrolled and progressive proliferation of a plasma cell clone. The disease leads to progressive morbidity and eventual mortality by lowering resistance to infection and causing significant skeletal destruction (with bone pain, pathological fractures, and hypercalcemia), anemia, renal failure, neurological complications and hyperviscosity syndrome.

The majority of patients with multiple myeloma produce a monoclonal protein, also called paraprotein, M-protein or M-component, which is an immunoglobulin (Ig) or a fragment of one that has lost its function (Kyle 2009, Palumbo 2011).[18,26] Normal immunoglobulin levels are compromised, leading to susceptibility of infections. The proliferating multiple myeloma cells displace the normal bone marrow leading to dysfunction in normal hematopoietic tissue and destruction of the normal bone marrow architecture, which is reflected by clinical findings such as anemia, paraprotein in serum or urine, and bone resorption seen as diffuse osteoporosis or lytic lesions shown in radiographs (Kyle 2003).[17] Furthermore, hypercalcemia, renal insufficiency or failure, and neurological complications are frequently seen (Palumbo 2011).[26] A small minority of patients with multiple myeloma are non-secretory.

At the time of diagnosis, multiple myeloma is a heterogeneous disease, with a course that varies on the basis of both disease- and host-related factors (eg, age, renal function, stage, chromosomal abnormalities). Multiple myeloma causes significant morbidity and mortality. It accounts for approximately 1% of all malignancies and 13% of hematologic cancers. Approximately 50,000 patients per year are diagnosed with multiple myeloma in the EU and US, and 30,000 patients per year die due to multiple myeloma (ACS 2013, Ferlay 2010).[1,10]

1.1.2. Treatment Options for Multiple Myeloma

Treatment choices for multiple myeloma vary with age, performance status, comorbidity, the aggressiveness of the disease, and related prognostic factors (Palumbo 2011).[26] 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 high-dose chemotherapy and autologous stem cell transplantation (ASCT). For those not considered suitable for high-dose chemotherapy and ASCT, longer-term treatment with multi-agent combinations including alkylators, high-dose steroids, and novel agents are currently considered as standards of care.

The availability of different efficacious multi-agent regimens has provided clinicians with the opportunity of tailoring treatment for each patient. Selection is based on patients' comorbidities and biologic age, while at the same time, taking into account the expected toxicity profiles of each treatment regimen (Gay 2011).[11]

1.1.3. Transplant-ineligible Population

In general, patients over the age of 65 or with significant comorbidities are usually not considered eligible for more intensive forms of first line therapy, and as a result the treatment approach often favors longer, less-intensive/toxic treatments (Gay 2011).[11] Treatment traditionally consists of systemic chemotherapy, with adjunctive use of radiation or surgery in selected cases associated with extramedullary disease (NCCN 2013, Palumbo 2009, Smith 2005).[23,29,34] For many years, the oral combination melphalan-prednisone (MP) was considered the standard of care for patients with multiple myeloma who were not eligible for ASCT (Gay 2011).[11] The advent of immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs) has led to a multiplicity of new treatment options for newly diagnosed patients not considered suitable for transplant based therapy.

The results of the Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide (FIRST) Study were presented at the American Society of Hematology Meeting in December 2013 (Facon 2013),[9] and most recently published in The New England Journal of Medicine (Benboubker 2014).[2] In this open-label Phase 3 study, non-transplant eligible patients with newly diagnosed myeloma were randomized to either melphalan-prednisone-thalidomide (MPT) or lenalidomide + low-dose dexamethasone (Rd). Patients who received Rd until disease progression had an improved outcome compared to those randomized to MPT, with a 28% reduction in the risk of progressive disease or death (median: 25.5 months, HR=0.72; p=0.00006). Secondary endpoints including duration of response and overall response were superior in the Rd cohorts. The safety profile of Rd was manageable, with reduced hematologic second primary malignancies compared with MPT. In the oral presentation at ASH 2013, the authors indicated that overall survival for patients who received Rd until disease progression was 59.4%, based on a preliminary survival analysis at 4 years (Facon 2013, 2014).[9]

1.2. Daratumumab

Daratumumab is a human IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38, such as plasma cells from patients with multiple myeloma. This target is distinct from those of other approved agents for multiple myeloma therapy.

For the most comprehensive nonclinical and clinical information as well as Reference Safety Information regarding daratumumab, refer to the latest version of the Investigator's Brochure (Daratumumab IB).[13]

1.2.1. Nonclinical Studies

Based on preclinical data, daratumumab may utilize multiple effector cell functions, resulting in immune mediated killing of tumor cells. In ex vivo experiments utilizing human bone marrow stromal cells co-cultured with primary multiple myeloma cells, complement-dependent cytotoxicity (CDC) occurs rapidly and demonstrates maximal myeloma cell killing by daratumumab within 1 hour of antibody-mediated activation of the complement proteins (de Weers 2011).[6] Daratumumab-induced antibody-dependent cell-mediated cytotoxicity

(ADCC) is slower in its action, with maximal ADCC by daratumumab observed at 4 hours in vitro (de Weers 2011).[6] Daratumumab has also been shown to induce antibody-dependent cellular phagocytosis (ADCP) in the presence of macrophages within 4 hours in vitro (Overdijk 2013).[25] The precise role of some or all of these effector functions in reducing tumor burden in patients is unknown.

In toxicology studies in cynomolgus monkeys and chimpanzees, the major observed toxicities were cytokine release syndrome and thrombocytopenia. A minor decrease in red blood parameters was also observed. Cytokine release was seen only following the first dose and was markedly reduced following implementation of a 10-mg predose of daratumumab. The effect on platelets and red blood cells was reversible.

1.2.2. Clinical Studies

1.2.2.1. Single-Agent Daratumumab Studies (GEN501 and MMY2002)

Two single-agent studies with daratumumab are ongoing (Studies GEN501 and MMY2002), as described in Table 1.

Table 1: Daratumumab Single-Agent Studies GEN501 and MMY2002

<table>
<tr><th>Study Number</th><th>Study Design</th><th colspan="2">Number of subjects Treated/
Treatment Regimen</th></tr>
<tr><td rowspan="4">GEN501</td><td rowspan="4">Open-label, Phase 1/2, first-in-human, single-agent study in subjects with multiple myeloma whose disease is relapsed or refractory to at least 2 prior lines of therapies

Population was heavily treated with prior treatment, including ASCT, chemotherapy based regimens, IMiDs, and PIs</td><td colspan="2"><u>Part 1</u>
n=32 total treated with daratumumab weekly

0.005-1 mg/kg (n=17)
2 mg/kg (n=3)
4 mg/kg (n=3)
8 mg/kg (n=3)
16 mg/kg (n=3)
24 mg/kg (n=3)</td></tr>
<tr><td colspan="2"><u>Part 2</u>
n=51 total treated</td></tr>
<tr><td>8 mg/kg (n=30)

Weekly for 8 weeks, followed by q2w for an additional 16 weeks, and monthly thereafter</td><td>16 mg/kg (n=21)

First dose, followed by a 3-week resting period, followed by weekly doses for 7 weeks, then q2w for an additional 14 weeks, and monthly thereafter</td></tr>
<tr><td></td><td></td></tr>
<tr><td rowspan="2">MMY2002</td><td rowspan="2">Open-label, multicenter, 2-stage, Phase 2 study of daratumumab for the treatment of subjects with multiple myeloma who have received at least 3 prior lines of therapy including a PI and an IMiD or whose disease is double refractory to both a PI and an IMiD</td><td colspan="2">n=34 total treated in Stage 1</td></tr>
<tr><td>8 mg/kg (n=18)
q4w</td><td>16 mg/kg (n=16)
qw for 8 weeks, then q2w for another 16 weeks, and then q4w thereafter</td></tr>
<tr><td colspan="4">ASCT= autologous stem cell transplantation; IMiD=immunomodulatory agent; PI=proteasome inhibitor; q2w=every 2 weeks; q4w=every 4 weeks</td></tr>
</table>

Among the 32 subjects treated in Part 1 of Study GEN501, the maximum tolerated dose (MTD) was not reached following intravenous (IV) infusions up to 24 mg/kg. Two subjects experienced dose-limiting toxicities (DLTs) in the lower dose cohorts (a subject in the 0.1-mg/kg group had Grade 3 anemia and Grade 4 thrombocytopenia, and a subject in the 1.0-mg/kg group had Grade 3 aspartate aminotransferase increased).

Among the 51 subjects treated in Part 2 of Study GEN501, serious adverse events (SAEs) were reported in 37% of subjects (43% of subjects in the 8-mg/kg group and 29% of subjects in the 16 mg/kg-group). The most frequently reported SAEs were pneumonia (6% subjects), and pyrexia (4% of subjects).

Among the 34 subjects treated in Stage 1 of Study MMY2002, SAEs were reported in 27% of subjects (33% of subjects in the 8 mg/kg group, and 19% of subjects in the 16 mg/kg group). The most frequently reported SAE was renal failure acute (6% of subjects).

1.2.2.2. Combination Daratumumab Studies

One study of daratumumab in combination with lenalidomide and dexamethasone (Study GEN503), and one study of daratumumab in combination with various backbone treatment regimens (Study MMY1001) are ongoing (Table 2).

Table 2: Daratumumab Combination Studies GEN503 and MMY1001

Study Number	Study Design	Treatment Regimen	Status/Estimated Start Date Number of subjects Treated/Planned
GEN503	Open-label, Phase 1/2 multicenter, dose-escalating study investigating the safety of daratumumab in combination with lenalidomide and dexamethasone in subjects with relapsed or refractory multiple myeloma	Phase 1: 2-16 mg/kg daratumumab, in combination with lenalidomide (25 mg daily Days 1-21 of 28 days) and dexamethasone (40 mg weekly)	Part 1: Ongoing (n=13 subjects treated) 2 mg/kg (n=3) 4 mg/kg (n=3) 8 mg/kg (n=4) 16 mg/kg (n=3)
		Phase 2: 16 mg/kg daratumumab, in combination with lenalidomide (25 mg daily Days 1-21 of 28 days) and dexamethasone (40 mg weekly)	Part 2: n=18 subjects treated approximately 30 subjects planned
MMY1001	Open-label, non-randomized, multicenter, Phase 1b study to evaluate the safety, tolerability, and dose regimen of daratumumab in combination with various backbone treatment regimens for multiple myeloma in either newly diagnosed or those who have received at least 2 prior therapies, depending on backbone treatment regimen	Daratumumab 16 mg/kg (initially, with possibility to de-escalate, if necessary) The backbone regimens to be combined with daratumumab include VELCADE-dexamethasone (VD), VMP, VTD, and Pom-dex	n=18 subjects treated[1] VTD (n=6) VMP (n=5) VD (n=1) Pom-dex (n=6) approximately 80 subjects planned

1. As of 21May2014

Pom-dex=pomalidomide-dexamethasone; VD=VELCADE-dexamethasone; VMP-VELCADE-melphalan-prednisone; VTD=VELCADE-thalidomide-dexamethasone

Based on preliminary efficacy data, 15 of 20 efficacy evaluable subjects in Study GEN503 have achieved a PR or better following treatment with daratumumab in combination with lenalidomide and dexamethasone.

The safety profile observed in Study GEN503 is consistent with historical safety data for lenalidomide and dexamethasone. Doses ranged from 2 mg/kg to 16 mg/kg daratumumab, in combination with the approved doses of lenalidomide (25 mg daily Days 1-21 of 28 days) and dexamethasone (40 mg weekly). No dose-limiting toxicity (DLT) drug-related safety signals have been observed in this heavily pre-treated population of subjects with advanced multiple myeloma. The Part 2 daratumumab dose was determined to be 16 mg/kg. Across all dose cohorts in Part 1 and in the 16 mg/kg expansion cohort for Part 2, the most frequently reported Grade 3 or higher adverse event was neutropenia (6 subjects), which is a known toxicity of lenalidomide. Eight SAEs have been reported. All SAEs were assessed by the investigator as not related to daratumumab. Four subjects experienced infusion-related reactions during the first infusion of daratumumab. These events were determined by the investigator to be related to daratumumab. In all instances, daratumumab was interrupted temporarily and restarted without complication or further incident.

Planned Phase 3 combination studies include a Phase 3 study (MMY3003) comparing daratumumab, lenalidomide, and dexamethasone with Rd and a Phase 3 study (MMY3004) comparing daratumumab, VELCADE, and dexamethasone with VD. Both studies are in patients with relapsed or refractory multiple myeloma and are planned to start in the second half of 2014.

1.3. Lenalidomide

Lenalidomide is an immunomodulatory (IMiD) agent that is thought to mediate antimyeloma activity by 3 main mechanisms: 1) direct antitumor effect; 2) inhibition of the microenvironment support for tumor cells; and 3) an immunomodulatory role (Kotla 2009).[15] Direct tumor effect is described both as growth inhibition of myeloma cell lines and induction of apoptosis. The microenvironment support is affected by downregulation of cell adhesion molecules (eg, intercellular adhesion molecule), thus inhibiting stromal cell interaction with tumor cells, and inhibition of growth factors (eg, insulin growth factor 1 and vascular endothelial growth factor) induced by myeloma cell adhesion. Finally, lenalidomide exhibits immunomodulatory activity including inhibition of proinflammatory signaling molecules (cytokines) such as tumor necrosis factor α, IL-1β, and IL-6, the latter of which is a known growth factor for myeloma cells (Vallet 2008).[37]

Importantly, it has also been shown that lenalidomide causes upregulation of natural killer (NK) cells in myeloma (Kotla 2009)[15] and enhances the effector cells of ADCC (Tai 2005, Tai 2008).[36,35]

Lenalidomide is currently approved in the US and EU for the treatment for relapsed/refractory myeloma. However, there is accumulating evidence that lenalidomide is an effective treatment strategy for new diagnosed patients as well. The Eastern Cooperative Oncology Group (ECOG) published a study in which patients with newly diagnosed myeloma were randomized to either

high-dose (160 mg/week) or low-dose (40 mg/week) dexamethasone in combination with lenalidomide (Rajkumar 2010).[31] Patients randomized to the low-dose dexamethasone treatment arm had an improved overall survival at one year (96% vs 87%). In terms of response rates, patients in the low-dose cohort had an overall response rate (≥PR) of 68.3%. Median time to progression was 26.1 months in the low dose group.

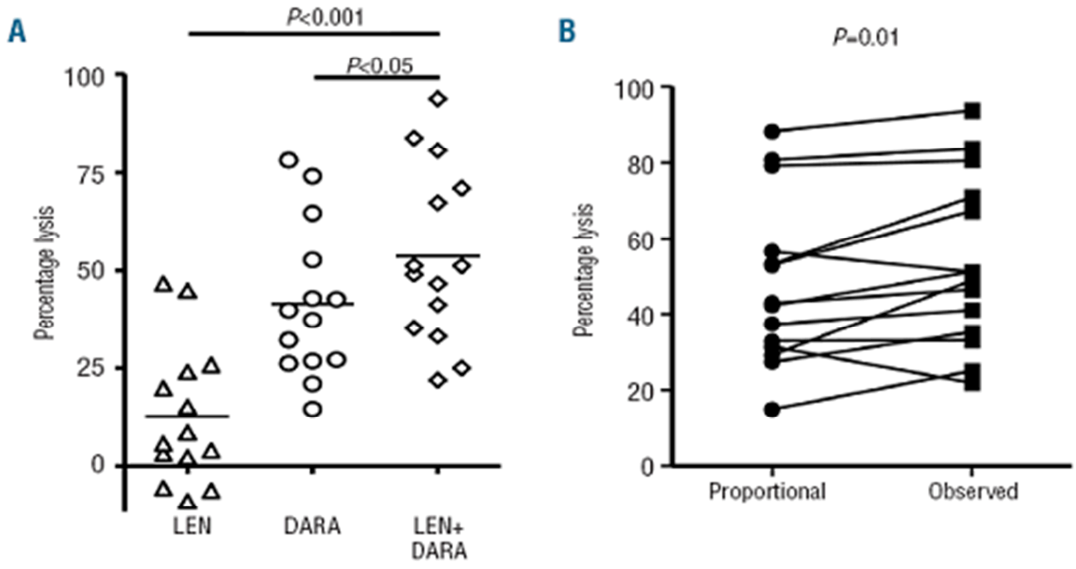
A large, randomized Phase 3 study (FIRST Study) compared Rd given until disease progression (Arm A) or for eighteen 28-day cycles (Arm B) with MPT (Arm C) in subjects newly diagnosed with multiple myeloma (Facon 2013, Benboubker 2014).[9,2] Continuous treatment with Rd (Arm A) significantly improved the primary endpoint of PFS compared with MPT (Arm C). Secondary endpoints (overall response rate [ORR], defined as PR or better, duration of response, and PFS2) consistently showed improvement in favor of Arm A over Arm C. The safety profile of Rd was manageable, with reduced hematologic second primary malignancies compared with MPT.

REVLIMID® (lenalidomide) in combination with dexamethasone was approved by both U.S. Food and Drug Administration and the European Commission for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant, on 18 February 2015 and 20 February 2015, respectively.

1.4. Lenalidomide and Daratumumab

Preclinically, using bone marrow mononuclear cells from patients with multiple myeloma, increased killing of tumor cells was demonstrated when daratumumab was combined with lenalidomide as compared with that of either agent alone as shown in (Figure 1A) (Van der Veer 2011a).[38] Notably, daratumumab and lenalidomide acted in a synergistic fashion to generate an extra effect (Figure 1B).

Figure 1: Improvement of Daratumumab-induced Antibody-dependent Cell-mediated Cytotoxicity by Lenalidomide in Bone Marrow Mononuclear Cells from Patients with Multiple Myeloma



Key: DARA = daratumumab; LEN = lenalidomide; MM = multiple myeloma.
(A) Bone marrow mononuclear cells of 14 patients with multiple myeloma were incubated for 47 hours with the control antibody, with lenalidomide (3 μM), and/or daratumumab (0.1 μg/mL). Surviving multiple myeloma cells were enumerated by Fluorescence-activated Cell Sorting analysis of CD138+ cells. The percentages of lysis of multiple myeloma cells treated with lenalidomide, daratumumab, and lenalidomide + daratumumab were calculated by the Tukey's post hoc analysis of repeated measures analysis of variance.
(B) The observed effect (% lysis) of the combination treatment was compared with the expected additive effect (proportional) of the combined treatments. Mixed model analysis supported the conclusion that the combination treatment was synergistic.

Finally, it was demonstrated that peripheral blood mononuclear cells isolated from patients during or just after lenalidomide treatment showed a significantly increased capacity to mediate daratumumab-dependent ADCC against multiple myeloma cells alone (Van der Veer 2011a).[38]

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

1.5. Overall Rationale for the Study

Multiple myeloma remains incurable with standard chemotherapy, despite the availability of multi agent therapy. Strategies directed at improving and maintaining response for longer periods of time and new treatment options directed at alternative mechanisms are also urgently needed for patients with multiple myeloma.

Recent studies have indicated that multiple drug combinations are superior over single- or double-agent combinations in treating multiple myeloma (Van der Veer 2011b).[39] The addition of new drugs to available regimens can mediate their clinical benefit because of the induction of a higher rate of initial CRs, which then improves relapse-free and overall survival. Contingent on the premise that the combined agents have non-overlapping and synergistic mechanism of actions, the immediate and effective targeting of the tumors with multiple agents appears to be a successful strategy in improving the clinical outcome of multiple myeloma therapy. Such a strategy is in agreement with the emerging concept that the genetic signature of multiple myeloma, and consequently the patient's susceptibility to a specific agent, will be highly heterogeneous, which may lead to drug resistance. Nevertheless, the CR rate of the best chemotherapeutic combinations is currently <50%, and all current combination therapies eventually induce drug resistance.

Based on data from ongoing studies with and the safety information in the label for lenalidomide, the expected safety profile of daratumumab in this combination therapy study is considered manageable. To date, 31 subjects have been treated in Study GEN503, an open-label, Phase 1/2 multicenter, dose-escalating study investigating the safety of daratumumab in combination with lenalidomide and dexamethasone in subjects with relapsed or refractory multiple myeloma. No DLTs have been reported, and the safety profile is consistent with what has been previously reported for lenalidomide monotherapy. Data from several clinical studies support the choice of 16 mg/kg as the daratumumab dose to be administered in this study. Based upon the pre-clinical synergy observed, and the promising clinical data in the relapsed/refractory setting, this is a rational combination to investigate in newly diagnosed patients.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective is to compare the efficacy of daratumumab when combined with lenalidomide and dexamethasone (DRd) to that of lenalidomide and dexamethasone (Rd), in terms of progression-free survival (PFS) in subjects with newly diagnosed myeloma who are not candidates for high dose chemotherapy and autologous stem cell transplant.

Secondary Objectives

The secondary objectives are:

- To evaluate clinical outcomes including:
  - Time to disease progression (TTP)
  - CR rate
  - MRD negativity rate
  - PFS2 (defined as time from randomization to progression on the next line of therapy or death, whichever comes first)

  - Overall survival
  - Time to next treatment
  - Stringent CR (sCR) rate
  - Overall response rate (partial response [PR] rate or better)
  - Proportion of subjects who achieve very good partial response (VGPR) or better
  - Time to response
  - Duration of response
- To evaluate the clinical efficacy of daratumumab combination with Rd in high-risk molecular subgroups
- To evaluate treatment effects on patient reported outcomes and heath economic/resource utilization
- To assess the safety and tolerability of daratumumab when administered in combination with Rd.
- To assess the pharmacokinetics of daratumumab in combination with Rd.
- To assess the immunogenicity of daratumumab.

Exploratory Objective

- To explore biomarkers predictive of response or resistance to therapy
- To assess durability of MRD negativity

2.2. Hypothesis

The primary hypothesis of this study is that daratumumab in combination with Rd will prolong PFS as compared with Rd alone in subjects with newly diagnosed multiple myeloma who are ineligible for high dose chemotherapy and autologous stem cell transplant.

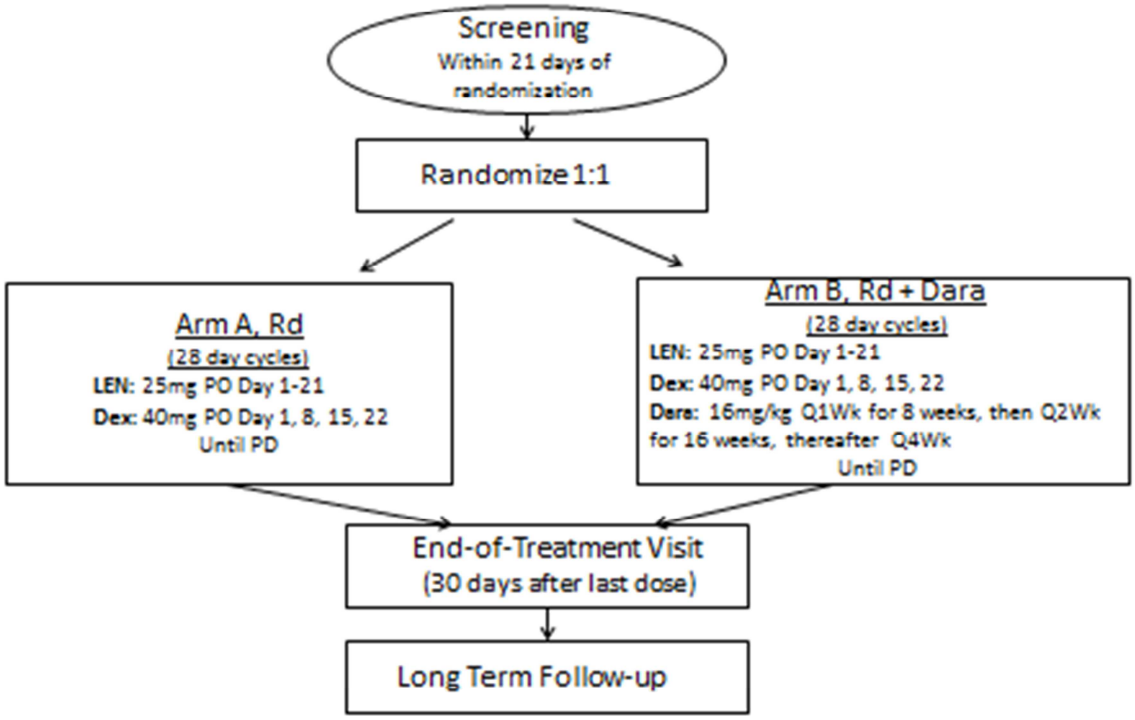
3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, open-label, active controlled, parallel-group, multicenter study in subjects at least 18 years of age with newly diagnosed multiple myeloma who are not candidates for high dose chemotherapy and ASCT. Approximately 730 subjects will be enrolled in this study with 365 subjects planned per treatment arm.

A diagram of the study design is provided in Figure 2.

Figure 2: Schematic Overview of the Study



Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 21 days before Cycle 1, Day 1. The Treatment Phase will extend from Day 1 of Cycle 1 until discontinuation of all study treatment. For subjects assigned to DRd, daratumumab will be administered weekly for the first 8 weeks (Cycles 1-2) of treatment and then every other week for 16 weeks (Cycles 3-6), then every 4 weeks (from Cycle 7 and beyond) until disease progression or unacceptable toxicity. This will equate to 9 consecutive weeks of dosing at the start of the study and a total of 23 doses in the first year. Lenalidomide will be administered at a dose of 25 mg orally (PO) on Days 1 through 21 of each 28-day cycle, and dexamethasone will be administered at a dose of 40 mg once a week in both treatment arms. Subjects in both treatment arms will continue lenalidomide and dexamethasone until disease progression or unacceptable toxicity. In the DRd arm, subjects will continue on daratumumab until disease progression or unacceptable toxicity. Randomization will be stratified by International Staging System (I vs II vs III), region (North America vs Other), and age (<75 vs ≥75), using an equal allocation ratio of 1:1.

Measures to prevent cytokine release syndrome will include preinfusion medication with dexamethasone, acetaminophen (paracetamol), and an antihistamine before each daratumumab infusion.

The Follow-up Phase will begin once a subject discontinues all study treatments. Subjects who discontinue for reasons other than disease progression must continue to have disease evaluations according to the Time and Events Schedule. The Follow-up Phase will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first. After the clinical cut-off (see below for definition), data collection will be reduced as per Section 9.1.4.

Two interim analyses are planned. The first interim analysis, with a purpose to evaluate safety, will be performed after a total of approximately 100 subjects have been treated for at least 8 weeks or discontinued the study treatment. The second interim analysis will be performed when 234 PFS events, which is 60% of the total planned events, have been accumulated. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. The significance level at this interim analysis to establish the superiority of DRd over Rd with regard to PFS will be determined based on the observed number of PFS events at the interim analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. If the experimental arm (DRd) is numerically worse than the control arm in terms of PFS (observed hazard ratio >1 favoring the control arm), then the study may be terminated for futility.

The primary PFS analysis will occur when approximately 390 PFS events have been observed. The date established for the primary PFS analysis will serve as the clinical cut-off date, after which data collection in the study will be reduced as per Section 9.1.4. Investigators will be informed when each interim analysis is to occur.

The end of the study will occur when 330 subjects have died, or 7 years after the last subject is randomized, whichever comes first. The sponsor will ensure that subjects benefiting from treatment with daratumumab will be able to continue treatment after the end of the study.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study to review efficacy and safety results at the planned interim analyses. After the interim review, they will make recommendations regarding the continuation of the study. In addition, the IDMC may also review cumulative safety data every 6 months besides the 2 interim analyses.

Assessment of tumor response and disease progression will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria. An assessment of MRD will be conducted on bone marrow samples. Safety evaluations will include adverse event monitoring, physical examinations, electrocardiogram (ECG) monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and ECOG performance status. Blood samples will be drawn for assessment of pharmacokinetic parameters.

3.2. Study Design Rationale

Rationale for Duration of Lenalidomide Administration

Lenalidomide and dexamethasone are commonly given in the front-line setting in the US. Based upon the FIRST Study (Facon 2013, Benboubker 2014),[9,2] the front-line treatment paradigm in the EU will likely evolve to include Rd in the future. The Facon study showed that treatment until progression conferred clinical benefit over treatment for a fixed duration of time. A retrospective analysis of 2 Phase 3 studies, one administering a lenalidomide based regimen and one administering a VELCADE based regimen, also showed that PFS1, PFS2, and overall survival (OS) were all significantly longer following continuous treatment to progression (Palumbo 2014).[27] This was observed regardless of the particular chemotherapy backbone. Taken together, these data support the principle of treatment until progression.

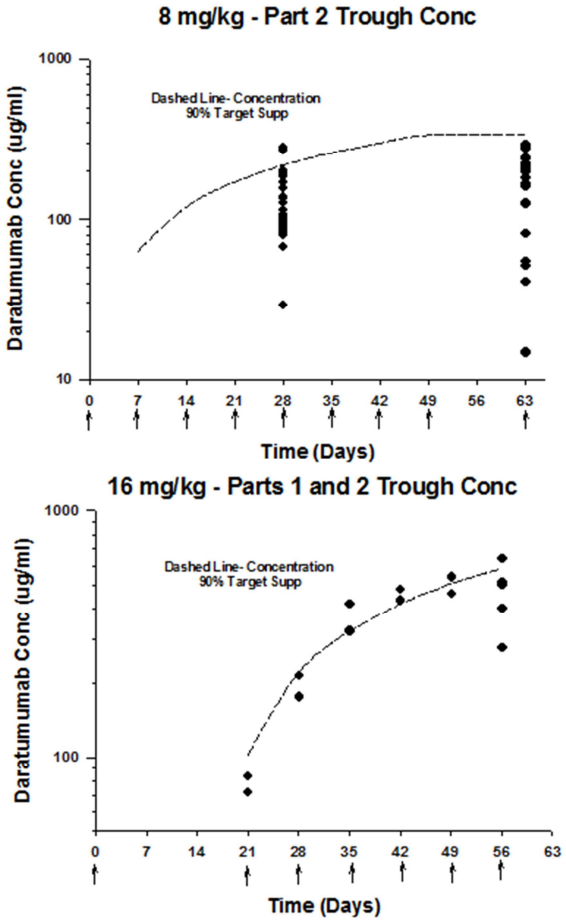
In the current study, treatment with Rd will continue until disease progression or unacceptable toxicity in the control arm (Arm A). This treatment duration is consistent with best current clinical practice based on the above published results.

In the experimental arm (Arm B), treatment with DRd will continue until disease progression or unacceptable toxicity. The protocol was initially designed to discontinue Rd after 24 months to isolate the efficacy and safety of daratumumab from continued exposure to Rd. Based on the data from the FIRST study, lenalidomide treatment until disease progression is emerging as the standard of care and is also consistent with the approved lenalidomide package insert (Hulin 2016; Revlimid USPI 2017).[14,33] Continuous Rd is currently being used as the backbone therapy in many Phase 3 studies evaluating active compounds in patients with myeloma (eg, bortezomib [Durie 2017],[8] carfilzomib, ixazomib, and elotuzumab [ongoing]). Results from the SWOG S0777 study evaluating a combined patient population of transplant eligible and ineligible subjects demonstrated improved median PFS with the addition of 6 months of bortezomib treatment to continuous Rd (43 months vs 30 months) with an acceptable safety profile despite the addition of a third agent to continuous Rd (Durie 2017).[8] Based on these develolpments, this amendment will allow for treatment to be consistent with the current standard of care.

Rationale for Daratumumab Dose

CD38, the target for daratumumab, is expressed on NK cells and clinical data has shown NK cell suppression to be a marker of on target drug activity. Clinical pharmacokinetic data have shown the 16 mg/kg dose to be the lowest dose that results in complete target suppression at all timepoints. This dose and schedule continuously suppressed NK cells throughout dosing. Daratumumab maximal target suppression is presented in Figure 3.

Figure 3: Daratumumab Maximal Target Suppression



8 mg/kg: Observed trough concentration values below predicted 90% suppression throughout dosing

16 mg/kg: Observed trough concentration values at 90% suppression throughout dosing

The ORR appeared higher for the 16 mg/kg dose compared with the 8 mg/kg dose, based on early preliminary data from Part 2 of Study GEN501 and from Study MMY2002 (both ongoing studies) as of a cutoff date of 24 January 2014. In Study GEN501, the ORRs (ie, PR or greater) were 11% and 40% for the 8 mg/kg (n=28) and 16 mg/kg (n=15) dose regimens, respectively. For Study MMY2002, the unconfirmed ORRs for the 8 mg/kg and 16 mg/kg dose regimens were similar to those observed in GEN501. In addition, VGPRs were observed for 7 of 30 subjects treated with the 16 mg/kg dose in the 2 studies. VGPR had not been observed at lower dose levels. These preliminary data support that full target saturation at the 16 mg/kg dose is needed to achieve higher and deeper response rates.

Rationale for DNA and Biomarker Collection

Biomarker samples will be collected to evaluate the depth of clinical response to daratumumab through evaluation of MRD, using DNA sequencing of immunoglobulin genes, and to determine response rates in specific molecular subgroups of multiple myeloma, using DNA/RNA sequencing of multiple myeloma cells to allow for assessment of high–risk genomics such as deletion 17p, t(4;14), t(14;20), t(14;16), deletion13, GEP signatures such as UAMS-70, and mutations in p53, BRAF, FGFR, IGH, PI3K, or other molecular subtypes associated with disease progression. Other biomarker goals include evaluation of potential mechanisms of resistance,

inter-individual variability in clinical outcomes or identification of population subgroups that respond differently to treatment.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 21 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. Subject must be at least 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place).

2. Criterion modified as per Amendment INT-2

   2.1 Subject must have documented multiple myeloma satisfying the CRAB (calcium elevation, renal insufficiency, anemia and bone abnormalities) criteria (see Attachment 1), monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma, and measurable disease.

   - Measurable disease, as assessed by central laboratory, defined by any of the following:
     - IgG myeloma: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
     - IgA, IgM, IgD, or IgE multiple myeloma: serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or
     - Light chain multiple myeloma without measurable disease in serum or urine: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.

3. Newly diagnosed and not considered candidate for high-dose chemotherapy with SCT due to:

   - Being age ≥65 years, OR
   - In subjects <65 years: presence of important comorbid condition(s) likely to have a negative impact on tolerability of high dose chemotherapy with stem cell transplantation. Sponsor review and approval of subjects under 65 years of age is required before randomization.

4. Subject must have an ECOG performance status score of 0, 1, or 2 (refer to Attachment 2).

5. Subject must have pretreatment clinical laboratory values meeting the following criteria during the Screening Phase:

   a) hemoglobin ≥7.5 g/dL (≥5 mM/L; prior red blood cell [RBC] transfusion or recombinant human erythropoietin use is permitted);

   b) absolute neutrophil count ≥1.0 x 10^9/L (granulocyte colony stimulating factor [GCSF] use is permitted);

   c) platelet count ≥70 x 10^9/L for subjects in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count >50 × 10^9/L (transfusions are not permitted to achieve this minimum platelet count);

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

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

   f) total bilirubin ≤2.0 x ULN, except in subjects with congenital bilirubinemia, such as Gilbert syndrome (direct bilirubin ≤2.0 x ULN);

   g) Criterion modified per Amendment INT-2

      g1) Creatinine clearance ≥30 mL/min (for lenalidomide dose adjustment for subjects with creatinine clearance 30-50 mL/min, refer to Section 6.2). Creatinine clearance can be calculated using the Cockcroft-Gault formula provided in Attachment 3; or for subjects with over- or underweight, creatinine clearance may be measured from a 24-hours urine collection using the formula provided in _ultralink236Attachment 3;

   h) Criterion modified per Amendment INT-2

      h1) corrected serum calcium ≤14 mg/dL (≤3.5 mM/L); or free ionized calcium ≤6.5 mg/dL (≤1.6 mM/L) (Attachment 4)

6. Criterion modified per Amendment INT-3

   6.1 Criterion modified per Amendment INT-2

   6.2 Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

   Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously. This includes one highly effective form of contraception (tubal ligation, intrauterine device [IUD], hormonal [progesterone-only birth control pills or injections or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing and must continue for 3 months after the last dose of daratumumab. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy. (Also see Attachment 5:

Lenalidomide Global Pregnancy Prevention Plan).

7. A man who is sexually active with a woman of childbearing potential must agree to use a latex or synthetic condom, even if he had a successful vasectomy. All men must also not donate sperm during the study, for 4 weeks after the last dose of lenalidomide, and for 3 months after the last dose of daratumumab.

8. A woman of childbearing potential must have 2 negative serum or urine pregnancy tests at Screening, first within 10 to 14 days prior to dosing and the second within 24 hours prior to dosing. For requirements during the Treatment Phase, please see Section 4.3.

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

4.2. Exclusion Criteria

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

1. Subject has a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma. Monoclonal gammopathy of undetermined significance is defined by presence of serum M-protein <3 g/dL; absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the M-protein; and (if determined) proportion of plasma cells in the bone marrow of 10% or less (Kyle 2003).[17] Smoldering multiple myeloma is defined as asymptomatic multiple myeloma with absence of related organ or tissue impairment end organ damage (Kyle 2003, Kyle 2007).[17,19]

2. Subject has a diagnosis of Waldenström's disease, or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions.

3. Subject has prior or current systemic therapy or SCT for multiple myeloma, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for 4 days) of corticosteroids before treatment.

4. Subject has a history of malignancy (other than multiple myeloma) within 5 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 5 years).

5. Subject has had radiation therapy within 14 days of randomization.

6. Subject has had plasmapheresis within 28 days of randomization.

7. Subject is exhibiting clinical signs of meningeal involvement of multiple myeloma.

8. Criterion modified as per Amendment INT-2

   8.1a) Subject has known chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) <50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal.

   8.1b) Subject has had known moderate or severe persistent asthma within the last 2 years (see Attachment 7), or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).

9. Criterion modified as per Amendment INT-2

   9.1) Subject is known to be seropositive for human immunodeficiency virus (HIV) or hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg] or antibodies to hepatitis B surface and core antigens [anti-HBs and anti-HBc, respectively]) or hepatitis C (anti-HCV antibody positive or HCV-RNA quantitation positive).

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

11. Subject has clinically significant cardiac disease, including:

    - myocardial infarction within 1 year before randomization, or an unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV
    - uncontrolled cardiac arrhythmia (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 4 Grade ≥3) or clinically significant ECG abnormalities
    - screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >470 msec

12. Subject has known allergies, hypersensitivity, or intolerance to corticosteroids, monoclonal antibodies or human proteins, lenalidomide, or their excipients (refer to respective package inserts or Investigator's Brochure), or known sensitivity to mammalian-derived products.

13. Subject has plasma cell leukemia (according to World Health Organization [WHO] criterion: ≥20% of cells in the peripheral blood with an absolute plasma cell count of more than 2×10^9/L) or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).
14. Subject is known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder). Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. Subject is taking any prohibited medications as per Section 8.3.
15. Subject is a woman who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study, within 4 weeks after the last dose of lenalidomide, or within 3 months after the last dose of daratumumab. Or, subject is a man who plans to father a child while enrolled in this study, within 4 weeks after the last dose of lenalidomide, or within 3 months after the last dose of daratumumab.
16. Subject has had major surgery within 2 weeks before randomization or has not fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study. Kyphoplasty or vertebroplasty is not considered major surgery.
17. Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before randomization or is currently enrolled in an interventional investigational study.
18. Subject has contraindications to required prophylaxis for deep vein thrombosis and pulmonary embolism.
19. Incidence of gastrointestinal disease that may significantly alter the absorption of oral drugs.

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 17.4, 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.

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. For restrictions related to concomitant medications, please refer to Section 8.3.

1. For women of childbearing potential, adequate contraception as specified in Section 4.1 must continue during the Treatment Phase, during any dose interruptions, for 4 weeks after the last dose of lenalidomide, and for 3 months after the last dose of daratumumab. All women must not donate ova during the study, for 4 weeks after the last dose of lenalidomide, and for 3 months after the last dose of daratumumab.

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

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

4. Because of the embryo-fetal risk of lenalidomide, all subjects must adhere to the local lenalidomide REMS program (when lenalidomide is supplied locally), or the lenalidomide Global Pregnancy Prevention Plan provided in Attachment 5 (when lenalidomide is supplied centrally and no local lenalidomide REMS program exists).

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

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

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Eligible subjects will be stratified by International Staging System (I vs II vs III see Attachment 8), region (North America vs Other), and age (<75 vs ≥75) and then randomized to treatment in a 1:1 ratio to either Treatment Arm A (Rd alone) or Treatment Arm B (daratumumab+Rd [DRd]). The method of randomization is randomly permuted blocks. An interactive web response system (IWRS) will be used. Each subject will be assigned a unique subject number.

Blinding

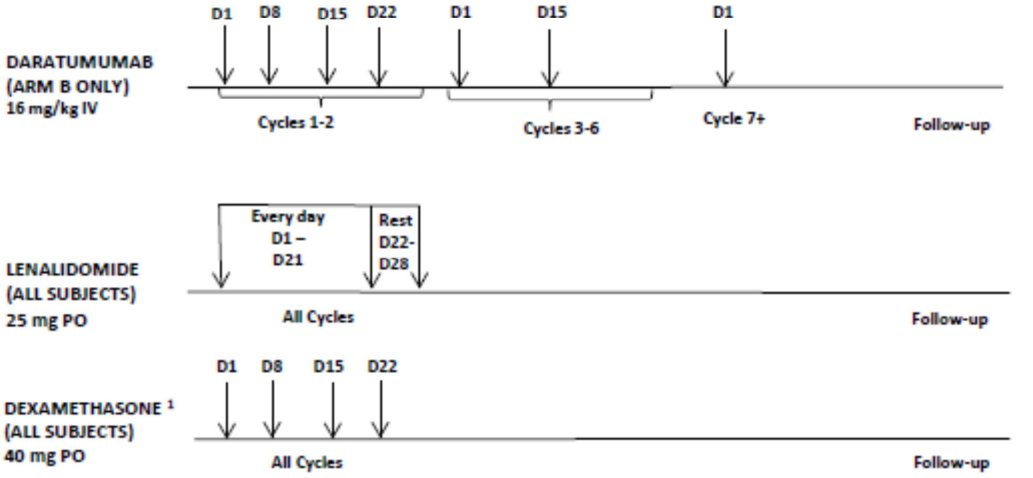
As this is an open study, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

In this protocol, the term "study drug" refers to daratumumab only, and "study treatment" refers to daratumumab, lenalidomide, and dexamethasone. Daratumumab is to be administered as described in the Time and Events Schedule. Each cycle is 28 days. The first visit of a cycle should be 4 weeks after the start of the previous cycle. The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. In Cycles 1 through 6, weekly or bi-weekly daratumumab infusions may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. In all cycles, weekly dexamethasone doses may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. Changes to within-cycle dosing should not impact Day 1 of the next cycle. Subjects will continue to receive study treatment according to the Time and Events Schedule until disease progression, unacceptable toxicity, or other reasons as listed in Section 10.2.

A schematic of study treatment administration is provided in Figure 4.

Figure 4: Schematic Overview Study Treatment Administration



1. On days when daratumumab is administered, dexamethasone will be administered to subjects in Arm B in the clinic and will serve as the treatment dose of steroid as well as the required pre-medication prior to daratumumab infusion.

6.1. Daratumumab (Arm B Only)

6.1.1. Daratumumab Preparation

The infusion solution will be prepared on the day of the planned infusion. Detailed instructions for preparation and administration of daratumumab will be supplied in the Site Investigational Product Procedures Manual (SIPPM) or equivalent document.

6.1.2. Daratumumab Administration

Daratumumab (16 mg/kg) will be administered by IV infusion to subjects in Arm B initially once every week for 8 weeks; then once every other week for 16 weeks; thereafter once every 4 weeks until documented progression, unacceptable toxicity, or study end. After the end of the study, the sponsor will ensure that subjects benefiting from treatment with daratumumab will be able to continue treatment.

Each subject's dose will be calculated based on the subject's weight rounded to the nearest kilogram. There is no cap on the absolute dose allowed, as long as the dose does not exceed 16 mg/kg. If a subject's weight changes by more than 10% from baseline, the dose of daratumumab will be re-calculated. For recommendations on daratumumab infusion rate, please refer to the SIPPM. All infusions will be performed as outpatient visits. Subjects will receive preinfusion medications and postinfusion medications as outlined in Section 6.1.3.

Every effort should be made to keep subjects on the planned dosing schedule. Time windows for daratumumab administration are outlined in Table 3.

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 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.

6.1.3. Prevention of Infusion Reactions

6.1.3.1. Preinfusion Medication

Preinfusion medications for subjects receiving daratumumab will be administered as described in the Time and Events Dose Administration Schedule. On daratumumab infusion days, subjects will receive the following medications prior to infusion:

- Acetaminophen (paracetamol) 650-1000 mg IV or orally (PO) approximately 1 hour or less prior to daratumumab infusion
- An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent but avoid IV use of promethazine) approximately 1 hour prior to infusion (see Attachment 9 for list of antihistamines that may be used); after Cycle 6, if a subject has not developed an infusion-related reaction and is intolerant to antihistamines, modifications are acceptable as per investigator discretion.

- Dexamethasone 40 mg IV (preferred) or PO, approximately 1 hour or less prior to daratumumab infusion. For subjects older than 75 years or underweight (body mass index [BMI] <18.5), dexamethasone 20 mg may be administered as appropriate (see Section 6.3). An equivalent intermediate-acting or long-acting corticosteroid may substitute (see Attachment 6 for conversion table). On days when subjects receive this dose of dexamethasone in the clinic, dexamethasone will not be self-administered at home. If weekly dexamethasone dosing has been reduced below 10 mg due to adverse events during study, a minimum of dexamethasone 10 mg IV should continue to be administered prior to daratumumab infusions.

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

6.1.3.2. Postinfusion Medication

For subjects with higher risk of respiratory complications (ie, subjects with mild asthma, or subjects with COPD who have a FEV1 <80%), the following postinfusion medications should be considered:

- Antihistamine (diphenhydramine or equivalent)
- Short-acting β_2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β_2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with COPD)

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 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. If an at-risk subject experiences no major infusion-related reactions, then these postinfusion medications may be waived after 4 full doses at the investigator's discretion.

6.1.4. Management of Infusion-related Reactions

Subjects in Arm B 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, and a defibrillator) must be available. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

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

- Subjects should be treated with acetaminophen, antihistamine, or corticosteroids. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors.
- In the event of a life-threatening infusion-related reaction (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.

If an infusion is paused, 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.

6.1.4.1. Infusion-Related Events 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 the onset, then the subject must be withdrawn from treatment.

6.1.4.2. 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.

6.2. Lenalidomide (Arm A and Arm B)

Lenalidomide will be self-administered at a dose of 25 mg PO each day on Days 1 through 21 of each 28 day cycle for subjects with creatinine clearance >50 mL/min. If creatinine clearance is between 30 and 50 mL/min, the dose of lenalidomide will be 10 mg every 24 hours. Once the creatinine clearance is >50 mL/min during the course of the treatment, lenalidomide can be increased to 25 mg. In both treatment arms, subjects will continue on lenalidomide until

progression of disease or unacceptable toxicity. Subjects in Arm B who discontinued treatment with Rd at 24 months may re-start treatment with Rd as per Amendment INT-4.

On daratumumab infusion days, it is recommended that lenalidomide should be administered either prior to or at the same time (preferred) as the premedications.

If a daily lenalidomide dose is missed, it may be taken if <12 hours have elapsed since the time that it should have been taken. If the next dose is scheduled to be taken within 12 hours, the missed lenalidomide dose should be skipped.

6.3. Dexamethasone (Arm A and Arm B)

Dexamethasone (or equivalent in accordance with local standards; see Attachment 6 for conversion table) will be administered at a total dose of 40 mg weekly. For subjects older than 75 years or underweight (BMI <18.5), the dexamethasone dose may be administered at a dose of 20 mg weekly. In both treatment arms, dexamethasone will be administered until the subject experiences disease progression or unacceptable toxicity, whichever comes first. Subjects in Arm B who discontinued treatment with Rd at 24 months may re-start treatment with Rd as per Amendment INT-4.

On days when subjects in Arm B receive an infusion of daratumumab, dexamethasone will not be self-administered but instead will be administered in the clinic. In this setting, dexamethasone will be utilized as the treatment dose of steroid for that particular day, as well as the required pre-medication prior to daratumumab infusion.

If a weekly dexamethasone dose is missed, it may be taken if <4 days have elapsed since the time that it should have been taken. If the next dose is scheduled to be taken within 3 days, the missed dexamethasone dose should be skipped.

6.4. Dose Delays and Dose Modification

Subjects who need to discontinue treatment with any one component of study treatment (lenalidomide, dexamethasone, or daratumumab) may continue to receive treatment with the other components of study treatment, as assigned.

6.4.1. Daratumumab Dose Modification

Dose modification of daratumumab is not permitted, but dose delay is the primary method for managing daratumumab-related toxicities.

6.4.1.1. Daratumumab-Related Toxicity Management

Refer to Section 6.1.3 for details on management of infusion-related reactions. ONLY if any of the following criteria are met and the event cannot be ascribed to lenalidomide, the daratumumab infusion must be held to allow for recovery from toxicity. The criteria for a dose delay are:

- Grade 4 hematologic toxicity
- Grade 3 thrombocytopenia with bleeding

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

Other than on Day 1 of a cycle, if a 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. A missed dose will not be made up.

Table 3: Daratumumab-Related Toxicity Management

Cycles	Frequency	Dose Held	Dosing Re-start
1 and 2	Weekly (q1wk)	>3 days	next planned weekly dosing date
3 to 6	Biweekly (q2wks)`	>1 week	next planned biweekly dosing date
7+	Every 4 weeks (Q4W)	>2 weeks	next planned every 4 weeks dosing date

Doses of daratumumab may be delayed up to 4 weeks (Cycle 1 to Cycle 6) or up to 6 weeks (Cycle 7 and beyond). Day 1 of a cycle should not be skipped; however, Day 1 of a cycle may be delayed, and Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. However, if a within-cycle dose is delayed, then the dates of the subsequent within-cycle doses should not be adjusted. Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 4 weeks (Cycle 1 to Cycle 6) or more than 6 weeks (Cycle 7 and beyond) will result in permanent discontinuation of daratumumab. If a dose delay occurs, then pharmacokinetic and pharmacodynamic assessments should be performed on the actual administration day of daratumumab, not on the original scheduled administration day.

6.4.1.2. Daratumumab Interruption or Missed Doses

A daratumumab dose that is held for more than the permitted time (Table 3) from the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the Sponsor at the earliest possible time. Subjects whose dose was delayed for more than 4 weeks (Cycle 1 to Cycle 6) or more than

6 weeks (Cycle 7 and beyond) should have study treatment discontinued, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

6.4.2. Lenalidomide Dose Reductions

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

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

Dose adjustments should be based on the highest grade of toxicity that is ascribed to lenalidomide. After initiation of lenalidomide, subsequent lenalidomide dose adjustment is based on individual subject treatment tolerance. If the investigator determines that an adverse event may be related to lenalidomide, dose adjustment can be done even if not specified in this protocol.

6.4.2.1. 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 • When count returns to $\geq 30 \times 10^9$/L	• Interrupt lenalidomide treatment, follow complete blood count weekly • Resume lenalidomide at the next lower dose
• For each subsequent drop in count to $<30 \times 10^9$/L • When count returns to $\geq 30 \times 10^9$/L	• Interrupt lenalidomide treatment • Resume lenalidomide at the next lower dose

6.4.2.2. 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, 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 • When count returns to $\geq 1.0 \times 10^9$/L and neutropenia is the only observed toxicity	• Interrupt lenalidomide treatment, consider G-CSF treatment, follow complete blood count weekly • Resume lenalidomide at 25 mg daily or initial starting dose
• When count returns to $\geq 1.0 \times 10^9$/L and dose-dependent hematological toxicities other than neutropenia are observed	• Resume lenalidomide at the next lower dose
• For each subsequent drop in count to $<1.0 \times 10^9$/L • When count returns to $\geq 1.0 \times 10^9$/L	• Interrupt lenalidomide treatment • Resume lenalidomide at the next lower dose level

6.4.2.3. 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 creatinine clearance of 50 mL/minute or less. The recommended doses for subjects with multiple myeloma and renal impairment are shown in Table 6.

Table 6: Lenalidomide Dose Adjustment for Renal Impairment

Category	Renal Function[a]	Dose
Moderate renal impairment	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

Key: CrCl = creatinine clearance.

[a] Estimated by creatinine clearance as calculated by the Cockcroft-Gault equation and adjusted for body weight in subjects with a body mass index >30 kg/m^2.

6.4.2.4. Other Adverse Events

For other Grade 3 or 4 non-hematologic and non-renal 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. Treatment with daratumumab and dexamethasone may continue.

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

6.4.3. Dexamethasone Dose Modifications

Dexamethasone may be reduced, if necessary, according to Table 7. For other Grade 3 or 4 non-hematologic and non-renal toxicities judged by the investigator to be related to dexamethasone alone, treatment with dexamethasone should be interrupted and restarted at the next lower dose level once the toxicity has resolved to Grade 2 or less. Treatment with

daratumumab and lenalidomide may continue. For complete details on dexamethasone, refer to the most current local product prescribing information.

Note that Table 7 represents suggested dose modifications of dexamethasone, but physician discretion and clinical judgment should prevail.

If weekly dexamethasone dosing has been reduced below 10 mg due to adverse events during study, a minimum of dexamethasone 10 mg IV should continue to be administered prior to daratumumab infusions.

Table 7: Recommended Dose Reduction for Dexamethasone

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 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%
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

7. TREATMENT COMPLIANCE

Study drug (daratumumab) will be administered by qualified site staff, and the details of each administration will be recorded in the electronic case report form (eCRF). Subjects will be

provided with a treatment diary which will be used to assess compliance with lenalidomide and dexamethasone treatment. Additional details are provided in the SIPPM or equivalent document.

8. CONCOMITANT THERAPY

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

Routine systemic use of the following concomitant medications will be collected in the eCRF and recorded in the source documents beginning with signing of the ICF to 30 days after the last dose of the last study treatment or until the start of subsequent anticancer treatment, if earlier: growth factors, transfusions, anti-infectives (antibacterials, antivirals, and antimycotics), steroids, anti-arrhythmics and other cardiac supportive therapy, anti-epileptics, centrally acting psychiatric medication, anti-histamines and other medications targeting postinfusion systemic reactions, bisphosphonates, and any anticancer therapy (including radiation). Concomitant medications to manage adverse events and SAEs will be recorded as per Section 12.3.1.

8.1. Recommended Therapies

8.1.1. Prevention of Deep Vein Thrombosis and Pulmonary Embolism

Lenalidomide has been associated with increased incidence of deep vein thrombosis and pulmonary embolism. Therefore, prophylaxis of venous thromboembolism (VTE) for all subjects is recommended according to IMWG guidelines as well as at the investigator's discretion (Palumbo 2008).[28] Both individual and myeloma-related risks of VTE should be taken into account in determining the type of thromboprophylaxis. In summary:

- If no risk factor, or any one risk factor is present, aspirin 81-325 mg once daily is recommended or dose per institutional standards
- If 2 or more risk factors are present, low molecular weight heparin (LMWH) (equivalent of enoxaparin 40 mg once daily) or full-dose warfarin, international normalized ratio (INR) 2-3, is recommended
- If any myeloma therapy-related risk factor is present, then LMWH (equivalent of 40 mg enoxaparin once daily) or full-dose warfarin (target INR 2-3) is recommended

8.1.2. Bisphosphonate Therapy

Bisphosphonate therapy is recommended to be continued per treatment guidelines (NCCN 2013).[23] 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.

Subjects who are currently using bisphosphonate therapy when they enter the study should continue the same treatment. If clinically indicated, subjects may initiate bisphosphonate therapy as soon as possible during Screening and no later than the end of Cycle 1. After Cycle 1, investigators should not prescribe bisphosphonates to subjects who have not received it before, unless it has been discussed with the sponsor and there is no sign of disease progression.

8.1.3. Therapy for Tumor Lysis Syndrome

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

8.1.4. Prophylaxis for Pneumocystis carinii

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

8.1.5. Prophylaxis for Herpes Zoster Reactivation

Prophylaxis for herpes zoster reactivation is recommended during the Treatment Phase, as per institutional guidelines.

8.1.6. 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

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

- Colony stimulating factors, erythropoietin, and transfusion of platelets and red blood cells. If erythropoietin is given, then this should be given according to the local lenalidomide label, 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
- Prophylactic antiemetics, with the exception of corticosteroids

8.3. Prohibited Therapies

Concomitant administration of any other antineoplastic therapy for the intention of treating multiple myeloma and other cancers not defined in the study protocol is prohibited, including medications that target CD38, as well as clarithromycin (Ghosh 2013).[12] Continuation of the

study treatment during or after emergency orthopedic surgery or radiotherapy because of the subject's benefit may occur only in the absence of disease progression and after review 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 by the sponsor.

Concomitant administration of investigational agents 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) should be avoided (other than those given for infusion-related reactions as described in Section 6.1.3.2 or for the treatment of adverse events [if no other treatment options are available]). Nonsteroidal anti-inflammatory agents should be used with caution in order to prevent myelom-related kidney disease.

Typically, IV contrast is NOT used in computed tomography (CT) scanning of the 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. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, pharmacokinetic, immunogenicity, biomarker, patient reported outcomes, and safety measurements applicable to this study.

All visit-specific PRO assessments should preferably be conducted/completed before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions. Refer to Section 9.7 for details.

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

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

The blood volume for the study is estimated at approximately 65 mL during screening and 360 mL during the first year (approximately 20-35 mL per cycle for routine testing, plus additional PK and biomarker samples). In the Follow-up Phase, subjects prior to PD will

continue to have approximately 20 mL blood drawn per month for serum disease evaluations. This includes laboratory assessments associated with safety, efficacy, and pharmacokinetic evaluations, as well as scientific research samples. 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. The Screening Phase begins when the first screening assessment is conducted (that was not performed as part of the subject's standard of care). During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in Time and Events Schedule. Screening procedures will be performed within 21 days before randomization; however, results of tests such as skeletal survey, radiologic tests (eg, magnetic resonance imaging [MRI] to document baseline size of known or suspected extramedullary plasmacytomas; ECG; chest x rays [or full chest CT scan]; or bone marrow aspirate or biopsy) performed up to 6 weeks (42 days) before randomization as routine standard of care for the subject's disease can be used. See Attachment 1 for the modified IMWG Diagnostic Criteria.

Subjects <65 years must have known presence of important comorbid condition(s) likely to have a negative effect on the tolerability of high dose chemotherapy with SCT. Documentation of the condition, for example diagnosis of concomitant infectious disease(s), should be provided. Sponsor review and approval of subjects under 65 years of age is required before randomization.

A negative pregnancy test for women of childbearing potential must be documented twice, once within 10-14 days before the first dose and a second time within 24 hours before the first dose of any component of the treatment regimen.

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

9.1.3. Treatment Phase

Details of the procedures performed during the Treatment Phase are outlined in the Time and Events Schedule. Subjects should start study treatment within 72 hours after randomization. A window of ±3 days is allowed for Day 1 of each cycle visits to the clinic. Each cycle is 28 days. The first visit of a cycle should be 4 weeks after the start of the previous cycle. The start of each cycle may occur ±3 days of the scheduled day in order to accommodate the schedule of the site or subject. Day 1 of subsequent cycles should be adjusted accordingly to maintain the 28-day cycle duration. In Cycles 1 through 6, weekly or bi-weekly daratumumab infusions may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. In all cycles, weekly dexamethasone doses may be given within ±1 day of the scheduled day in order to accommodate the schedule of the site or subject. Changes to within-cycle dosing should not impact Day 1 of the next cycle. 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. If disease progression is diagnosed, then the subject will discontinue study treatment, complete the End-of-Treatment Visit, and enter the Follow-up Phase. If disease progression has not occured at the time of the End-of-Treatment visit, disease evaluations must continue until disease progression is confirmed. Subsequent anti-myeloma treatment will not be started until after disease progression is confirmed by the Sponsor.

End-of-Treatment Visits

Unless a subject withdraws consent for study participation or is lost to follow up, an End-of-Treatment Visit is to occur within 4 weeks after the last dose of all study treatments. Every effort should be made to conduct the End-of-Treatment Visit before the subject starts subsequent treatment. If a subject is unable to return to the site for the End-of-Treatment Visit, then the subject should be contacted to collect information on adverse events that occur up to 30 days after the last dose of study treatment. Additional information on reporting of adverse events is presented in Section 12.

9.1.4. Follow-up Phase

The Follow-up Phase will begin once a subject discontinues all study treatments. Subjects who discontinue before disease progression must continue to have disease evaluations. Ideally, the timing of disease evaluations should follow the Time and Events Schedule until confirmed PD, death, the start of a new anticancer therapy, withdrawal of consent, lost to follow-up, or the end of the study. After disease progression is documented, subsequent anticancer therapy, PFS2 (per investigator judgment), second primary malignancies and survival status will be obtained at least every 16 weeks ±2 weeks. Every 16-week follow-up contacts should be scheduled from the date of confirmed progression. In subjects for whom disease progression will not be documented (eg, received subsequent anticancer treatment or refused disease evaluations, but agreed to follow-up contacts), the every 16-week follow-up should be scheduled from the date of the End-of-Treatment Visit.

A clinical cut-off will be established after the primary PFS analysis (390 PFS events). Following the clinical cut-off date, disease assessments will no longer be required and data collection will be limited to the following:

- For subjects still receiving study treatment: study treatment administration, adverse events, SAEs, laboratory data associated with SAEs
- For all subjects: all subsequent anticancer treatment, PFS2 (based on investigator judgment), second primary malignancies, and survival follow-up

If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and documented in the eCRF.

The end of the study occurs after 330 subjects have died, or for a maximum of 7 years after the last subject is randomized, whichever occurs first. The sponsor will ensure that subjects

benefiting from treatment with daratumumab will be able to continue treatment after the end of the study.

9.2. Efficacy

9.2.1. Evaluations

Disease response and progression will be based on assessments from IMWG Guidelines as defined in Section 9.2.1.1. Previous studies have demonstrated potential interference of therapeutic monoclonal antibodies with detection of endogenous myeloma M-protein on serum immunofixation (IFE) (McCudden 2010).[22] Daratumumab detection on serum immunofixation has been demonstrated in subjects treated with 16 mg/kg, and may interfere with the traditional IMWG criteria of negative serum IFE for complete response or stringent complete response. 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 with VGPR, and a negative endogenous M-protein by serum M-protein quantitation by electrophoresis (SPEP), reflex IFE testing will be performed to confirm the presence of daratumumab on IFE.

9.2.1.1. Response Categories

Disease evaluations must be performed every 28 days for the first 2 years and then every 8 weeks until disease progression (or other reasons as per Section 10). A window of ±7 days is allowed. If treatment has been delayed for any reason, the disease evaluations must be performed according to schedule, regardless of any changes to the dosing regimen.

Disease evaluations will be performed by a central laboratory (unless otherwise specified). This study will use the IMWG consensus recommendations for multiple myeloma treatment response criteria (Durie 2006, Rajkumar 2011)[7,32] presented in Table 8. For quantitative immunoglobulin, M-protein, and immunofixation 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 complete response or stringent complete response, will be considered CR/sCR.

Disease progression must be consistently documented across clinical study sites using the criteria in Table 8. For patients with measurable disease by SPEP or UPEP at baseline, increases in serum free light chains (FLC) or the FLC ratio alone do not meet criteria for progressive disease.

Table 8: International Uniform Response Criteria Consensus Recommendations

Response	Response Criteria
Stringent complete Response (sCR)	• CR as defined below, *plus* • Normal FLC ratio, *and* • Absence of clonal PCs by immunohistochemistry, immunofluorescence[a] or 2- to 4-color flow cytometry
Complete response (CR)*	• Negative immunofixation on the serum and urine, *and* • Disappearance of any soft tissue plasmacytomas, *and* • <5% PCs in bone marrow
Very good partial Response (VGPR)*	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or* • ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours
Partial response (PR)	• ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours • If the serum and urine M-protein are not measurable, a decrease of ≥50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥50% reduction in bone marrow PCs is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% • In addition to the above criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR, or progressive disease
Progressive disease (PD)†	• Increase of 25% from lowest response value in any one of the following: • Serum M-component (absolute increase must be ≥0.5 g/dL), • Urine M-component (absolute increase must be ≥200 mg/24 hours), • Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥10%) • Bone marrow plasma cell percentage: the absolute percentage must be >10% • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the PC proliferative disorder

EBMT = European Group for Blood and Marrow Transplantation; FLC = free light chain; PC = plasma cell

All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither.

Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.

For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

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

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

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

Clinical Relapse

Clinical relapse is defined using the definition of clinical relapse in the IMWG criteria (Durie 2006, Rajkumar 2011).[7,32] 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; >2.875mM/L)
4. Decrease in hemoglobin of more than 2 g/dL (1.25 mM) or to less than 10 g/dL
5. Rise in serum creatinine by more than or equal to 2 mg/dL (≥177 mM/L)
6. Hyperviscosity

In some 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.

For continuation of treatment, the IMWG response will be determined on an ongoing basis by the investigator. For data analysis and reporting, however, the sponsor will use a validated computer algorithm that has been shown to provide consistent review of the data necessary to determine disease progression and response according to the IMWG criteria. For CR/sCR, the IMWG criteria require subjects to have a negative SPEP and serum IFE. As an immunoglobulin, daratumumab can be picked up by SPEP and serum IFE and may cause false positive SPEP and IFE results. A reflex assay has been developed by the sponsor to confirm daratumumab interference on these assays.

Serum free light chain assay test results will be analyzed by the central laboratory for the assessment of stringent complete response (sCR), according to the most recently published IMWG criteria (Durie 2006).[7] 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, lost to follow-up, or the end of study, whichever occurs first. Disease evaluations scheduled for treatment days should be collected before study treatment is administered.

9.2.1.2. Myeloma Protein Measurements in Serum and Urine

Blood and 24-hour urine samples for M-protein measurements will be sent to and analyzed by a central laboratory. Only 1 serum and one 24-hour urine sample per time point are required by the central laboratory to perform the following tests. If the 24-h urine collection (UPEP) began before informed consent was obtained as part of routine patient care, the sample can be used in this study as long as it was sent to the central lab for analysis after the informed consent was obtained.

- Serum quantitative immunoglobulins (QIgs)
  - All subjects will be evaluated for IgG, IgA, IgM, IgE, and IgD at Screening. Every 3 months during treatment and at the EOT visit, subjects with IgD or IgE disease will be evaluated for IgG, IgA, IgM, IgE, and IgD and subjects with IgG, IgA, or IgM disease will be evaluated for IgG, IgA, and IgM.
- Serum M-protein quantitation by electrophoresis (SPEP)
- Serum immunofixation at Screening and thereafter when a CR is suspected or maintained. If daratumumab interference is suspected based on SPEP and IFE results, additional reflex IFE testing may be performed.
- Serum free light chain assay (monthly for subjects with free light chain (FLC) disease, all others per Time and Events Schedule)
- 24-hour urine M-protein quantitation by electrophoresis (UPEP)
- Urine immunofixation at Screening and thereafter when a CR is suspected or maintained.

Blood and 24-hour urine samples will be collected as specified in the Time and Events Schedule until the development of confirmed disease progression. After subjects have completed 24 months of study treatment, the timing of collection for SPEP and UPEP (and the timing of collection of FLC for subjects with light chain multiple myeloma) will change from every 4 weeks to every 8 weeks. Disease progression based on 1 of the laboratory tests alone must be confirmed by at least 1 repeat investigation performed 1 to 3 weeks later. Disease evaluations will continue beyond relapse from CR until disease progression is confirmed. Serum and urine immunofixation test and serum free light chain assay will be performed at Screening and thereafter when a CR is suspected (when serum or 24-hour urine M-protein electrophoresis [by SPEP or UPEP] are 0 or nonquantifiable) or maintained. However, for subjects with light chain multiple myeloma, serum free light chain assay will be performed routinely. Serum immunofixation (IFE) assay samples will be split into 2 aliquots, with 1 reserved for potential follow-on testing if daratumumab interference with IFE is suspected. As daratumumab is a monoclonal IgG antibody, additional serum samples may be utilized to monitor for potential daratumumab interference with the IFE.

9.2.1.3. Serum Calcium Corrected for Albumin

Blood samples for calculating serum calcium corrected for albumin will be collected and analyzed centrally (as specified in the Time and Events Schedules) until the development of confirmed disease progression. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mM/L) can indicate disease progression or relapse if it is not attributable to

any other cause (see disease response criteria). 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 4.

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.

9.2.1.4. β_2-microglobulin and Albumin

Blood samples for β_2 microglobulin and albumin are to be collected at Screening, and will be analyzed by the central laboratory.

9.2.1.5. Bone Marrow Examination

Bone marrow aspirate or biopsy will be performed at Screening for clinical characterization (morphology, IHC or immunofluorescence or 2- to 4- color flow cytometry, and cytogenetics), to establish baseline multiple myeloma clonality to monitor for MRD and to perform molecular subtyping to monitor daratumumab activity in high-risk molecular subgroups. Good quality slides are required for morphological examination to determine plasma cell percentage in the bone marrow. Assessment by flow cytometry alone is not sufficient. Bone marrow examination for disease assessment will be performed locally; however, a portion of the bone marrow aspirate must be sent to the central laboratory for analysis of MRD and molecular subtyping. A fresh bone marrow aspirate at screening is required if at all possible, by exception non-decalcified diagnostic tissue (bone marrow aspirate slides or FFPE tissue) may be supplied for MRD assessment instead. Additional bone marrow aspirates will be performed to confirm sCR and CR (only one analysis is required, with either IHC or immunofluorescence or 2- to 4- color flow cytometry included in the analysis) and to monitor for MRD at time points detailed in Table 9. If feasible, a bone marrow aspirate may be collected from subjects at disease progression to evaluate mechanisms of daratumumab resistance.

Bone marrow assessments to be performed locally and centrally are summarized in Table 9.

Table 9: Bone Marrow Testing

	Local Testing	Central Testing
Screening	Disease characterization (morphology, and either immunohistochemistry, immunofluorescence, or flow cytometry). Cytogenetic analysis by conventional karyotype or FISH.	MRD and molecular subtyping: a portion of bone marrow aspirates collected at screening will be sent to a central laboratory. If a fresh bone marrow aspirate will not be performed at screening because the procedure has already been done within 42 days prior to randomization, then the unstained or stained, non-decalcified diagnostic tissue (3-5 bone marrow aspirate smears, or 3-5 touch-prep slides from biopsy, or 3-5 bone marrow clot slides) should be collected for MRD assessment at baseline.
During Treatment	At time of suspected CR/sCR: Evaluate Plasma cell percentage in the bone marrow to confirm CR Evaluate clonality of plasma cells (by flow cytometry, IHC or IF**) in the bone marrow to confirm sCR *(If sCR criteria are not met, repeat local testing for sCR with subsequent bone marrow testing.)*	A portion of bone marrow aspirates collected at time of suspected CR/sCR, and 12, 18, 24 and 30 (+/-1) months post C1D1, will be analyzed for MRD*.
Disease Progression	Not applicable.	If feasible, a bone marrow aspirate is requested to be collected from subjects at disease progression and sent to central laboratory to evaluate mechanisms of daratumumab resistance.

CR=complete response; FISH=fluorescence in situ hybridization; MRD=minimal residual disease; sCR=stringent complete response

*If one of these time points occurs within 1 month of suspected CR/sCR, a repeat bone marrow will not be requested. These bone marrow tests will only be required if patient's response is near CR or better by blood and urine evaluations.
**Immunohistochemistry or immunofluorescence (both require kappa/lambda ratio from analysis of ≥100 cells) or 2- to 4-color flow cytometry are acceptable methods to evaluate plasma cell clonality.

9.2.1.6. Minimal Residual Disease Assessment

Minimal Residual Disease (MRD) assessment by next-generation sequencing (NGS) is a relatively new and effective tool in the assessment of patients with multiple myeloma (Ladetto 2014).[20] Several studies have demonstrated that MRD status is correlated with PFS and OS (Martinez-Lopez 2014).[21] In this study, bone marrow samples will be collected when a bone marrow aspirate is performed at Screening and at the subsequent timepoints outlined in Table 9 and Time and Events Schedule.

9.2.1.7. Assessment of Lytic Disease

A complete skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease) is to be performed and evaluated locally by X-ray or low-dose CT during the Screening Phase. Please note that the same methodology used at Screening should be used throughout the study for comparison purposes. During the Treatment Phase and before disease progression is confirmed, imaging should be performed whenever clinically indicated based on symptoms, to document response or progression. Magnetic resonance imaging (MRI) may be included as an additional assessment at the discretion of the investigator; however, focal lesions identified by MRI alone cannot be counted as lytic disease. If a radionuclide bone scan was used at Screening in addition to the complete skeletal survey, then both methods must be used to document disease status. These tests must be performed at the same time. However, a radionuclide bone scan does not replace a complete skeletal survey.

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 radiographs, depending on the symptoms that the subject experiences. If the diagnosis of disease progression is obvious by radiographic investigations, then no repeat confirmatory imaging is necessary. In instances where changes may be more subtle, repeat imaging may be performed in 1 to 3 weeks per investigator discretion.

9.2.1.8. Documentation of Extramedullary Plasmacytomas

Sites of known extramedullary plasmacytomas must be documented during the Screening Phase. Clinical examination or MRI may be used to document extramedullary sites of disease. Computed tomography scan evaluations are an acceptable alternative if there is no contraindication to the use of intravenous 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 every 4 weeks (by physical examination) for subjects with a history of plasmacytomas or as clinically indicated during treatment for other subjects until development of confirmed CR or confirmed disease progression. If assessment can only be performed radiologically, then evaluation of extramedullary plasmacytomas may be done every 12 weeks. 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 8). 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.

9.2.2. Endpoints

Primary Endpoints

The primary endpoint is PFS, which is defined as the duration from the date of randomization to either progressive disease, or death, whichever occurs first. Disease progression will be determined according to the IMWG criteria (Durie 2006, Rajkumar 2011).[7,32] For subjects who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy. Relapse from CR by positive immunofixation or trace amount of M-protein is not considered to be progressive disease and is not included in the PFS calculation.

The primary PFS analysis will occur once the targeted number of PFS events (390) is reached. At that time, for subjects without disease progression, disease assessments are no longer required per protocol but may continue to be performed according to the standard of care.

Secondary Endpoints

The secondary efficacy endpoints include:

- Time to disease progression (TTP) is defined as the time from the date of randomization to the date of first documented evidence of PD, as defined in the IMWG criteria. For subjects who have not progressed, data will be censored at the date of the disease evaluation before the start of any subsequent anti-myeloma therapy.
- CR rate, defined as the percentage of subjects achieving CR, as defined:
  - Negative immunofixation of serum and urine, and
  - Disappearance of any soft tissue plasmacytomas, and
  - <5% plasma cells (PCs) in bone marrow
  - For those subjects with negative SPEP and suspected daratumumab interference on immunofixation, a reflex assay using anti-idiotype antibody will be utilized to confirm daratumumab interference and rule out false positive immunofixation. Subjects who have confirmed daratumumab interference, but meet all other clinical criteria for CR or sCR, will be considered CR/sCR.
- MRD negativity rate, defined as the proportion of subjects assessed as MRD negative, at any timepoint after the date of randomization.
- Progression-free Survival on Next line of Therapy (PFS2), defined as the time from randomization to progression on the next line of treatment or death, whichever comes first. Disease progression will be based on investigator judgment. For those subjects who are still alive and not yet progressed on the next line of treatment, they will be censored on the last date of follow-up.

- OS, 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.
- sCR rate, defined as the percentage of subjects achieving CR in addition to having a normal FLC ratio and an absence of clonal cells in bone marrow by immunohistochemistry, immunofluorescence, 2-4 color flow cytometry.
- Time to next treatment, defined as the time from randomization to the start of the next-line treatment.
- Overall response rate (ORR), defined as the proportion of subjects who achieve PR or better, according to the IMWG criteria, during or after the study treatment.
- Proportion of subjects who achieve VGPR or better, defined as the proportion of subjects achieving VGPR and CR (including sCR) according to the IMWG criteria during or after the study treatment at the time of data cutoff.
- Time to response, defined as the time between the randomization and the first efficacy evaluation that the subject has met all criteria for CR or PR. For subjects without response (CR/PR), data will be censored either at the date of progressive disease or, in the absence of progressive disease, at the last disease evaluation before the start of subsequent anti-myeloma therapy.
- Duration of response, calculated from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, as defined in 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.
- To evaluate clinical efficacy of DRd in high risk molecular subgroups compared to Rd alone.
- To evaluate the impact of DRd compared to Rd on patient-reported perception of global health.

Exploratory Endpoints

- Biomarkers predictive of response or resistance to daratumumab.
- Durability of MRD negativity.

9.3. Pharmacokinetics and Immunogenicity

9.3.1. Evaluations

For all subjects in Arm B, pharmacokinetic samples to determine serum concentration of daratumumab will be obtained according to the Time and Events Schedule. Venous blood samples (5 mL per sample) will be collected to determine serum concentration of daratumumab and the serum will be divided into 3 aliquots (1 aliquot for pharmacokinetic analysis, 1 aliquot for antibodies to daratumumab analysis [when appropriate], and 1 aliquot as a backup). Samples collected for determining serum concentrations of daratumumab in this study may be retained to address questions about drug characteristics that may arise at a later time point.

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 antibodies to daratumumab using validated immunoassay methods by or under the supervision of the sponsor's bioanalytical facility.

9.3.3. Pharmacokinetic Parameters

The pharmacokinetic parameters are defined as:

CL	Total systemic clearance of drug after IV administration
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
V	Volume of distribution

Pharmacokinetic samples to determine serum concentration of daratumumab will be obtained from all subjects. Pharmacokinetic endpoints include:

- Minimum observed concentration (Cmin)
- Maximum observed concentration (Cmax)

If sufficient data are available, then other pharmacokinetic parameters may be calculated, including but not limited to total systemic clearance of drug after IV administration (CL) and volume of distribution (V).

9.3.4. Immunogenicity Assessments (Antibodies to daratumumab)

Venous blood samples drawn from all subjects in the DRd arm will be assessed for the generation of antibodies to daratumumab (immunogenicity), according to the Time and Events Schedule. Additionally, blood samples to assess immunogenicity should also be collected at the final visit for subjects who discontinue treatment. Subjects who discontinue treatment will also be asked to return for immunogenicity evaluation during the 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 antibodies to daratumumab 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, including exploring the relationship between serum concentrations of daratumumab and endpoints of clinical efficacy. If these analyses are performed, then the details and results will be presented in a separate report.

9.5. Biomarkers

Biomarker assessments will focus on 2 main objectives including evaluating the ability of daratumumab + Rd to reduce MRD in subjects who achieve a complete response (compared to Rd alone) and to determine the clinical benefit (ORR, PFS, and OS) of daratumumab + Rd in high-risk molecular subtypes (del17p, t(4;14), t(14;16), specific gene signatures, specific mutations). Bone marrow aspirates will be collected at screening and following treatment as outlined in the Time and Events Schedule. Baseline bone marrow aspirate samples will be subjected to DNA and RNA sequencing in order to classify subjects into high-risk molecular subgroups and to establish the myeloma clone for MRD monitoring. A fresh bone marrow aspirate at Screening is required if at all possible, by exception non-decalcified diagnostic tissue (please see Table 9 Bone Marrow Testing for further information) may be supplied for MRD assessment instead. For subjects who achieve a CR or sCR, bone marrow aspirates will be utilized for assessment of MRD by next-generation sequencing (NGS) of immunoglobulin heavy and light chains (Vij 2013).[40] If this methodology is unavailable, or determined to be scientifically inferior, then alternative methods for MRD assessment may be utilized. In cases where daratumumab is suspected of interfering with serum IFE and preventing clinical CR response calls, subjects with VGPR will also be evaluated for MRD by NGS.

In addition to planned bone marrow aspirate assessments, a whole blood sample will be collected from subjects as outlined in the Time and Events Schedule for processing to plasma and PBMCs. These samples may be used to evaluate specific subsets of immune cells such as cytotoxic T cells, regulatory T cells, MDSCs, and activated NK cells. Cells may also be used for additional phenotypic and functional profiling. Proteomic analysis may also be used to evaluate changes in cytokines, complement proteins, soluble CD38, soluble CD59, IFNγ, granzyme, perforin, and other proteins associated with ADCC/CDC/ADCP to evaluate potential biomarkers of response and resistance.

Potential mechanisms of tumor resistance, such as changes in antigen (CD38) expression or increased expression in complement inhibitory proteins (CD46, CD55, and CD59) in multiple myeloma cells, may be monitored in subjects if a bone marrow aspirate sample is deemed feasible for collection at progressive disease. In addition, changes in expression patterns of genes associated with ADCC, CDC, or other mechanisms of action of daratumumab may be evaluated.

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 the Time and Events Schedule.

9.6. Medical Resource Utilization

Medical resource utilization (MRU) data, including primary non-protocol driven hospitalizations, outpatient visits, and emergency room visits, should be collected in the eCRF (Hospitalization/Outpatient Visits CRF) by the Investigator and study-site personnel for all subjects throughout the study. Please see CRF completion guidelines.

9.7. 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 and the EQ-5D-5L instruments will be used. Both questionnaires will be completed at the timepoints outlined in the Time and Events Schedule. All visit-specific PRO assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions. All PRO measures will be completed using an electronic device (ePRO). For more details refer to the ePRO user manual.

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 (Wisloff 1996, Wisloff 1997).[41,42] 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 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) (Herdman 2011).[13] 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.

9.8. Safety Evaluations

Safety will be measured by adverse events, laboratory test results, ECGs, vital sign measurements, physical examination findings, and assessment of ECOG performance status score. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

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

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. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

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

The tests below will be performed by the local laboratory unless otherwise noted.

- Hematology Panel

  -hemoglobin

  -white blood cell (WBC) count with absolute neutrophils and lymphocytes
  -platelet count

- Serum Chemistry Panel

-blood urea nitrogen (BUN) or urea	-alkaline phosphatase
-creatinine	-lactic acid dehydrogenase (LDH)
-glucose	-uric acid
-aspartate aminotransferase (AST)	-total; direct bilirubin (not required except in case of congenital bilirubinemia, such as Gilbert disease)
-alanine aminotransferase (ALT)	-total protein
-creatinine clearance (calculated or measured)	-sodium*
	-potassium*

*Sodium and potassium assessment was added in Protocol Amendment 2, however collection of sodium and potassium results will be done retrospectively from the date of subject consent for the duration of the study, if collected as part of routine care.

Serum or urine 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 and throughout the Treatment Phase, as specified in the Time and Events Schedule. Where lenalidomide is supplied locally, subjects must adhere to the local lenalidomide REMS program. Where lenalidomide is supplied centrally and no local lenalidomide REMS program exists, then subjects must adhere to the lenalidomide Global Pregnancy Prevention Plan in Attachment 5.

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

Calcium and albumin adjusted calcium:

These parameters will be part of the efficacy evaluations as specified in Section 9.2.1.3, and will be analyzed by the central laboratory. Measurement of calcium and albumin should follow the schedule for disease assessments. Measurement of free ionized calcium is an acceptable alternative to corrected serum calcium for determining hypercalcemia.

Daratumumab Interference with Indirect Antiglobulin Test (IAT) results:

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 a patient 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. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab IAT interference by treating reagent RBCs with dithiothreitol (DTT) (Chapuy 2015[4], Chapuy 2016).[5]

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

a) Providing ABO/RhD compatible, phenotypically or genotypically matched units
b) Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using dithiothreitol (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.

Pulmonary Function Test

Subjects with known or suspected COPD must have a FEV1 test during screening. Refer to Section 6.1.3.2 for details on subjects with higher risk of respiratory complications.

Electrocardiogram (ECG)

ECGs 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, then the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

Vital Signs

Vital signs (pulse/heart rate, temperature, and blood pressure) will be performed as specified in the Time and Events Schedule. It is recommended that blood pressure (sitting) and pulse measurements be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones). Only vital signs associated with an adverse event will be entered in the eCRF; all measurements will be recorded in the source documents.

Physical Examination and ECOG Performance Status

A complete physical examination (including neurological examination) should be performed during the Screening Phase. Thereafter, only a symptom and disease directed physical examination is required. Height will be measured at screening only; weight will be measured regularly as specified in the Time and Events Schedule. Abnormalities will be recorded in the appropriate sections of the eCRF. ECOG Performance Status (Attachment 2) will be used to evaluate the impact of the disease status on the activities of daily living. When scheduled, ECOG

assessments along with PRO questionnaires should be obtained prior to any other study procedures planned for the same day.

9.9. Sample Collection and Handling

If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (or equivalent)/sodium heparin of 10 U/mL and charged with a volume equal to the dead space volume of the lock. If a mandarin (obturator) is used, blood loss due to discard is not expected. Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

For samples collected from the central laboratory, sample dates and times must be recorded on the laboratory requisition form. 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/WITHDRAWAL

10.1. Completion

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

10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study. After treatment discontinuation, the subject will move into the Follow-up Phase. The End-of-Treatment Visit and Follow-up visit assessments should continue as specified in the Time and Events Schedule. 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.

Subjects who need to discontinue treatment with any one component of study treatment (lenalidomide, dexamethasone, or daratumumab) may continue to receive treatment with the other components of study treatment, as assigned.

A subject's study treatment should be discontinued if:

- The investigator believes that for safety 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
- The subject experiences unacceptable toxicity, including infusion-related reactions described in Section 6.1.4
- The subject's dose of daratumumab is held for more than 4 weeks in Cycles 1- 6 or for more than 6 weeks in Cycle 7 and beyond (unless Sponsor approves continuation)
- The subject experiences disease progression (please see below). Relapse from CR is not considered as disease progression

A subject who experiences a second primary malignancy that can be treated by surgery may continue to receive the assigned study treatment and the subject should continue to be followed for subsequent progression of multiple myeloma. Subjects who require radiation therapy for treatment of second primary malignancy must have study treatment discontinued unless, upon consultation with the Sponsor and review of data, continuation is agreed upon. Subjects who require systemic treatment of a new malignancy must end study treatment but should continue to be followed for PFS2 and OS.

Before subjects discontinue study treatment due to disease progression, sites will document disease progression (for example by completing a disease progression form or by contacting the IWRS) as soon as possible and within 48 hours. The medical monitor will confirm that treatment should be discontinued. After confirmation from the sponsor, study treatment may be discontinued and the subject entered into Follow-up.

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

10.3. Withdrawal From the Study

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

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

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

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study treatment assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study, assessments outlined in the End-of-Treatment Visit should be obtained.

Withdrawal From the Use of Samples in Future Research

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

11. STATISTICAL METHODS

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

11.1. Subject Information

The primary analysis population will be the intent-to-treat (ITT) population, which will include all randomized subjects. Safety will be evaluated for the population of all treated subjects. The pharmacokinetic analyses will be performed on the pharmacokinetic evaluable population. Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, and range. Categorical variables will be summarized using frequency tables. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries.

11.2. Sample Size Determination

The sample size calculation is performed on the basis of the following assumption. Based on the published data, the median PFS for Rd arm is assumed to be approximately 24 months. Assuming that DRd can reduce the risk of the disease progression or death by 25%, ie, assuming the hazard ratio (DRd vs Rd) of 0.75, a total of 390 PFS events is needed to achieve a power of 80% to detect this hazard ratio with a log-rank test (two-sided alpha is 0.05). With a 21-month accrual period and an additional 24-month follow-up, the total sample size needed for the study is approximately 730 (365/arm) subjects. The sample size calculation has taken into consideration an annual dropout rate of 5%.

Long-term survival follow-up will continue until 330 deaths have been observed or 7 years after the last subject is randomized. Therefore, this study will achieve approximately 80% power to detect a 27% reduction in the risk of death (hazard ratio = 0.73) with a log-rank test (two-sided alpha = 0.05).

11.3. Efficacy Analyses

Response to study treatment and progressive disease will be evaluated by a computer algorithm. For the primary endpoint of PFS, the primary analysis will consist of a stratified log rank test for the comparison of the PFS distribution between the 2 treatment arms. The Kaplan-Meier method will be used to estimate the distribution of overall PFS for each treatment. The treatment effect (hazard ratio) and its two-sided 95% confidence intervals are to be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

Other time-to-event efficacy endpoints, including TTP, PFS2, OS, and time to subsequent anti myeloma treatment, will be analyzed similarly. For overall survival, the final analysis will occur after 330 deaths have been observed. Earlier analyses, in which overall survival are analyzed,

will be considered as interim analyses, and the stopping boundary will be determined using the observed number of deaths at the time of the analyses and a modified linear alpha-spending function per the Lan-DeMets method. At the interim PFS analysis (234 PFS events), a total alpha of 0.0001 (2-sided) will be spent. Cumulative total alpha (2-sided) spent at each subsequent analysis of OS will be the total alpha allocated to OS multiplied by the proportion of the number of deaths observed at the time of the analysis out of the total planned number of deaths (330). Comparison between the 2 treatment arms of overall response rates, VGPR rate, and other binary endpoints will be conducted using the stratified Cochran Mantel Haenszel test. The Mantel-Haenszel odds ratio will be provided along with its two-sided 95% confidence interval, and will be provided as the measure of treatment effect. Duration of response will be provided descriptively without formal statistical comparison.

Strong control of familywise Type I error rate will be controlled at a two-sided significance level of 0.05 for the following major secondary endpoints: TTP, CR rate, MRD negativity rate, PFS2 and OS. A hierarchical testing procedure will be used. Details about this hierarchical procedure will be specified in the statistical analysis plan for this study prior to any efficacy analysis.

11.4. Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed on the pharmacokinetic-evaluable population, defined as subjects who have received one dose of daratumumab and at least one 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 Cmin and Cmax. If sufficient data are available, then other pharmacokinetic parameters may be calculated, including but not limited to CL and V.

If sufficient data are available, then population pharmacokinetic analysis of serum concentration time data of daratumumab, will be performed using nonlinear mixed-effects modeling. The potential population PK analysis may also include PK 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 antibodies to daratumumab will be summarized for all subjects who receive a dose of daratumumab and have appropriate samples for detection of antibodies to daratumumab.

11.6. Pharmacokinetic/Pharmacodynamic Analyses

If sufficient data are available, then population pharmacokinetic analysis serum concentrations of serum concentration-time data of daratumumab will be performed using nonlinear mixed-effects

modeling. If the population pharmacokinetic analysis is conducted, then details will be given in a population pharmacokinetic analysis plan 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. Analyses will be performed and stratified by clinical covariates or molecular subgroups using the appropriate statistical methods (eg, parametric or non-parametric, univariate or multivariate, analysis of variance, 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 in addition to genes and pathways attenuated following treatment with daratumumab. In order to remove any confounding influence of prognostic factors, any predictive biomarker identified in this study could be verified in a prospective clinical study with a control treatment arm.

Any biomarker measures will be listed, tabulated, and where appropriate, plotted. Subjects will be grouped by prescribed dose. Complete responders will be utilized to investigate the prognostic effect of MRD on PFS. MRD analysis will include evaluation of data from other studies to determine if decreased MRD is seen with daratumumab + Rd based chemotherapy regimen compared with the Rd based chemotherapy alone.

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.

In addition, due to the small sample sizes of high-risk subgroups within the multiple myeloma subject population, a meta-analyses may be performed across daratumumab Phase 3 studies to evaluate clinical efficacy of daratumumab with standard of care agents in pre-specified subgroups of multiple myeloma subjects. The meta-analysis protocol will pre-specify the objective of the meta-analysis, the criteria for inclusion and exclusion of studies, the hypotheses and endpoints, and statistical methods including a method for investigation of heterogeneity. This meta-analytic approach, supported by high-quality data from the individual studies, should be able to provide definitive evidence on the effectiveness of daratumumab in the subpopulation of multiple myeloma subjects with high-risk molecular abnormalities. In a similar fashion, a meta-analysis examining MRD negativity in daratumumab treated subjects in frontline, newly diagnosed multiple myeloma (MMY3006, MMY3007, MMY3008) may also be performed.

11.8. Patient Reported Outcomes

EORTC-QLQ-C30 scores will be evaluated for all domains except “financial problems” among subjects with at least one post-baseline assessment and 50% completion of the relevant items for a domain. Descriptive analyses followed by mixed model repeated measures will be used to analyze each domain score. No adjustment for multiple comparisons will be made.

EQ-5D-5L scores will be summarized at each time point.

11.9. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The severity assessment for an adverse event or serious adverse event should be completed using the NCI CTCAE Version 4. All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment arm.

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

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus post treatment cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. 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.

Parameters with predefined NCI CTCAE toxicity grades will be summarized. Change from baseline to the worst toxicity grade experienced by the subject during the study will be provided as shift tables. Worst toxicity grade during treatment will be presented, according to NCI CTCAE (version 4). Clinically relevant changes (i.e. causing a treatment intervention and/or need for concomitant therapy) will be also recorded on the adverse event eCRF. All other lab abnormalities need not be recorded as adverse events.

Electrocardiogram (ECG)

Electrocardiogram data will be summarized and listed.

Vital Signs

Descriptive statistics of baseline temperature, pulse/heart rate, and blood pressure (systolic and diastolic) values will be summarized.

11.10. Interim Analysis

Two interim analyses are planned. The first interim analysis, with a purpose to evaluate safety, will be performed after a total of approximately 100 subjects have been treated for at least 8 weeks or discontinued the study treatment. The second interim analysis will be performed

when 234 PFS events, which is 60% of the total planned events, have been accumulated. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. The significance level at this interim analysis to establish the superiority of DRd over Rd with regard to PFS will be determined based on the observed number of PFS events at the interim analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. If the experimental arm (DRd) is numerically worse than the control arm in terms of PFS (observed hazard ratio >1 favoring the control arm), then the study may be terminated for futility, with a conditional power of less than 20% under the alternative hypothesis given the observed interim data.

11.11. Data Monitoring Committee

An IDMC, consisting of 2 clinicians and 1 statistician who are independent experts not otherwise participating in the study, will be established to review efficacy and safety results at the planned interim analyses. After the interim review, they will make recommendations regarding the continuation of the study. In addition, the IDMC may also review cumulative safety data every 6 months besides the 2 interim analyses. The details will be provided in a separate IDMC charter.

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.

Suspected Unexpected Serious Adverse Reactions (SUSARs)

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between 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). Refer to Section 12.3.3 for SUSAR Reporting Requirements.

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 within the Reference Safety Information included in the Investigator's Brochure.

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.

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. Any adverse event or serious adverse event not listed in the NCI CTCAE Version 4 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 and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug. No MTD has been reached for daratumumab. However, if the dose exceeds the maximum tested dose of 24 mg/kg, then it will be considered as overdose in this study.
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject exposure to the sponsor study drug, eg, name confusion)

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

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study treatment, unless the subject withdraws consent for study participation, or starts subsequent anticancer therapy. For subjects who have received subsequent 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 daratumumab need to be reported. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study treatment, must be reported using the 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.

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). 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. Anticipated events will be recorded and reported as described in Attachment 10.

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

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual serious adverse events the sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the investigational institute where required). The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Subjects (or their designees, if appropriate) will be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study and for at least 6 months (Arm B) after treatment ends 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
- Blood type (and IAT testing as described in Section 9.8 for subjects in Arm B)

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 eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

12.3.3. Suspected Unexpected Serious Adverse Reactions

The sponsor assumes responsibility for appropriate reporting of all Suspected Unexpected Serious Adverse Reactions (SUSAR) [serious adverse events that are unlisted (unexpected) and associated with the use of the study drug] to the regulatory authorities in accordance with GCP. The sponsor will also report to the investigator (and the head of the investigational institute where required) all serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

12.3.4. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment and promptly be withdrawn from the study. The subject should be referred to a physician experienced in teratology for evaluation and advice. Investigators should follow the local label for guidance on subject education and ensure that all subjects adhere to the local lenalidomide REMS program (when lenalidomide is supplied locally), or the lenalidomide Global Pregnancy Prevention Plan provided in Attachment 5 (when lenalidomide is supplied centrally and no local lenalidomide REMS program exists). Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

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

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 on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on 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 in a vial. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

14.2. Packaging

Daratumumab is supplied in glass vials containing daratumumab at a concentration of 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

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

Daratumumab will be diluted in a sterile, pyrogen-free physiological saline solution (0.9% NaCl) prior to IV administration. Refer to the Investigational Product Preparation Instructions and Investigational Product Procedures Manual for details regarding dose preparation, storage, and handling of diluted solutions.

14.5. Drug Accountability

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

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, 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. 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 Brochure for daratumumab
- Site Investigational Product Procedures Manual
- Laboratory manual
- PRO questionnaires and user guidelines
- eCRF completion guidelines
- Sample ICF
- Subject diaries
- Subject wallet card indicating blood type (and IAT testing for Arm B; see Section 9.8)
- Other manuals and guidance documents as needed

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

The primary safety profile of daratumumab is consistent with infusion-related reactions; see Section 6.1.3 for prevention details. 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. Anemia was also reported in Study GEN501. Free hemoglobin was mildly elevated, but other parameters did not support hemolysis. No bleeding events were observed. Routine safety laboratory measurement of RBCs and platelets will be closely monitored in this study.

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

The blood volume for the study is estimated at approximately 65 mL during screening and 360 mL during the first year (approximately 20-35 mL per cycle for routine testing, plus additional PK and biomarker samples). In the Follow-up Phase, subjects prior to PD will continue to have approximately 20 mL blood drawn per month for serum disease evaluations. These blood volumes are not burdensome and fall within the normal range of a single blood donation.

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), 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).

Furthermore, where required, progress reports/written summaries of the study status will be submitted to the IRB/IEC annually, or more frequently if requested.

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, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

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

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

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

16.2.4. Privacy of Personal Data

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

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

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for

study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

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

Exploratory biomarker/PK/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 Study (Withdrawal From the Use of Samples in Future Research).

16.2.6. Country Selection

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

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and 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 (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

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

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

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

17.3. Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and 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 documentation must be available for the following to confirm data collected in the eCRF: 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 treatment administration information; and date of study completion and reason for early discontinuation of study treatment or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

Subject- and investigator-completed scales and assessments designated by the sponsor (EORTC QLQ-C30 and EQ-5D-5L) will be recorded directly into an electronic device or other tool 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 provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. Data must be entered into eCRFs in English. Study site personnel must complete the eCRF 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. The investigator must verify that all data entries in the eCRFs are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the eCRF (if applicable) and complete the query.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- 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).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

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

study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database, and direct transmission of PRO data to the ePRO vendor database and then to the sponsor's database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRFs 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 eCRFs 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 eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and

study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents 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 documentation 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.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed after 330 deaths have occurred or 7 years after the last subject is randomized, whichever is first. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject 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 and comparison with the eCRFs. 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 eCRF data from all study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. 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/or disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: Modified IMWG Diagnostic Criteria for Multiple Myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma[a] AND any one or more of the following myeloma defining events:

Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

- Hypercalcemia: serum calcium >0.25 mM/L (>1 mg/dL) higher than ULN or >2.75 mM/L (>11 mg/dL)
- Renal insufficiency: creatinine clearance[b] <40mL/min or serum creatinine >177 μM/L (>2 mg/dL)
- Anemia: hemoglobin >2 g/dL below the lower limit of normal or hemoglobin <10 g/dL[c]
- Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT[d]

Note: Subjects only meeting SLiM CRAB are not eligible.

Footnotes:

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

b) Measured or estimated by validated equations.

c) Hemoglobin measurement performed as part of standard of care within 42 days before randomization is acceptable for screening for CRAB criteria; but must be performed within 21 days before randomization for other eligibility requirements.

d) 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.

Reference: Rajkumar 2014 [30]

Attachment 2: 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 1982[24]

Attachment 3: Calculated and Measured Creatinine Clearance

Cockcroft-Gault formula:

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

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

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

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

Formula to measure creatinine clearance:

$$CrCl = \frac{U_{Cr} \times U_{vol}}{P_{Cr} \times T_{min}}$$

$$\text{Corrected CrCl} = CrCl \times \frac{1.73}{BSA}$$

Notes: U_{Cr}, Urine creatinine concentration; U_{vol}, Urine volume from 24hrs collection; P_{Cr}, plasma creatinine concentration; T_{min}, collection time in minutes (24h x 60min); BSA, body surface area.

If the body mass index of a subject is >30kg/m^2, lenalidomide dosing should be based on the CrCl calculated with adjusted body weight.

Attachment 4: Serum Calcium Corrected for Albumin

If calcium is expressed in mg/dL and albumin is expressed in g/dL:
Corrected calcium (mg/dL) =
serum calcium (mg/dL) + 0.8•(4 - serum albumin [g/dL])

If calcium is expressed in mM/L and albumin is expressed in g/L:
Corrected calcium (mM/L) =
serum calcium (mM/L) + 0.02•(40 - serum albumin [g/L])

Source: Burtis 1999[3]

Attachment 5: Lenalidomide Global Pregnancy Prevention Plan

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

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

1.1 Pregnancy Prevention Risk Management Plans

1.1.1 Lenalidomide Pregnancy Prevention Risk Management Plan

1.1.1.1 Lenalidomide Pregnancy Risk Minimisation Plan for Celgene Clinical Trials

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

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

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

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

Risks Associated with Pregnancy

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

Criteria for females of childbearing potential (FCBP)

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

Counseling

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

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

The investigator must ensure that for females of childbearing potential:

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

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

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

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

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

Contraception

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

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

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

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

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

Pregnancy testing

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

Before starting study drug

Female Patients:

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

Male Patients:

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

During study participation and for 28 days following study drug discontinuation

Female Patients:

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

Male Patients:

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

Additional precautions

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of study drug.
- Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.

1.1.1.3 Lenalidomide Education and Counseling Guidance Document

To be completed prior to each dispensing of study drug.

Protocol Number: _____

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

(Check the appropriate box to indicate risk category)

Female: □

If female, check one:

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

Male: □

Do Not Dispense study drug if:

- **The patient is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**

- **The patient states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual contact) [at least 28 days prior to therapy, during therapy and during dose interruption].**

FCBP:

1. I verified that the required pregnancy tests performed are negative.
2. I counseled FCBP regarding the following:
   - Potential risk of fetal exposure to lenalidomide: If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. The teratogenic potential of lenalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking lenalidomide.
   - Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to therapy, during therapy, during dose interruption and 28 days after discontinuation of study drug].
   - That even if she has amenorrhea she must comply with advice on contraception
   - Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
     - Highly effective methods:
       - Intrauterine device (IUD)
       - Hormonal (birth control pills, injections, implants)
       - Tubal ligation
       - Partner's vasectomy
     - Additional effective methods:
       - Male condom
       - Diaphragm
       - Cervical Cap
   - Pregnancy tests before and during treatment, even if the patient agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10 to 14 days and the second within 24 hours of the start of study drug.
   - Frequency of pregnancy tests to be done:
     - Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
     - If the patient missed a period or has unusual menstrual bleeding.

  - When the patient is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.

- Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug and for 28 days after stopping study drug.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
- Do not break, chew, or open study drug capsules.
- Return unused study drug to the study doctor.

3. Provide Lenalidomide Information Sheet to the patient.

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

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

MALE:

1. I counseled the Male patient regarding the following:
   - Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP).
   - To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 28 days after stopping study drug.
   - Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant.
   - NEVER share study drug with anyone else.

- Do not donate blood, semen or sperm while taking study drug and for 28 days after stopping study drug.
- Do not break, chew, or open study drug capsules.
- Return unused study drug capsules to the study doctor.

2. Provide Lenalidomide Information Sheet to the patient.

Investigator/Counselor Name (Print): _____

(circle applicable)

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

(circle applicable)

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

1.1.1.4 Lenalidomide Information Sheet

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

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

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

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

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

   - **Do not take study drug if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting study drug
     - while taking study drug
     - during dose interruptions of study drug
     - for 28 days after stopping study drug
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days and again 24 hours prior to the first dose of study drug
     - weekly for the first 28 days

  - every 28 days after the first month or every 14 days if you have irregular menstrual periods
  - if you miss your period or have unusual menstrual bleeding
  - 28 days after the last dose of study drug (14 and 28 days after the last dose if menstrual periods are irregular)

- **Stop taking study drug if you become pregnant during treatment**
  - If you suspect you are pregnant at any time during the study, you must stop study drug immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation
- **Do not breastfeed while taking study drug**
- The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not of childbearing potential:

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

If you are a male:

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

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

2. **Restrictions in sharing study drug and donating blood:**
   - **Do not share study drug with other people. It must be kept out of the reach of children and should never be given to any other person.**
   - **Do not donate blood** while you take study drug and for 28 days after stopping study drug.

- **Do not break, chew, or open study drug capsules.**
- You will get no more than a 28-day supply of study drug at one time.
- Return unused study drug capsules to your study doctor.

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

Attachment 6: Conversion Table for Glucocorticosteroid Dose

Generic Name	Oral or Intravenous Dose (mg)
Dexamethasone	0.75
Methylprednisolone	4
Prednisolone	5
Prednisone	5
Betamethasone	0.6

Attachment 7: Asthma Guidelines

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

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Components of Control		Classification of Asthma Control								
		Well Controlled			Not Well Controlled			Very Poorly Controlled		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
	Symptoms	≤ 2 days/week but not more than once on each day		≤ 2 days/ week	> 2 days/week or multiple times on ≤2 days/week		> 2 days/ week	Throughout the day		
Impairment	Nighttime awakenings	≤ 1x/month		≤ 2x/month	> 1x/month	≥ 2x/month	1-3x/week	> 1x/week	≥ 2x/week	≥ 4x/week
	Interference with normal activity	None			Some limitation			Extremely limited		
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			> 2 days/week			Several times per day		
	Lung function FEV_1 or peak flow FEV_1/FVC	N/A	> 80% > 80%	> 80%	N/A	60-80% 75-80%	60-80%	N/A	< 60% < 75%	< 60%
	Validated questionnaires ATAQ ACQ ACT			0 ≤ 0.75 ≥ 20			1-2 ≥ 1.5 16-19			3-4 N/A ≤ 15
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2/year					
		Consider severity and interval since last exacerbation								
	Reduction in lung growth/ Progressive loss of lung function	Evaluation requires long-term follow-up								
		• Maintain current step • Regular follow-up every			Step up 1 step	Step up at least 1 step	• Step up 1 step •	• Consider short course of oral steroids • Step up 1-2 steps		• Consider short course of oral

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

Attachment 8: International Staging system

International Staging System		
Stage	**Criteria**	**Median Survival (months)**
I	Serum $ß_2$ microglobulin <3.5 mg/L, serum albumin ≥3.5 g/dL	62
II	Not I or III[a]	44
III	Serum $ß_2$ microglobulin ≥5.5 mg/L	29

[a] There are 2 possibilities for Stage II:
1) Serum $ß_2$ microglobulin <3.5 mg/mL but serum albumin <3.5 g/dL, or
2) Serum $ß_2$ microglobulin 3.5 – 5.4 mg/L irrespective of the serum albumin

Attachment 9: The Family of antihistamine medications

The following antihistamines may be used for daratumumab preinfusion medication (including, but not limited to):

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

  * The IV use of promethazine should be avoided.

Attachment 10: Anticipated Adverse Events

Anticipated Event

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

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

- Anaemia
- Bleeding
- Bone diseases
- Hypercalcaemia
- Hyperuricemia
- Hyperviscosity syndrome
- Infection
- Neutropenia
- Renal failure or insufficiency
- Thrombocytopenia

Reporting of Anticipated Events

All adverse events will be recorded in the CRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

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

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Ming Qi

Institution: Janssen Research & Development

Signature: [redacted] Date: 25 May 2017
(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: 22 May 2017

Janssen Research & Development

Statistical Analysis Plan For the First Interim Analysis

A Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High Dose Therapy

Protocol 54767414MMY3008; Phase 3

JNJ54767414 (daratumumab)

Status:	Approved
Date:	24 February 2016
Prepared by:	Janssen Research & Development
Document No.:	EDMS-ERI-120250925

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase/serum glutamate pyruvate transaminase
AST	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
CRF	case report form
CSR	Clinical Study Report
DPS	data presentation specification
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
IA	interim analysis
IMWG	International Myeloma Working Group
ISS	International Staging System
ITT	intent-to-treat
IWRS	interactive web response system
LDH	lactate dehydrogenase
LLOQ	lower limits of quantification
MedDRA	Medical Dictionary for Regulatory Activities
M-protein	monoclonal protein, monoclonal paraprotein
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse
ORR	Overall response rate
OS	Overall survival
RBC	Red blood cell count
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SPEP	serum protein electrophoresis
TEAEs	treatment-emergent adverse events
TTP	Time to disease progression
UPEP	urine protein electrophoresis
VGPR	Very good partial response
WBC	White blood cell count

1. INTRODUCTION

This interim statistical analysis plan (IA1 SAP) contains definitions of analysis sets, derived variables, and statistical methods for the first planned interim analysis specified in the protocol 54767414MMY3008.

1.1. Overview of Trial Design

This is a randomized, open-label, active controlled, parallel-group, multicenter study in subjects at least 18 years of age with previously untreated multiple myeloma who are not candidates for high dose chemotherapy and ASCT. Approximately 730 subjects will be enrolled in this study with 365 subjects planned per treatment arm.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 21 days before Cycle 1, Day 1. The Treatment Phase will extend from Day 1 of Cycle 1 until discontinuation of all study treatment. For subjects assigned to DRd, daratumumab will be administered weekly for the first 8 weeks (Cycles 1-2) of treatment and then every other week for 16 weeks (Cycles 3-6), then every 4 weeks (from Cycle 7 and beyond) until disease progression or unacceptable toxicity. This will equate to 9 consecutive weeks of dosing at the start of the study and a total of 23 doses in the first year. Lenalidomide will be administered at a dose of 25 mg orally (PO) on Days 1 through 21 of each 28-day cycle, and dexamethasone will be administered at a dose of 40 mg once a week for both treatment arms. Subjects in the DRd arm will receive lenalidomide/dexamethasone for a maximum of 2 years (subjects will continue to receive dexamethasone as a premedication for daratumumab administration even after the lenalidomide/dexamethasone treatment is discontinued); those in the Rd arm will continue lenalidomide/dexamethasone until disease progression or unacceptable toxicity. In the DRd arm, subjects will continue on daratumumab until disease progression or unacceptable toxicity. Randomization will be stratified by International Staging System (I vs II vs III), region (North America vs Other), and age (<75 vs ≥ 75), using an equal allocation ratio of 1:1.

Measures to prevent infusion-related reactions will include preinfusion medication with dexamethasone, acetaminophen (paracetamol), and an antihistamine before each daratumumab infusion.

The Follow-up Phase will begin once a subject discontinues all study treatments. Subjects who discontinue for reasons other than disease progression must continue to have disease evaluations according to the Time and Events Schedule. The Follow-up Phase will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first. After the clinical cut-off (see below for definition), data collection will be reduced.

Two interim analyses are planned. The first interim analysis, with a purpose to evaluate safety, will be performed after a total of approximately 100 subjects have been treated for at least 8 weeks or discontinued the study treatment. The second interim analysis will be performed when 234 PFS events, which is 60% of the total planned events, have been accumulated. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. The

significance level at this interim analysis to establish the superiority of DRd over Rd with regard to PFS will be determined based on the observed number of PFS events at the interim analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. If the experimental arm (DRd) is numerically worse than the control arm in terms of PFS (observed hazard ratio > 1 favoring the control arm), then the study may be terminated for futility.

The primary PFS analysis will occur when approximately 390 PFS events have been observed. The date established for the primary PFS analysis will serve as the clinical cut-off date, after which data collection in the study will be reduced. Investigators will be informed when each interim analysis is to occur.

The end of the study will occur when 330 subjects have died, or 5 years after the last subject is randomized, whichever comes first. The sponsor will ensure that subjects benefiting from treatment with daratumumab will be able to continue treatment after the end of the study.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study to review efficacy and safety results at the planned interim analyses. After the interim review, they will make recommendations regarding the continuation of the study. In addition, the IDMC may also review cumulative safety data every 6 months besides the 2 interim analyses.

Assessment of tumor response and disease progression will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria. An assessment of MRD will be conducted on whole blood and bone marrow samples. Safety evaluations will include adverse event monitoring, physical examinations, electrocardiogram (ECG) monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and ECOG performance status. Blood samples will be drawn for assessment of pharmacokinetic parameters.

1.2. Objective of First Interim Analysis

The objective of the first planned interim analysis is to evaluate safety of daratumumab in combination with Rd versus Rd alone.

1.3. Timing of First Interim Analysis

The first interim analysis will occur after 100 subjects have been treated for at least 8 weeks or discontinued the study treatment.

1.4. Safety Evaluation at First Interim Analysis

Safety evaluation at the first interim analysis will focus on assessment of study treatment discontinuation, adverse events, serious adverse events, Grade ≥ 3 adverse events, adverse events leading to study treatment discontinuation, infusion-related reactions, and deaths within 30 days of last study treatment. The detailed analyses of safety are described in Section 4.

1.5. Interim Analysis Committee (IAC)

An IDMC, consisting of two clinicians and one statistician for this study, will serve as an interim analysis committee (IAC) and perform IAC function in addition to its periodic safety monitoring responsibility (i.e., every 6 months). The IDMC members and roles and responsibilities of IDMC members are specified in the IDMC charter. After the first interim data review, the IDMC will make recommendations regarding the continuation of the study. The possible decisions or actions based on the first interim analysis will be:

- To continue the study without modification until second interim analysis
- To continue the study without modification, and plan an additional safety review
- To halt enrollment pending discussions with the Sponsor
- To stop the study for safety

1.6. Statistical Support Group (SSG)

The first interim analysis will be performed in cooperation with a statistical support group (SSG). A statistical support group is an external organization independent of sponsor, whose name and members are identified in the IDMC Charter. The role and responsibility of SSG (including SSG statistician) are specified in the IDMC charter.

1.7. Level of Unblinding

Prior to the scheduled first interim analysis meeting, the SSG group will prepare the data package and send the data package to the IDMC members. Due to limited availability of safety data for the combination of daratumumab with Rd to date, and to ensure the IDMC have a comprehensive evaluation of safety, the data available for IDMC review will be unblinded with respect to both treatment groups and individual subject. However, all participating investigators and the Sponsor's study team will be blinded to the aggregated data until analysis of the primary endpoint of PFS, which will occur after 390 PFS events have occurred.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

For analyses of data by cycle, if data are collected by date (i.e., AE onset), the corresponding study evaluations will be assigned to actual sequential cycles, which are derived from the study treatment administration data. The start date of a particular cycle is defined as the date of the first scheduled dose, and the end date of a cycle is the start date of the next cycle minus 1. For the last cycle, the end date is defined as the end of treatment visit date or 27 days after the last dose if the end of treatment visit date is not available. If data (e.g., laboratory and vital sign, etc.) are collected by cycle, the nominal cycle will be used to summarize data.

2.2. Pooling Algorithm for Analysis Centers

All participating centers in the study will be pooled together for analyses.

2.3. Study Treatment and Study Drug

In this study, study treatment refers to lenalidomide, dexamethasone, and daratumumab and study drug refers to daratumumab.

2.4. Study Treatment Dosing Date

Study treatment dosing date is the date on which a subject actually received study treatment (partial or complete) and will be recorded in the study treatment administration dataset.

For subjects who receive DRd treatment, the first study treatment date is defined as the earliest date of non-zero dose of the following administration: lenalidomide, dexamethasone or daratumumab. The last study treatment date is defined as the latest date of non-zero dose of the following administration: lenalidomide, dexamethasone or daratumumab.

For subjects who receive Rd treatment, the first study treatment date is defined as the earliest date of non-zero dose of the following administration: lenalidomide or dexamethasone. The last study treatment date is defined as the latest date of non-zero dose of the following administration: lenalidomide or dexamethasone.

2.5. Baseline Measurement

Baseline measurement is defined as the closest non-missing measurement taken on or prior to the first study treatment (including time if time is available).

2.6. Imputation of Missing/Partial Dates

Unless specified otherwise, no data imputation will be applied for missing safety evaluations, and all available data for all subjects will be presented. For analysis and reporting purpose, missing/partial dates in medical history (date of initial MM diagnosis), adverse event (AE onset date; AE end date), concomitant therapies (start date; end date), and subsequent anti-cancer therapies (start date) will be imputed.

The detailed imputation rules along with other derived variables are specified in the data presentation specification (DPS).

2.7. General Analysis Method

In general, continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median and range. Categorical variables will be summarized using frequency and percentage.

2.8. Analysis Sets

The following analysis sets are defined.

- Intent-to-treat (ITT): is defined as subjects who have been randomly assigned to the DRd or Rd group. Analyses of demographics and baseline characteristic will be based on this population.
- Safety population: is defined as subjects who have received at least 1 administration of any study treatment (daratumumab, lenalidomide, or dexamethasone). This population will be used for all safety analyses. The safety analyses grouping will be according to treatment actually received.

3. SUBJECT INFORMATION

3.1. Demographics and Baseline Characteristics

Unless specified otherwise, all demographic and baseline characteristics variables will be summarized for the ITT population. No statistical comparisons between the 2 treatment groups are planned.

Subject demographic and baseline characteristic variables: age (< 65 years, 65 to < 75 years, and ≥75 years), sex, ethnicity, race, weight (kg), height (cm), and ECOG performance status will be summarized by treatment group and overall.

Baseline disease characteristics including type of multiple myeloma, measurable disease, ISS Staging, time since initial diagnosis (months), number of lytic bone lesions (None, 1-3, 4-10, more than 10), presence of diffuse myeloma-related osteopenia (Yes, No), number and percentage of subjects with extramedullary plasmacytomas (0, ≥1), bone marrow % plasma cells (<10, 10 – 30, >30), bone marrow cellularity (hypocellular, normocelluar, hypercellular, indeterminate), bone marrow % cellularity, baseline ECG overall conclusion (normal, abnormal but not clinically significant, abnormal and clinically significant)
will be tabulated by treatment group and overall.

3.2. Disposition Information

The number of subjects who are randomized to each treatment group will be summarized. The number and percentage of subjects who are treated will be reported. For all treated subjects (defined as subjects who have received at least 1 administration of any study treatment), the number and percentage of subjects who discontinued treatment including reason for discontinuation as indicated by the investigators will be summarized.

3.3. Extent of Exposure

Extent of exposure to study treatments will be summarized and presented based on the safety population.

The number and percentage of subjects treated within each cycle will be summarized by treatment group. The maximum number of treatment cycles received for each subject will be summarized by frequency and descriptive statistics (mean, standard deviation, median, and range). Duration of study treatment, defined as the number of days from the date of the first administration of study treatment to the date of the last dose, will be summarized.

The dose intensity, which is defined as the sum of total dose administered in all cycles divided by the number of treatment cycles, will be calculated for each study treatment (daratumumab, lenalidomide, dexamethasone) accordingly

4. SAFETY

Safety assessment will be evaluated at the first interim analysis through AEs. Safety analyses will be based on the safety population and presented by the treatment actually received.

4.1. Adverse Events

AEs will be monitored throughout the study. All AEs will be recorded in standard medical terminology and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. For AE reporting, the verbatim term used in the eCRF by investigators to identify adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Unless otherwise specified, at each level of subject summarization in reporting the incidence of the AE, a subject is counted once if one or more events were recorded.

All summaries of AEs will be based on treatment-emergent adverse events (TEAEs), which is defined as any AE that occurs after the first administration of study treatment (e.g., daratumumab, lenalidomide, or dexamethasone) through 30 days after the last study treatment administration; or any AE that is considered reasonably related to study treatment regardless of the start date of the event; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered reasonably related to study treatment by the investigator.

The incidence of TEAEs will be summarized overall, by MedDRA system organ class (SOC) and preferred term, by toxicity grade, and by relationship to study treatment administration. Specifically, the following AE summaries will be presented by treatment group:

4.1.1. Overview of Adverse Events

An overview of TEAEs will be provided for each treatment group and relatedness to study treatment. The overview will include summaries of subjects with any TEAE, subjects by maximum toxicity grade of TEAE, subjects with any serious TEAE, subjects who terminated study treatment due to a TEAE, and deaths due to a TEAE.

4.1.2. Adverse Events by System Organ Class

Incidence of TEAEs by MedDRA SOC and preferred term will be provided.

4.1.3. Serious Adverse Events (SAEs)

For subject who had any treatment-emergent serious adverse events, a list of subject ID, treatment group, MedDRA preferred term/verbatim term, study day of AE, AE duration, AE seriousness, AE toxicity grade, relationship to study treatment, action taken with study treatment and outcome for all the treatment-emergent adverse events of this subject will be provided.

4.1.4. Infusion-Related Reactions

Infusion-related reactions based on investigator assessment will be summarized by treatment group.

4.1.5. Treatment Discontinuations Due to Adverse Events

For the treatment-emergent adverse events leading to study treatment discontinuation, a list of subject ID, treatment group, MedDRA preferred term/verbatim term, study day of AE, AE duration, AE seriousness, AE toxicity grade, relationship to study treatment, action taken with study treatment and outcome will be provided.

4.1.6. Deaths

A listing will be generated for all patients who died within 30 days of last dose of study treatment. The primary cause of death will be provided.

Janssen Research & Development

Statistical Analysis Plan

Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High Dose Therapy

Protocol 54767414MMY3008 Amendment INT-4 Phase 3

JNJ-54767414 (daratumumab)

Status: Approved
Date: 3 October 2018
Prepared by: Janssen Research & Development
Document No.: EDMS-ERI-120250925, 2.0

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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LIST OF IN-TEXT TABLES

AMENDMENT HISTORY

Unique Identifier for SAP Version	Date of SAP Version	Author	Changes from the Previous Version
1.0	24 February 2016	[redacted]	The initial version for the first interim analysis
2.0	3 October 2018	[redacted]	1. Updated per the latest protocol 2. Added the efficacy part

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ASCT	Autologous Stem Cell Transplant
AST	aspartate aminotransferase
BSA	body surface area
CI	confidence interval
CR	complete response
CrCL	creatinine clearance
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
DPS	data presentation specification
DRd	Daratumumab, lenalidomide, dexamethasone
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FISH	fluorescence in situ hybridization
FLC	free light chain
IA	interim analysis
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
IMWG	International Myeloma Working Group
IRR	infusion-related reaction
ISS	International Staging System
ITT	intent-to-treat
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
M-protein	monoclonal protein, monoclonal paraprotein
MRD	minimal residual disease
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse
ORR	overall response rate
OS	overall survival
PD	progressive disease
PBMC	peripheral blood mononuclear cell
PFS	progression-free survival
PP	per-protocol
PR	partial response
Rd	lenalidomide, dexamethasone
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
sCR	stringent complete response
SD	stable disease
SD	standard deviation
SOC	system organ class
SPEP	serum protein electrophoresis
TEAEs	treatment-emergent adverse events
TTR	time to response
TTP	time to disease progression
UPEP	urine protein electrophoresis
VGPR	very good partial response
WBC	white blood cells

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the planned analyses as specified in the protocol JNJ-54767414MMY3008, Amendment INT-4.

1.1. Overview of Trial Design

This is a randomized, open-label, active controlled, parallel-group, multicenter study in subjects at least 18 years of age with previously untreated multiple myeloma who are not candidates for high dose chemotherapy and ASCT. The primary objective is to evaluate if daratumumab in combination with Rd prolongs progression-free survival (PFS) compared with Rd alone. The secondary objectives are to compare the 2 treatment groups with respect to time to disease progression (TTP), complete response (CR) or better rate, MRD negativity rate, progression-free survival on next line of therapy (PFS2), overall survival (OS), time to next treatment, overall response rate (ORR), very good partial response (VGPR) or better rate, sCR rate, time to response, duration of response as well as to assess the safety and tolerability of daratumumab when administered in combination with Rd.

Approximately 730 subjects will be randomized in this study with 365 subjects planned per treatment arm (DRd or Rd). Randomization will be stratified by International Staging System (I vs II vs III), region (North America vs Other), and age (<75 vs ≥75). Within each stratum, subjects will be randomized using an equal allocation ratio of 1:1.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 21 days before Cycle 1 Day 1. The Treatment Phase will extend from Day 1 of Cycle 1 until discontinuation of all study treatment. For subjects assigned to DRd, daratumumab will be administered weekly for the first 8 weeks (Cycles 1-2) of treatment and then every other week for 16 weeks (Cycles 3-6), then every 4 weeks (from Cycle 7 and beyond) until disease progression or unacceptable toxicity. This will equate to 9 consecutive weeks of dosing at the start of the study and a total of 23 doses in the first year. Lenalidomide will be administered at a 25 mg or 10 mg orally (PO) on Days 1 through 21 of each 28-day cycle, and dexamethasone will be administered at a dose of 40 mg or 20 mg once a week for both treatment arms (per age, for more detail refer to protocol Section 6. Dosage and Administration). Those in the Rd arm will receive lenalidomide will be administered at a dose of 25 mg or 10 mg orally (PO) on Days 1 through 21 of each 28-day cycle, and dexamethasone will be administered at a dose of 40 mg or 20 mg once a week until disease progression or unacceptable toxicity. Subjects in both treatment arms will continue lenalidomide and dexamethasone until disease progression or unacceptable toxicity. In the DRd arm, subjects will continue on daratumumab until disease progression or unacceptable toxicity.

The Follow-up Phase will begin once a subject discontinues all study treatments. Subjects who discontinue for reasons other than disease progression must continue to have disease evaluations according to the Time and Events Schedule which will continue until confirmed progression disease (PD), death, lost to follow up, consent withdrawal, subsequent anticancer therapy, or

study end, whichever occurs first. After the clinical cut-off (see below for definition), data collection will be reduced as per protocol Section **Error! Reference source not found.**.

Two interim analyses are planned (for detail refer to Section 1.4).

The primary PFS analysis will occur when approximately 390 PFS events have been observed. The date established for the primary PFS analysis will serve as the clinical cut-off date, after which data collection in the study will be reduced. Investigators will be informed when each interim analysis is to occur. All available data prior to that time will be included in each of the respective analyses.

The end of the study will occur when 330 subjects have died, or 7 years after the last subject is randomized, whichever comes first. The sponsor will ensure that subjects benefiting from treatment with daratumumab will be able to continue treatment after the end of the study.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study to review efficacy and safety results at the planned interim analyses (more detail information including the timing refer to section 1.4). After the interim reviews, they will make recommendations regarding the continuation of the study. In addition, the IDMC may also review cumulative safety data every 6 months besides the 2 interim analyses.

Assessment of tumor response and disease progression will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria. An assessment of MRD will be conducted on bone marrow samples. Safety evaluations will include adverse event monitoring, physical examinations, electrocardiogram (ECG) monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status. Blood samples will be drawn for assessment of pharmacokinetic parameters.

1.2. Statistical Hypotheses for Trial Objectives

The primary efficacy endpoint of this study is PFS. The null hypothesis is that there is no difference in PFS between daratumumab in combination with Rd and Rd alone in subjects with newly diagnosed multiple myeloma who are ineligible for high dose chemotherapy and autologous stem cell transplant.

The secondary endpoints such as ORR, VGPR or better rate, CR or better rate, MRD negativity rate, OS, TTP, PFS2, sCR rate, time to next treatment, time to response and duration of response will be evaluated as well.

1.3. Sample Size Determination

The sample size calculation is performed on the basis of the following assumption. Based on the published data, the median PFS for Rd arm is assumed to be approximately 24 months. Assuming the addition of daratumumab can reduce the risk of the disease progression or death by 25%, i.e., assuming the hazard ratio (DRd vs. Rd) of 0.75, a total of 390 PFS events is needed to achieve a power of 80% to detect this hazard ratio with a log-rank test (two-sided alpha is

0.05). With a 21-month accrual period and an additional 24-month follow-up, the total sample size needed for the study is approximately 730 (365/arm) subjects. The sample size calculation has taken into consideration an annual dropout rate of 5%.

Long-term survival follow-up will continue until 330 deaths have been observed or 7 years after the last subject is randomized, whichever is first. Therefore, this study will achieve approximately 80% power to detect a 27% reduction in the risk of death (hazard ratio = 0.73) with a log-rank test (two-sided alpha = 0.05) if 330 death events are observed at the study end.

1.4. Interim Analyses

Two interim analyses are planned. The first interim analysis, with a purpose to evaluate safety, has been performed after a total of approximately 100 subjects have been treated for at least 8 weeks or discontinued the study treatment. The second interim analysis will be performed when approximately 234 PFS events, which is 60% of the total planned events (390 PFS events), have been accumulated to evaluate the cumulative interim safety and efficacy of daratumumab in combination with Rd. The significance level at this interim analysis to establish the superiority of DRd over Rd with regard to PFS will be determined based on the observed number of PFS events at the interim analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. If the experimental arm (DRd) is numerically worse than the control arm in terms of PFS (observed hazard ratio >1 favoring the control arm), then the study may be terminated for futility.

More details about the conduct of these interim analyses can be found in a stand-alone IDMC charter.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

For analyses of data by cycle, if data are collected by date (e.g., AE onset), the corresponding study evaluations will be assigned to actual sequential cycles, which are derived from the study treatment administration data. The start date of a particular cycle is defined as the date of the first scheduled dose of any component of the study treatment, and the end date of a cycle is the start date of the next cycle minus 1. For the last cycle, the end date is defined as the end of treatment visit date or the minimum of last study treatment date plus 30 days and subsequent antimyeloma therapy minus 1 day, if the end of treatment visit date is not available.

In general, if data (e.g., laboratory and vital sign etc.) are collected by cycle, the nominal cycle will be used to summarize data. However, due to possible cycle delays, assessment performed in the same cycle may not be well aligned in time scale for different subjects.

2.2. Pooling Algorithm for Analysis Centers

All participating centers in the study will be pooled together for analyses.

2.3. Study Treatment and Study Drug

In this study, study treatment refers to lenalidomide, dexamethasone, and/or daratumumab. Study drug refers to daratumumab.

2.4. Study Treatment Dosing Date

Study treatment dosing date is the date on which a subject actually receives study treatment (partial or complete) and will be recorded in the study treatment administration dataset.

For subjects who receive DRd treatment, the first study treatment date is defined as the earliest date of non-zero dose of the following administration: lenalidomide, dexamethasone or daratumumab. The last study treatment date is defined as the latest date of non-zero dose of the following administration: lenalidomide, dexamethasone or daratumumab.

For subjects who receive Rd treatment, the first study treatment date is defined as the earliest date of non-zero dose of the following administration: lenalidomide or dexamethasone. The last study treatment date is defined as the latest date of non-zero dose of the following administration: lenalidomide or dexamethasone.

2.5. Baseline Measurement

Baseline measurement is defined as the closest non-missing measurement taken on or prior to the first study treatment administration (including time if time is available, with exception of parameters associated with disease-related efficacy assessment such as SPEP, UPEP, kappa, lambda, kappa/lambda ratio, serum calcium, and albumin).

2.6. Unique Lab Value

In general, in instances when there are multiple records at a given visit date for lab parameters associated with disease assessment, the following rules will be applied to select the unique lab value for analysis: a) multiple records from both central and local lab, central lab value always takes precedence over local lab value; b) multiple records from central lab, select the latest value by time, visit number, or sequence number as the unique lab value; c) multiple records from local lab, select the latest lab value by time, visit number, or sequence number as the unique local lab value.

2.7. Imputation of Partial Dates

Unless specified otherwise, no data imputation will be applied for missing safety and efficacy evaluations. For analysis and reporting purpose, partial dates in adverse event (AE onset date; AE end date), concomitant therapies (start date; end date), MM diagnosis date, and start date of subsequent antimyeloma therapy will be imputed.

2.7.1. Missing/Partial Adverse Event Onset Date

If the onset date of an adverse event is missing completely or partially, the following imputation rules will be used.

- When month and year are present and the day is missing,
  - If the onset month and year are the same as the month and year of first study treatment, the day of first study treatment or the day-component of the AE end date (possibly imputed) is imputed, whichever is earlier
  - If the onset month and year are not the same as the month and year of first study treatment, then the first day of the month is imputed
- When only a year is present,
  - If the onset year is the same as the year of first study treatment. If AE end date is available and is prior to first study treatment, the day and month of AE end date are imputed. Otherwise, the day and month of first study treatment are imputed
  - If the onset year is different from the year of first study treatment, the 1st of January is imputed
- If the onset date is completely missing, the earlier one of the date of first study treatment and the AE end date is imputed as the onset date.

No imputation will be done for partial or missing AE onset time.

2.7.2. Missing/Partial Adverse Event End Date

If the end date of an adverse event is missing completely or partially, the following imputation rules will be used.

- If month and year are present and the day of the month is missing, the last day of the month is imputed.
- If only a year is present, the 31st of December is used.
- If the imputed date is later than the date of death (if available), the date of death will be used as the imputed date instead.
- If the year of end date is missing, no imputation will be applied.

No imputation will be done for partial or missing AE end time.

2.7.3. Partial Concomitant Medication Start/End Date

In case of partially missing concomitant medication start/end dates, the following imputation rules will be applied. If the date is completely missing, no imputation will be performed.

- If only the day is missing, the 15th day of the month will be used
- If both the day and month are missing, the 30th of June will be used.

- If the medication was taken prior to study start, and the imputed start date is after first treatment date, further adjust of the imputed start date as the day prior to first dosing date; If the medication was taken after study start, and the imputed start date is prior to first dosing date, further adjust the imputed start date as first dosing date. Also adjust the imputed medication end date so that it is on or after first dosing date.

2.7.4. Partial Multiple Myeloma Diagnosis Date

For partial date of original multiple myeloma diagnosis, the following imputation rules will apply:

- If only the day is missing, set to 15th (as imputed date), and pick minimum of imputed date, date of collection and date of randomization
- If both the day and month are missing, set to January 1, and pick minimum of imputed date, date of collection and date of randomization
- If year is missing, no imputation will be applied.

If the imputed date of original diagnosis is after the randomization date, further adjust the imputed start date as the day before the randomization date.

2.7.5. Partial Subsequent Anticancer Therapy Start Date

If year or month of subsequent anticancer therapy start date is missing or no components of the start date are present, no imputation will be performed.

If only the day is missing, the following steps apply:

- If the month and year of the start date are the same as the month and year of last dosing date, the day of last dosing date or the day-component of the stop date of subsequent anticancer therapy is imputed, whichever is earlier.
- If the start month and year are not the same as the month and year of last dosing date, the first day of the month is imputed.

No imputation will be applied for missing or partial subsequent anticancer therapy end date.

2.8. General Analysis Method

In general, continuous variables will be summarized using descriptive statistics such as mean, standard deviation (SD), median and range. Categorical variables will be summarized using frequency and percentage. For time-to-event variables, which is defined as from randomization to the date of the event, the Kaplan-Meier method will be used for descriptive summaries. For the calculation of time-to-event and duration-of-event variables, the difference between the start date and the end date plus 1 day will be used.

2.9. Analysis Sets

The following analysis sets are defined.

- Intent-to-treat (ITT): defined as subjects who have been randomly assigned to the DRd or Rd group. Analyses of demographics, baseline characteristics and efficacy endpoints will be primarily analyzed based on this population.
- Safety population: defined as subjects who have received at least 1 administration of any study treatment (partial or complete). This population will be used for all safety analyses. The safety analyses grouping will be according to treatment actually received.
- Response-evaluable: defined as subjects who have a confirmed diagnosis of multiple myeloma and measurable disease at baseline or screening visit. In addition, subjects must have received at least one administration of study treatment and have adequate post-baseline disease assessments. Measurable disease is defined as follows:
  - IgG myeloma: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
  - 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
  - Light chain multiple myeloma without measurable disease in serum or urine: Serum immunoglobulin free light chain (FLC) level ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.

This population will be used as sensitivity analyses for selective response-related secondary endpoints such as CR or better rate.

- Per-protocol (PP) population: defined as subjects who are randomized and meet all eligibility criteria.
- Pharmacokinetics-evaluable: is defined as subjects assigned to DRd group who received at least 1 administration of daratumumab and have at least 1 pharmacokinetic sample concentration value after the first infusion. All pharmacokinetics analyses are based on the pharmacokinetic evaluable population.
- Immune response-evaluable: is defined as subjects assigned to DRd group who have at least 1 immunogenicity sample obtained after their first daratumumab administration.
- Molecular genetic evaluable: defined as subjects who meet one of the following biomarker criteria for risk assessment based on the next generation sequencing (NGS) data:
  - Standard risk: subjects that are negative (=molecular aberration absent) for all del17p, t(14;16), t(4;14).
  - High risk: subjects that are positive (=molecular aberration present) for any of del17p, t(14;16), t(4;14).
- Cytogenetic evaluable: defined as subjects who meet one of the following cytogenetic risk categories:
  - Standard risk: subjects that are negative for del17p, t(14;16), t(4;14) by FISH/Karyotype.
  - High risk: subjects that are positive for any of del17p, t(14;16), t(4;14) by FISH/Karyotype.

2.10. Definition of Subgroups

The following pre-specified subgroup analyses are to be performed at the 2nd IA for the efficacy and safety endpoints (Table 1). Additional subgroup analyses may be performed, if requested and deemed necessary by IDMC for making their decision.

Table 1: Subgroup Analyses of Efficacy and Safety Endpoints

Subgroup	Definition	Analysis Type
Sex	Male, Female	E, S
Age	<75 years, ≥75 years	E, S
Race	White, Others	E, S
Baseline renal function (CrCl)	E: >60 mL/min, ≤60 mL/min S: <30, 30 to <60, 60 to <90, ≥90 mL/min	E, S
Baseline hepatic function	Normal, Impaired [a]	E, S
Region	North America, Others	E, S
International Staging System (ISS)	I, II, III	E
Type of MM	IgG, Non-IgG	E
Cytogenetic risk	High risk [b], Standard risk	E
ECOG performance score	0, 1, ≥2	E

E: efficacy (PFS, ORR, CR or better rate); S: TEAE
[a] Includes mild (total bilirubin ≤ ULN and AST > ULN or ULN < total bilirubin ≤ 1.5×ULN), moderate (1.5×ULN < total bilirubin ≤ 3×ULN), severe (total bilirubin > 3×ULN).
[b]. High risk is defined as positive for any of del17p, t(14;16) or t(4;14) by FISH/Karyotype.

2.11. Other General Definitions

2.11.1. Treatment Emergent Adverse Events

Treatment emergent adverse events (TEAEs) are defined as any AE with onset date and time on or after that of the first dose of study drug infusion through 30 days after the last dose of study drug or the day prior to start of subsequent therapy, whichever is earlier; or any AE that is considered related to (probably, possibly, or very likely) study drug regardless of the start date of the event. AEs with missing or partial onset date and time will be considered as treatment-emergent unless the onset date and time of an AE can be determined as earlier than that of the first dose, or later than 30 days after last dose.

2.11.2. Linking of Treatment Emergent Adverse Events

All event records of the same preferred term from the same subject are to be linked by the onset date and the end date. If an event is followed by another event of the same preferred term with an onset date (or date/time) the same as or 1 day (or 1 minute if applicable) after the end date (or date/time) of the previous record and any features of the adverse event (i.e.: toxicity grades/seriousness/action taken) are different between these two records, these 2 records should be linked together and considered as 1 event, the maximal toxicity grade of the 2 records would be used for the analysis.

3. SUBJECT INFORMATION

3.1. Demographics and Baseline Characteristics

Unless specified otherwise, all demographic and baseline characteristics variables will be summarized for the ITT population. No statistical comparison between the 2 treatment groups is planned.

The distribution of subject enrollment will be presented for each treatment group according to region and country.

Subject demographic and baseline characteristic variables: age (<65 years, 65 to <70 years, 70 to <75 years, and ≥75 years), sex, ethnicity, race, weight (kg), height (cm), body surface area (BSA, m^2) and ECOG performance status will be summarized by treatment group and overall. A listing of subject demographic and baseline characteristics will be provided as well.

Baseline disease characteristics including type of multiple myeloma (IgG, IgA, IgM, IgD, IgE, light chain only, biclonal, or negative immunofixation), type of measurable disease (Serum only (IgG, IgA, Other - IgD, IgM, IgE and biclonal), Serum and urine, Urine only, Serum FLC only, or not evaluable), ISS staging at baseline (I, II, III), time since initial MM diagnosis (months), number of lytic bone lesions (None, 1-3, 4-10, more than 10), presence of diffuse myeloma-related osteopenia (Yes, No), number of extramedullary plasmacytomas (0, ≥1), presence of extramedullary plasmacytomas (Yes, No), bone marrow biopsy/aspirate % plasma cells (<10, 10 – 30, >30), bone marrow biopsy % plasma cells (<10, 10 – 30, >30), bone marrow aspirate % plasma cells (<10, 10 – 30, >30), standard-risk and high-risk cytogenetic abnormalities (del17p, t(4;14), t(14;16)), will be summarized and tabulated by treatment group and overall.

A descriptive summary of selected hematology and biochemistry laboratory analytes at baseline will be provided for each treatment group and overall. In addition, baseline toxicity grade of each selected laboratory analyte in hematology and chemistry panel will be summarized by treatment group using frequency based on the safety population.

Medical history collected at baseline or screening visit will be summarized by system-organ class and preferred term for each treatment group and overall.

A summary of stratification factors (ISS staging, region, and age) used in the randomization based on IWRS will be provided to evaluate whether or not randomization process was appropriately executed in the study. The stratified log-rank test and stratified cox model use these stratification factors in randomization.

3.2. Disposition Information

An overview of subject disposition in the study will be provided. The overview includes a summary of total number of subjects who are randomized to each treatment group, the number

and percentage of subjects who are randomized but not treated in each treatment group, and total number of subjects who are treated in each treatment group. For all treated subjects (defined as subjects who have received at least 1 administration of any study treatment), the number and percentage of subjects who discontinued treatment including reason for discontinuation as indicated by the investigators will be summarized. The similar summaries will be presented for all randomized subjects who discontinued from study.

A list of subjects who discontinued study treatment will be provided for safety subjects. This listing will include subject ID, treatment group, date of treatment discontinuation, study day of last dose, reason for discontinuation as well as the specific adverse events (MedDRA preferred term/verbatim term) if discontinuation due to AEs and primary cause of death if discontinuation due to death. A similar list of subjects who discontinued study will be provided for ITT subjects.

3.3. Extent of Exposure

Extent of exposure to study treatments will be summarized and presented based on the safety population.

The number and percentage of subjects treated within each cycle will be summarized by treatment group. The maximum number of treatment cycles received for each subject will be summarized by frequency and descriptive statistics.

Duration of study treatment, defined as the number of months from the date of the first administration of study treatment to the date of the last administration of study treatment, will be summarized.

The number of daratumumab administrations will be summarized for subjects treated with DRd. The total dose administered for daratumumab (mg/kg), lenalidomide (mg), and dexamethasone (mg) will be summarized overall, by cycle of daratumumab treatment.

The dose intensity, which is defined as the sum of total dose administered in all cycles divided by the number of treatment cycles, will be calculated for each study treatment and summarized accordingly. Additionally, the daratumumab dose intensity will be summarized by cycles of daratumumab treatment.

The relative dose intensity (%) defined as the ratio of total actually received dose and total planned dose (planned dose level times the number of administered infusions/medications) will be calculated for each study treatment and summarized by treatment group using descriptive statistics.

The number of subjects with treatment dose delay within the cycle, dose reduced, dose re-escalated per protocol, or dose skipped for lenalidomide and dexamethasone will be summarized for each treatment group. The reasons (AE or other) for treatment dose delay within the cycle, dose reduced, dose re-escalated per protocol, or dose skipped for lenalidomide and dexamethasone will be reported. In addition, a summary of study treatment dose modifications by cycle will be provided.

3.4. Protocol Deviations

Major protocol deviations will be summarized for the ITT population by the following types (not limited) of deviation for each treatment group:

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Efficacy assessment deviation
- Safety assessment deviation

A listing of subjects with major protocol deviations including subject ID, type of deviation, and reasons for deviation will be provided.

3.5. Prior, Concomitant and Subsequent Therapies

With the study population of newly diagnosed multiple myeloma subjects who are not candidates for high dose chemotherapy and ASCT, prior systemic use of corticosteroids is limited to a short course (equivalent of dexamethasone 40mg/day for 4 days) for purposes other than multiple myeloma. If any, a listing of all prior systemic use of corticosteroids will be provided.

Concomitant medications collected in the CRF page during the study will be summarized by therapeutic class, pharmacologic class, and drug name for each treatment group. A similar summary will be provided for subjects who received growth factor support, pre-infusion medication and post-infusion medication, respectively. In addition, systemic steroids as concomitant medication use during the study will be summarized. Additionally, prophylactic antiviral medication use will be tabulated.

The total number of subjects who received subsequent antimyeloma therapy will be reported for subjects in safety population in each treatment group. A summary of subsequent antimyeloma therapy will be presented by therapeutic class, pharmacologic class and drug name. In addition, for subjects who received subsequent antimyeloma therapy, their best response to the first subsequent antimyeloma therapy will be summarized.

4. EFFICACY

A validated computerized algorithm, which is based on the IMWG response criteria (Durie 2006, Rajkumar 2011)[1, 2] and has been used and validated by an independent review committee (IRC) in Study MMY2002, will be used to determine response and disease progression for each subject. As a sensitivity analysis, investigator assessment of response and disease progression using the IMWG response criteria will also be performed.

4.1. Analysis Specifications

4.1.1. Level of Significance

All statistical hypothesis tests and 95% confidence interval presented will be 2-sided.

The primary hypothesis is to be tested at the 0.05 significance level (overall). The exact significance level at the second interim analysis is to be determined by the observed number of events per the O'Brien-Fleming alpha spending function. Assuming 234 PFS events are observed at the second interim analysis, the alpha to be spent will be 0.0076 (2-sided) for the interim analysis and 0.0476 (2-sided) for the primary PFS analysis (390 PFS events occur). If the observed two-sided p-value is smaller than this significance level as specified above, the superiority of DRd versus Rd with respect to PFS will be established.

If the primary endpoint of PFS is statistically significant, the following secondary endpoints ordered below will be sequentially tested, each with an overall two-sided alpha of 0.05, by utilizing a hierarchical testing approach as proposed by Tang and Geller (1999) that strongly controls Type I error rate:

1) CR or better rate
2) VGPR or better rate
3) MRD negativity rate (10^{-5})
4) Overall response rate (ORR)
5) Overall survival (OS)

These secondary endpoints will be tested at the 2nd IA and the primary PFS analysis. The primary PFS analysis will be skipped if PFS is positive at the 2nd IA. If this is the case, the protocol will be amended to add an analysis for secondary endpoints at a similar timing as the planned primary PFS analysis (note that OS will also be tested at its protocol-specified final analysis). The significance level at the second interim and the primary PFS analyses will be determined by the alpha-spending function specific to endpoints:

- For ORR, VGPR or better rate, CR or better rate, and MRD negativity rate (10^{-5}), the information fraction is expected to be 80% at the 2nd IA. The O'Brien-Fleming alpha-spending function as implemented by the Lan-DeMets method will be used for alpha spending: 0.0244 (two-sided) at the 2nd IA and 0.0428 (two-sided) at the primary PFS analysis.
- For OS, a modified linear alpha spending function will be used to determine the alpha level at three looks (2nd IA, primary PFS analysis, and final OS analysis). The alpha level will be 0.0001 for the first OS look, and linear spending function will be used to determine the alpha level for the second and last looks. For example, if 59% targeted OS events are observed at the second look, the corresponding alpha level will be 0.0295.

If the null hypothesis for any of these endpoint fails to be rejected at the second interim analysis, then any subsequent endpoint(s) listed above will not be tested until the next analysis time point (e.g., primary PFS analysis), if applicable. If the null hypothesis for an endpoint is rejected at the

second interim analysis, it will remain being rejected and will not be re-tested at any subsequent time points, if any.

4.1.2. Data Handling Rules

There is no imputation planned for missing efficacy endpoint values.

4.2. Primary Efficacy Endpoint

The primary efficacy endpoint is progression-free survival (PFS) based on the computerized algorithm.

4.2.1. Definition

PFS is defined as the duration from the date of randomization to either progressive disease, according to the IMWG response criteria, or death, whichever occurs first. Subjects who start subsequent antimyeloma therapies for multiple myeloma without disease progression will be censored at the last disease assessment before the start of subsequent therapies. Subjects who withdrew consent from the study before disease progression will be censored at the last disease assessment before withdrawal of consent to study. Subjects who are lost to follow-up will be censored at the last disease assessment before subjects are lost to follow-up. Subjects who have not progressed and are still alive at the cutoff date for analysis will be censored at the last disease assessment. Subjects without any post-baseline disease assessment will be censored at the randomization.

Determination of dates of PFS event and dates for censoring is summarized in Table 2 as follows.

Table 2: PFS Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
Disease progression prior to start of subsequent antimyeloma therapy	Earliest date that indicates disease progression	PFS event
Death without subsequent antimyeloma therapy	Date of death	PFS event
No post-baseline disease assessment	Randomization	Censored
Other (e.g., withdrawal of consent to study participation, lost to follow-up, start of subsequent antimyeloma therapy etc.)	Date of last disease assessment prior to withdrawal of consent to study participation, lost to follow-up, or subsequent antimyeloma treatment	Censored

4.2.2. Analysis Methods

Analysis of PFS will be based on the ITT population. The Kaplan-Meier method will be used to estimate the distribution of overall PFS for each treatment group. The median PFS with 95% CI will be provided. In addition, the number and percentage of subjects who had a PFS event or were censored will be reported. The Kaplan-Meier PFS curve will also be plotted by treatment group.

The primary treatment comparison of the distribution of overall PFS will be based on a stratified log-rank test. The p-value from a stratified log-rank test will be reported. Hazard ratio and its 95% confidence interval will be estimated based on a stratified Cox's regression model with treatment as the sole explanatory variable. Stratification factors used in the analyses include ISS staging (I, II, III), region (North America vs other), and age (<75 years vs ⩾75 years).

In addition, 12, 24 and 36-months of PFS rate with 95% CI will be estimated by Kaplan-Meier method and reported for each treatment group.

Additionally, reasons for PFS event and censoring will be summarized for ITT population.

4.2.3. Sensitivity Analysis of PFS

The following sensitivity analysis is planned to evaluate the robustness of the primary endpoint analysis of PFS.

4.2.3.1. Progressive Disease Based on Investigator Assessment

A sensitivity analysis of PFS, in which progressive disease is based on investigator assessment according to the IMWG response criteria, will be performed in a similar manner as described in the Section 4.2.2.

The PFS definition used in the sensitivity analysis is similar to that defined in the Section 4.1.2, except for date of progressive disease and date of censoring. The date of progressive disease is the date of initial disease progression recorded in the Disease Progression CRF page or earliest date of confirmed progressive disease recorded in the Evaluation of Response CRF page, based on investigator assessment. Similarly, the censoring date is the latest date of disease response recorded in the Evaluation of Response CRF page, based on investigator assessment.

In addition, reasons for PFS and censoring based on investigator assessment will be summarized for ITT population.

4.2.3.2. Not Censored for Start of Subsequent Anticancer Therapies

A sensitivity analysis of PFS derived from the algorithm by not censoring data due to start of subsequent anticancer therapies for subjects, who have not developed a confirmed progressive disease, will be performed in a similar manner as described in Section 4.2.2.

The PFS definition used in the sensitivity analysis is similar to that defined in Section 4.2.1, except for censoring data due to start of subsequent anticancer therapies. Subjects who start subsequent anticancer therapies for multiple myeloma without disease progression will NOT be censored at the last disease assessment before the start of subsequent therapies. If there is no confirmed progressive disease, the subjects will be censored at the last disease assessment before subjects are lost to follow-up or withdrawal of consent to study.

Determination of dates of PFS event and dates for censoring is summarized in Table 3 as follows.

Table 3: PFS Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
Disease progression	Earliest date that indicates disease progression	PFS event
Death	Date of death	PFS event
No post-baseline disease assessment	Randomization	Censored
Other (e.g., withdrawal of consent to study participation, lost to follow-up, start of subsequent anticancer therapy etc.)	Date of last disease assessment	Censored

4.2.3.3. Censored for Death/PD after Missing More Than One Disease Evaluation

A sensitivity analysis of PFS derived from the algorithm by censoring for death or progression after missing consecutive evaluations will be performed in a similar manner as described in Section 4.2.2.

The PFS definition used in the sensitivity analysis is similar to that defined in Section 4.2.1, except for death or progression after missing more than one disease evaluation. For any PFS (death or progression) event identified by the computer algorithm, if the event date and the latest date of scheduled disease evaluation (includes serum M-protein, urine M-protein, serum FLC and corrected calcium only) immediately preceding the event differs more than 2.5 disease evaluation intervals, which indicates that subject missed at least one scheduled disease evaluation, then this event will not be considered as a PFS event in the sensitivity analysis. Instead, the subject will be censored at the date of last disease evaluation (includes serum M-protein, urine M-protein, serum FLC and corrected calcium only) prior to the PFS event originally identified.

4.2.3.4. Per-protocol Analysis of PFS

A sensitivity analysis of PFS derived from the algorithm based on Per-protocol population will be performed in a similar manner as described in Section **Error! Reference source not found.**.

4.2.3.5. Unstratified Analysis of PFS

A sensitivity analysis of PFS by using unstratified log-rank test and unstratified Cox's regression model will be performed in a similar manner as described in Section 4.2.2.

4.3. Secondary Endpoints

Secondary efficacy endpoints include overall response rate (ORR), VGPR or better rate, CR or better rate, MRD negativity rate, OS, TTP, PFS2, sCR rate, time to subsequent antimyeloma treatment, time to response and duration of response.

4.3.1. CR or Better Rate

4.3.1.1. Definition

CR or better rate is defined as the proportion of subjects with a response of CR or better (i.e., CR or sCR) based on the computerized algorithm, according to IMWG response criteria, during or after the study treatment.

4.3.1.2. Analysis Methods

CR or better rate will be calculated for each treatment group based on the ITT and response-evaluable population. The number and percentage of subjects in the following response categories will be presented by treatment group: stringent complete response (sCR), complete response (CR), sCR+CR, very good partial response (VGPR), VGPR or better (sCR+CR+VGPR), partial response (PR), overall response (sCR+CR+VGPR+PR), stable disease (SD), progressive disease (PD), and not evaluable (NE). The corresponding 95% exact CI will be provided.

Stratified CMH test will be used to test treatment difference in ORR, VGPR or better rate, CR or better rate and sCR rate. The CMH estimate of odds ratio and its 95% confidence interval and p-value for testing treatment difference will be reported. Stratification factors used in the analysis include ISS staging (I, II, III), region (North America vs. Other), and age ($<$75 years vs. $\geqslant$75 years).

A sensitivity analysis, which disease response is based on investigator assessment according to the IMWG response criteria, will be performed in a similar manner as described above.

4.3.2. VGPR or Better Rate

4.3.2.1. Definition

VGPR or better rate is defined as the proportion of subjects with a response of VGPR or better (i.e., VGPR, CR or sCR) based on the computerized algorithm, according to IMWG response criteria, during or after the study treatment.

4.3.2.2. Analysis Methods

Similar statistical methods will be applied as described in Section 4.3.1.2for CR or better rate analysis.

4.3.3. MRD Negativity Rate

For this study, three threshold values, 10^{-4}, 10^{-5} and 10^{-6}, will be used to evaluate MRD negativity status and its predictive value for PFS.

4.3.3.1. Definition

MRD negativity rate is defined as the proportion of subjects who have negative MRD at any time point after the date of randomization and prior to subsequent antimyeloma therapy. MRD

positive subjects include subjects of which all tested results were found to be MRD positive, or indeterminate, or unavailable (calibration failure or missing).

4.3.3.2. Analysis Methods

The MRD negativity rate will be calculated for each treatment group based on the ITT population. The corresponding 95% exact CI will be provided.

For each threshold value, Fisher's exact test will be used to test if the MRD negativity rate is the same between the two treatment groups in the previously untreated myeloma setting.

For the purpose of hierarchical testing (Section 4.1.1), the threshold value of 10^{-5} will be employed using ITT populations.

The durability of MRD negativity may be examined for each treatment group by the proportion of subjects remaining MRD negative 12 months after initial MRD negativity if data becomes available.

4.3.4. Overall Response Rate (ORR)

4.3.4.1. Definition

ORR is defined as the proportion of subjects who achieve a partial response or better (i.e., PR, VGPR, CR or sCR) based on the computerized algorithm, according to IMWG response criteria, during or after the study treatment.

4.3.4.2. Analysis Methods

Similar statistical methods will be applied as described in Section 4.3.1.2 for CR or better rate analysis.

4.3.5. Overall Survival

4.3.5.1. Definition

Overall survival (OS) is measured from the date of randomization to the date of death due to any cause. Subjects who are lost to follow-up will be censored at the time of lost to follow-up. Subjects who are still alive at the clinical cut-off date for the analysis will be censored at the last known alive date. The date of last known alive will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

4.3.5.2. Analysis Methods

OS, including 12, 24 and 36-months survival rate, will be analyzed for the ITT population. The Kaplan-Meier method will be used to estimate the distribution of OS for each treatment group. Median OS with 95% CI will be provided. In addition, the number and percentage of subjects who had died or were censored will be reported. Additionally, the survival rate with 95% CI at 12, 24 and 36-months will be estimated using Kaplan-Meier method for each treatment group.

Due to the expected small number of death events at the second interim analysis, the distribution of OS for the 2 treatment groups will be compared based on an un-stratified log-rank test. A p-value from an un-stratified log-rank test will be reported. Hazard ratio and its 95% confidence interval will be estimated based on an un-stratified Cox's regression model with treatment as the sole explanatory variable.

In addition, a summary of reasons for censoring of overall survival will be provided.

If the null hypothesis of OS is not rejected at the second interim analysis, for OS at the primary PFS analysis when 360 PFS events observed, the alpha to be spent will be determined by a linear alpha spending function based on the observed number of deaths at that time, i.e., the cumulative alpha to be spent will be the total alpha (0.05) multiplied by the proportion of the observed number of deaths out of the total planned number of deaths (330, expected at time of the final OS). See Section 4.1.1 for more details on alpha spending and type I error control.

4.3.6. Time to Disease Progression (TTP)

4.3.6.1. Definition

TTP is defined as the time between the date of randomization and the date of first documented evidence of confirmed PD, as defined in the IMWG response criteria, or death due to PD, whichever occurs first. Subjects who start subsequent antimyeloma therapies for multiple myeloma without disease progression will be censored at the last disease assessment before the start of subsequent therapies. Subjects who withdraw consent to study or are lost to follow-up or die without disease progression will be censored at the last disease assessment. Subjects who have not progressed at the cutoff date for analysis will be censored at the last disease assessment. Subjects without any post-baseline disease assessment will be censored at the randomization.

Determination of dates of TTP event and dates for censoring is summarized in Table 4 as follows.

Table 4: TTP Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
Disease progression prior to start of subsequent anticancer therapy	Earliest date that indicates disease progression	TTP event
Death due to disease progression prior to start of subsequent anticancer therapy	Date of death	TTP event
No post-baseline disease assessment	Randomization	Censored
Other (e.g., withdrawal of consent to study participation, lost to follow-up, start of subsequent anticancer therapy etc.)	Date of last disease assessment prior to subsequent anticancer treatment	Censored

4.3.6.2. Analysis Methods

Similar statistical methods will be applied as described in Section 4.2.2for PFS analysis, including descriptive and comparison of the distribution of overall TTP.

4.3.7. Progression-free Survival on Next Line of Therapy (PFS2)

4.3.7.1. Definition

Progression-free survival on next line of therapy (PFS2) is defined as the time from randomization to progression on next line of therapy or death, whichever comes first. Any deaths are considered as PFS2 events. Subjects who start next line of therapy without disease progression on study treatment will be censored at the last disease assessment before starting next line of therapy. For subjects who start next line of therapy after progression on study treatment, are still alive and not yet progress on next line of therapy, they will be censored on the last date of follow-up. Subjects without any post-baseline follow-up will be censored at the randomization.

Determination of dates of PFS2 event and dates for censoring is summarized in Table 5 as follows.

Table 5: PFS2 Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
No post-baseline disease assessment	Randomization	Censored
Alive and no disease progression on study treatment	Date of last disease assessment prior to start of 1st line on next therapy	Censored
Disease progression on study treatment and progress on the 1st line of next therapy or any death	Minimum of earliest date that indicates progression on the 1st line of next therapy and date of death	PFS2 event
Other	Minimum of start date of 2nd line of next therapy minus 1 and last date of follow-up	Censored

4.3.7.2. Analysis Methods

Similar statistical methods will be applied as described in Section 4.2.2 for PFS analysis.

4.3.8. sCR Rate

4.3.8.1. Definition

sCR rate is defined as the proportion of subjects with a response of sCR based on the computerized algorithm, according to IMWG response criteria, during or after the study treatment.

4.3.8.2. Analysis Methods

Similar statistical methods will be applied as described in Section 4.3.3.2 for CR or better rate analysis.

4.3.9. Time to Subsequent Antimyeloma Treatment

4.3.9.1. Definition

Time to subsequent antimyeloma treatment is defined as the time from randomization to the start of subsequent antimyeloma treatment. Death due to PD without start of subsequent

therapy will be considered as event. Subjects who withdrew consent to study or are lost to follow, or die due to causes other than disease progression will be censored at the date of death or the last date known to be alive.

4.3.9.2. Analysis Methods

The Kaplan-Meier method will be used to estimate the distribution of time to subsequent antimyeloma treatment for the ITT population. Median time to subsequent antimyeloma treatment with 95% CI will be tabulated for each treatment group. In addition, a Kaplan-Meier curve for time to subsequent antimyeloma treatment will be plotted. The hazards ratio and its 95% CI will be obtained through a stratified Cox's regression model with treatment as the sole explanatory variable. Treatment comparison will be made via a stratified log-rank test.

4.3.10. Time to Response

4.3.10.1. Definition

Time to response (i.e., time to first response) is defined as the time between the date of randomization and the first efficacy evaluation that the subject has met all criteria for PR or better based on the computerized algorithm for patients who had PR or better as their best response.

4.3.10.2. Analysis Methods

For subjects who achieve a confirmed response, descriptive statistics (n, mean, standard deviation, median, and range) will also be provided to summarize time to response, time to first response, time to VGPR or better response and time to CR or better response.

4.3.11. Duration of Response

4.3.11.1. Definition

Duration of response (DOR) is defined for subjects with a confirmed response (PR or better) as the time between first documentation of response and disease progression based on the computerized algorithm, according to IMWG response criteria, or death due to PD, whichever occurs first. Responders without disease progression will be censored at the censoring time point for TTP.

4.3.11.2. Analysis Methods

No formal statistical comparison of DOR between the 2 treatment groups is planned. Analysis of DOR will be based on subjects who achieved a confirmed response of PR or better. Median DOR with 95% CI will be estimated based on the Kaplan-Meier method for each treatment group. The Kaplan-Meier duration of response curve will be plotted by treatment group.

4.4. Subgroup Analysis of Efficacy Endpoints

For assessment of internal consistency and investigation of homogeneity of the treatment effect across subgroups, subgroup analyses of the primary and selected secondary efficacy endpoints will be conducted based on pre-specified subgroups defined in Section 2.10.

A forest plot of subgroup analysis on PFS and selected secondary endpoints (e.g. ORR) will be generated, respectively.

Additionally, the primary endpoint of PFS and secondary endpoint of TTP may be explored by responder vs non-responder for each treatment group.

4.5. Functional Status and Well-being

4.5.1. Definition

Functional status and well-being will be assessed using 2 PRO measures, the EORTC QLQ-C30 and the EQ-5D-5L.

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 instrument contains 28 items using a verbal rating scale with 4 response options: “Not at All,” “A Little,” “Quite a Bit,” and “Very Much” (scored 1 to 4). Two additional items use response options (1 to 7): 1 = Very Poor, to 7 = Excellent. All scale and item scores will be linearly transformed to be in the range from 0 to 100 according to the algorithm in EORTC QLQ-C30 scoring manual, version 3.0 (Fayers et al, 2001). A higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

The EQ-5D-5L is a generic 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). 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 (but allows for values less than 0 by UK scoring algorithm).

4.5.2. Analysis Methods

Compliance rates for completion of EORTC QLQ-C30 and EQ-5D-5L at each time point will be generated based on number of expected.

Key PRO endpoints

- EORTC QLQ-C30 global health status/quality of life subscale
- EQ-5D-5L utility score
- EQ-5D-5L visual analog scale (VAS)

The change from baseline at each time point will be summarized descriptively by treatment group.

A distribution based method will be used to define worsening/improvement in scores, i.e., half standard deviation away from the mean score at baseline combining both treatment groups. Time to worsening and time to improvement will be derived. Death due to disease progression will be considered as worsening. Subjects who have not met the definition of worsening/improvement will be censored at the last PRO assessment. Subjects without baseline assessment or post-baseline assessment will be censored at date of randomization.

Time to improvement will be descriptively reported. Time to worsening will be estimated using Kaplan-Meier methods. The hazard ratio for DRd relative to Rd and its associated 95% confidence interval (CI) will be calculated based on the stratified Cox proportional hazards model by the stratification factor at randomization.

A mixed effects model with repeated measures analysis will be conducted estimating change from baseline at each time point between two treatments. ITT subjects who have a baseline value and at least one post-baseline value are included in the analysis. Change from baseline will be fitted to a mixed effects model including subjects as a random effect, and baseline value, treatment group, time in week, treatment-by-time interaction, and stratification factors as fixed effects. Line plot of LS mean of change from baseline with standard error over time will be displayed by treatment arm.

Secondary PRO endpoints

These may include other QLQ-C30 scales:

- functional scales: physical, role, cognitive, emotional, and social
- symptom scales: fatigue, pain, and nausea and vomiting
- single-item score: dyspnea, loss of appetite, insomnia, constipation, diarrhea, and financial difficulties

The change from baseline at each time point may be summarized descriptively by treatment group.

Time to worsening/improvement and mixed effect model analysis, as described for the key PRO endpoints, may be performed as appropriate. Line plot of LS mean of change from baseline with standard error over time may be displayed by treatment arm.

5. SAFETY

Safety assessment will be evaluated through AEs and clinical hematology and chemistry laboratory tests. Safety analyses will be based on the safety population and presented by the treatment actually received.

5.1. Adverse Events

All adverse events whether serious or non-serious, will be reported from the time a signed and dated informed consent form (ICF) is obtained until 30 days after the last dose of study treatment, until the subject withdraws consent for study participation, or until the subject starts subsequent antimyeloma therapy, whichever occurs first. AEs will be recorded in standard medical terminology and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. For AE reporting, the verbatim term used in the CRF by investigators to identify adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

Unless otherwise specified, at each level (e.g., system organ class and/or preferred term) of subject summarization in reporting the incidence of the AE, a subject is counted once if one or more events were recorded. For summarizing new onset events, all event records of the same preferred term from the same subject are to be linked by the onset date and the end date. If an event is followed by another event of the same preferred term with an onset date (or date/time) the same as or 1 day (or 1 minute if applicable) after the end date (or date/time) of the previous record and any features of the adverse event (i.e.: toxicity grades/seriousness/action taken) are different between these two records, these 2 records should be linked together and considered as one event. A Grade 5 event will be linked to previous event of the same preferred term if the onset date of grade 5 record is the same or one day after the end date of previous record.

All summaries of AEs will be based on treatment-emergent adverse events (TEAEs), which are defined as any AE that occurs after start of the first study treatment through 30 days after the last study treatment; or the day prior to start of subsequent antimyeloma therapy, whichever is earlier; or any AE that is considered drug-related (very likely, probably, or possibly related) regardless of the start date of the event; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered drug-related by the investigator.

The incidence of TEAEs will be summarized overall, by MedDRA system organ class (SOC) and preferred term, by toxicity grade, and by relationship, to study treatment administration. Specifically, the following AE summaries will be presented by treatment group.

5.1.1. Overview of TEAEs

An overview of TEAEs reported through the study will be provided for each treatment group. The overview will include summaries of subjects with TEAEs, with TEAEs related to study treatment, with TEAEs of maximum toxicity grade of 1 to 5, SAEs, TEAEs leading to discontinuation of all study treatment.

5.1.2. All TEAEs

- Incidence of TEAEs by MedDRA SOC and preferred term.
- Most commonly reported (>10%) TEAE by MedDRA SOC and preferred term.

5.1.3. Toxicity Grade 3 or 4 TEAEs

- Incidence of toxicity Grade 3 or 4 TEAEs, by MedDRA SOC and preferred term
- List of subjects with any toxicity Grade 3 or 4 TEAEs
- Most commonly reported (>5%) Grade 3 or 4 TEAE by MedDRA SOC and preferred term

5.1.4. Study Treatment-Related TEAEs

- Incidence of TEAEs considered by the investigator to be related to study treatment, by MedDRA SOC, preferred term and relationship to study treatment
- Incidence of TEAEs with toxicity Grade 3 or 4 considered by the investigator to be related to study treatment, by MedDRA SOC and preferred term and relationship to study treatment

5.1.5. Serious Adverse Events (SAEs)

- Incidence of treatment-emergent SAEs, by MedDRA SOC and preferred term
- Incidence of treatment-emergent SAEs considered by the investigator to be related to study treatment, by MedDRA SOC, preferred term and relationship to treatment
- Most commonly reported (>2%) SAEs by MedDRA SOC and preferred term
- List of subjects with any treatment-emergent SAEs

5.1.6. TEAEs Leading to Dose Modifications

Incidence of TEAEs leading to dose modifications will be summarized by MedDRA SOC and preferred term. The summaries will be presented by all grades and Grade 3 or 4 for each treatment. This table will include TEAEs leading to cycle delays or dose modification of at least 1 of the study treatments, the dose modifications include dose delay within the cycle, dose reduced (not applicable to daratumumab), dose re-escalated per protocol (not applicable to daratumumab), or dose skipped.

5.1.7. TEAEs Leading to Discontinuation of Any Study Treatment

A summary of number of subjects who discontinued any study treatment because of 1 or more TEAEs by MedDRA system-organ class and preferred term will be provided. The summaries will be presented by all grades and Grade 3 or 4 for each treatment group. The AEs leading to discontinuation of any study treatment are based on AEs recorded in the AE CRF page with an action taken of drug withdrawal for any study treatment.

A listing of subjects who discontinued any study treatment because of TEAEs will be provided

5.1.8. TEAEs Leading to Discontinuation of All Study Treatment

A summary of number of subjects who discontinued all study treatment because of 1 or more TEAEs by MedDRA system-organ class and preferred term will be provided. A listing of subjects who discontinued all study treatment because of TEAEs will be provided, this listing includes TEAEs leading to discontinuation of all study treatment for those subjects indicated as having discontinued study treatment due to an adverse event on the end of treatment CRF page.

5.2. Deaths

5.2.1. Death Due to TEAEs

The number of subjects who died due to treatment-emergent adverse events will be summarized by preferred term and relationship to study treatment for each treatment group. The TEAEs included in this table are AEs with outcome death or toxicity grade of 5 recorded in the AE CRF page.

A listing of subjects who died due to treatment-emergent adverse events will be provided.

5.2.2. Deaths

A summary of all deaths and cause of death will be tabulated overall and by treatment group. Specifically, the number of subjects who died during the study will be summarized for the ITT population. The primary cause of death collected on the death information CRF page will be reported. If the primary cause of death is AE, the number of subjects who have related AE and unrelated AE will be further reported.

Subjects who died within 30 days of last study treatment dose and within 60 days of first study treatment dose, respectively, based on the safety population.

A listing of all deaths will be provided.

5.2.3. Adverse Events by Subgroups

The following subgroup analysis of adverse events will be performed based on subgroups specified in Section 2.10:

- Overview of TEAEs
- All TEAEs
- Toxicity Grade 3 or 4 TEAEs
- SAEs.

5.3. Adverse Events of Clinical Interest

The adverse events of clinical interest would be focus on below items (detail would be defined on the DPS or below sections),

- IRR
- Infections and Infestations
  - Opportunistic infections
  - Virus infections
- Hemorrhage events
- Interferences for blood typing
- Tumor lysis syndromes
- Intravascular hemolysis
- Cytopenia
  - Neutropenia events
  - Thrombocytopenia events
  - Anaemia
  - Lymphopenia
- Second Primary Malignancies

5.3.1. Infusion-Related Reactions (IRR)

Subjects with any IRR associated with daratumumab administration will be summarized by MedDRA system-organ class and preferred term. The summaries will be presented by all grades, Grade 3, 4, and 5. In addition, the total number of subjects with IRR in more than 1 infusion will be reported. Additionally, the timing of IRR associated with daratumumab administration will be evaluated through a summary of IRR by event onset time.

A listing of subjects with Grade 3 or higher treatment-emergent infusion-related reactions associate with daratumumab administration will be provided. In addition, subjects with treatment-emergent infusion-related reactions results in discontinuation of daratumumab will be listed.

5.3.2. Infections and infestations

Infections and infestations refer to adverse events with SOC of infections and infestations. A summary of number of subjects with 1 or more toxicity Grade 3 or 4 treatment-emergent infections and infestations by MedDRA preferred term and relationship to treatment will be provided. Additional summary analyses may include by onset time (i.e., $\leq$ 6 months vs. 6-$\leqslant$12 months vs. 12-$\leq$24 months vs. >24 months) and/or exposure-adjusted incidence rate of infections/infestations.

5.3.2.1. Opportunistic Infections

Opportunistic Infections to adverse events with PT terms which would be defined on the DPS. The summaries will be presented by all grades and Grade 3 or 4 for each treatment group.

5.3.3. Cytopenia

Cytopenia includes Neutropenia events, Thrombocytopenia events, Anaemia and Lymphopenia. The four types of Cytopenia to adverse events with PT terms which would be defined on the DPS. The summaries will be presented by all grades and Grade 3 or 4 for each treatment group.

5.3.4. Hemorrhage

Hemorrhage defined by Standardized MedDRA Queries (SMQ) with the first subcategory SMQ of hemorrhage terms (exclude laboratory terms). The summaries will be presented by all grades and Grade 3 or 4 for each treatment group.

5.3.5. Second Primary Malignancies

A listing of subjects who reported second primary malignancies during the study will be provided. This listing will include diagnosis, study day of diagnosis, recurrence of a prior existing malignancy (yes, no) and pathology diagnosis (biopsy, aspirate etc.) etc. information whenever a second primary malignancy is observed. In addition, cumulative study treatment exposure, the treatment for second primary malignancy and the outcome information will also be presented in the listing.

5.4. Clinical Laboratory Tests

The evaluation of clinical laboratory tests will focus on the following selected laboratory analytes:

Hematology panel:

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

Blood chemistry panel:

- alkaline phosphatase
- creatinine
- uric acid
- glucose
- bilirubin
- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)

- sodium
- potassium
- corrected calcium
- phosphate
- creatinine clearance

Blood samples for serum hematology are taken at the screening visit, on Days 1, 8, 15, and 22 of Cycles 1-2, Days 1 and 15 of Cycles 3-6, Day 1 of Cycles 7+, and at the End-of-Treatment visit. Blood sample for biochemistry are taken at the screening visit, on Day 1 of each treatment cycle and at the End-of-Treatment visit.

Descriptive statistics (mean, standard deviation, median, range) will be used to summarize observed laboratory values and change from baseline in observed value at each scheduled visit for each treatment group. Line plot of mean with standard error for each laboratory analyte over time will be displayed by treatment group for hemoglobin, neutrophils, lymphocytes, platelets, WBC, AST, ALT, creatinine, and creatinine clearance.

The worst toxicity grade in hematology and chemistry during the treatment will be summarized by treatment group and toxicity grade. Shift tables from baseline to worst toxicity grade during the treatment will be provided for each laboratory analyte listed above. These tables will summarize the number of subjects with each baseline CTC grade and changes to the maximum CTC grade.

5.5. Vital Signs and Physical Examination Findings

Vital signs (systolic and diastolic blood pressure, heart rate, and temperature) values at baseline will be summarized.

Post baseline physical examination findings were collected as AEs, and therefore will not be summarized.

5.6. Electrocardiogram (ECG)

Electrocardiograms (ECG) will be performed at Screening, Day 1 of Cycle 3 and Cycle 6 immediately after end of daratumumab infusion, and End-of-Treatment visit.

The number and percentage of subjects with normal or abnormal 12-lead ECG results will be summarized.

5.7. ECOG Performance Score

ECOG performance status, which evaluates the effect of the disease status on the activities of daily living, will be assessed at Screening, Day 1 of Cycle 3, Cycle 6, Cycle 9 and Cycle 12 for the first year, every 6th cycle thereafter until EOT (PD), post-PD collected at Week 8 and 16. Descriptive statistics will be used to summarize ECOG performance status at baseline, Day 1 of each treatment cycle (including change from baseline), worst score during treatment (including

change from baseline), and End-of-Treatment visit (including change from baseline) for each treatment group. Shift table from baseline to worst score during the treatment will be provided.

6. PHARMACOKINETICS/IMMUNOGENICITY/PHARMACODYNAMICS

Unless specified otherwise, descriptive statistics (e.g., number of observations, mean, standard deviation, median, and range) will be used to summarize pharmacokinetics and pharmacodynamics data. In addition, coefficient variation and geometric mean will be provided in the pharmacokinetic concentration summary.

6.1. Pharmacokinetics

6.1.1. Sampling Timepoints

For subjects assigned to DRd, blood samples to assess serum concentration (pharmacokinetics) of daratumumab will be obtained at Day 1 of Cycle 1, 6 and 12, End-of-Treatment and Post-Treatment Week 8. On a daratumumab dosing day, blood samples need to be collected before (up to 2 hours but not after the start of infusion) and after (up to 2 hours but not before the end of infusion) daratumumab administration.

6.1.2. Pharmacokinetic Parameters

The pharmacokinetic parameters are defined as:

- Minimum observed concentration (C_{min}) - the concentration observed immediately before infusion.
- Maximum observed concentration (C_{max}) - the concentration observed after the end of infusion

For daratumumab, the pharmacokinetic evaluations include C_{min} and C_{max}.

6.1.3. Analysis Methods

Pharmacokinetic analyses will be performed on the pharmacokinetic-evaluable population. All serum concentrations below the lowest quantifiable concentration or missing data will be recorded as such in the concentration data set. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented.

Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point. A plot of mean (±SD) daratumumab serum peak and trough concentrations over time will be provided.

If sufficient data are available, population pharmacokinetic analysis of serum concentration-time data of daratumumab may be performed using nonlinear mixed-effects modeling. If population pharmacokinetic analysis is conducted, it may include data from other clinical studies; details will be provided in a population pharmacokinetic analysis plan and results will be presented in a separate report.

6.2. Immunogenicity

6.2.1. Sampling Timepoints

Samples to assess the generation of antibodies to daratumumab (immunogenicity) will be obtained from all subjects in the DRd group at Cycle 1 Day 1 predose, End-of Treatment, and Post-Treatment Week 8. 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 immune response analysis.

6.2.2. Analysis Methods

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 antibodies to daratumumab. In addition, subjects who are positive for antibodies to daratumumab will also be listed.

6.3. Pharmacokinetic/Pharmacodynamic Analyses

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

7. BIOMARKER

Biomarker studies are designed to identify markers predictive of response (or resistance) to daratumumab. 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. Results of biomarker analyses may be presented in a separate report.

Blood samples will be drawn from all subjects in both treatment groups to better understand the mechanism of action and mechanism of resistance of daratumumab. Minimal residual disease (MRD) will be assessed from bone marrow aspirates for all subjects who achieve a CR/sCR. Molecular subtyping will be done to evaluate daratumumab response rates in high-risk multiple myeloma subpopulations.

7.1. Minimal Residual Disease (MRD)

Bone marrow aspirates will be collected to monitor MRD in those subjects who attain or suspect to have a CR/sCR. MRD will be monitored using next generation sequencing (NGS) on bone marrow aspirate.

7.1.1. Sampling Timepoints

Samples are requested at time of suspected CR/sCR and at 12, 18, 24 and 30 months post C1D1 (+/-1 month). If one of these time points occurs within 1 month of suspected CR, a repeat bone marrow will not be requested. These bone marrow tests will only be required if patient's response is near CR or better by blood and urine evaluations (for detail timepoint refer to protocol Section 9.2.1.5).

7.1.2. Analysis Methods

Details on MRD negativity rate analyses are described in Section 4.3.4.

In addition, to evaluate the relationship between MRD negativity and clinical endpoints (e.g. PFS) may be explored.

7.2. Molecular Subtyping

7.2.1. Sample collection and characterization

Viable, frozen CD38+ bone marrow aspirate samples were collected at baseline for DNA/RNA sequencing analysis. Peripheral blood mononuclear cell (PBMC) samples were collected at baseline to use as controls.

7.2.2. Molecular Subtypes

A portion of the bone marrow aspirate samples collected as specified in the Section 7.2.1 will be utilized for translocation/mutation/genomic analysis using exome-sequencing and RNA-sequencing to assess whether specific molecular subgroups having chromosomal aberrations such as del17p, t(4;14), t(14;16), are responsive to daratumumab treatment. PBMC samples will be sent for exome sequencing and used as controls for mutation and copy number analysis.

7.2.3. High-risk/Standard-risk Molecular Subgroup Analysis

High-risk and standard-risk molecular subgroups have been defined in Section 2.9.

To determine if daratumumab combined with Rd (DRd) will lead to improved clinical responses in high-risk molecular subgroups, the following exploratory analysis will be conducted by using the similar analysis methods specified in Sections 4.3.1.2 and 4.2.2.

- To evaluate ORR and MRD negativity rate for subjects in high-risk molecular subgroup and subjects with specific molecular subtyping such as del17p, t(14;16), t(4;14)
- To evaluate PFS and OS for subjects in high-risk molecular subgroup and subjects with specific molecular subtyping such as del17p, t(14;16), t(4;14)

If subgroup size allows, these results will also be compared with the subjects treated with DRd in the standard-risk molecular subgroup, to explore whether subjects treated with DRd in high risk molecular subgroup will have similar clinical outcome as subjects in standard risk subgroup.

8. MEDICAL RESOURCE UTILIZATION

Medical resource utilization (excluding study infusion administration) will be descriptively summarized by treatment group. Frequencies of hospitalization, outpatient visits, type of hospitalization or outpatient visit, reasons for hospitalization or outpatient visit, durations of hospitalization or outpatient visit will be calculated and tabulated.

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ATTACHMENTS

ATTACHMENT 1: Additional Exploratory Analysis to Support HEMAR

1. DEFINITION OF SUBGROUPS

Subgroup analyses will be performed using the criteria listed below to determine whether the treatment effect is consistent among subgroups. Analyses will be conducted for the ITT population and for the following subgroups:

- For subjects who reached CR/sCR as their best response
- For subjects who reached VGPR as their best response
- For subjects who reached PR as their best response
- For subjects who reached PD as their best response
- For subjects who had baseline ECOG of 2
- For subjects who achieved MRD negativity (10^{-4}, 10^{-5} and 10^{-6})

Subgroup analyses will be performed if data warrants.

2. TIME-TO-EVENT ENDPOINTS FOR SUBGROUP ANALYZES

Kaplan-Meier estimates will be used to estimate distribution of time to event by treatment arm based on all ITT population. Data will be calculated and summarized with descriptive statistics. The following time-to-event endpoints will be analyzed by pre-defined subgroups as defined in section 2.10 and in section 1, Appendix:

- PFS
- TTP
- Time to subsequent antimyeloma treatment
- PFS2
- OS
- Time to best response
- DOR

2.1. Subgroup Analysis by Center for PFS, OS and EQ-5D and EORTC QLQ C30

3. EXPOSURE ADJUSTED INCIDENCE RATES (EAIR)

3.1. Restriction on the first event

The analysis restricts on the occurrence of the first event per patient and ignores the existence of later (multiple) events as these cannot be assumed to occur independent of previous events (e.g.: patients suffering from infections may have in general a higher risk of having other complications and may even have a higher risk of getting other infections). The occurrence of multiple events is subject to another analysis considering the absolute number of adverse events per patient.

For these reasons the EAIR should be interpreted as *'rate until the first event occurs'*. Rates estimated from several patients can be averaged on the level of a preferred term (PT), of a system organ class (SOC), or on a global level (see below).

The interpretation of EAIRs is simple and consistent on the preferred-term level only, and can be expressed as "*Average number of TEAEs per preferred-term emerging per person-month of exposure*".

The aforementioned considerations apply in the same way to EAIRs estimated on the global level: when EAIRs are collapsed into the global estimate (first analyses), the estimate can be interpreted as the "Average number of TEAEs emerging per person-month *and PT*", because estimation has been performed on a *'per PT'*-basis (per *average* or *typical* PT among all PTs).

Comparing EAIRs on the level of the SOC or on the global level involves data destruction because a patient's information is reduced to the first TEAE only (and possibly to a TEAE of marginal relevance among many TEAEs with higher clinical relevance).

The EAIR analysis focuses on the 'speed' by which TEAEs emerge. The analysis restricts on the first event of a patient because independence of TEAEs cannot be assumed. The necessity to restrict on the first event entails considerable data destruction when deriving SOC-specific EAIRs or the EAIR on a global level. To overcome this, the *'per PT'*-analysis, which is reported in both Tables identically, is preferable.

Comparing EAIRs between the analyses outlined below on a SOC-specific or a global level demonstrates that the *'per PT'*- method makes the interpretation of results more difficult. However, it can be suggested that this method provides a more robust approach when the two treatment arms are to be compared on a SOC-specific or global level. A t-Test like comparison of PT-specific estimates between the two treatment arms may provide a more robust, comprehensive and easy-to-communicate way of visualizing and comparing results.

3.2. Duration of exposure: censored & non-censored

The incidence rate for a patient is derived from the duration of exposure to treatment of that patient. When averaging incidence rates, a patient's duration of exposure is given either A) by the time when the event has occurred (non-censored data), or B) by the total duration of treatment in case the patient does not show the adverse event in question (censored data). Depending on whether a patient has an adverse event or not, the duration of exposure enters the denominator in its non-censored or censored form, respectively.

3.3. Incidence rate per patient

The incidence rate for a specific event of a patient *i* is the reciprocal of time *t* when the first event occurs:

$$EAIR_i = \frac{1}{t_i}.$$

3.4. Average EAIR

The *EAIR* averaged over all patients is

$$EAIR = \frac{\sum_{i=1}^{n} TEAE_i}{\sum_{i=1}^{n} t_i},$$

whereby

a) a TEAE enters the sum in the nominator unweighted ($TEAE_i$ =1, otherwise $TEAE_i$ =0), and
b) the duration of exposure enters the denominator as described before: $t_i = \begin{cases} time\ of\ TEAE \text{ if occurring (non-censored data)} \\ total\ duration\ of\ treatment \text{ if no event occurs (censored data)} \end{cases}$.

3.5. EAIRs on the level of a SOC and on the global level on a 'per-PT' basis

3.5.1. Average EAIR per PT

The *EAIR* for a specific PT is an average over all patients, i.e.

$$EAIR_{PT} = \frac{\sum_{i=1}^{n} TEAE_{PT,i}}{\sum_{i=1}^{n} t_{PT,i}},$$

whereby the number of TEAEs and durations of exposure enter the nominator and the denominator.

3.5.2. Average EAIR per SOC

The average *EAIR* per SOC considers the first event of each patient within the SOC. The denominator includes the exposure time of each adverse event of all PTs within the SOC, per patient, i.e.

$$EAIR_{SOC} = \sum_{i=1}^{n} TEAE_{SOC,i} \sum_{PT=1}^{n\ PTs\ per\ SOC} \frac{1}{t_{PT,i}},$$

where $TEAE_{SOC,i}$ is the first event per patient per SOC and $t_{PT,i}$ is the exposure time for a specific preferred term of a given patient.

Note: This *EAIR* is an incidence rate per *average (or typical)* preferred term in that SOC (cf. 3.6.1).

3.5.3. Average EAIR on a global level

The average *EAIR* on a global level only considers the first event per patient across all events. The denominator includes the exposure times of all PTs, i.e.

$$EAIR_{global} = \sum_{i=1}^{n} TEAE_i \sum_{PT=1}^{n\ PTs} \frac{1}{t_{PT,i}},$$

where $TEAE_i$ is the first event of a patient overall and the $t_{PT,i}$'s are PT-specific exposure times of that patient.

Note: This EAIR is an incidence rate *per average (or typical)* preferred term.

3.6. Second analyses

3.6.1. Average EAIR per PT

The *EAIR* for a specific PT is an average over all patients as described before, i.e.

$EAIR_{PT} = \frac{\sum_{i=1}^{n} TEAE_{PT,i}}{\sum_{i=1}^{n} t_{PT,i}}$,
whereby the number of TEAEs and durations of exposure enter the nominator and the denominator.

3.6.2. Average EAIR per SOC

The average *EAIR* per SOC considers the first event per patient per SOC only, and only one (the corresponding) exposure time in the denominator (confer before, where the denominator in the $EAIR_{SOC}$ depends on the number of PTs per SOC):

$$EAIR_{SOC} = \frac{\sum_{i=1}^{n} TEAE_{SOC,i}}{\sum_{i=1}^{n} t_{SOC,i}},$$

Note: This EAIR is an incidence rate *per SOC*.

3.6.3. Average EAIR on a global level

The average *EAIR* on a global level considers the overall first event per patient only, and only one (the corresponding) exposure time in the denominator (confer before, where the denominator in the $EAIR_{SOC}$ depends on the overall number of PTs):

$$EAIR_{global} = \frac{\sum_{i=1}^{n} TEAE_{i}}{\sum_{i=1}^{n} t_{i}},$$

whereby $TEAE_i$ represents the first TEAE among all TEAEs of patient i and t_i as before (time when TEAE occurs (non-censored data) or total duration of treatment if no event occurs (censored data))

4. ADDITIONAL TIME TO EVENT ANALYSES

In case of different exposure times, time adjustment for AE is necessary. Hazard Ratio and Kaplan-Meier curves will be conducted including number of patients at risk for the following safety endpoints:

- Any TEAE
- Any Serious TEAE
- Any TEAE leading to death
- Any Grade 3 or 4 TEAE
- Any Grade 3 or higher TEAE
- Any TEAE leading to treatment discontinuation

Detailed description by preferred term:

- TEAEs by preferred term with prevalence>=10%/
- Grade 3 or 4 TEAEs preferred term with prevalence>=5%
- Grade 3 or higher TEAEs by preferred term prevalence>=5%
- Serious TEAEs preferred term with prevalence>=2%
- TEAEs leading to treatment discontinuation preferred term with prevalence>=1%
- TEAE leading to death preferred term without prevalence cut-off

ATTACHMENT 2: Multiple Myeloma IMWG Algorithm

PD and Response Algorithm
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The issues addressed by the program are:

1. Whether or not the disease progressed and date* of progression
2. The date* of censoring for subjects whose disease never progressed
3. Reason(s) for PD
4. The date* and category of best and first response
5. Duration of response

* Day post-randomization for randomized subjects.

1. Determination of PD and Relapse from CR

1.1. IMWG Criteria

1.1.1. Progressive Disease

PD is to be used for calculation of time to disease progression and progression-free survival for all subjects including those experiencing CR.

PD is defined as satisfying any one of the criteria listed below. These are identical to the IMWG criteria as described in the protocol. Further explanations (noted in superscript) pertaining to particular PD criteria are provided in Section 1.2, Clarifications and Modifications.

a. Increase (1.2.2) of ≥25% in the level of serum M-protein and absolute increase (1.2.2) must be ≥0.5 g/dL (5 g/L) (1.2.3; 1.2.4).

b. Increase (1.2.2, 1.2.18) of ≥25% in the 24-hour urinary light chain excretion (urine M-protein) and absolute increase (1.2.2) must be ≥200 mg/24 hours (1.2.3).

c. Only in subjects without measurable serum and urine M-protein levels: increase (1.2.2) of ≥25% in the difference between involved and uninvolved FLC levels (1.2.20) and absolute increase (1.2.2) must be >10 mg/dL (1.2.3).

d. Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels: increase (1.2.2) of ≥25% in the level of bone marrow plasma cells percentage and absolute increase (1.2.2) must be ≥10% (1.2.3).

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e. Definite increase [1.2.8] in the size of existing bone lesions [1.2.9] or soft tissue plasmacytomas [1.2.9; 1.2.10].

f. Definite development of new bone lesions [1.2.11] or soft tissue plasmacytomas [1.2.12, 1.2.13].

g. Development of hypercalcemia [1.2.14; 1.2.15; 1.2.16] (corrected serum calcium >2.875 mmol/L or >11.5 mg/dL) that can be attributed solely to the PC proliferative disorder.

1.1.2. Relapse from CR

Relapse from CR is to be used for calculation of disease-free survival for subjects experiencing CR.

Relapse from CR is defined as satisfying any one of the criteria listed below (a, b, or c). These are identical to the IMWG criteria as described in the protocols. Further explanations (noted in superscript) pertaining to particular relapse from CR criteria are provided in Section 1.2, Clarifications and Modifications.

a. Reappearance of serum or urinary M-protein by immunofixation or electrophoresis [1.2.3; 1.2.7].

b. Development of ≥5% plasma cells in the bone marrow.

c. Appearance of any other sign of progression (i.e., new plasmacytomas, lytic bone lesion, or hypercalcemia) [1.2.11; 1.2.12; 1.2.13; 1.2.14; 1.2.15].

1.2. Clarifications and Modifications

In order to allow these rules to be applied consistently and to be programmed, the Sponsor has added certain clarifications and modifications for using the IMWG criteria.

1.2.1. Measurable disease is defined in the protocol by at least one of the following measurement: (1) serum M-protein ≥ 1g/dL (≥ 10 g/L) or ≥ 0.5 g/dL (≥ 5 g/L) for subjects with IgA, IgD, IgE or IgM multiple myeloma; (2) urine M-protein ≥ 200 mg/24h; (3) serum FLC assay: involved FLC level ≥ 10 mg/dL (≥ 100 mg/L) provided serum FLC ratio is abnormal.

1.2.2. The reference point for calculating increase and % of increase for M-protein, FLC and bone marrow plasma cells will be the lowest response value and the "lowest response value" does not need to be a confirmed value.

1.2.3. Requires 2 consecutive (i.e., no intermediate values that do not meet the definition of PD) assessments made at any time before the institution of any new therapy (i.e., subsequent anti-cancer therapy). If a subject has an unconfirmed PD

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followed by death due to PD within 30 days of unconfirmed PD, or PD (the same parameter as of initial observed PD) observed within 4 weeks after start of subsequent anti-cancer therapy, the unconfirmed PD will be considered as PD.

1.2.4. If nadir serum M-protein is ≥ 50g/L (≥5 g/dL), M-protein increases of ≥ 10g/L (1g/dL) is sufficient for progressive disease. It does not require meeting "increase of ≥ 25% in the level of serum M-protein".

1.2.5. Any 2 consecutive increase of serum M-protein ≥5 g/L (≥0.5 g/dL) is consistent with progressive disease, assuming that increase of ≥25% is met or not applicable, even if the serum M-protein level is below measurable disease threshold.

1.2.6. The baseline value for assessing disease progression is the last pretreatment measurement (it applies to SPEP, UPEP, FLC, plasmacytomas and bone lesions except as noticed in Section 1.2.10). For example, if there is a screening value and a Cycle 1 Day 1 value (prior to start of treatment) for M-protein, the program ignores the screening value and uses Cycle 1 Day 1 as the reference point for assessing PD for the first post-treatment results.

1.2.7. The program disregards serum M-protein and urine paraprotein measurements prior to Day 5 after dosing. These tests are considered too soon after dosing to be regarded as legitimate on-treatment values.

1.2.8. The program computes the date of progression as the earliest date of any of the tests listed in Section 1.1.1 (a, b, e, f or g for subjects with measurable serum or/and urine M-protein; or a, b, c, e, f or g for subjects without measurable serum and urine M-protein) that indicate PD. Similarity, the program computes the date of relapse from CR as the earliest date of any of the tests listed in Section 1.1.2 (a, b, or c) that indicate relapse from CR.

1.2.9. For PD due to bone lesions, the algorithm will rely on information collected on the eCRF regarding skeletal survey (i.e., increase in the size of lytic bone lesions or increase in the total number of lytic bone lesions) and other radiology reports. At any time, study sites may report progressive disease based on an increase in the size or number of lytic bone lesions. The algorithm accepts this determination as definitive.

1.2.10. Plasmacytomas/bone lesions that are first reported during the first week on study are treated as baseline plasmacytomas/bone lesions. The rationale for this rule is that plasmacytomas/bone lesions take time to develop, so anything reported within 1 week of first dose almost certainly existed before the start of study drug.

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In the case that no pre-treatment value for plasmacytomas/bone lesion is available, the first post-treatment value is used as baseline.

1.2.11. For plasmacytomas, the Sponsor has defined "definite increase in size" as an increase of over 50% in the sum of the products of the two longest perpendicular diameters when available, using the smallest previous product as the reference point.

1.2.12. New post-baseline bone lesions are evidence of PD. If no baseline bone lesions are available, then any subsequent data that report a bone lesion will be considered as development of new bone lesions.

1.2.13. New post-baseline plasmacytomas are evidence of PD, even if the measurements are not available. If no baseline plasmacytoma data are available, then any subsequent data that report a plasmacytoma will be considered as a "new" plasmacytoma and will be considered as evidence of PD.

1.2.14. Hypercalcemia will be based on corrected calcium values as long as they are available (i.e., corrected calcium values are collected or serum calcium and albumin are collected). If corrected calcium values are not available, free-ionized calcium values will be used if they are available. Hypercalcemia based on free-ionized calcium will be defined as >1.5 mmol/L.

1.2.15. For subjects who have hypercalcemia at baseline, the program will never assess PD due to "development of hypercalcemia". A subject is considered to have hypercalcemia at baseline if he or she meets one of the following criteria:

a. For subjects with corrected calcium values, any corrected calcium value >ULN which occurs on or before Day 4 (relative to first dose).
Note: if subject had central and local assessments done on the same day, the central record takes precedence.

b. For subjects without corrected calcium values in all visits, but with free-ionized calcium values on or before Day 4, any free-ionized calcium value >ULN which occurs on or before Day 4 (relative to first dose).

1.2.16. For subjects with normal calcium at baseline, if the first PD criteria met is a post-baseline hypercalcemic value, then the following programming algorithm will be applied:

a. The program will first search for evidence of progression in other parameters within the following 56 days. If PD is determined in other parameters within the following 56 days, then the subject is assessed as PD. The date of PD is the date of the initial

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hypercalcemic value and hypercalcemia is indicated as the reason or one of the reasons for PD.

b. If PD is not determined in other parameters within 56 days, the program will search for the next available corrected calcium/free-ionized calcium value. If the second value also meets the criteria for hypercalcemia, the subject is assessed as PD. The date of PD is the date of the initial hypercalcemic value and hypercalcemia is indicated as the reason or one of the reasons for PD.

c. If there is no more follow-up calcium value, then the subject is assessed as PD.

d. Any PD identified through a), b) or c) will be flagged and reviewed by clinical to ensure that hypercalcemia can be attributed solely to the plasma cell proliferative disorder. Hypercalcemia due to other reasons will not be considered as PD in the algorithm.

1.2.17. Descriptive (or non-numeric) results from bone marrow aspirate or bone marrow biopsy will be given a numeric interpretation based on the following conventions:

a. Percentage plasma cells reported as a range on the CRF page will be assigned the mean value (i.e., lower range plus upper range divide by 2) that will be analyzed by the programming algorithm (e.g., an amount reported as 10-15% would be interpreted as 12.5%).

b. Percent plasma cells reported as <x% will be interpreted as (x-1)% and percent plasma cells reported as >x% will be interpreted as x%.

c. Other conventions include:

Reported as:	Interpreted as:
"Not significantly present"	4%
"Sheets of plasma cells not seen"	4%

1.2.18. Imputation of UPEP and SPEP values: If the serum immunofixation result is "Not Detected" and the SPEP value is missing or not done, then SPEP value is treated as 0. If the urine immunofixation is "Not Detected" and the UPEP is missing or not done, then UPEP value is treated as 0.

1.2.19. a. Spurious UPEP values are not used in the determination. Determination of a spurious value is as follows: If at least 4 values exist in the neighborhood (+/- 94 days) of the value of interest, the mean and standard deviation of the values is computed (not including the value of interest in the calculation). The value of interest is compared to the mean +/- 3 standard deviations. If the value < mean-3*standard deviation or the value > mean+3*standard deviation then the value is considered spurious. The last two values available for a particular subject

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are never considered as spurious. The baseline value for a subject is also never considered as spurious.

b. If the first PD criteria met is two consecutive UPEP values and subject has started subsequent anticancer therapy, this subject is assessed as PD and date of PD is the date of first UPEP assessment. Otherwise, if the first PD criteria met is two consecutive UPEP values and subject has not started subsequent anticancer therapy, then the following programming algorithm will be applied:

    1) The program will first search for evidence of progression in other parameters within the following 94 days. If PD is determined in other parameters within the following 94 days, then the subject is assessed as PD. The date of PD is the date of the initial UPEP value.
    2) If PD is not determined in other parameters within 94 days and no more UPEP values are available, then the subject is assessed as PD due to UPEP.
    3) Otherwise, the third UPEP value is considered. If the third value meets the criteria for PD, the subject is assessed as PD due to UPEP. If the third value does not meet the criteria for PD, but other parameters indicate PD within the next 94 days, the subject is assessed as PD due to UPEP at the time of the initial UPEP value.
    4) Otherwise, the fourth UPEP value is considered. If the fourth value meets the criteria for PD, the subject is assessed as PD due to UPEP. If the fourth value does not meet the criteria for PD, the subject is not assessed as PD due to UPEP. If no fourth UPEP value is available, the subject is not assessed as PD.

1.2.20. Difference between involved and uninvolved FLC level is defined as absolute value of kappa FLC level minus lambda FLC level in the serum.

1.2.21. Development of plasma cell leukemia is considered as disease progression. The date of PD is the date of event onset.

2. Determination of Date of Censoring and Reason for PD

The date of last post-baseline efficacy measure is used as the censoring date for all subjects without progressive disease. Subjects that have no post-baseline efficacy data are censored at the date of randomization for randomized subjects.

The reason(s) for PD is defined as the initial reason(s) that caused the program to indicate PD as well as any other criteria that were met by the time of confirmation of PD. Indicator variables for each reason (SPEP, UPEP, FLC, bone marrow, bone lesion [increase in number, increase in size], extramedullary plasmacytoma [new extramedullary plasmacytoma, increase in size], hypercalcemia and plasma cell leukemia) are created.

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3. Determination of Response Category and Duration of Response

3.1. IMWG Criteria

According to IMWG criteria, response categories include complete response (CR), stringent complete response (sCR), very good partial response (VGPR), partial response (PR), stable disease (SD), and progressive disease (PD) (defined in Section 1). Although minimal response (MR) is not officially a response category in the IMWG criteria, consensus recommendations state that for subjects with relapsed and /or refractory myeloma, MR should be reported separately in clinical trials. Categories of sCR, CR, VGPR, PR, and SD are determined using the IMWG criteria and MR adopted from the EBMT criteria for subjects with relapsed refractory myeloma as outlined below.

Further explanations (noted in superscript) pertaining to particular response criteria are provided in Section 3.2, Clarifications and Modifications. The definition for duration of response is also covered in Section 3.2.18.

3.1.1. Definition of CR

Requires all of the following:

a. Negative immunofixation of serum and urine [3.2.4; 3.2.5; 3.2.6; 3.2.19].

b. Disappearance of any soft tissue plasmacytomas.

c. <5% plasma cells in the bone marrow [3.2.7].

3.1.2. Definition of sCR

Requires all of the following:

a. CR as defined above.

b. Normal FLC ratio [3.2.8].

c. Absence of clonal bone marrow plasma cell (PCs) by immunohistochemistry, immunofluorescence [3.2.9] or 2- to 4-color flow cytometry.

3.1.3. Definition of VGPR

Requires any of the following:

a. Serum and urine M-component detectable by immunofixation but not on electrophoresis [3.2.5; 3.2.11;3.2.12], or

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b. ≥90% reduction [3.2.10] in serum M-protein plus urine M-protein <100 mg/24 hours [3.2.5; 3.2.11]

c. If the serum and urine M-protein are not measurable, a reduction [3.2.10] of >90% in the difference between involved and uninvolved FLC levels [3.2.5; 3.2.13] is required.

d. In addition to the above criteria, if present at baseline, ≥50% reduction [3.2.10] in the size of soft tissue plasmacytomas is also required.

3.1.4. Definition of PR

Requires all of the following:

a. ≥50% reduction [3.2.10] of serum M-protein [3.2.5] and reduction [3.2.10] in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours [3.2.5].

b. If the serum and urine M-protein are not measurable, a reduction [3.2.10] of ≥50% in the difference between involved and uninvolved FLC levels [3.2.5; 3.2.13] is required.

c. In addition to the above criteria, if present at baseline, ≥50% reduction [3.2.10] in the size of soft tissue plasmacytomas is also required.

3.1.5. Definition of SD

Not meeting the criteria for sCR, CR, VGPR, PR, or PD.

3.2. Clarifications and Modifications

As was the case with PD, developing a program to assess response requires adding certain clarifications, minor modifications and additions to the IMWG criteria.

3.2.1. Only subjects with measurable disease at baseline are eligible for assessment of response (i.e., considered in the response-evaluable population). Measurable disease is defined in Section 1.2.1; only legitimated on treatment serum M-protein and urine paraprotein measurements are used for assessment of response. The legitimated on treatment measurements is defined in Section 1.2.6.

3.2.2. CR, sCR, VGPR, PR, MR and SD response categories require no known evidence of progressive or new bone lesions if radiographic studies were performed. Once the program has determined PD for a subject, no subsequent response assessments are performed. For example, a subject who progresses at week 6 cannot have a first response or best response that starts after week 6.

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3.2.3. Subjects with measurable disease (defined in Section 1.2.1) in serum (SPEP) and urine (UPEP) need to be followed by both SPEP and UPEP for response assessment and categorization; Except for assessment of CR or better, subjects with measurable disease restricted to the SPEP will need to be followed only by SPEP (i.e., urine M-protein need not show a reduction, but the available urine M-protein values must not meet the criteria for PD); correspondingly, subjects with measureable disease restricted to the UPEP will need to be followed only UPEP (i.e., serum M-protein need not show a reduction, but the available serum M-protein values must not meet the criteria for PD). For example, a subject who has baseline values of 0.1 g/dL of IgG M-protein and 300 mg/24 hrs of urine paraprotein and who subsequently maintains values of 0.1 g/dL and 120 mg/24 hrs will be regarded as achieving a PR; Subjects with measurable disease in either SPEP or UPEP or both will be assessed for response only based on these two tests and not by the FLC assay.

3.2.4. To be considered CR, both serum and urine immunofixation must be carried out and be negative regardless of the size of baseline M-protein in the serum or urine; subjects with negative UPEP values pretreatment still require UPEP testing to confirm CR.

3.2.5. Requires 2 consecutive (i.e., no intermediate values that do not meet the definition of response) assessments made at any time before the institution of any new therapy (i.e., subsequent anti-cancer therapy).

3.2.6. For coding CR in subjects in whom the only measurable disease is by serum FLC levels: it requires a normal FLC ratio (Kappa/Lambda) in addition to CR criteria. However, a normal FLC ratio is not required if the involved FLC level decrease to below detectable level (Kappa<0.5 mg/L or Kappa<0.67 mg/L based on new reagent lot; or lambda<0.6 mg/L). The default reference range of 0.26 to 1.65 will be used to determine normal FLC ratio, if the reference range from central/local laboratory is not available.

3.2.7. If all criteria for confirmed CR were met, except that bone marrow aspirate and biopsy were not performed, and baseline bone marrow evaluation showed <5% plasma cells, then the algorithm accepts this as a CR. If both bone marrow aspirate and bone marrow biopsy were performed at baseline, then both values must have <5% plasma cells for the rule to be applied. For subjects without measurable disease at baseline or subjects whose baseline bone marrow plasma cells percentage is >5%, bone marrow confirmation is required for CR response.

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3.2.8. Normal FLC ratio is required for all subjects regardless of whether disease at baseline was measurable on serum, urine, both or neither. However, a normal FLC ratio is not required if the involved FLC level decrease to below detectable level (Kappa<0.5 mg/L or Kappa<0.67 mg/L based on new reagent lot; or lambda<0.6 mg/L). The default reference range of 0.26 to 1.65 will be used to determine normal FLC ratio (Kappa/Lambda), if the reference range from central/ local laboratory is not available.

3.2.9. 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.

3.2.10. Reductions are based on changes from baseline.

3.2.11. VGPR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both or neither. For coding VGPR in subjects in whom the only measurable disease is by SPEP, it is not required that UPEP value must meet VGPR criteria, but UPEP test must be performed and not meeting PD criteria whenever SPEP meet VGPR criteria; correspondingly, for coding VGPR in subjects with measureable disease restricted to the UPEP, it is not required that SPEP value must meet VGPR criteria, but SPEP test must be performed and not meeting PD criteria whenever UPEP meet VGPR criteria.

3.2.12. Serum and urine M-protein via SPEP and UPEP must be reported as 0, not detected, or below level of quantification and positive serum or urine immunofixation.

3.2.13. Difference between involved and uninvolved FLC level is defined as absolute value of kappa FLC level minus lambda FLC level in the serum.

3.2.14. Skeletal survey is not required for assessment of response unless clinically indicated. However, if skeletal survey is performed, there should be no indication of disease progression before confirmation of response.

3.2.15. The date of first/best response is the earliest date that all available and required response criteria are met. The date of serum immunofixation response is the initial date of response, not the date of confirmation. The date of urine immunofixation response is the initial date of response, not the date of confirmation. The latest date of response (date at which all criteria were met) among all the relevant response criteria will also be stored in the analysis dataset.

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3.2.16. Duration of response (DOR) applies to subjects achieving at least PR by IMWG criteria, and is measured from start of achieving PR (first observation of PR before confirmation) to the time of disease progression, with deaths owing to causes other than progression not counted, but censored. DOR is derived as (date of PD or date of censoring – date of first response + 1).

3.2.17. If the first two or more scheduled assessments are missing followed immediately by a confirmed PD (> study day 56), the best response should be SD instead of PD. If best response is assessed as SD, date of best response is not assigned.

3.2.18. Occasionally, the results of the urine immunofixation and UPEP may conflict. If the urine IFE is negative and the UPEP has any value less than 200 mg/24 hrs, the UPEP is disregarded and the urine results are treated as satisfying the requirement for a CR. Similarly, if serum IFE becomes and remains negative, appearance of low level of paraprotein (≤0.5 g/dL or 5 g/L) in SPEP will be disregarded.

3.2.19. A DIRA result of NEGATIVE is treated as equivalent to a negative immunofixation of serum. Since there is no repeat of the DIRA test, we consider a single DIRA test as equivalent of two consecutive immunofixation of serum tests if that indicates a CR.

3.2.20. Subjects with at least one post-baseline disease assessment corresponding to the type of measurable disease at baseline and also not falling into any response category or progressive disease are assigned as response category- stable disease (SD).

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4. References

1. BGM Durie *et al*. International uniform response criteria for multiple myeloma. *Leukemia 2006*
2. Rajkumar *et al*. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood 2011*

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Facon T, Kumar S, Plesner T, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. N Engl J Med 2019;380:2104-15. DOI: 10.1056/NEJMoa1817249

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Additional Methods

Key Exclusion Criteria

Patients with monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, primary amyloidosis, Waldenström's macroglobulinemia, plasma cell leukemia or POEMS syndrome, prior systemic therapy including stem-cell transplantation for treatment of myeloma, and malignancy within 5 years of randomization were not eligible.

Pre- and Post-infusion Medications

During daratumumab infusion days, patients received acetaminophen 650 to 1,000 mg intravenously or orally, diphenhydramine 25 to 50 mg (or equivalent) intravenously or orally, and dexamethasone 40 mg intravenously or orally approximately 1 hour prior to daratumumab infusion. For patients older than 75 years of age or with body mass index less than 18.5 kilograms per square meter, dexamethasone was administered at a dose of 20 mg once weekly.

Post-infusion medications were administered for patients with higher risk of respiratory complications (i.e., those with mild asthma or patients with chronic obstructive pulmonary disease who have forced expiratory volume in 1 second <80%); these medications included diphenhydramine (or equivalent), short-acting β_2 adrenergic receptor agonists such as salbutamol aerosol, and control medications for lung disease (e.g., inhaled corticosteroids ± long-acting β_2 adrenergic receptor agonists for patients with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for patients with chronic obstructive pulmonary disease).

Definition of Relative Dose Intensity

The relative dose intensity (RDI) for daratumumab was influenced by dose skipping. For lenalidomide and dexamethasone, as dose adjustments were also permitted, RDI was affected by dose reduction or escalation or dose skipping. RDI was established by calculating the administered cumulative dose and comparing to cumulative planned dose (assuming C1D1 dose was 100% dosing for entire treatment).

Minimal Residual Disease

Baseline bone marrow aspirate samples were subjected to next-generation sequencing in order to establish the myeloma clone for minimal residual disease monitoring. For patients who achieved a complete response or a stringent complete response, bone marrow aspirates were utilized for assessment of minimal residual disease by next-generation sequencing of immunoglobulin heavy and light chains. Minimal residual disease analysis was not possible for 11.1% of patients who achieved complete response or better, due to lack of samples (3.0%), unsuccessful assay run (2.7%), or calibration failure (5.4%). The calibration success rate of the minimal residual disease assay was 91.9%.

Additional Statistical Analyses

The significance level at this interim analysis to establish the superiority of daratumumab, lenalidomide, and dexamethasone over lenalidomide and dexamethasone with regard to PFS was determined based on the observed number of PFS events at the interim analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. Assuming 234 PFS events are observed at the second interim analysis, the alpha to be spent will

be 0.0076 (2-sided) for the interim analysis and 0.0476 (2-sided) for the primary PFS analysis (390 PFS events occur). If the daratumumab group was found to be numerically worse than the control group in terms of PFS (observed hazard ratio greater than 1 favoring the control arm), then the study was to be terminated for futility, with a conditional power of less than 20% under the alternative hypothesis given the observed interim data.

If the primary endpoint of PFS is statistically significant, the following secondary endpoints ordered below will be sequentially tested, each with an overall two-sided alpha of 0.05, by utilizing a hierarchical testing approach as proposed by Tang and Geller[1] that strongly controls Type I error rate:

1) CR or better rate

2) VGPR or better rate

3) MRD negativity rate (10^{-5})

4) Overall response rate (ORR)

5) Overall survival (OS)

If the null hypothesis for any of these endpoint fails to be rejected at the second interim analysis, then any subsequent endpoint(s) listed above will not be tested until the next analysis time point (e.g., primary PFS analysis), if applicable. If the null hypothesis for an endpoint is rejected at the second interim analysis, it will remain being rejected and will not be re-tested at any subsequent time points, if any.

These secondary endpoints will be tested at the second interim analysis and the primary PFS analysis and the significance level for these analyses will be determined by the alpha-spending function specific to endpoints:

For ORR, VGPR or better rate, CR or better rate, and MRD-negativity rate (10^{-5}), the information fraction is expected to be 80% at the second interim analysis. The O'Brien-Fleming alpha-spending function as implemented by the Lan-DeMets method will be used for alpha spending: 0.0244 (two-sided) at the second interim analysis and 0.0428 (two-sided) at the primary PFS analysis.

For OS, a modified linear alpha-spending function will be used to determine the alpha level at 3 analyses. The alpha level will be 0.0001 for the first OS analysis, and a linear spending function will be used to determine the alpha level for the second and last analyses. For example, if 59% of the targeted OS events are observed at the second analysis, the corresponding alpha level will be 0.0295.

Per protocol, the 3 OS analyses were defined as follows: the first interim OS analysis was performed at the current interim analysis (240 PFS events); the second interim OS analysis will occur when approximately 260 deaths have been accumulated which will be about the same time as when the primary PFS analysis (390 PFS events) would have occurred; the final OS analysis will occur when 330 deaths have been observed or 7 years after the last patient is randomized.

Definitions of Efficacy Endpoints

Progression-free survival was defined as the duration from the date of randomization to either progressive disease, in accordance with the International Myeloma Working Group criteria,[2,3] or death, whichever occurred first. For patients who have not progressed, data were censored at the date of the disease evaluation before the start of any subsequent anti-myeloma therapy.

Time to progression was defined as the time from the date of randomization to the date of first documented evidence of disease progression, as defined by the International Myeloma Working Group criteria. For patients who have not progressed, data were censored at the date of the disease evaluation before the start of any subsequent anti-myeloma therapy.

Complete response rate, defined as the percentage of patients achieving a complete response, was defined by negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and less than 5% plasma cells in bone marrow. For patients with negative serum M-protein quantitation by electrophoresis and suspected daratumumab interference on immunofixation, a reflex assay using an anti-idiotype antibody was utilized to confirm daratumumab interference and to rule out false positive immunofixation. Patients with confirmed daratumumab interference who met all other clinical criteria for complete response or stringent complete response were considered as having complete response or stringent complete response.

The rate of negative status for minimal residual disease was defined as the proportion of patients assessed as having negative status for minimal residual disease at any time point after the date of randomization.

Progression-free survival on the next line of therapy (progression-free survival 2) was defined as the time from randomization to progression on the next line of treatment or death, whichever occurred first. Disease progression was based on investigator judgment. For patients who were still alive and had not yet progressed on the next line of treatment, data were censored on the last date of follow-up.

Overall survival was measured from the date of randomization to the date of the patient's death. If the patient was alive or the vital status was unknown, the patient's data was censored at the date the patient was last known to be alive.

Stringent complete response rate was defined as the percentage of patients achieving complete response in addition to having a normal free light-chain ratio and absence of clonal cells in bone marrow, as assessed by immunohistochemical analysis, immunofluorescence analysis, or two- to four-color flow cytometry.

Overall response rate was defined as the proportion of patients who achieved partial response or better, according to International Myeloma Working Group criteria, during or after trial treatment.

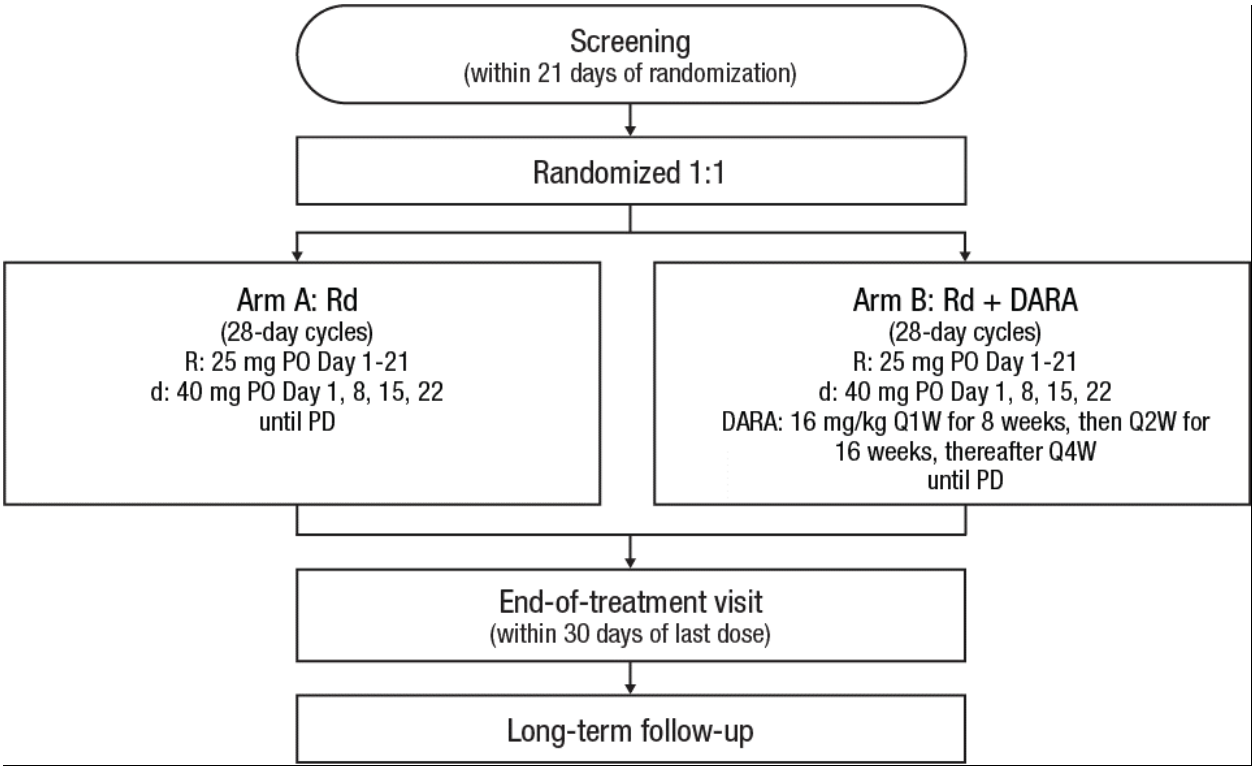
Proportion of patients who achieved very good partial response or better was defined as the proportion of patients achieving very good partial response and complete response (including

stringent complete response), according to International Myeloma Working Group criteria, during or after the trial treatment at the time of data cutoff.

Time to response was defined as the time between randomization and the first efficacy evaluation at which the patient met all criteria for either complete response/stringent complete response or partial response, as applicable. For patients without response, data were censored either at the date of progressive disease or, in the absence of progressive disease, at the last disease evaluation before the start of subsequent anti-myeloma therapy.

Duration of response was calculated from the date of initial documentation of a response (partial response or better) to the date of first documented evidence of progressive disease, as defined in the International Myeloma Working Group criteria. For patients who did not progress, data were censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.

Figure S1. Trial Design.



Rd, lenalidomide and dexamethasone; R, lenalidomide; PO, orally; d, dexamethasone; PD, progressive disease; DARA, daratumumab; Q1W, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks.

Figure S2. CONSORT Patient Flow Diagram.

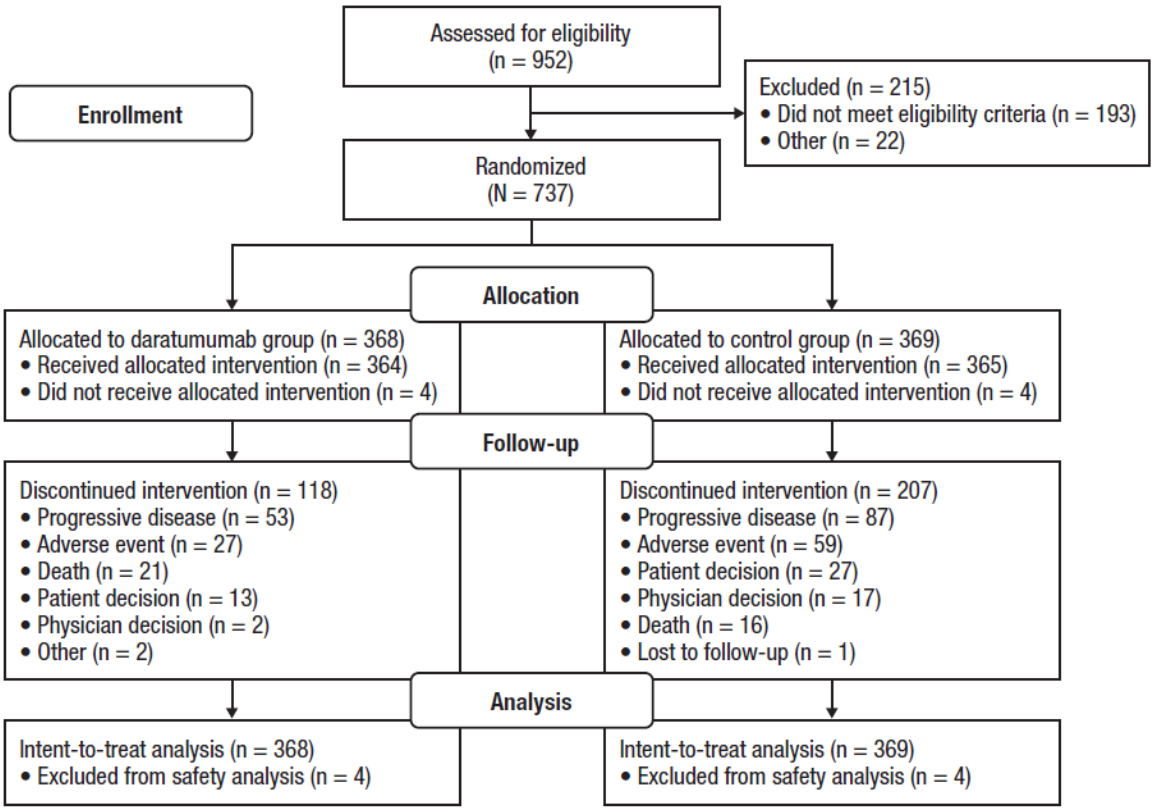
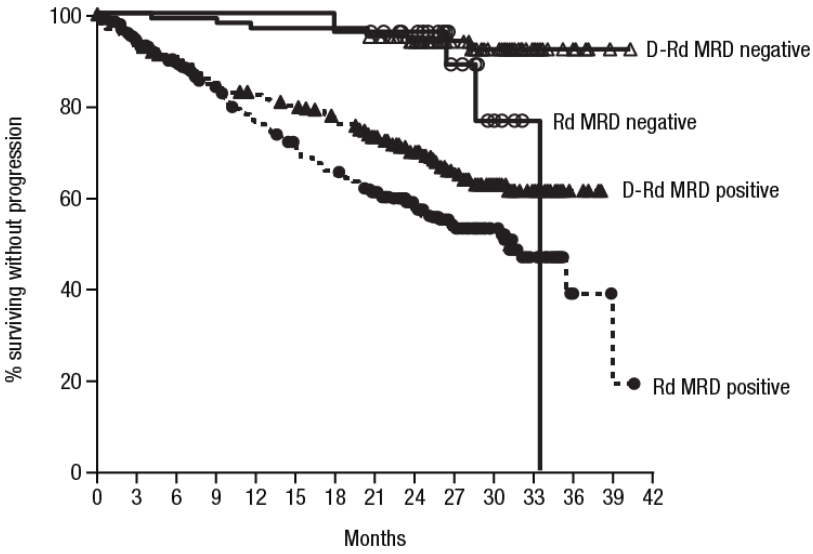


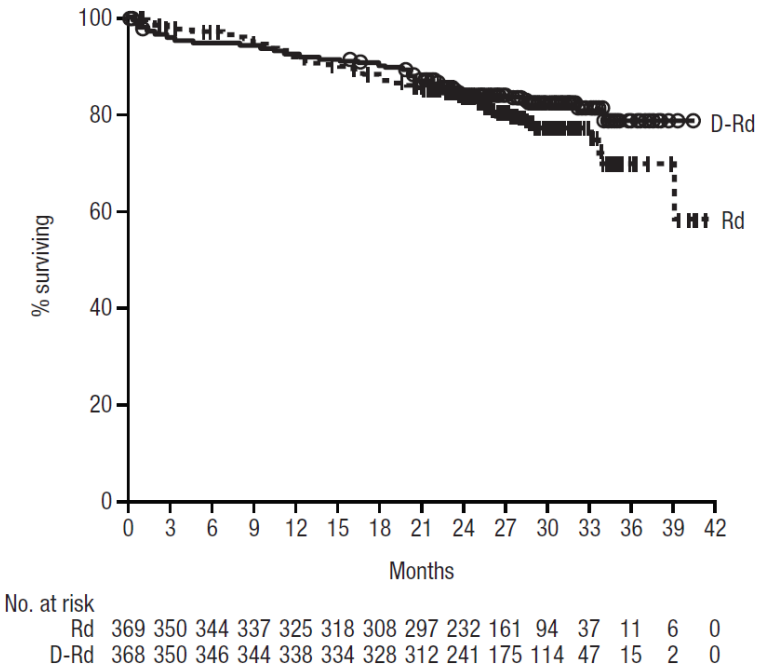
Figure S3. Progression-free Survival by Minimal Residual Disease Status in the Intention-to-Treat Analysis Set.



No. at risk															
Rd MRD negative	27	27	27	27	27	27	27	25	21	12	5	1	0	0	0
D-Rd MRD negative	89	89	88	88	86	86	86	84	70	55	33	12	5	1	0
Rd MRD positive	342	305	280	253	227	209	192	175	128	82	45	17	3	2	0
D-Rd MRD positive	279	258	247	232	223	214	204	187	133	91	53	23	6	0	0

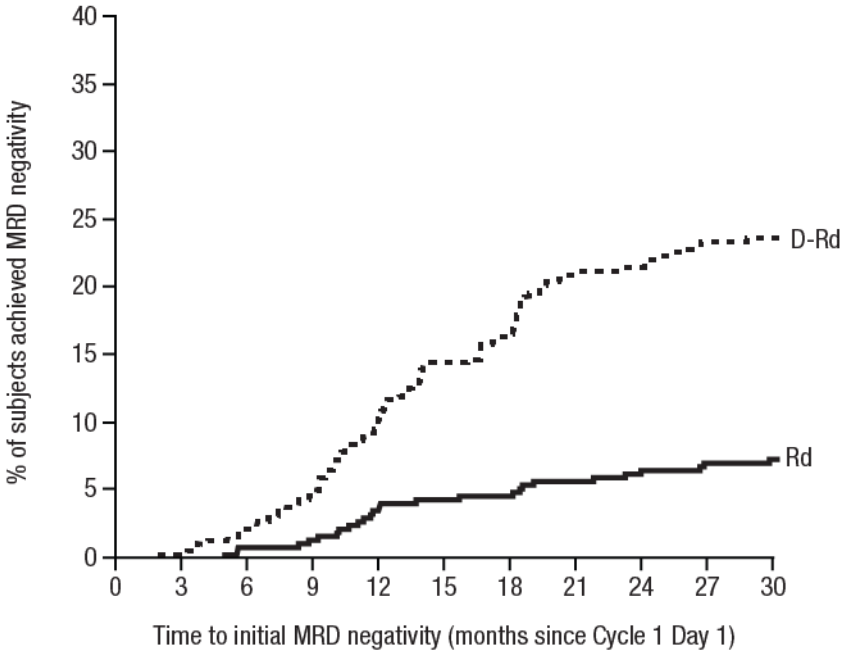
D-Rd, daratumumab plus lenalidomide and dexamethasone; MRD, minimal residual disease; Rd, lenalidomide and dexamethasone.

Figure S4. Overall Survival in the Intention-to-Treat Analysis Set.



D-Rd, daratumumab plus lenalidomide and dexamethasone; Rd, lenalidomide and dexamethasone; HR, hazard ratio; CI, confidence interval.

Figure S5. Rate of Accumulation of Minimal Residual Disease–Negative Events (10^{-5}) in the Intention-to-Treat Analysis Set.



D-Rd, daratumumab plus lenalidomide and dexamethasone; Rd, lenalidomide and dexamethasone; MRD, minimal residual disease.

Table S1. International Staging System Criteria.[4]

Stage	Criteria	Median Survival (months)*
I	Serum ß$_2$-microglobulin <3.5 mg/L, serum albumin ≥3.5 g/dL	62
II	Not I or III†	44
III	Serum ß$_2$-microglobulin ≥5.5 mg/L	29

*Survival statistics may not be current; based on Greipp PR, et al. *J Clin Oncol* 2005;23:3412-20.
†There are 2 possibilities for stage II: 1) serum ß$_2$-microglobulin <3.5 mg/L but serum albumin <3.5 g/dL, or 2) serum ß$_2$-microglobulin 3.5–5.4 mg/L irrespective of the serum albumin.

Table S2. Recommended Lenalidomide Dose Adjustment Schedules for Neutropenia and Thrombocytopenia.

Neutropenia

Neutrophil Count	Recommended Course of Action
• When count first falls to $<1.0 \times 10^9$/L • When count returns to $\geq 1.0 \times 10^9$/L and neutropenia is the only observed toxicity	• Interrupt lenalidomide treatment, consider G-CSF treatment, follow complete blood count weekly • Resume lenalidomide at 25 mg daily or initial starting dose
• When count returns to $\geq 1.0 \times 10^9$/L and dose-dependent hematological toxicities other than neutropenia are observed	• Resume lenalidomide at the next lower dose
• For each subsequent drop in count to $<1.0 \times 10^9$/L • When count returns to $\geq 1.0 \times 10^9$/L	• Interrupt lenalidomide treatment • Resume lenalidomide at the next lower dose level

Thrombocytopenia

Platelet Count	Recommended Course of Action
• When count first falls to $<30 \times 10^9$/L • When count returns to $\geq 30 \times 10^9$/L	• Interrupt lenalidomide treatment, follow complete blood count weekly • Resume lenalidomide at the next lower dose
• For each subsequent drop in count to $<30 \times 10^9$/L • When count returns to $\geq 30 \times 10^9$/L	• Interrupt lenalidomide treatment • Resume lenalidomide at the next lower dose

Table S3. International Uniform Response Criteria Consensus Recommendations.

Response	Response Criteria
sCR	• CR as defined below, plus • Normal free light-chain ratio, and • Absence of clonal plasma cells by immunohistochemistry, immunofluorescence,* or two- to four-color flow cytometry
CR†	• Negative immunofixation on the serum and urine, and • Disappearance of any soft tissue plasmacytomas, and • <5% plasma cells in bone marrow
VGPR†	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, or • ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours
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 free light-chain levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light-chain assay is also not measurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% • In addition to the above criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
SD	• Not meeting criteria for CR, VGPR, PR, or PD
PD‡	• Increase of 25% from lowest response value in any one of the following: o Serum M-component (absolute increase must be ≥0.5 g/dL), o Urine M-component (absolute increase must be ≥200 mg/24 hours), o Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved free light-chain levels (absolute increase must be >10 mg/dL) o Only in patients without measurable serum and urine M-protein levels and without measurable disease by free light-chain levels: bone marrow plasma cell percentage (absolute percentage must be ≥10%) o Bone marrow plasma cell percentage (absolute percentage must be 10%) o Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas o Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease; IMWG, International Myeloma Working Group.

Note: All response categories (sCR, CR, VGPR, PR, and PD) require two consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither.

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

*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 a kappa/lambda ratio of >4:1 or <1:2.

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

‡Clarifications to IMWG criteria for coding PD: bone marrow criteria for PD are to be used only in patients without measurable disease by M-protein and by free light-chain levels; "25% increase" refers to M-protein, free light-chain, 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.

Table S4. Treatment Exposure in the Safety Population.

	Daratumumab Group (N = 364)	**Control Group (N = 365)**
Median duration of study treatment – mo (range)	25.3 (0.1-40.4)	21.3 (0.03-40.6)
Median total number of cycles received – no. (range)	27 (1-44)	22 (1-43)
Median relative dose intensity – % (range)		
Daratumumab	98.4 (3.2-107.0)	–
Lenalidomide	76.2 (7.9-240.9)	91.4 (4.8-234.2)
Dexamethasone	84.2 (11.0-110.7)	90.7 (18.9-154.5)

Table S5. Infusion-related Reactions in Two or More Patients.

Event	**Daratumumab Group (N = 364)**		
	Any Grade	Grade 3	Grade 4
Any infusion-related reaction – no. (%)	149 (40.9)	9 (2.5)	1 (0.3)
Dyspnea	34 (9.3)	3 (0.8)	0
Cough	27 (7.4)	0	0
Chills	27 (7.4)	0	0
Hypertension	12 (3.3)	2 (0.5)	1 (0.3)
Pyrexia	12 (3.3)	0	0
Nausea	9 (2.5)	0	0
Throat irritation	9 (2.5)	0	0
Bronchospasm	8 (2.2)	1 (0.3)	0
Headache	8 (2.2)	0	0
Chest discomfort	8 (2.2)	0	0
Rhinorrhea	7 (1.9)	0	0
Vomiting	7 (1.9)	0	0
Rash	7 (1.9)	0	0
Hypotension	6 (1.6)	0	0
Nasal congestion	6 (1.6)	0	0
Tachycardia	4 (1.1)	1 (0.3)	0
Decreased oxygen saturation	4 (1.1)	1 (0.3)	0

Sneezing	4 (1.1)	0	0
Throat tightness	4 (1.1)	0	0
Wheezing	4 (1.1)	0	0
Flushing	4 (1.1)	0	0
Hypoxia	3 (0.8)	2 (0.5)	0
Oropharyngeal pain	3 (0.8)	0	0
Hot flush	3 (0.8)	0	0
Erythema	3 (0.8)	0	0
Hypersensitivity	3 (0.8)	0	0
Malaise	2 (0.5)	1 (0.3)	0
Tremor	2 (0.5)	0	0
Sinus tachycardia	2 (0.5)	0	0
Increased lacrimation	2 (0.5)	0	0

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4. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. J Clin Oncol 2005;23:3412-20.

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1. Identifying information.

2. The work under consideration for publication.

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4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

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Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
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Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Tahamtan
2. Surname (Last Name): Ahmadi
3. Date: 01-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Genmab	☐	☑	☐	☑	Employment and Equity ownership

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

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Section 6. Disclosure Statement

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Dr. Ahmadi reports personal fees and other from Genmab outside the submitted work.

Evaluation and Feedback

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Michael
2. Surname (Last Name): Attal
3. Date: 20-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 5. Relationships not covered above

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Attal has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Nizar
2. Surname (Last Name): Bahlis
3. Date: 31-January-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Janssen	☑	☑	☐	☐	Consultancy, Honoraria, and Research funding

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Amgen	☑	☑	☐	☐	Consultancy, Honoraria, and Research funding
Celgene	☑	☑	☐	☐	Consultancy, Honoraria, and Research funding

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

Section 5. Relationships not covered above

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Bahlis reports grants and personal fees from Janssen, during the conduct of the study; grants and personal fees from Amgen, grants and personal fees from Celgene, outside the submitted work; .

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Supratik
2. Surname (Last Name): Basu
3. Date: 31-January-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Basu has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Christopher
2. Surname (Last Name): Chiu
3. Date: 01-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Janssen	☐	☑	☐	☑	Employment and Equity ownership

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Chiu reports personal fees and other from Janssen outside the submitted work.

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Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
Issued: The patent has been issued by the agency
Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Thierry
2. Surname (Last Name): Facon
3. Date: 24-April-2019

4. Are you the corresponding author? ☑ Yes ☐ No

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Janssen	☐	☑	☐	☐	Membership on an entity's Board of Directors or advisory committees and SpeakersBureau

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Celgene	☐	☑	☐	☐	Membership on an entity's Board of Directors or advisory committees and Speakers Bureau

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Janssen	☐	☑	☐	☐	Membership on an entity's Board of Directors or advisory committees and Speakers Bureau
Takeda	☐	☑	☐	☐	Membership on an entity's Board of Directors or advisory committees and Speakers Bureau
Amgen	☐	☑	☐	☐	Membership on an entity's Board of Directors or advisory committees
Sanofi	☐	☑	☐	☐	Membership on an entity's Board of Directors or advisory committees
Karyopharm	☐	☑	☐	☐	Membership on an entity's Board of Directors or advisory committees
Oncopeptides	☐	☑	☐	☐	Membership on an entity's Board of Directors or advisory committees
Roche	☐	☑	☐	☐	Advisory committee

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

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Dr. Facon reports personal fees from Janssen, during the conduct of the study; personal fees from Celgene, personal fees from Janssen, personal fees from Takeda, personal fees from Amgen, personal fees from Sanofi, personal fees from Karyopharm, personal fees from Oncopeptides, personal fees from Roche, outside the submitted work; .

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Laurent
2. Surname (Last Name): Frenzel
3. Date: 21-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Frenzel has nothing to disclose.

Evaluation and Feedback

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Hartmut
2. Surname (Last Name): Goldschmidt
3. Date: 01-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Janssen	☑	☑	☐	☐	Consultancy, Honoraria, Membership on an entity's Board of Directors or Advisory committees and Research funding

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

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Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Adaptive Biotechnology	☐	☑	☐	☐	Consultancy and Membership on an entity's Board of Directors or advisory committees

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Amgen	☑	☑	☐	☐	Consultancy, Membership on an entity's Board of Directors or advisory committees and Research funding
Bristol-Myers Squibb	☑	☑	☐	☐	Consultancy, Honoraria, Membership on an entity's Board of Directors or Advisory committees and Research funding
Celgene	☑	☑	☐	☐	Consultancy, Honoraria, Membership on an entity's Board of Directors or Advisory committees and Research funding
Janssen	☑	☑	☐	☐	Consultancy, Honoraria, Membership on an entity's Board of Directors or Advisory committees and Research funding
Sanofi	☑	☑	☐	☐	Consultancy, Membership on an entity's Board of Directors or advisory committees and Research funding
Takeda	☑	☑	☐	☐	Consultancy, Membership on an entity's Board of Directors or advisory committees and Research funding
Chugai	☐	☑	☐	☐	Honoraria and research funding
Mundipharma	☑	☐	☐	☐	Research funding
Novartis	☑	☑	☐	☐	Honoraria and Research funding
Art Tempi	☐	☑	☐	☐	Honoraria

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Cyrille
2. Surname (Last Name): Hulin
3. Date: 31-January-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

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Janssen	☑	☑	☐	☐	Honoraria and Research funding
Amgen	☐	☑	☐	☐	Honoraria

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Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments	
Takeda	☐	☑	☐	☐	Honoraria	

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

Section 5. Relationships not covered above

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Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
Issued: The patent has been issued by the agency
Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Rachel
2. Surname (Last Name): Kobos
3. Date: 01-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Janssen	☐	☑	☐	☐	Employment

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Kobos reports personal fees from Janssen outside the submitted work.

Evaluation and Feedback

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4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Shaji
2. Surname (Last Name): Kumar
3. Date: 06-March-2019

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Janssen	☑	☑	☐	☐	Membership on an entity's Board of Directors or advisory committees and Research Funding

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
AbbVie	☑	☑	☐	☐	Membership on an entity's Board of Directors or advisory committees and Research Funding

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Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Celgene	☑	☑	☐	☐	Membership on an entity's Board of Directors or advisory committees and Research Funding
KITE	☑	☑	☐	☐	Membership on an entity's Board of Directors or advisory committees and Research Funding

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

Section 5. Relationships not covered above

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Section 6. Disclosure Statement

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Dr. Kumar reports grants and personal fees from Janssen during the conduct of the study; grants and personal fees from AbbVie, grants and personal fees from Celgene, grants and personal fees from KITE, outside the submitted work.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Xavier
2. Surname (Last Name): Leleu
3. Date: 04-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Janssen	☐	☑	☐	☐	Honoraria

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Amgen	☐	☑	☐	☐	Honoraria
Takeda	☐	☑	☐	☐	Honoraria
Janssen	☐	☑	☐	☐	Honoraria

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Bristol-Myers Squibb	☐	☑	☐	☐	Honoraria
Novartis	☐	☑	☐	☐	Honoraria
Roche	☐	☑	☐	☐	Honoraria
Merck	☐	☑	☐	☐	Honoraria
Mundipharma	☐	☑	☐	☐	Honoraria
Gilead	☐	☑	☐	☐	Honoraria
AbbVie	☐	☑	☐	☐	Honoraria
Karyopharm	☐	☑	☐	☐	Honoraria
Celgene	☐	☑	☐	☐	Honoraria
Incyte	☐	☑	☐	☐	Honoraria

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Leleu reports personal fees from Janssen, during the conduct of the study; personal fees from Amgen, personal fees from Takeda, personal fees from Janssen, personal fees from Bristol-Myers Squibb, personal fees from Novartis, personal fees from Roche, personal fees from Merck, personal fees from Mundipharma, personal fees from Gilead, personal fees from AbbVie, personal fees from Karyopharm, personal fees from Celgene, personal fees from Incyte, outside the submitted work; .

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4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Joseph
2. Surname (Last Name): Mace
3. Date: 01-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

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Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Mace has nothing to disclose.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Margaret
2. Surname (Last Name): Macro
3. Date: 01-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

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Janssen	☑	☑	☐	☐	Honoraria and Research Funding

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Celgene	☐	☑	☑	☐	Honoraria and Travel
Janssen	☑	☑	☑	☐	Honoraria, Research funding and Travel
Takeda	☑	☑	☑	☐	Honoraria, Research funding and Travel

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Amgen	☐	☑	☑	☐	Honoraria and Travel	

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Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

1. Identifying information.

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4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

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Personal Fees: Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting , lectures, speakers bureaus, expert testimony, employment, or other affiliations
Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
Issued: The patent has been issued by the agency
Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Philippe
2. Surname (Last Name): Moreau
3. Date: 31-January-2019

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Janssen	☐	☑	☐	☐	Honoraria, Membership on an Board of Directors or advisory committees and Speakers Bureau

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

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Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Amgen	☐	☑	☐	☐	Honoraria, Membership on an entity's Board of Directors or advisory committees and Speakers Bureau

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Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Celgene	☐	☑	☐	☐	Honoraria, Membership on an entity's Board of Directors or advisory committees and Speakers Bureau
Janssen	☐	☑	☐	☐	Honoraria, Membership on an entity's Board of Directors or advisory committees and Speakers Bureau
AbbVie	☐	☑	☐	☐	Honoraria, Membership on an entity's Board of Directors or advisory committees and Speakers Bureau
Takeda	☐	☑	☐	☐	Honoraria, Membership on an entity's Board of Directors or advisory committees

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

Section 5. Relationships not covered above

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☐ Yes, the following relationships/conditions/circumstances are present (explain below):

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Dr. Moreau reports personal fees from Janssen, during the conduct of the study; personal fees from Amgen, personal fees from Celgene, personal fees from Janssen, personal fees from AbbVie, personal fees from Takeda, outside the submitted work; .

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Hareth
2. Surname (Last Name): Nahi
3. Date: 31-January-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Nahi has nothing to disclose.

Evaluation and Feedback

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Section 1. Identifying Information

1. Given Name (First Name): Michael
2. Surname (Last Name): O'Dwyer
3. Date: 01-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

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Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments	
Janssen	☐	☑	☐	☐	Consultancy	

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Section 1. Identifying Information

1. Given Name (First Name): Robert
2. Surname (Last Name): Orlowski
3. Date: 31-January-2019

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

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Bristol-Myers Squibb	☐	☑	☐	☐	Consultancy and Membership on an entity's Board of Directors or advisory committees

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Celgene	☐	☑	☐	☐	Consultancy and Membership on an entity's Board of Directors or advisory committees
Kita Pharma	☐	☑	☐	☐	Consultancy and Membership on an entity's Board of Directors or advisory committees
Sanofi-Aventis	☐	☑	☐	☐	Consultancy and Membership on an entity's Board of Directors or advisory committees
Takeda	☐	☑	☐	☐	Consultancy
Amgen	☑	☑	☐	☐	Consultancy, Membership on an entity's Board of Directors or advisory committees and Research Funding
BioTheryX	☑	☐	☐	☐	Research Funding
Spectrum Pharma	☑	☐	☐	☐	Research Funding

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Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Janssen	☐	☑	☐	☐	Consultancy and Honoraria

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

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Janssen	☐	☑	☐	☑	Consultancy, Equity ownership and Honoraria

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

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Dr. Perrot reports personal fees from Janssen during the conduct of the study; personal fees and other from Janssen outside the submitted work.

Evaluation and Feedback

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Torben
2. Surname (Last Name): Plesner
3. Date: 31-January-2019

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

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Janssen	☐	☑	☐	☐	Consultancy

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

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Celgene	☐	☐	☐	☑	Independent Response Assessment Committee

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Section 1. Identifying Information

1. Given Name (First Name): Ming
2. Surname (Last Name): Qi
3. Date: 01-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Janssen	☐	☑	☐	☐	Employment

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Hang
2. Surname (Last Name): Quach
3. Date: 01-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

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Dr. Quach has nothing to disclose.

Evaluation and Feedback

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Noopur
2. Surname (Last Name): Raje
3. Date: 01-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

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Amgen	☐	☑	☐	☐	Consultancy
Celgene	☐	☑	☐	☐	Consultancy
Bristol-Myers Squibb	☐	☑	☐	☐	Consultancy

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Janssen	☐	☑	☐	☐	Consultancy
Takeda	☐	☑	☐	☐	Consultancy
Astrazeneca	☑	☐	☐	☐	Research Funding

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Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
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Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Mourad
2. Surname (Last Name): Tiab
3. Date: 01-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Tiab has nothing to disclose.

Evaluation and Feedback

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4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Clarissa
2. Surname (Last Name): Uhlar
3. Date: 01-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Janssen	☐	☑	☐	☐	Employment

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Section 5. Relationships not covered above

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Dr. Uhlar reports personal fees from Janssen outside the submitted work.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Saad
2. Surname (Last Name): Usmani
3. Date: 01-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Janssen	☑	☑	☐	☐	Consultancy and Research funding

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
AbbVie	☐	☑	☐	☐	Consultancy
Amgen	☑	☑	☐	☐	Consultancy and Research funding
Celgene	☑	☑	☐	☐	Consultancy and Research funding

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Genmab	☐	☑	☐	☐	Consultancy
Merck	☑	☑	☐	☐	Consultancy and Research funding
MundiPharma	☐	☑	☐	☐	Consultancy
Janssen	☑	☑	☐	☐	Consultancy and Research funding
Seattle Genetics	☑	☑	☐	☐	Consultancy and Research funding
Bristol-Myers Squibb	☑	☐	☐	☐	Research funding
Pharmacyclics	☑	☐	☐	☐	Research funding
Sanofi	☑	☐	☐	☐	Research funding

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

Section 5. Relationships not covered above

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Section 6. Disclosure Statement

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Dr. Usmani reports grants and personal fees from Janssen, during the conduct of the study; personal fees from AbbVie, grants and personal fees from Amgen, grants and personal fees from Celgene, personal fees from Genmab, grants and personal fees from Merck, personal fees from MundiPharma, grants and personal fees from Janssen, grants and personal fees from Seattle Genetics, grants from Bristol-Myers Squibb, grants from Pharmacyclics, grants from Sanofi, outside the submitted work; .

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This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Rian
2. Surname (Last Name): Van Rampelbergh
3. Date: 01-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Janssen	☐	☑	☐	☐	Employment

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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Dr. Van Rampelbergh reports personal fees from Janssen outside the submitted work.

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Royalties: Funds are coming in to you or your institution due to your patent

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Christopher
2. Surname (Last Name): Venner
3. Date: 01-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

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Janssen	☑	☑	☐	☐	Honoraria and Research funding

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Amgen	☐	☑	☐	☐	Honoraria

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Takeda	☐	☑	☐	☐	Honoraria	

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Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

Definitions.

Entity: government agency, foundation, commercial sponsor, academic institution, etc.
Grant: A grant from an entity, generally [but not always] paid to your organization
Personal Fees: Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting , lectures, speakers bureaus, expert testimony, employment, or other affiliations
Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
Issued: The patent has been issued by the agency
Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Jianping
2. Surname (Last Name): Wang
3. Date: 01-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Janssen	☐	☑	☐	☐	Employment

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Wang reports personal fees from Janssen outside the submitted work.

Evaluation and Feedback

Please visit http://www.icmje.org/cgi-bin/feedback to provide feedback on your experience with completing this form.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

1. Identifying information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Katja
2. Surname (Last Name): Weisel
3. Date: 01-February-2019

4. Are you the corresponding author? ☐ Yes ☑ No

Corresponding Author's Name: Thierry Facon

5. Manuscript Title: Daratumumab Plus Lenalidomide and Dexamethasone for Untreated Myeloma

6. Manuscript Identifying Number (if you know it): 18-17249

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Janssen	☑	☑	☐	☐	Consultancy, Honoraria and Research funding

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication**.

Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below.

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Janssen	☑	☑	☐	☐	Consultancy, Honoraria and Research funding
Celgene	☐	☑	☐	☐	Consultancy

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Name of Entity	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Amgen	☐	☑	☐	☐	Consultancy, Honoraria and Research funding
Bristol-Myers Squibb	☐	☑	☐	☐	Consultancy and Honoraria
Juno	☐	☑	☐	☐	Consultancy
Sanofi	☑	☑	☐	☐	Consultancy and Research funding
Takeda	☐	☑	☐	☐	Consultancy and Honoraria

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☑ No other relationships/conditions/circumstances that present a potential conflict of interest

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Dr. Weisel reports grants and personal fees from Janssen, during the conduct of the study; grants and personal fees from Janssen, personal fees from Celgene, personal fees from Amgen, personal fees from Bristol-Myers Squibb, personal fees from Juno, grants and personal fees from Sanofi, personal fees from Takeda, outside the submitted work; .

ICMJE Form for Disclosure of Potential Conflicts of Interest

Evaluation and Feedback

Please visit http://www.icmje.org/cgi-bin/feedback to provide feedback on your experience with completing this form.

Data Sharing Statement

Facon T, Kumar S, Plesner T, et al. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. N Engl J Med. DOI: 10.1056/NEJMoa1817249.

Question	Authors' Response
Will the data collected for your study be made available to others?	Yes
Would you like to offer context for your decision?	—
Which data?	—
Additional information about data	—
How or where can the data be obtained?	The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.
When will data availability begin?	With publication
When will data availability end?	—
Will any supporting documents be available?	—
Which supporting documents?	—
Additional information about supporting documents	—
How or where can supporting documents be obtained?	—
When will supporting documents availability begin?	—
When will supporting documents availability end?	—
To whom will data be available?	—
For what type of analysis or purpose?	—
By what mechanism?	—
Any other restrictions?	—
Additional information	The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/

	transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

This statement was posted on May 30, 2019, at NEJM.org.