Janssen Research & Development

Statistical Analysis Plan

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

Protocol 54767414MMY2004; Phase 2

JNJ-54767414 (daratumumab)

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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
BUN	blood urea nitrogen
C	cycle
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CR	complete response
CrCl	creatinine clearance
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
D-R	daratumumab-lenalidomide
DRC	Data Review Committee
D-RVd	daratumumab-lenalidomide-bortezomib-dexamethasone
DOR	duration of response
ECG	electrocardiogram
ECOG	European cooperative oncology group
eCRF	electronic case report form
FISH	fluorescence in situ hybridization
HDT	high-dose chemotherapy
IFE	immunofixation
Ig	immunoglobulin
IMWG	international multiple 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
MM	multiple myeloma
MRD	minimal residual disease
MRU	medical resource utilization
NCI CTC	national cancer institute common terminology criteria
NCI-CTCAE	national cancer institute common terminology criteria for adverse events
NE	not evaluable
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
RBC	red blood cell
RVd	lenalidomide-bortezomib-dexamethasone
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
sCR	stringent complete response
SD	stable disease
SMQ	standardized MedDRA queries
SOC	system organ class
SRI	safety run-in subjects

TEAE	treatment-emergent adverse event
TTP	time to disease progression
TTR	time to response
VGPR	very good partial response
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the planned analysis for study protocol 54767414MMY2004: comparing Daratumumab, Lenalidomide, Bortezomib, and Dexamethasone (D-RVd) versus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in subjects with newly diagnosed multiple myeloma eligible for high-dose chemotherapy (HDT) and autologous stem cell transplantation (ASCT).

1.1. Trial Objectives

1.1.1. Primary Objective

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

1.1.2. Secondary Objectives

The secondary objectives are:

- To evaluate CR and sCR rate following induction, ASCT, post-ASCT consolidation, and maintenance treatment

- To evaluate overall response rate and rate of VGPR or better following induction, ASCT, post-ASCT consolidation, and maintenance treatment

- To evaluate duration of and time to sCR and time to CR

- To evaluate time to VGPR or better

- To evaluate time to PR or better

- To assess negative MRD rate following induction, post-ASCT consolidation, and maintenance treatment

- To evaluate clinical outcomes including:

    – Time to progression

    – Progression-free survival

    – Overall survival (OS)

    – Duration of response

- To assess the safety and tolerability of D-RVd

- To assess the pharmacokinetics of daratumumab

- To assess the immunogenicity of daratumumab

- To evaluate patient-reported outcomes (PROs)

- To evaluate stem cell yield after mobilization

- To assess time to absolute neutrophil count (ANC) recovery, defined as the date of the first of 3 consecutive laboratory values (obtained on different days) where the ANC is >0.5 x 10^9/L

- To assess time to platelet count recovery, defined as the date of the first of 3 consecutive laboratory values (obtained on different days) where the platelet count is >20 x 10^9/L and at least 7 days after the most recent prior platelet transfusion

- To evaluate the tolerability of daratumumab when administered as a rapid infusion during maintenance treatment (ie, an accelerated infusion rate whereby 20% of the daratumumab dose is administered over 30 minutes and the remaining 80% is administered over 60 minutes for a total dose administration time 90 minutes)

1.1.3.   Exploratory Objective

The exploratory objectives are:

- To evaluate PFS on next-line therapy (PFS2)

- To evaluate the clinical efficacy of D-RVd in high-risk cytogenetic subgroups currently defined as del(17p), t(4;14), t(14;16)

- To explore immune modulatory effects of D-RVd as compared with RVd through immune profiling (NK, T, and B cells) and T-cell receptor sequencing

- To collect medical resource utilization (MRU) data that may be used in future economic modeling (the construction and reporting of the economic model will be conducted separately from this study)

- To evaluate serum concentrations and potential immunogenicity of daratumumab with respect to infusion-related reactions (IRRs) in the setting of rapid infusion during maintenance.

1.2.   Trial Design

This is a multicenter, randomized, open-label, active-controlled, Phase 2 study in subjects with newly diagnosed multiple myeloma eligible for HDT and ASCT. Initially, there will be a safety run-in phase in up-to-16 subjects to assess potential dose-limiting toxicities (DLTs) that may be associated with the addition of daratumumab to the RVd regimen. The main study consists of 4

phases: a 28-day screening phase; an induction/consolidation phase (which is inclusive of four 21-day induction treatment cycles followed by stem cell mobilization, HDT, and ASCT, followed by two 21-day consolidation treatment cycles); a 24-month maintenance phase that starts after the post-ASCT consolidation disease evaluation; and a long-term follow-up phase. All subjects will be followed in the long-term follow-up phase for at least 1 year after last dose of study treatment and will continue until death, withdrawal of consent for study participation, or the end of study definition is met. The end of study is defined as when all subjects have completed at least 1 year of long-term follow up, or until death or withdrawal of consent for study participation, whichever occurs first.

Initially, a safety run-in phase will be performed at selected study sites. In this safety run-in phase, a total of 8 to 16 subjects will be enrolled and assigned to receive D-RVd to assess potential DLTs during Cycle 1 of treatment. Subjects who experience a DLT during the safety run-in will be withdrawn from the study (based on investigator's judgment and best clinical practice). If the stopping boundaries are crossed after 8, 12, or 16 subjects, all subjects will be withdrawn from the study, and the study will be stopped. Unless the study is stopped due to DLTs, subjects enrolled in the safety run-in phase will continue in the study and follow the visit schedule and procedures described for the main study (except PRO assessments and MRU data collection).

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

- D-RVd group: RVd with daratumumab 16 mg/kg IV weekly during induction treatment (Days 1, 8, and 15 of Cycles 1 through 4) and every 3 weeks during consolidation treatment (Day 1 of Cycles 5 and 6), followed by every 4 or 8 weeks during maintenance treatment

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

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

Disease response and progression will be based on assessments according to the IMWG guidelines. Efficacy evaluations include: M-protein measurements (serum and urine), immunofixation (IFE) (serum and urine), serum FLC, serum calcium corrected for albumin,

examination of bone marrow aspirate or biopsy, skeletal survey (assessment of lytic bone disease), and documentation of extramedullary plasmacytomas. Minimal residual disease in the bone marrow aspirate will also be assessed.

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

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

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

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

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

1.3. Statistical Hypotheses for Trial Objectives

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

1.4. Sample Size Justification

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

1.5.   Randomization and Blinding

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by ISS stage I, II, or III, and by CrCL (30-50 mL/min and >50 mL/min). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject.

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 with the exception of Cycle 4. For the last cycle, the end date is defined as the end of treatment visit date, or the earlier of the last study treatment date plus 30 days or the first subsequent anti-myeloma therapy start date 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.

2.2.   Pooling Algorithm for Analysis Centers

Data from participating centers in the study will be pooled together for analyses purpose.

2.3.   Analysis Sets

The following analysis sets are defined.

- Safety run-in (SRI) analysis set: is defined as all subjects enrolled to safety run-in treatments.

- Intent-to-treat analysis set (ITT): is defined as all randomized and SRI subjects. Analyses of demographics, baseline characteristic and time-to-event variables (e.g., PFS and OS) will be based on this analysis set.

- Safety analysis set: is defined as all randomized and SRI subjects who received at least 1 dose (partial or complete) of study treatment (Daratumumab, Lenalidomide, Bortezomib or Dexamethasone). This analysis set will be used for all safety analyses. The safety analysis grouping will be according to treatment actually received.

- Response-evaluable set: is defined as all randomized and SRI 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 1 administration of study treatment and have at least 1 post-baseline disease assessment. Measurable disease is defined as follows:

  - Immunoglobulin G (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 Ig free light chain (FLC) level ≥10 mg/dL and abnormal serum Ig kappa/lambda FLC ratio

  Analyses of the primary endpoint of sCR response and any secondary response-related endpoints such as ORR, time to response, and duration of response will be based on this analysis set.

- Pharmacokinetics-evaluable: defined as all subjects assigned to D-RVd 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 analysis set.

- Immune response-evaluable: defined as subjects assigned to D-RVd who have at least 1 immunogenicity sample obtained after their first daratumumab administration.

- Cytogenetic evaluable: defined as subjects who meet one of the following cytogenetic risk categories based on FISH:

  - Standard risk: subjects that are negative for del(17p), t(4;14) and t(14;16)

  - High risk: subjects that are positive for any of del(17p), t(4;14) and t(14;16)

2.4. Definition of Subgroups

If deemed necessary, the following subgroup analyses may be performed for the primary endpoint, selected secondary efficacy endpoints or safety endpoints, depending on the number of subjects in each subgroup as shown in Table 1. Given that SRI only has 16 subjects, subgroup analyses will not be performed for the group.

Table 1: Subgroup Definition

Subgroup	Definition
Sex	Male, Female
Age	<65 years, ≥65 years
Type of MM	IgG, Non-IgG
ECOG performance score	0, ≥1
ISS Stage[a]	I, II, III
Baseline creatinine clearance[a]	CrCl [30-50 mL/min or >50 mL/min]
Cytogenetics	high risk vs. standard risk according to FISH

[a] IWRS data is used

Additionally, if deemed necessary, patients who have consolidation therapy with HDT/ASCT after 4 cycles of induction therapy are considered as a separate ASCT subgroup for analysis purpose.

Subgroup analysis may be performed for subjects who had 4-week daratumumab dosing vs. those who had 8-week daratumumab dosing during maintenance period if deemed necessary.

2.5.   Study Day and Relative Day

Study treatment refers to Daratumumab, Lenalidomide, Bortezomib and Dexamethasone (D-RVd) and Lenalidomide, Bortezomib and Dexamethasone (RVd). Study drug refers to Daratumumab.

Study treatment dosing date is the date on which a subject receives study treatment (partial or complete) and will be recorded in the study treatment administration dataset.

The first study treatment date is defined as the earliest date of non-zero dose of the following administration: Daratumumab, Lenalidomide, Bortezomib or Dexamethasone. The last study treatment date is defined as the latest date of non-zero dose of all the study treatment administrations.

Study Day 1 or Day 1 refers to the start of the first study treatment administration date. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- (Visit date) - (date of Study Day 1) + 1, if visit date is ≥ date of Study Day 1
- (Visit date) - (date of Study Day 1),   if visit date < date of Study Day 1

A subject is considered as treated in a cycle if he/she receives any nonzero dose of Daratumumab, Lenalidomide, Bortezomib or Dexamethasone in that cycle.

2.6.   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).

2.7.   Treatment Phases

The study consists of 4 treatment phases: induction (Cycles 1 to 4), ASCT, consolidation (Cycles 5-6), and maintenance (Cycles 7-32). Definition of treatment phases are as follows:

- o Induction (Cycles 1 to 4): start of induction is the first dose date of study treatment. The end of induction is 1 day before PBSC apheresis if subject had ASCT. If subject discontinued the study early before ASCT, the end of induction is the end of Cycle 4 visit date if available; or the latest of treatment discontinuation date, the last dose date and the last non-follow-up visit date

- o ASCT: start of ASCT is the PBSC apheresis date. The end of ASCT is 1 day before C5D1 date if subject took Cycle 5 treatment. If subject discontinued the study early during ASCT, the end of ASCT is the latest of the last ASCT date, treatment discontinuation date and the last non-follow-up visit date

- o Consolidation (Cycles 5-6): start date of consolidation is C5D1 date. End date of consolidation is the post-ASCT disease evaluation date or 1 day before C7D1. If subject discontinued early before post-ASCT disease evaluation or C7D1, the end of consolidation is the latest of treatment discontinuation date, the last dose date and the last non-follow-up visit date

- o Maintenance (Cycles 7-32): start date of maintenance is C7D1 date. End of maintenance is the later of the last dose date and the last non-follow-up visit date. If subject discontinued the treatment earlier, end of maintenance is the latest of treatment discontinuation date, the last dose date and the last non-follow-up visit date

- o Follow-up phase: the follow-up phase starts 1 day after the end-of-treatment visit to the trial completion/discontinuation date.

When the start date of a phase is not available, the end date of that phase should be set to missing.

2.8.   Unique Laboratory Value

In general, in instances when there are multiple records at a given visit date for laboratory parameters associated with disease assessment, the following rules will be applied to select the unique laboratory value for analysis:

a) When there are multiple records from both central and local labs, central lab value always takes precedence over local lab value

b) When there are multiple records from central lab for a treatment phase, select the latest value as the unique lab value within the treatment phase

c) When there are multiple records from local lab for a treatment phase, select the latest lab value as the unique lab value within the treatment phase.

For local lab data regarding disease-related efficacy assessment such as SPEP, UPEP, kappa, lambda, kappa/lambda ratio, serum calcium, albumin and etc., only qualitative data will be used for analysis. Due to different local lab has different reference ranges, quantitative data from local labs will not be used for analysis.

2.9. Imputation of Missing/Partial Dates

Unless specified otherwise, no data imputation will be applied for missing safety and efficacy evaluations. For analysis and reporting purpose, missing or partial dates in adverse event (AE onset date; AE end date), multiple myeloma diagnosis date, and concomitant therapies (start date; end date) will be imputed.

Additional imputation rules will be specified in the data presentation specification (DPS).

2.9.1. 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 is imputed. If the imputed start date is later than end date, the day-component of the AE end date (possibly imputed) is imputed

    - 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 or no components of the onset date are 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 the 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.

2.9.2. 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 year of the end date is missing, no imputation will be applied

- 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.

No imputation will be done for partial or missing AE end time.

2.9.3. 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 day as the 15th day of the month, and pick the earliest day of the imputed date, the date of data collection, and the date of randomization for randomized subjects and the first dose date of study treatment for SRI subjects.

- If both the day and month are missing, set to January 1 and pick the earliest day of the imputed date, date of data collection, and the date of randomization for randomized subjects and the first dose date of study treatment for SRI subjects.

- If year is missing, no imputation will be applied.

2.9.4. 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 study treatment date, further adjust the imputed start date to make the day prior to the first dose date of study treatment.

- If the medication was taken after study start, and the imputed start date is prior to the first dose date of study treatment, further adjust the imputed start date as the first dose date. Also adjust the imputed medication end date so that it is on or after the first dose date of study treatment.

2.9.5. Partial Subsequent Antimyeloma Therapy Start Date

If year or month of subsequent antimyeloma 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 of study treatment, the earlier of the last dosing date and the day-component of the stop date of subsequent antimyeloma therapy is used for imputation.

- If the start month and year are not the same as the month and year of last dosing date of study treatment, the first day of the month is imputed.

No imputation will be applied for missing or partial subsequent antimyeloma therapy end date.

2.10. General Analysis Method

In general, continuous variables will be summarized using descriptive statistics such as mean, standard deviation (SD), median and range (maximum and minimum). Categorical variables will be summarized using frequency and percentage. For time-to-event variables including PFS, OS, etc., Kaplan-Meier method will be used for descriptive summaries, and Kaplan-Meier plots.

Summary tabulations for subject disposition, duration of follow-up time and baseline characteristics will be presented side-by-side by the randomized treatment groups (RVd, D-RVd), safety run-in treatment (D-RVd), all D-RVd combined from randomized D-RVd and safety run-in, and grand total from the randomized and the safety run-in subjects.

For each efficacy parameter, separate summary tabulations will be presented with one by the randomized treatment groups (RVd, D-RVd), and another one by randomized D-RVd, safety run-in D-RVd and all D-RVd.

Safety parameters including AEs will be presented side-by-side by the randomized treatment groups (RVd, D-RVd), safety run-in treatment (D-RVd), and all D-RVd.

3.   INTERIM ANALYSIS AND DATA REVIEW/MONITORING COMMITTEES

3.1.   Safety Run-in Data Review Committee (DRC)

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

3.2.   Interim Analysis

There is no interim efficacy analysis planned for this study. However, interim safety analyses are planned to monitor data at an ongoing basis to ensure the continuing safety of the study subjects.

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

One interim safety analysis is planned for the main study. The interim safety analysis will occur after at least 50 subjects are treated for at least 4 cycles and undergo stem cell mobilization (or are evaluated for mobilization feasibility) in the main study. Subsequent interim safety analysis will occur every 6 months afterwards. Details on the interim safety analysis can be found in its SAP.

3.3.   Independent Data Monitoring Committee (DMC)

An independent DMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in the main study. The committee will meet periodically during the main study to review interim safety data. The DMC will make recommendations regarding the continuation of the main study. The details will be provided in a separate DMC charter.

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

4.   SUBJECT INFORMATION

4.1.   Demographics and Baseline Characteristics

The following parameters will be summarized using ITT analysis set. No statistical comparison among treatment groups is planned.

- Demographic and baseline characteristic variables: age (continuous), age category (<65 years, and ≥ 65 years), sex, ethnicity, race, weight (kg), height (cm), body surface area (BSA) (m^2), and ECOG performance status (0, 1, 2, >2)

- Baseline disease characteristics: type of myeloma (IgA, IgD, IgE, IgG, IgM, light chain, biclonal, serum free light chain only), ISS staging (I, II, III) collected from eCRF not IWRS, type of measurable disease (serum, urine, FLC, NE), cytogenetics profile (del(17p), t(4;14), t(14;16)), time since initial diagnosis of MM (days), number of lytic bone lesions (None, 1-3, 4-10, more than 10), presence of diffuse myeloma-related osteopenia (Yes, No), number extramedullary plasmacytomas (0, ≥ 1), bone marrow biopsy/aspirate % plasma cells (<10, $10-59$, ≥ 60), and bone marrow biopsy/aspirate cellularity (hypocellular, normocellular, hypercellular, indeterminate)

- Medical history collected at baseline or screening visit will be summarized by system-organ class and preferred term

- A summary of stratification factors (ISS staging, creatinine clearance (CrCl [30-50 mL/min or >50 mL/min])) used in the randomization based on IWRS will be provided to evaluate whether or not randomization process was appropriately executed in the study. These IWRS captured stratification factors in randomization will be included in the stratified Cochran-Mantel-Haenszel (CMH) test, log-rank test and stratified Cox's regression models.

- Baseline vital signs: pulse, systolic blood pressure, and diastolic blood pressure

- Baseline ECG overall interpretation: normal, abnormal and clinically significant, or abnormal and not clinically significant.

4.2. Disposition Information

The number and percentage of subjects who enrolled and discontinued study treatment will be summarized using the ITT analysis set, together with reasons of discontinuation reported on eCRF by different treatment phases (induction, ASCT, consolidation and maintenance) and overall. The number of subjects who discontinued from study and the reported reasons on eCRF will be presented similarly.

4.3. Extent of Exposure

Extent of exposure to study treatments will be summarized based on the safety analysis set including the following:

- The number and percentage of subjects treated within each cycle

- Maximum number of treatment cycles received by treatment phases (induction, consolidation and maintenance)

- Total number of treatment cycles received

- 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 dose

- The duration of Daratumumab infusion (hours) for first infusion, second infusion, and subsequent infusions

- Total number of Daratumumab infusions per cycle by treatment phases (induction, consolidation and maintenance)

- Total dose administered overall and by treatment cycle for Daratumumab (mg/kg), Lenalidomide (mg), Bortezomib (mg/m^2), or Dexamethasone (mg)

- Dose intensity for each treatment, which is calculated as the sum of total doses (mg/kg, or mg/m^2, or mg) received in all cycles divided by the number of treatment cycles

- Relative dose intensity (%), which is defined as the ratio of the total actually received dose and total planned dose. Total planned dose is calculated as the sum of planned dose level over the number of recorded infusions or dose administrations (zero & non-zero dosing records included. For each dose administration, the planned dose is 16 mg/kg for Daratumumab, 1.3 mg/m^2 for Bortezomib, and 20 mg for Dexamethasone. The lenalidomide planned dose is 25 mg for Cycles 1 to 6, and 10 mg for Cycles 7 to 9. From Cycle 10 on, the planned dose is 15 mg per administration.

- Number of subjects with cycle delay, dose skipped (not administered), adjusted, stopped and interrupted for Daratumumab, Lenalidomide, Bortezomib, and Dexamethasone as well as the respective reasons.

4.4. Protocol Deviations

The incidence of major protocol deviations will be summarized based on the ITT analysis set. A listing of all major protocol deviations will be provided.

4.5. Prior, Concomitant Medications and Subsequent Therapies

Prior medications are the medications or therapies administered before the first dose of study treatment, or prior is marked as "Yes" on eCRF page. Concomitant medications are therapies recorded throughout the study with start date on or after the first dose date of study treatments until 30 days following completion of the last dose of study treatments. Prior and concomitant

medications will be summarized by World Health Organization (WHO) drug therapeutic class, pharmacologic class, and generic name based on ITT analysis set.

With the study population of newly diagnosed subjects with multiple myeloma, pre-study therapies are limited to prior systemic use of corticosteroids and radiation therapy for multiple myeloma. If any, a listing of all prior systemic use of corticosteroids, and prior radiotherapy will be provided for the ITT analysis set.

Pre- and post-infusion medications will be summarized separately. This will be provided using the ITT analysis set.

The total number of subjects who received subsequent antimyeloma therapy will be reported for ITT analysis set. 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.

4.6.   Autologous Stem Cell Transplantation (ASCT)

The number (%) of subjects who undergone stem cell mobilization and who undergone transplant will be summarized. Stem cell yield (10^6 CD34 cells/kg), the number of CD34+ cells transplanted (10^6/kg), days to engraftment for neutrophils (0.5×10^9/L) and days to engraftment for platelets (20×10^9/L) will be summarized by mean, standard deviation, median, minimum and maximum based on ITT analysis set.

Days to engraftment for neutrophils were assessed by investigators as the time to absolute neutrophil count (ANC) recovery, defined as the date of the first of 3 consecutive laboratory values (obtained on different days) where the ANC is $>0.5 \times 10^9$/L.

Days to engraftment for platelets were assessed by investigators as the time to platelet count recovery, defined as the date of the first of 3 consecutive laboratory values (obtained on different days) where the platelet count is $>20 \times 10^9$/L and at least 7 days after the most recent prior platelet transfusion.

When subjects' neutrophils or platelets did not drop below the specified threshold, some investigators have captured engraftment days as 0. As such, 0 engraftment day will not be included in the summary of data.

The ASCT related information will be listed.

5.   EFFICACY

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

Response to study treatment and progressive disease will be evaluated by a validated computer algorithm to calculate IMWG response. As a sensitivity analysis, investigator assessments of response and disease progression using the IMWG response criteria will also be performed.

All response related efficacy analyses including time to response and duration of response will be based on the response-evaluable analysis set, and time to events including PFS, time to disease progression (TTP), PFS2, and OS will be based on the ITT analysis set.

5.1.   Analysis Specifications

5.1.1.   Level of Significance

The primary hypothesis will be tested at 1-sided 10% significant level. All the secondary and exploratory analysis are to be tested at a 2-sided 5% significance level.

5.1.2.   Data Handling Rules

There is no imputation planned for missing efficacy endpoint values.

5.2.   Primary Efficacy Endpoint

5.2.1.   Definition

The primary endpoint is the proportion of subjects achieving a sCR by the end of post-ASCT consolidation treatment, as determined by the validated computer algorithm using the IMWG criteria.

5.2.2.   Analysis Methods

The number and percentage of subjects with sCR as the best response achieved by the end of post-ASCT consolidation treatment will be tabulated based on the response-evaluable analysis set. The proportion of sCR response will be compared between the two randomized treatment groups using the stratified CMH test. A Mantel-Haenszel odds ratio, along with its 2-sided 95% confidence interval and the p-value from the CMH chi-square test will be reported.

Stratification factors used in the analysis include ISS Stage (I, II, or III), and creatinine clearance (CrCl [30-50 mL/min or >50 mL/min]) from IWRS at randomization.

5.2.3. Sensitivity Analysis

As a sensitivity analysis, a landmark sCR analysis will be performed for the post-consolidation sCR rate defined as the percentage of response-evaluable subjects who achieved or maintained sCR status within 30 days of post-ASCT consolidation disease evaluation visit. The sCR status is assessed using the computerized algorithm according to IMWG response criteria, and must be achieved prior to start of subsequent therapies. Subjects must not die or progress by post-ASCT consolidation disease evaluation visit. The same stratified CMH chi-square test as the primary analysis will be implemented for the sensitive analysis and comparison will be made between the two randomized treatment groups.

For subjects entered maintenance phase but with missing post-ASCT consolidation disease evaluation visit, the date of the visit will be imputed by the median date from the end of Cycle 6 to the post-ASCT consolidation disease evaluation visit among the subjects with none missing post-ASCT consolidation disease evaluation visit date.

In addition, sCR rate will be summarized for D-RVd treated subjects by randomized and safety run-in subjects.

5.3. Secondary Efficacy Endpoints

5.3.1. Response Rate and Overall Response Rate (ORR)

5.3.1.1. Definition

Best response:
The proportion of subjects achieving a complete response (CR), very good partial response (VGPR), partial response (PR) or stable disease (SD) as best response by the end of post-ASCT consolidation treatment will be determined by the validated computer algorithm using the IMWG criteria, respectively.

ORR is defined as the proportion of subjects who achieve PR or better response (i.e., PR, VGPR, CR or sCR), according to IMWG response criteria. The proportion of subjects achieving sCR or CR, and the proportion of subjects achieving VGPR or better (i.e., VGPR, CR or sCR) will be determined by the validated computer algorithm using the IMWG criteria.

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The proportion of subjects achieving sCR/CR/VGPR/PR/SD response as best response, CR or better, VGPR or better and ORR will also be determined for the following timepoints in addition to post-ASCT consolidation treatment:

- At the end of induction prior to ASCT
- At the end of ASCT prior to consolidation
- At the end of maintenance therapy.

5.3.1.2.   Analysis Methods

The number and percentage of subjects with each response of sCR/CR/VGPR/PR/SD, CR or better, VGPR or better, and ORR as best response at the end of each treatment phase will be summarized along with its corresponding 95% CI based on the response-evaluable analysis set. The proportion of subjects with sCR, CR or better, VGPR or better, and ORR will be compared between the two randomized treatment groups using the stratified CMH test. A Mantel-Haenszel odds ratio, along with its 2-sided 95% confidence interval and the p-value from the CMH chi-squared test will be reported. Stratification factors used in the analysis include ISS Stage (I, II or III), and creatinine clearance (CrCl [30-50 mL/min or >50 mL/min]) from IWRS at randomization.

A sensitivity analysis of each response category, in which disease response is based on investigator assessment according to the IMWG response criteria, will be performed in a similar manner.

5.3.2.   Duration of sCR, CR and Duration of Response (DOR)

5.3.2.1.   Definition

Duration of response is defined for subjects with a confirmed response (PR or better) as the duration from the date of initial documentation of a response (PR or better) according to the IMWG criteria to the date of first documented evidence of progressive disease according to the IMWG criteria or death due to progressive disease. Responders without disease progression will be censored at the censoring timepoint as defined in Section 5.3.5 for time to progression (TTP).

Duration of sCR and duration of CR are defined similarly as the DOR with the response targeting on sCR and CR, respectively.

5.3.2.2.   Analysis Methods

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.

Kaplan-Meier estimates will be generated and Kaplan-Meier curves for the duration of response will be produced. No formal statistical comparison of DOR between the 2 randomized treatment groups is planned.

Duration of sCR and duration of CR will be analyzed similarly as DOR.

A sensitivity analysis of DOR, duration of sCR and duration of CR, in which disease response and progression are based on investigator assessment according to the IMWG response criteria, will be performed in a similar manner.

5.3.3.   Time to Response

5.3.3.1.   Definitions

Time to response of sCR is defined as the time from the date of the first dose of study treatment for SRI subjects, and the date of randomization for randomized subjects, to the date of the a c h i e v i n g s C R based on the computerized algorithm, which was confirmed by a repeated measurement as required by the IMWG criteria. Subjects without sCR will be censored at the censoring date for TTP as defined in Section 5.3.5.

Time to response of CR or better, VGPR or better, and PR or better are defined similarly as specified above.

5.3.3.2.   Analysis Methods

Kaplan-Meier method will be used to estimate the cumulative distribution function of response over time for subjects with response of sCR, CR or better, VGPR or better, and PR or better based on the response-evaluable analysis set. Median time to response with 95% CI will be tabulated. Kaplan-Meier estimates and curves for each response variable will be provided.

In addition, descriptive statistics (n, mean, standard deviation, median, range) will be provided to summarize time to sCR, CR or better, VGPR or better, and PR or better response.

A sensitivity analysis of time to response based on investigator assessment according to the IMWG criteria will be performed.

5.3.4.   Progression-Free Survival

5.3.4.1.   Definition

PFS is defined as the duration from the date of the first dose of study treatment for SRI subjects and the date of randomization for the randomized subjects to the date of first documented evidence of progressive disease based on the computerized algorithm according to

the IMWG response criteria or death due to any cause, whichever occurs first throughout the entire study. 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 clinical cut-off date for analysis will be censored at the last disease assessment. Subjects without any post-baseline disease assessment will be censored at the first dose date of study treatment for SRI subjects and at the randomization date for randomized subjects.

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 prior to start of subsequent antimyeloma therapy and in the absence of PD	Date of death	PFS event
No post-baseline disease assessment	First dose date for SRI subjects and randomization date for randomized subjects	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

5.3.4.2. Analysis Methods

Kaplan-Meier method will be used to estimate the distribution of PFS based on ITT analysis set. The estimated median PFS with 95% CI will be provided. The number and percentage of subjects who had a PFS event or were censored will be reported. In addition, PFS rates with 95% CI will be estimated by 12-month interval through Kaplan-Meier method. Kaplan-Meier PFS curves will also be generated.

The comparison between the two randomized treatment groups of the distribution of overall PFS will be based on a stratified log-rank test for the ITT analysis set. 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 Stage (I, II or III), and creatinine clearance (CrCl [30-50 mL/min or >50 mL/min]) from IWRS at randomization.

Reasons for PFS censoring will be summarized for ITT analysis set.

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 above.

5.3.5. Time to Disease Progression (TTP)

5.3.5.1. Definition

TTP is defined as the time from the date of the first dose of study treatment for SRI subjects and the date of randomization for the randomized subjects to the date of first documented evidence of confirmed progressive disease, as defined in the IMWG response criteria, or death due to progressive disease, 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 clinical cut-off date for analysis will be censored at the last disease assessment. Subjects without any post-baseline disease assessment will be censored at the date of the first dose of study treatment for SRI subjects and the date of randomization for the randomized subjects. The TTP definition is similar to PFS except that death not due to progressive disease will be censored.

5.3.5.2. Analysis Methods

Similar statistical methods will be applied to TTP as described for the PFS analysis.

A sensitivity analysis of TTP, in which progressive disease is based on investigator assessment according to the IMWG response criteria, will be performed in a similar manner.

5.3.6. Overall Survival (OS)
5.3.6.1. Definition

Overall survival (OS) is measured from the date of the first dose of study treatment for SRI subjects, and the date of randomization for the randomized subjects, to the date of death due to any cause. Subjects who withdraw consent from the study or are lost to follow-up will be censored at the time of withdrawal or 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 date of being alive. The date of

last known alive will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

5.3.6.2.   Analysis Methods

The Kaplan-Meier method will be used to estimate the distribution of OS for each treatment group for the ITT analysis set. 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. 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 primary analysis, the distribution of OS for the 2 randomized 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.

5.3.7.   Progression-free Survival on Next Line of Therapy (PFS2)
5.3.7.1.   Definition

Progression-free survival on next line of therapy (PFS2) is defined as the time from the date of the first dose of study treatment for SRI subjects, or date of randomization for the randomized subjects, to the progression on the next line of therapy or death due to any cause, whichever comes first. Any deaths are considered as PFS2 events regardless if the death occurs before 2nd line of subsequent therapy or not. The disease progression on the next line of therapy will be based on investigator judgment.

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 those subjects who start next line of therapy after progression on study treatment, are still alive and not yet progressed 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 first dose date of study treatment for SRI subjects, and at the date of randomization for randomized subjects.

Otherwise, subject will be censored at the minimum of 2nd line of next therapy start date minus 1 and last date of follow-up for subjects who had subsequent anticancer therapy, or censored at the last date of follow-up for subjects who did not have subsequent anticancer therapy.

Determination of dates of PFS2 and dates for censoring is summarized in Table 3 as follows.

Table 3:   PFS2 Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
No post-baseline disease assessment	First dose date of study treatment for SRI subjects and the date of randomization for randomized subjects	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

5.3.7.2.   Analysis Methods

PFS2 will be analyzed based on ITT analysis set similarly to PFS.

5.4.   Functional Status and Well-being

5.4.1.   Definition

Functional status and well-being will be assessed using three PRO measures, EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-MY20. The PROs will be scored based on the instrument developer guidelines.

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.

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 Likert 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 EORTC Myeloma Module EORTC QLQ-MY20 is meant for use among a wide range of patients with multiple myeloma, varying in disease stage and treatment modality. The myeloma module incorporates a single item scale to assess body image, and three multi-item scales assessing disease symptoms, side effects of treatment and future perspective. The raw and standardized scores for symptom, side effects, future perspective and body image single item scale will be calculated as described in the scoring manual.

5.4.2.   Analysis Methods

Compliance rates for completion of EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-MY20 at each scheduled time point will be generated based on number of expected.

<u>Key PRO endpoints</u>

- EQ-5D-5L VAS and utility score
- EORTC QLQ-C30 global health status/quality of life subscales as follows
    - 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
- EORTC QLQ-MY20 body image, disease symptoms, side effects of treatment and future perspective

The change from baseline at each scheduled time point will be summarized descriptively (n, mean, standard deviation, range, median, range) by treatment groups. Line plot of mean with standard error over time will be displayed by treatment group.

A mixed effects model with repeated measures analysis will be conducted estimating change from baseline at each time point between two randomized treatment groups. 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 month, treatment-by-time interaction, and stratification factors as fixed effects.

A distribution-based method will be used to define improvement/worsening in scores, i.e., half standard deviation away from the mean score at baseline combining both randomized treatment groups.

Time to improvement will be summarized by using descriptive statistics such as mean, standard deviation, median and range.

For randomized subjects, time to worsening will be estimated using Kaplan-Meier methods. The hazard ratio for D-RVd relative to RVd and its associated 95% confidence interval (CI) will be calculated based on the stratified Cox proportional hazards model by the stratification factors at randomization. Death due to disease progression will be considered as worsening. Subjects who have not met the definition of worsening will be censored at the last PRO assessment. Subjects without baseline assessment or post-baseline assessment will be censored at date of randomization.

5.5. Subgroup Analyses

Subgroup analyses of the primary and selected secondary efficacy endpoints will be performed based on subgroups defined in Section 2.4 if deemed necessary.

Descriptive summaries and forest plot for the computer algorithm assessed response rates will be provided for the subgroups specified in Section 2.4. The subgroup analyses will be performed if there is adequate number of subjects in each subgroup.

6. SAFETY

Safety evaluation will include adverse events (AEs), death, clinical laboratory tests (hematology and serum chemistry), vital signs, 12-lead ECG, physical exam findings, and ECOG performance status.

Safety analyses will be performed based on the safety analysis set. AEs will be summarized with 4 groups displayed side by side. The 4 groups are randomized D-RVd, randomized RVd, safety run-in D-RVd, and All D-RVd. 12-lead ECG and ECOG performance status will be summarized by randomized D-RVd, randomized RVd, and safety run-in D-RVd.

6.1. 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 electronic case report forms (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 are defined as any AE that occurs after the first administration of study treatment (e.g., Daratumumab, Lenalidomide, Bortezomib, or Dexamethasone) through 30 days after the last study treatment administration or the day prior to start of subsequent therapy, whichever is earlier, or any AE that is considered related to study treatment (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 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 maximum toxicity grade, and by relationship to study treatment administration.

6.1.1.   Overview of TEAEs

An overview of TEAEs will be provided and will include the number and percentage (incidence) of subjects with any AEs, subjects with any toxicity grade 3 or higher AEs, subjects with any treatment-related AEs, subjects with any toxicity grade 3 or higher treatment-related AEs, subjects with any SAEs, subjects with any treatment-related SAEs, subjects with any AEs leading to study treatment discontinuation, subjects with any treatment-related AEs leading to study treatment discontinuation, and subjects with any AEs with outcome of death

6.1.2.   All TEAEs

- Incidence of TEAEs by SOC, preferred term, and maximum toxicity grade (1-2 and 3-4)
- Incidence of most common (at least 20%) TEAEs by SOC, and preferred term

6.1.3.   Toxicity Grade 3 or 4 TEAEs

- Incidence of toxicity grade of 3-4 TEAEs, by SOC, preferred term and maximum toxicity grade

- Incidence of most common (at least 10%) TEAEs with toxicity grade of 3-4, by SOC, and preferred term

6.1.4.   Study Treatment-Related TEAEs

- Incidence of treatment-related TEAEs by SOC, preferred term and maximum toxicity grade (1-2 and 3-4)
- Incidence of treatment-related TEAEs by SOC, preferred term and relationship
- Incidence of treatment-related TEAEs with grade of 3-4 by SOC, preferred term and relationship
- Incidence of TEAEs related to daratumumab by SOC, preferred term and maximum toxicity grade (1-2 and 3-4)

6.1.5.   Serious Adverse Events (SAEs)

- Incidence of treatment-emergent SAEs, by SOC and preferred term

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- Incidence of most common (at least 5%) treatment-emergent SAEs, by SOC and preferred term
- Incidence of treatment-emergent SAEs related to study treatments by SOC, preferred term, and relationship
- Incidence of treatment-emergent SAEs related to daratumumab by SOC and preferred term

6.1.6. TEAEs Leading to Discontinuation of Any Study Treatment

- Incidence of TEAEs leading to any study treatment discontinuation (Daratumumab, Lenalidomide, Bortezomib, or Dexamethasone) by SOC, preferred term and maximum toxicity grade (1-2, 3-4)
- List of subjects who discontinued any study treatment due to AEs including subject ID, preferred term/verbatim term, study day of onset, toxicity grade, relationship to study treatment, action taken and outcome

6.1.7. TEAEs Leading to Cycle Delays or Dose Modifications

- Incidence of TEAEs leading to any treatment cycle delays or dose modifications of at least one of the study treatments (Daratumumab, Lenalidomide, Bortezomib, or Dexamethasone) by SOC, preferred term and maximum toxicity grade (1-2, 3-4) where dose modifications include dose skipping (not administered) or dose adjustment or dose stopped

6.2. Deaths

- Incidence of subjects who died due to TEAEs by SOC, preferred term
- List of subjects whose primary cause of death is at least one AE during the study

6.3. Adverse Events of Clinical Interest

- **Infusion-related reaction (IRR)**
  - Incidence of infusion-related reactions (IRRs) reported with Daratumumab by SOC, preferred term and maximum toxicity grade during all cycles
  - Incidence of IRRs reported with Daratumumab by SOC, preferred term and maximum toxicity grade during Cycle 1
  - Incidence of IRRs reported with Daratumumab by SOC, preferred term and event onset time
  - List of subjects with IRRs reported with Daratumumab including subject ID, MedDRA preferred term/verbatim, study day of event, toxicity grade, relationship to study treatment, action taken with study treatment and outcome

- **Infections and infestations**

  refer to adverse events with SOC of infections and infestations

  - Incidence of infections and infestations TEAEs with grade 3-4 by SOC, preferred term and maximum toxicity

- **Peripheral neuropathies (PNs)**

  refer to adverse events with high level term (HLT) of peripheral neuropathies NEC

  - Incidence of PNs by MedDRA high level term and preferred term, and maximum toxicity

- **Hemorrhage events**

  refer to the adverse events defined by Standardized MedDRA Queries (SMQ) with the first subcategory SMQ of hemorrhage terms (exclude laboratory terms)

  - Incidence of hemorrhage by MedDRA high level term and preferred term, and maximum toxicity

- **Tumor lysis syndrome**

  Tumor lysis syndrome (TLS) events refer to the adverse events defined by narrow Standardized MedDRA Queries (SMQ) of tumor lysis syndrome (haemorrhagic tumor necrosis, tumor lysis syndrome, or tumor necrosis)

  - TLS events will be listed

- **Second primary malignancies**

  - Summary of second primary malignancies
  - List of subjects who reported second primary malignancies during the study along with diagnosis, study day of diagnosis, recurrence of a prior existing malignancy (yes, no) and pathology diagnosis (biopsy, aspirate, etc.) information at time a second primary malignancy observed, cumulative study treatment exposure, the treatment for second primary malignancy and the outcome information

- **TEAEs by subgroups:**

  The following summaries based on subgroups specified in Section **Error! Reference source not found.** will be provided if deemed necessary:

    - Overview of TEAEs
    - All TEAEs

- Toxicity Grade 3 or 4 TEAEs
- SAEs.

6.4. Clinical Laboratory Tests

The evaluation of clinical safety laboratory tests will focus on the following selected laboratory analytes:

Hematology:

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

Chemistry:

- sodium	- total bilirubin
- potassium	- alkaline phosphatase
- creatinine and creatinine clearance (CrCl)	- calcium and albumin-adjusted calcium
- glucose	- albumin
- aspartate aminotransferase (AST)	- blood urea nitrogen (BUN)
- alanine aminotransferase (ALT)	- lactic acid dehydrogenase (LDH)

Since safety laboratory tests for the trial is provided by local labs, they are reported according to each local lab normal ranges. A listing of subjects with any laboratory results outside the reference ranges (any grade 3 and above laboratory results) will be provided.

6.5. Vital Signs and Physical Examination

Baseline vital signs (systolic and diastolic blood pressure, heart rate, and temperature) values will be summarized. Similar analyses will be performed for weight at Day 1 of each treatment cycle.

Post baseline physical examination findings were collected as AEs, and therefore will not be summarized.

6.6. 12-lead Electrocardiogram (ECG)

The number and percentage of subjects with normal or abnormal 12-lead ECG results will be summarized by scheduled study visits.

6.7. ECOG Performance Status

Frequencies of ECOG performance status (0, 1, 2, >2) over time will be summarized. In addition, shift from baseline to worst score during treatment may be provided.

7. PHARMACOKINETICS/IMMUNOGENICITY/PHARMACODYNAMIC

Unless specified otherwise, descriptive statistics (e.g., number of observations, mean, SD, median, and range) will be used to summarize pharmacokinetics and pharmacodynamics data at protocol specified timepoints. In addition, coefficient variation and geometric mean will be provided in the pharmacokinetic concentration summary.

7.1. Pharmacokinetics

7.1.1. 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 Cmin and Cmax.

7.1.2. 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 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. Plot of mean (± standard deviation) 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.

7.2. Immunogenicity

7.2.1. Sampling Timepoints

Samples to assess the generation of antibodies to daratumumab (immunogenicity) will be obtained from all subjects treated with D-RVd at predose of Cycles 1, 4, 5 and at post-treatment Weeks 4 and 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.

7.2.2. Analysis Methods

The incidence of antibodies to daratumumab (immunogenicity) will be summarized for all subjects who receive at least one 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. A listing of daratumumab concentrations at the time of each immunogenicity sample will be provided.

7.3. 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.

8. 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.

Minimal residual disease (MRD) will be assessed for all subjects who achieve a CR/sCR.

8.1. Minimal Residual Disease (MRD)

Bone marrow aspirates will be collected at baseline from all patients, as well as during treatment period in those subjects who attain or suspect to have a CR/sCR (including subjects with VGPR or better and suspected daratumumab interference) at 4 timepoints: at the end of induction prior to ASCT, at post-ASCT consolidation, 12 and 24 months (±3 weeks) during maintenance treatment. MRD will be monitored using ClonoSEQ Assay 2.0 on bone marrow aspirate. The clonoSEQ assay has a sensitivity of 1 cancer cell in the background of ≥100,000 white blood cells ($<10^{-5}$) or greater, and will be utilized in this study to assess MRD.

8.1.1. Definition

Post-ASCT consolidation MRD negative rate is defined as the proportion of subjects who achieved negative MRD at any time up to the post-ASCT consolidation disease evaluation visit, prior to subsequent antimyeloma therapy, after the first dose of study treatment for SRI subjects, and after randomization for the randomized subjects. MRD positive subjects include subjects of which all tested results were found to be MRD positive, or indeterminate, or unavailable (calibration failure or missing).

8.1.2. Analysis Methods

The MRD negative rate by using threshold of $<10^{-5}$ will be analyzed similarly to the sCR rate based on ITT analysis set.

In addition, MRD negative rate up to the end of induction, up to 12-month of maintenance, and up to 24-month of maintenance will be presented in the same manner as the post-ASCT consolidation.

Time to MRD negativity will be descriptively summarized by treatment groups, as well as the proportion of subjects with durable MRD negativity (i.e., lasted at least 6 months, or 12 months after the start of any MRD negativity) if sufficient data becomes available. Six-month durable MRD-negative is defined as MRD negative and confirmed by at least 6 months apart without MRD positive in between. One-year durable MRD-negative is defined as MRD negative and confirmed by at least 1 year apart without MRD positive in between.

A sensitivity analysis of MRD negative rate by using threshold of $<10^{-4}$ will be performed in a similar manner as described above. If data allow, an exploratory analysis using threshold of $<10^{-6}$ will also be performed.

9. 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.

10. REFERENCES

1. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467–1473. Corrigenda/Erratum in: Leukemia. 2007; 21:1134-1135.

2. Rajkumar SV, Harousseau J-L, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011; 4691-4695.

3. Sonneveld P, Avet-Loiseau H, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood. 2016 Jun 16;127(24):2955-62.

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SIGNATURES

Signed by	Date	Justification
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