Janssen Research & Development

Statistical Analysis Plan

A Phase 3 Study Comparing Daratumumab, VELCADE (bortezomib), Lenalidomide, and Dexamethasone (D-VRd) with VELCADE, Lenalidomide, and Dexamethasone (VRd) in Subjects with Untreated Multiple Myeloma and for Whom Hematopoietic Stem Cell Transplant is Not Planned as Initial Therapy

Protocol 54767414MMY3019; Phase 3

JNJ-54767414 (Daratumumab)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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AMENDMENT HISTORY

Unique Identifier for SAP Version	Date of SAP Version	Author	Changes from the Previous Version
1.0	28 February 2019	Diana Chen Wang, Jim	Signed off version
2.0	14 May 2021	Liu, Black, Wang, Jim	Changes made: 1. Updated per the protocol amend 4 2. Updated the supplementary and sensitivity analysis per ICH E9, including the mitigation on COVID-19 impact 3. Updated overall MRD negativity rate and cytogenetic risk category definitions 4. Corrected some typos.
3.0	28 May 2021	Jim Wang Ke Zhang	Updated per FDA feedbacks received on 27 May 2021: • Further clarification on adaptive approach on the final PFS events, increasing from 162 to 205 • Added OS as exploratory endpoint at the primary MRD analysis • Updated censoring rules in the primary PFS analysis method • Added proportional hazard assumption assessment on the PFS analysis.

ABBREVIATIONS

AE	adverse event
ALT/SGPT	alanine aminotransferase
AST/SGOT	aspartate aminotransferase
BSA	body surface area
CI	confidence interval
C_{max}	maximum concentration
C_{min}	minimum concentration
COVID-19	Coronavirus Disease 2019
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
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FLC	free light chain
IA	interim analysis
IDMC	Independent Data Monitoring Committee
IMWG	International Myeloma Working Group
IRR	injection-related reaction
ISS	International Staging System
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimum residual disease
NCI	National Cancer Institute
NGS	next generation sequencing
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PFS	progression-free survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
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
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
Tmax	time to maximum concentration
TTP	time to disease progression
TTR	time to response
VGPR	very good partial response
WBC	white blood cells
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of the analysis sets, derived variables and statistical methods for the planned analysis for the clinical study report (CSR) of the Phase 3 study comparing daratumumab, VELCADE (bortezomib), lenalidomide, and dexamethasone (D-VRd) with VELCADE, lenalidomide, and dexamethasone (VRd) in subjects with untreated multiple myeloma and for whom hematopoietic stem cell transplant is not planned as initial therapy, as specified in the protocol JNJ-54767414MMY3019, Amendment 4.

1.1. Trial Objectives

The primary objective is to determine if the addition of daratumumab to VRd (D-VRd) will improve overall minimal residual disease (MRD) negativity rate compared with VRd alone.

The key secondary objectives are

a. To determine if the addition of daratumumab to VRd will improve clinical outcome as measured by:
   - Progression-free survival (PFS)
   - Durability of MRD negativity
   - CR or better rate

b. To assess the safety profile of D-VRd

Other secondary efficacy objectives include: MRD negativity rate at 1 year, overall response rate (ORR), very good partial response (VGPR) or better rate, time to response (TTR), duration of response (DOR), time to next treatment (TTN), progression-free survival on the next line of therapy (PFS2), and overall survival (OS).

Following secondary endpoints will be evaluated as well:

- To evaluate patient-reported outcomes (PROs) and medical resource utilization
- To evaluate the pharmacokinetics (PK) of daratumumab
- To determine the immunogenicity of daratumumab and recombinant human hyaluronidase PH20 (rHuPH20)
- To evaluate clinical efficacy (i.e., overall MRD negativity rate and PFS) of daratumumab when added to VRd in cytogenetic high-risk subgroups

The exploratory objectives are to explore time to MRD negativity, the correlation of MRD negative status and clinical outcomes such as PFS and OS.

1.2. Trial Design

This is a randomized, open-label, multicenter, Phase 3 study evaluating subjects with newly diagnosed multiple myeloma for whom hematopoietic stem cell transplant is not planned as initial therapy. At randomization, subjects will be stratified by International Staging System (ISS) Stage (I, II, or III, based on β-2 microglobulin and albumin by central laboratory), and age/transplant

eligibility (<70 years ineligible, or age <70 years and refusal to transplant, or age ≥70 years). Approximately 360 subjects (180/arm) will be randomized in a 1:1 ratio in 2 arms. Subjects in Arm A will receive VRd alone for eight 21-day cycles followed by Rd alone until disease progression or unacceptable toxicity. Subjects in Arm B will receive D-VRd for eight 21-day cycles and will continue to receive D-Rd therapy until disease progression or unacceptable toxicity.

The study will consist of 3 phases: A Screening Phase, a Treatment Phase (Intervention Phase), and a Follow-up Phase (Post-Intervention Phase). The Screening Phase will be up to 28 days before randomization. Subjects will receive either D-VRd or VRd for 8 cycles. No subject will receive bortezomib after completion of the first 8 cycles of VRd. After completing 8 cycles of therapy, subjects will continue with D-Rd or Rd until disease progression or unacceptable toxicity. Subjects who discontinue treatment with any one component of study treatment (bortezomib, lenalidomide, dexamethasone, or daratumumab) may continue to receive treatment with the other components of study treatment, as randomized. Subjects will enter the Follow-up Phase once they have documented disease progression, or unacceptable toxicity and all treatment is discontinued. In the Follow-up Phase, subjects who discontinued before disease progression must continue to have disease evaluations until confirmed PD, death, withdrawal of consent, lost to follow-up, or the end of the study. After disease progression is documented, follow-up will be obtained at least every 16 weeks until the final PFS analysis. Subsequent antimyeloma treatment, PFS2 (per investigator judgment), second primary malignancies, and survival will also be recorded.

The primary analysis of the overall MRD negativity rate will be performed at approximately 18 months after the last patient subject is administered their first dose of study treatment. Long-term follow-up for PFS will continue until 162 PFS events have been observed. An interim analysis for PFS is planned, when 98 PFS events (60% of total planned PFS events) are expected to have been accumulated.

Assessment of tumor response and disease progression will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria[0]. An assessment of MRD will be conducted on 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 and immunogenicity parameters.

An IDMC will be commissioned for this study to review safety and efficacy results before the final analysis of PFS. After each review at the primary MRD analysis and the interim analysis of PFS, the IDMC will make recommendations regarding the unblinding of study results and/or the continuation of the study without unblinding. The IDMC will also review cumulative safety data after the first 100 subjects have been treated for at least 1 cycle or discontinued, and thereafter every 6 months. Refer to protocol Section 9.8 for details.

1.3. Statistical Hypotheses for Trial Objectives

The primary endpoint of this study is the overall MRD negativity rate. The null hypothesis is that there is no difference in overall MRD negativity rate between daratumumab in combination with VRd and VRd alone in subjects with newly diagnosed multiple myeloma who are not intended for initial transplant.

1.4. Sample Size Justification

Based on the available data from Studies CASTOR, POLLUX, and ALCYONE, approximately 64% of MRD negative subjects at a threshold of 10^{-4} were also MRD negative at a threshold of 10-5. The IFM2009-TE NDMM study showed a 49% overall MRD negativity rate at 10^{-4} for all the VRd subjects without transplant. Thus, the anticipated overall MRD negativity rate (10^{-5}) for the control arm in this study is estimated to be at most 35%. This study assumes that the addition of daratumumab to VRd would lead to a 15% absolute increase in overall MRD negativity rate (50% D-VRd vs. 35% VRd alone). A sample size of 360 subjects (180 each arm) is needed to achieve a power of 80% to detect such a treatment difference at a 2-sided alpha of 0.05.

This sample size will also provide approximately 80% power to detect a 37% reduction in the risk of progression or death (HR=0.63, translating to an improvement in median PFS from 43 months to 68 months) with a log-rank test at a 2-sided alpha of 0.05. To ensure adequate power for PFS, an adaptive approach may be used to determine the timing of the final PFS analysis (162 events). If the observed HR for PFS at the interim analysis (i.e., 60% of events) is higher than expected, the final analysis of PFS may be delayed until approximately 205 events have been observed (roughly 3 years later). If the HR of 0.7 is observed for PFS at the interim, 205 events will provide approximately 80% conditional power (CP) for the final analysis of PFS. The event size for the final analysis of PFS will not be decreased from 162. The ADDPLAN®[2] targeting the CP=80% subject to the maximum number of events 205 has been used to plan the adaptive design. To maintain a strong control of the type I error rate for the PFS analysis, an inverse normal p-value combination method3 will be used if the number of events for the final analysis is increased to approximately 205. The method allows flexible adaptations at an IA and creates a valid test that controls the type I error rate in a strong sense analytically. In this proposed design, the adaptation is the potential adjustment of the required number of events for the final analysis.

Using the approach proposed by Wassmer (2006)[3], if the number of events for the final analysis is increased, final test statistic Z_f, is weighted combination of log-rank test statistics LR_1 and LR_2. LR_2 is performed on the full analysis set and LR_1 is calculated on the interim full analyis set

$$Z_f = \sqrt{t}\,LR_1 + \sqrt{1-t}\left(\left(\sqrt{\frac{d_2}{d_2-d_{IA}}}\right)LR_2 - \left(\sqrt{\frac{d_{IA}}{d_2-d_{IA}}}\right)LR_1\right)$$

where t is the fixed information fraction of 0.6, d_2= total number of accumulated events (for stage 1 and stage 2), and d_{IA} is the actual number of PFS events at the interim analysis.

1.5. Randomization and Blinding

Central randomization will be implemented in this study. Eligible subjects will be stratified by ISS (Stage I, II, or III, based on β-2 microglobulin and albumin by central laboratory), and age/transplant eligibility (<70 years ineligible, or age <70 years and refusal to transplant, or age ≥70 years), and then assigned randomly to 1 of 2 treatment groups in a 1:1 ratio based on an algorithm implemented in the interactive web response system (IWRS) before the study. The randomization will be balanced by using randomly permuted blocks. Based on the randomization code, the IWRS will assign a unique intervention code, which will dictate the intervention assignment and matching study drug kit for the subject.

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

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 certain 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. To address this, by-week windowing rules may be applied in the overtime data summaries by study week.

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

Study treatment refers to bortezomib, lenalidomide, dexamethasone and daratumumab. Study drug refers to daratumumab.

2.4. Analysis Sets

2.4.1. Intent-To-Treat (ITT) Analysis Set

This set consists of subjects who have been randomly assigned to the D-VRd or VRd group. Demographics, baseline characteristics, baseline disease characteristic and efficacy endpoints will be primarily analyzed based on this analysis set.

2.4.2. Modified Intent-To-Treat (mITT) Analysis Set

This set consists of ITT subjects who have not permanently discontinued study treatment/ trial, or have died due to COVID-19 on or before the primary MRD analysis cutoff date, if the difference between this analysis set and ITT is more than 10%, this analysis set will be used as supplementary analyses for selected endpoints.

2.4.3. Safety Analysis Set

This set consists of subjects who have received at least 1 administration of any study treatment (partial or complete). This analysis set will be used for all safety analyses. The safety analyses grouping will be based on the treatment actually received.

2.4.4. MRD-evaluable Analysis Set

This set consists of CR or better subjects who have a successful baseline calibration, and also have at least one post-baseline MRD sample with positive or negative result. If the difference between this analysis set and CR or better subjects is more than 10%, this analysis set may be used as sensitivity analyses for selected MRD related endpoints.

2.4.5. Pharmacokinetic Analysis Set

This set consists of all subjects randomized to D-VRd group who received at least 1 administration of daratumumab and have at least 1 pharmacokinetic sample concentration value after their first daratumumab administration. All pharmacokinetics analyses are based on the pharmacokinetic analysis set.

2.4.6. Immunogenicity Analysis Set

For daratumumab, immunogenicity analysis will be performed on the daratumumab immunogenicity analysis set, defined as all subjects randomized to D-VRd who receive at least one dose of daratumumab and have at least one sample for detection of anti-daratumumab antibodies obtained after the first dose daratumumab.

- For rHuPH20, immunogenicity analysis of rHuPH20 will be performed on the rHuPH20 immunogenicity analysis set, defined as all subjects assigned to D-VRd who receive at least 1 dose of daratumumab and have at least 1 sample for detection of anti-rHuPH20 antibodies obtained after the first dose of daratumumab.

2.5. Definition of Subgroups

The pre-specified subgroups are summarized in Table 1. Additional exploratory subgroup analyses may be performed, if requested and deemed necessary by IDMC for their analyses and decision making.

Table 1: Subgroups

Subgroup	Definition of Group	Analysis Type
Sex	• Male • Female	E, S
Age	• S: <65, 65-<70, ≥70 years • E: <70, ≥70 years	E, S
Baseline renal function	• <30 mL/min/ 1.73m^2 • 30 to <60 mL/min/1.73m^2 • 60 to <90 mL/min/1.73m^2 • ≥90 mL/min/1.73m^2 Based on estimated glomerular filtration rate (e-GFR) (mL/min/1.73m^2) values for the modified diet in renal disease (MDRD)	S
Region	• Europe • North America • Other	E, S
Weight	• ≤65 kg • > 65 and ≤ 85 kg • >85 kg	E
Baseline ECOG performance score	• 0 • ≥1	E
Baseline International Staging System (ISS)[a]	• I • II • III	E
Cytogenetic risk	• High-risk [b] • Standard-risk	E

E= efficacy (MRD negativity rate, PFS, CR or better rate), ECOG= Eastern Cooperative Oncology Group, NCI=National Cancer Institute, S=Safety

[a] Baseline ISS will be derived based on the combination of serum β2-microglobulin and albumin

[b] High risk is defined by FISH testing of subjects having t (4; 14); t (14; 16) and/or 17p deletion.

2.6. Study Day and Relative Day

Study Day 1 refers to the date of first study treatment. 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

2.7. Baseline

The baseline value is defined as the closest non-missing value 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 and vital sign).

2.8. Imputation Rules for Missing Date/Time of Onset/Resolution

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 AE (AE onset date/time; AE resolution date/time), concomitant therapies (onset date; resolution date), multiple myeloma diagnosis date, and onset date of subsequent antimyeloma therapy will be imputed.

2.8.1. Adverse Event Onset/Resolution Date/Time

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the first study treatment.
  - The day of the first study treatment, if the month/year of the onset of AE is the same as month/year of the first study treatment and month/year of the AE resolution date is different
  - The day of the first study treatment or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the first study treatment and month/year of the AE resolution date are same
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the first study treatment
  - Month and day of the first study treatment, if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the first study treatment
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

If the resolution date of an AE is missing completely or partially, the following imputation rules will be used:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.

Completely missing resolution dates will not be imputed.

AE onset/resolution dates with missing times will be imputed as follows:

- A missing time of onset of an AE will be set to the earlier of:

  - 00:01 as long as the onset date is after the first study treatment
  - The time of first study treatment if this is on the same day of the AE occurred.
- The missing time of the resolution of an AE will be set to 23:59.
- If a missing time is associated with a partial or missing date, the date will be imputed first prior to imputing the time. If a missing time is associated with a completely missing date, the missing time will not be imputed.

2.8.2. Concomitant Medication Onset/Resolution Date

In case of partially missing dates, the imputation will be done as follows:

- If the date is completely missing, no imputation will be performed.
- Otherwise, the following rules will be applied to impute partially missing dates (onset date, resolution date). 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 onset date is after first treatment date, further adjust the imputed onset date as the day prior to the first treatment date; if the medication was taken after study start, and the imputed onset date is prior to the first treatment date, further adjust the imputed onset date as the first treatment date. Also adjust the imputed medication resolution date so that it is on or after the first treatment date.

2.8.3. Prior 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 15 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.

2.8.4. Subsequent Antimyeloma Therapy Onset 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, the day of last dosing date or the day-component of the stop date of subsequent antimyeloma 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 antimyeloma therapy end date.

3. INTERIM ANALYSIS

There is no interim analysis planned for the overall MRD negativity rate. After the primary analysis of MRD negativity rate, disease assessment will continue for the secondary endpoint PFS, for which one interim analysis is planned after approximately 98 events (i.e., 60% of the total 162 events) have been accumulated. The significance levels at this interim analysis of PFS to establish the superiority (or declare the futility) of daratumumab plus VRd over VRd alone will be determined based on the observed number of PFS events at this analysis using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha- and beta-spending method.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Unless specified otherwise, all demographic and baseline characteristics variables will be summarized for the ITT analysis set. No statistical comparison between the 2 treatment groups is planned. Table 2 presents a list of the demographic variables that will be summarized by treatment group and overall.

Table 2: Demographic Variables

Continuous Variables	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Surface Area (BSA) (m^2)	
Categorical Variables	
Age (<65, 65-<70, ≥70 years)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female, undifferentiated, unknown)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Not reported)	
Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported)	
Enrollment distribution (by region and country)	
ECOG performance status (0, 1, 2)	
Weight (≤65 kg, >65 and ≤ 85, >85 kg)	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'

Table 3 presents a list of the baseline characteristics variables that will be summarized by treatment group and overall.

Table 3: Baseline Characteristics Variables

Continuous Variables	**Summary Type**
Time since initial multiple myeloma diagnosis (months)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Selected hematology laboratory analytes (hemoglobin, platelets, absolute lymphocyte count, white blood cell count, absolute neutrophil count)	
Selected chemistry laboratory analytes (AST, ALT, Alkaline phosphatase, creatinine clearance, total bilirubin, corrected serum calcium)	
Vital sign parameters (pulse, systolic blood pressure, diastolic blood pressure, temperature)	
Categorical Variables	
Type of multiple myeloma (IgG, IgA, IgM, IgD, IgE, free light chain only, biclonal, or negative immunofixation)	Frequency distribution with the number and percentage of subjects in each category.
Type of measurable disease (IgG, IgA, Other (IgD, IgM, IgE and biclonal), Serum and urine, Urine only, or Serum FLC)	
ISS staging at screening by central laboratory assessment (I, II, III)	
Number of lytic bone lesions (None, 1-3, 4-10, more than 10)	
Presence of extramedullary plasmacytomas (Yes, No)	
Bone marrow % plasma cells (<10, 10-30, >30-60, >60)	
Bone marrow cellularity (hypercellular, normocellular, hypocellular, indeterminate) by biopsy or aspirate	
Standard-risk or high-risk cytogenetic abnormalities (del17p, t(4;14), t(14;16))	
Baseline toxicity grade (1, 2, 3, 4) of selected hematology laboratory analytes	
Baseline toxicity grade (1, 2, 3, 4) of selected chemistry laboratory analytes	
Medical history collected at baseline or screening visit (by system organ class, preferred term)	
ECG overall interpretation at baseline (normal, abnormal and clinically significant, abnormal and not clinically significant, not evaluable)	
Transfusions during screening (by transfusion categories)	
Stratification factors (ISS staging, age/transplant eligibility)	

In addition, the following listings will be provided:

- Subjects who did not meet study inclusion/exclusion criteria
- Subject demographic and baseline characteristics

4.2. Disposition Information

The number and percentage of subjects in the following disposition categories will be summarized throughout the study by treatment group and overall.

- Subjects who are randomized to each treatment group
- Subjects who are randomized but not treated in each treatment group
- Subjects who are treated in each treatment group
- Treated subjects (defined as subjects who have received at least 1 administration of any study treatment) who discontinued treatment, including reason for discontinuation as indicated by the investigators

- Randomized subjects who discontinued from study, including reason for discontinuation as indicated by the investigators.

Listings of subjects will be provided for the following categories:

- Treated subjects who discontinued study treatment
- Randomized subjects who discontinued study

4.3. Extent of Exposure

Extent of exposure to study treatments will be summarized and presented based on the safety analysis set.

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 days 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 (continuous and categorical variables) will be summarized for subjects treated with D-VRd. The total dose administered for daratumumab (mg), bortezomib (mg/m^2), lenalidomide (mg), and dexamethasone (mg) will be summarized overall, by cycle, and by Cycles 1-2, Cycles 3-8 and Cycles 9+ for daratumumab.

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 for Cycles 1-2, Cycles 3-8, and Cycles 9+.

The relative dose intensity (%) defined as the ratio of total dose actually received and total planned dose (planned dose level times the number of administered injections/medications) will be calculated for each study treatment and summarized by treatment group using descriptive statistics.

The number of subjects with treatment cycle delay, dose modifications for each study treatment will be summarized for each treatment group. The reasons (AE or other, including COVID-19) for treatment cycle delay, dose delays or skipping for each study treatment as well as dose reduction for bortezomib, lenalidomide, and dexamethasone will also be reported. In addition, a summary of study treatment dose modifications by cycle will be provided.

4.4. Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical study. Subjects with major protocol deviations will be identified prior to database lock and the subjects with major protocol deviations will be summarized by category for ITT analysis set.

- Entered but did not satisfy criteria

- Developed withdrawal criteria but not withdrawn
- Received wrong treatment or incorrect dose
- Received a disallowed concomitant treatment
- Other, including COVID-19 related

A listing of all major protocol deviations including subject ID, type of deviation, and reasons for deviation will be provided. A similar listing will be presented for all COVID-19 related minor protocol deviations.

4.5. Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary September 2017 version.

Concomitant medications collected in the eCRF 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-injection medication and post-injection medication, respectively.

In addition, systemic steroids as concomitant medication use during the study will be summarized.

Additionally, prophylactic antiviral medication use will be tabulated.

4.6. Subsequent Antimyeloma Therapy

The total number of subjects who received subsequent antimyeloma therapy will be reported for safety analysis set in each treatment group. A summary of subsequent antimyeloma therapy will be presented by therapeutic class, pharmacologic class and drug name, coded using the WHO Drug Dictionary September 2017 version.

5. EFFICACY

Efficacy assessment will be performed by the sponsor using a validated computerized algorithm, following the IMWG criteria. Detailed rules for response/PD assessment will be provided in a separated attachment: Disease Progression and Response Assessment. As a sensitivity analysis, investigator assessment of response and disease progression using the IMWG response criteria will also be summarized.

All the efficacy analyses will be based on the ITT analysis set unless specified otherwise.

5.1. Analysis Specifications

5.1.1. Level of Significance

All statistical hypothesis tests and 95% confidence intervals presented will be 2-sided.

The primary hypothesis is to be tested at the 0.05 significance level (overall).

If the primary endpoint of overall MRD negativity rate is statistically significant, the key secondary endpoints (i.e., CR or better rate, PFS, and durable MRD negativity rate) 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)[4] that strongly controls family wise Type I error rate.

Due to the short follow-up time at the primary MRD data cut, PFS and durable MRD negativity data will be premature, we may perform the hierarchical test on them starting at the interim PFS data cut (98 events occurred). The final PFS analysis (162 events occurred) will be skipped if the PFS interim result crosses the pre-specified stopping boundary. The significance level at each data cut will be determined by the alpha-spending function specific to endpoints:

- For CR or better rate, the information fraction is expected to be 80% at the primary MRD cut. 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 primary MRD cut and 0.0428 (two-sided) at the interim PFS cut.
- For PFS, the exact significance level at the interim analysis and final PFS analysis is to be determined by the observed number of events per the O'Brien-Fleming alpha spending function. Assuming 98 PFS events are observed at the interim analysis, the alpha to be spent will be 0.0076 (2-sided) for the interim analysis and 0.0476 (2-sided) for the final PFS analysis (162 PFS events occur).

  To ensure adequate power for PFS, an adaptive approach may be used to determine the timing of the final PFS analysis. If the observed HR for PFS at the interim analysis (i.e., 60% of events) is higher than expected (e.g., 0.7 or higher), the final analysis of PFS may be delayed until approximately 205 events have been observed. To control the overall type I error rate, the inverse normal test with the same fixed weights (i.e., information fractions of interim and final analyses) as originally planned will be used to combine the log-rank statistics before and after the interim analysis.

- For durable MRD negativity rate, the information fraction is expected to be 80% at the interim PFS cut. 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 interim PFS cut and 0.0428 (two-sided) at the final PFS cut.

If the null hypothesis for any of these endpoint fails to be rejected at the interim analysis, then any subsequent endpoint(s) listed above will not be tested until the next analysis time point (e.g., final PFS analysis), if applicable. If the null hypothesis for an endpoint is rejected at any interim analysis, it will remain being rejected and will not be re-tested at any subsequent time points, if any.

5.1.2. Data Handling Rules

There is no imputation planned for missing efficacy endpoint values.

5.2. Primary Efficacy Endpoint(s)

5.2.1. Definition

The primary endpoint is overall MRD negativity rate, defined as the proportion of subjects who achieve CR or better response and have MRD negative status (at 10^{-5}) by bone marrow biopsy/aspirate after randomization but prior to progressive disease (PD), subsequent anti-myeloma therapy, or both.

MRD positive subjects include subjects of which all tested samples were found to be MRD positive or indeterminate. For subjects with missing MRD samples, failure to calibrate baseline MRD, or otherwise unevaluable samples, MRD status will be considered as MRD positive.

5.2.2. Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 5 components:

- Treatments:
  - Daratumumab, bortezomib, lenalidomide and dexamethasone (D-VRd, investigational treatment) for eight 21-day cycles followed by daratumumab, lenalidomide, and dexamethasone (VRd) therapy until disease progression or unacceptable toxicity
  - Bortezomib, lenalidomide and dexamethasone (VRd) for eight 21-day cycles followed by lenalidomide and dexamethasone (Rd, control treatment) until disease progression or unacceptable toxicity
- Population: subjects with untreated multiple myeloma and for whom hematopoietic stem cell transplant is not planned as initial therapy
- Variable: MRD negativity status (yes or no, yes defined as achieving CR or better response and MRD negative status (at 10^{-5}) by bone marrow biopsy/aspirate any time after treatment assignment but prior to either of the intercurrent events: subsequent antimyeloma therapy or progressive disease)
- Population-level summary: odds ratio (OR) of D-VRd vs. VRd
- Intercurrent events:
  - Subsequent antimyeloma therapy
  - Progressive disease.

Composite strategy will be used to count for the intercurrent events as reflected in the variable definition.

5.2.3. Analysis Methods

For this study, threshold value of 10^{-5} will be used for the primary MRD negativity analysis. Other threshold values (10^{-4} and 10^{-6}) may also be explored.

MRD negativity on or after disease progression or switch to subsequent anti-myeloma therapy without confirmed progression on study treatment, will not be considered as MRD negative in the analysis.

The overall MRD negativity rate will be calculated for each treatment group based on the ITT analysis set. The corresponding 95% exact CI will be provided. Reasons for missing or unevaluable MRD status will be tabulated by treatment group.

The stratified Cochran Mantel Haenszel (CMH) estimate of odds ratio and its 95% confidence interval and p-value from Fisher's exact test will be used to test if the MRD negativity rate is the same between the two treatment groups. Stratification factors used in the analysis include ISS staging (I, II, III) and age/transplant eligibility (<70 years ineligible, <70 years and refusal to transplant, ≥70 years).

Following supplementary analyses may be performed in a similar manner as described above:

- Overall MRD negativity rate based on the "modified ITT" analysis set (if ≥10% subjects who have discontinued study treatment/ study or died due to COVID-19)
- Overall MRD negativity rate based on the CR or better subjects only.

The following exploratory analysis may be conducted,

- Exploratory analyses correlating MRD negativity with long-term clinical endpoints (e.g., PFS) are described in Section 8.1.2.
- Overall MRD negativity based on the MRD evaluable analysis set (if ≥10% different from the CR or better subjects)

5.3. Major Secondary Endpoints

The major secondary efficacy endpoints include CR or better rate, PFS and durable MRD negativity rate.

5.3.1. CR or Better Rate

5.3.1.1. Definition

CR or better rate is defined as the proportion of subjects achieving CR or sCR based on the computerized algorithm, according to IMWG response criteria, during or after the study treatment prior to the start of subsequent antimyeloma therapy.

5.3.1.2. Estimand

The estimand corresponding to the major secondary endpoint, CR or better rate, in the study, is defined similarly as the primary endpoint in Section 5.2.2, except:

- Variable: CR or better response (yes or no, yes defined as achieving CR or better response any time after treatment assignment but prior to subsequent antimyeloma therapy)
- Intercurrent events:
  - Subsequent antimyeloma therapy

Composite strategy will be used to count for the intercurrent events as reflected in the variable definition.

5.3.1.3. Analysis Methods

CR or better responses after switch to subsequent anti-myeloma therapy will not be counted as CRs in the analysis.

The CR or better rate will be calculated for each treatment group based on the ITT analysis set. The corresponding 95% exact CI will be provided. The stratified 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), and age/transplant eligibility (<70 years ineligible, <70 years and refusal to transplant, ≥70 years).

5.3.2. Progression-free Survival (PFS)

5.3.2.1. Definition

PFS is defined as the duration from the date of randomization to either progressive disease (PD) or death due to any cause, whichever comes first. Disease progression will be determined according to the International Myeloma Working Group (IMWG) criteria. Subjects who start subsequent anti-myeloma 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. 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 date of randomization.

Determination of dates of PFS event and dates for censoring is summarized in Table 4 as follows.

Table 4: PFS Event and Censoring Method

Situation	Outcome	Date of Event or Censoring
Disease progression prior to start of subsequent antimyeloma therapy	PFS event	Earliest date that indicates disease progression
Death (due to any cause) *	PFS event	Date of death
Disease progression or death immediately preceded by 2 or more consecutive missed disease assessments	Censored	At the last adequate disease assessment before the consecutive missed disease assessments
No postbaseline disease assessment	Censored	Date of randomization
Other, such as: • Withdrawal of consent to study participation • Lost to follow-up • Start of subsequent antimyeloma therapy prior to disease progression or death	Censored	Date of last disease assessment prior to withdrawal of consent to study participation, lost to follow-up, start of subsequent antimyeloma therapy

*Subjects who died after consent withdrawal will be censored at the date of consent withdrawal for PFS analysis

5.3.2.2. Estimand

The estimand corresponding to the major secondary endpoint PFS for this study is defined by the following 5 components:

- Treatments:
  - Daratumumab, bortezomib, lenalidomide and dexamethasone (D-VRd, investigational treatment) for eight 21-day cycles followed by daratumumab, lenalidomide, and dexamethasone (VRd) therapy until disease progression or unacceptable toxicity
  - Bortezomib, lenalidomide and dexamethasone (VRd, control treatment) for eight 21-day cycles followed by lenalidomide and dexamethasone (Rd) until disease progression or unacceptable toxicity
- Population: subjects with untreated multiple myeloma and for whom hematopoietic stem cell transplant is not planned as initial therapy
- Variable: progression-free survival
- Population-level summary: hazard ratio (HR) of D-VRd vs. VRd
- Intercurrent events:
  - Start of subsequent antimyeloma therapy prior to disease progression or death
  - COVID-19 infection with the outcome of death prior to disease progression.

Hypothetical strategy will be applied to the intercurrent events of subsequent antimyeloma therapy prior to disease progression or death, as if the subjects would not have experienced such an intercurrent event. Treatment policy will be used for COVID-19 infection with the outcome of death prior to disease progression, whether such an intercurrent event has occurred or not is irrelevant.

5.3.2.3. Analysis Methods

Analysis of PFS will be based on the ITT analysis set. 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 reasons for PFS censoring will be summarized accordingly. The Kaplan-Meier PFS curve will also be plotted by treatment group.

If a subsequent antimyeloma therapy started prior to disease progression or death, the PFS date would be censored at the date of last disease assessment before the start of subsequent antimyeloma therapy, as described in Table 4 of PFS events and censor methods in Section 5.3.2.1.

The 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) and age/transplant eligibility (<70 years ineligible, <70 years and refusal to transplant, ≥70 years). In addition, landmark PFS rate with 95% CI will be estimated by Kaplan-Meier method and reported for each treatment group.

The proportional hazard (PH) assumption of the PFS analysis will be examined graphically (log-log plot of S(t)) and/or numerically (e.g., good of fitness test by Schoenfeld residual). If the PH assumption is not met, additional analyses may be performed to address the issue, such as the

Inverse probability of censoring weighting (IPCW) analysis to take the confounding factors (e.g., daratumumab-containing subsequent therapy) into account because non-PH may be caused by potential treatment change (or crossover).

Additionally, following sensitivity or supplementary analyses may be performed in a similar manner as described above:

Sensitivity

- Unstratified analysis of PFS
- Progressive disease is based on investigator assessment according to the IMWG response criteria

Supplementary

- Not censor the events after the start of subsequent antimyeloma therapies
- Censor the death due to COVID-19
- Censor the subjects who permanently discontinue treatment/study due to COVID-19 (censor at last disease evaluation before treatment/study discontinuation).

5.3.3. Durable MRD Negativity Rate

5.3.3.1. Definition

Durable MRD negativity rate is defined as the proportion of subjects who achieve CR or better response and have achieved MRD negative status (at 10^{-5}) at two bone marrow biopsy/aspirate examinations that are a minimum of one year apart (and the two examinations should be prior to progressive disease (PD), subsequent anti-myeloma therapy, or both), without any examination showing MRD positive status in between.

5.3.3.2. Estimand

The estimand corresponding to the major secondary endpoint, durable MRD negativity rate, in the study, is defined same as the primary endpoint in Section 5.2.2, except the variable definition:

- Variable: durable MRD negativity status (yes or no, yes defined as achieving CR or better response and MRD negative status (at 10^{-5}) at two bone marrow biopsy/aspirate examinations that are a minimum of one year apart without any examination showing MRD positive status in between, and prior to either of the intercurrent events: subsequent antimyeloma therapy or progressive disease).

5.3.3.3. Analysis Methods

The durable MRD negativity rate will be calculated for each treatment group based on the ITT analysis set. The corresponding 95% exact CI will also be provided.

Chi-square estimate of the common odds ratio with 95% confidence interval and p-value from Fisher's exact test for treatment difference will be reported.

5.4. Other Efficacy Variable(s)

Other efficacy endpoints include MRD negativity rate at one year and other timepoints (i.e., 18, 24, 30, or 36 months), overall survival (OS), overall response rate (ORR), VGPR or better rate, Progression-free survival on the next line of therapy (PFS2), time to response (TTR), time to subsequent antimyeloma treatment, and duration of response (DOR).

5.4.1. Definitions

MRD negativity rate at one year is defined as the proportion of subject who achieved CR or better response and MRD negative status (at 10^{-5}) by bone marrow biopsy/aspirate at 12 months after the first dose of study treatment and prior to progressive disease (PD), subsequent anti-myeloma therapy, or both. But the subjects who have achieved MRD negative status on or after PD or the start of subsequent anti-myeloma therapy, will not be considered as MRD negative. Similar definitions apply to the MRD negativity rates at other scheduled time points, which are 18, 24, 30, or 36 months after the first dose of study treatment.

Overall response rate (ORR) is defined as the proportion of subjects who achieve PR or better responses (i.e., PR, VGPR, CR, or sCR) based on the computerized algorithm, in accordance with the IMWG criteria, during or after the study treatment but before the start of subsequent anti-myeloma therapy.

VGPR or better rate is defined as the proportion of subjects achieving VGPR, CR, and sCR based on the computerized algorithm, in accordance with the IMWG criteria, during or after the study treatment but before the start of subsequent anti-myeloma therapy.

Progression-free survival on the next line of therapy (PFS2) is defined as the time from randomization to progression on the next line of treatment or death (due to any cause), whichever comes first. Disease progression will be based on investigator judgment. Subjects who are still alive and not yet progressed on the next line of treatment will be censored on the last date of follow-up. Subjects who withdraw consent or lost to follow-up prior to any subsequent antimyeloma therapy will be censored at the date of last disease assessment during the course of study. Subjects without any post-baseline follow-up will be censored at the randomization.

Overall survival (OS) is defined as the time from the date of randomization to the date of the subject's 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 died after consent withdrawal will be considered as having an OS event. If the subject is alive at the cutoff date for the analysis or the survival status is unknown, then the subject's data will be censored at the date the subject was last known to be 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.

Time to response (TTR, i.e., time to the first response) is defined as the time between the randomization and the first efficacy evaluation at which the subject meets all criteria for PR or better based on the computerized algorithm, according to IMWG response criteria.

Time to subsequent antimyeloma treatment is defined as the time from randomization to the start of subsequent antimyeloma treatment. Death due to PD without the start of any 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 PD will be censored at the date of death or the last date known to be alive.

Duration of response is defined as the duration from the date of initial documentation of a response (PR or better) to the date of first documented evidence of PD based on computerized algorithm, according to IMWG response criteria, or death due to PD, whichever occurs first. Subjects who have not progressed or who die due to causes other than disease progression will be censored at the last disease evaluation before the start of subsequent antimyeloma therapy.

5.4.2. Analysis Methods

The analysis of MRD negativity rate at 1 year and other timepoints (i.e., 18, 24, 30, or 36 months), ORR and VGPR or better rate will be performed in a similar manner as described in the Section 5.3.1.3.

The analysis of OS, PFS2, time to subsequent antimyeloma therapy, and DOR will be performed in a similar manner as described in the Section 5.3.2.2. At the primary MRD analysis, OS analysis will be exploratory and descriptive. The Kaplan-Meier curves of OS will also be provided by treatment group.

Time to first response will be analyzed for subjects who achieve a response (PR or better) and descriptive statistics (N, mean, SD, median, and range) will be provided.

6. SAFETY

Safety assessment will be evaluated through AEs, clinical laboratory tests, vital sign measurements, physical examination findings, ECG, and assessment of ECOG performance status. Safety analyses will be based on the safety analysis set and presented by treatment group.

6.1. 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. Adverse Events will be recorded in standard medical terminology and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0. The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the latest 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. If the event occurs on the day of the first study treatment and either event time or time of study drug are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered as treatment-emergent unless it is known to be prior to the first study treatment based on partial onset date or resolution date.

The following AE summaries will be presented by treatment group.

- An overview of TEAEs, including subjects with TEAEs, treatment-emergent SAEs, TEAEs related to study treatment, TEAEs leading to discontinuation of any study treatment, AE of maximum grade of 1 to 5, deaths due to TEAE

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and relationship to study treatment
- TEAEs by SOC, PT and maximum toxicity grade
- Most common (>10%) TEAEs by SOC and PT

- Treatment-emergent SAEs by SOC and PT
- Treatment-emergent SAEs by SOC, PT, and relationship to study treatment
- Treatment-emergent SAEs by SOC, PT, and maximum toxicity grade
- Most common (>2%) Treatment-emergent SAEs by SOC and PT

- Toxicity grade 3 or 4 TEAEs by SOC and PT
- Toxicity grade 3 or 4 TEAEs by SOC, PT, and relationship to study drug
- Most common (>5%) toxicity grade 3 or 4 TEAEs by SOC and PT

- TEAEs leading to discontinuation of any study treatment by SOC, PT, and toxicity grade 3/4. 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.

- TEAEs leading to discontinuation of all study treatments by SOC, PT, and toxicity grade 3/4. This summary 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.

- TEAEs leading to cycle delays or dose modifications by SOC, PT, and toxicity grade 3/4. This summary includes TEAEs leading to cycle delays or dose modification of at least one of the study treatments, the dose modifications include dose delays, dose skipping, or dose reduction.

6.2. Deaths

6.2.1. 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.

6.2.2. All Deaths

A summary of all death 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 safety analysis set. The primary cause of death collected on the death information CRF page will be reported. If the primary cause of death is an AE, the number of subjects who have a related AE and unrelated AE will be further reported. The similar summaries will be presented for subjects who died within 30 days of last study treatment dose and within 60 days of first study treatment dose, respectively.

6.3. Adverse Events of Clinical Interest

6.3.1. Injection-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 an IRR in more than 1 injection will be reported. Additionally, the timing of an IRR associated with daratumumab administration will be evaluated through a summary of an IRR by event onset time.

A listing of subjects with Grade 3 or higher treatment-emergent IRR associated with daratumumab administration will be provided. In addition, subjects with treatment-emergent IRR results in discontinuation of daratumumab will be listed.

6.3.2. Local Injection Site Reactions

Subjects with any local injection-site reactions associated with daratumumab administration will also be summarized by MedDRA system-organ class and preferred term. The summaries will be presented by any grade and Grade 3 or 4. A listing of subjects with treatment-emergent injection-site reactions associated with daratumumab administration will also be provided.

6.3.3. 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., ≤6 months vs. 6- ≤12 months vs. >12 months).

6.3.4. Peripheral Neuropathies

Peripheral neuropathies (PNs) refer to adverse events with high level term (HLT) of peripheral neuropathies NEC. Incidences of PNs will be summarized by MedDRA high level term and preferred term. The summaries will be presented by all grades and Grade 3 or 4 for each treatment group.

6.3.5. Hemorrhage Events

Hemorrhage events refer to the adverse events defined by Standardized MedDRA Queries (SMQ) with the first subcategory SMQ of hemorrhage terms (exclude laboratory terms). Incidences will be summarized by MedDRA system-organ class and preferred term. The summaries will be presented by all grades and maximum toxicity grade for each treatment group.

6.3.6. Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) events refer to the adverse events defined by narrow Standardized MedDRA Queries (SMQ) of tumor lysis syndrome (hemorrhagic tumor necrosis, tumor lysis syndrome, or tumor necrosis). A listing of subjects who reported any treatment-emergent TLSs during the study will be provided.

6.3.7. 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.) 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.

6.3.8. Coronavirus Disease 2019 (COVID-19)

Subjects who reported COVID-19 infection and death during the study may be summarized and listed.

6.4. Adverse Events by Subgroups

The following subgroup analysis of adverse events will be performed based on subgroups specified in Section 2.5:

- Overview of TEAEs
- All TEAEs
- Toxicity Grade 3 or 4 TEAEs
- Treatment-emergent SAEs.

6.5. 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
  - lactate dehydrogenase (LDH)
  - creatinine clearance
  - blood urea nitrogen or urea
  - total protein

Blood samples for serum hematology and chemistry are taken at the screening visit, on Days 1, 8, and 15 of Cycles 1-8, Day 1 of Cycles 9+, and at the End-of-Treatment visit. All clinical laboratory tests will be displayed for the subjects included in the safety analysis set.

Descriptive statistics (mean, SD, 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.

Applicable laboratory results will be graded according to NCI-CTCAE version 5.0. 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.

A listing of markedly abnormal laboratory results outside the reference ranges will be provided for selected laboratory analytes.

6.6. Vital Signs and Physical Examination Findings

Vital signs (systolic and diastolic blood pressure, heart rate, and temperature) are measured at screening visit, at Day 1, 8, and 15 of Cycles 1-8, and Day 1 of Cycles 9+. The values and change from baseline of each parameter will be summarized at each scheduled time point by treatment group.

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

6.7. Electrocardiogram (ECG)

The interpretation of the electrocardiogram (ECGs) as determined by a qualified physician (investigator or qualified designee) will be displayed by the number and percentage of subjects meeting the normality criteria. The interpretation will be summarized at baseline and the post-baseline timepoints by treatment group.

6.8. ECOG Performance Score

ECOG performance status evaluates the effect of the disease status on the activities of daily living will be assessed at screening visit, at Day 1 of Cycle 4, 8, 11, and 14 for the first year, every 6 cycle thereafter until PD, and 8 weeks and 16 weeks post-PD. Descriptive statistics will be used to summarize ECOG performance status at baseline, scheduled post-baseline timepoints (including change from baseline), worst score during post injection period (including change from baseline) for each treatment group. Shift table from baseline to worst score during the post injection period may be provided.

6.9. Other Safety Parameters

For subjects with known or suspected chronic obstructive pulmonary disease (COPD), a listing will be provided for force expiratory volume in 1 second (FEV1), and the overall interpretation as determined by the site personnel.

7. PHARMACOKINETICS/PHARMACODYNAMICS

Unless specified otherwise, descriptive statistics (e.g., number of observations, mean, SD, 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.

7.1. Pharmacokinetics

7.1.1. Sampling Timepoints

For subjects randomized to D-VRd, blood samples to assess serum concentration of daratumumab (pharmacokinetics) will be obtained at Day 1 predose of Cycles 1, 3, 9 and 12, Day 4 of Cycles 1 and 3, and Post-treatment Week 8.

7.1.2. Pharmacokinetic Parameters

The pharmacokinetic parameters are defined as:

- Minimum observed concentration (C_{min}): the concentration observed immediately before daratumumab administration.
- Maximum observed concentration (C_{max}): the concentration observed at Day 4 after daratumumab administration.

For daratumumab, the pharmacokinetic evaluations include C_{min} and C_{max}.

7.1.3. Analysis Methods

Pharmacokinetic data from subjects in the pharmacokinetic analysis set will be presented by visit and timepoint. 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. Data from subjects outside the prespecified visit window will be reported, but not included in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the data presentation specification.

Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point. Individual and mean (±SD) daratumumab serum peak and trough concentrations over time will be plotted. And daratumumab serum concentrations at each sampling time point would be summarized by baseline body weight (≤50 kg, ≤ 65 kg, >65 to ≤ 85 kg, > 85 kg, >120 kg).

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. Immune Response

7.2.1. Sampling Timepoints

Samples to assess the generation of antibodies to daratumumab and recombinant human hyaluronidase PH20 (rHuPH20) will be obtained from all subjects in the D-VRd group at Day 1 pre-dose of Cycle 1, Cycle 9, and Cycle 12, and Post-Treatment Week 8. In addition, if an injection-related reaction occurs associated with the second or later daratumumab administration, 2 separate blood sample should be drawn as soon as possible after the reaction for determination of anti-daratumumab antibodies and anti-rHuPH20 antibodies.

7.2.2. Analysis Methods

Immunogenicity data from subjects in the daratumumab immunogenicity analysis set will be presented by visit and timepoint, and summarized using descriptive statistics. Immunogenicity data from subjects in the rHuPH20 immunogenicity analysis set will be presented by visit and

timepoint, and summarized using descriptive statistics. Scatter plots for onset and duration of ADA for both immunogenicity sets will also be presented.

In addition, subjects who are positive for anti-daratumumab or anti-rHuPH20 antibodies will also be listed. A listing of sample level anti-daratumumab and anti-rHuPH20 antibodies with the concurrent daratumumab concentrations will also be provided. Additional analyses may be performed to assess the clinical relevance of anti-daratumumab or anti-rHuPH20 antibodies.

7.3. Pharmacokinetic/Pharmacodynamic Relationships

If sufficient data are available, other pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of daratumumab and clinical efficacy/safety endpoints. 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. Molecular subtyping will be done through next generation sequencing (NGS) to evaluate daratumumab response rates in risk-stratified multiple myeloma subpopulations.

8.1. Minimal Residual Disease (MRD)

Bone marrow aspirates will be collected at baseline from all patients, as well as on treatment in those subjects who attain or suspect to have a CR/sCR to monitor MRD. MRD will be monitored using ClonoSEQ Assay 2.0 on bone marrow aspirate.

8.1.1. Sampling Timepoints

For all subjects, a fresh bone marrow aspirate will be obtained at baseline, as well as on treatment for subjects who were suspected to have a CR/sCR, at the time of the suspected CR/sCR, the landmark time points: 12, 18, 24, 30, and 36 months (+/-1 month) after first dose of study treatment, and yearly (+/-1 month) thereafter until PD.

8.1.2. Analysis Methods

Details on overall MRD negativity rate analyses are described in Section 5.2.

In addition, exploratory landmark analyses will be conducted to correlate overall MRD negativity results (as either binary or continuous values) with long-term clinical endpoints such as PFS. Subgroup analysis of PFS by MRD negativity status may also be performed. Similar analysis may be performed for subjects who achieved CR or better.

9. FUNCTIONAL STATUS AND WELL-BEING

9.1.1. Definition

Functional status and well-being will be assessed using three patient-reported outcomes (PROs) measure: the EORTC- QLQ-C30, EORTC QLQ-MY20, and the EQ-5D-5L. They will be scored based on the instrument developer guidelines. No imputation will be done for the PRO data.

The EORTC QLQ-C30 includes 30 items, within a 1-week recall, resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 Global Health Status scale (GHS), 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

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 Multiple Myeloma Module (QLQ-MY20) has 20-items that make up 4 scales: disease symptoms, side effects of treatment, future perspective, and body image. Scoring and interpretation are similar to the EORTC QLQ-C30.

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 (VAS) 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 (UK scoring algorithm allows for values less than 0).

9.1.2. Analysis Methods

Analysis of PRO data will be performed on the ITT analysis set. For subjects with multiple records at the same visit, the closest one to the visit date will be selected as the scheduled assessment. Compliance rates for completion of EORTC QLQ-C30, EORTC QLQ-MY20, and EQ-5D-5L at each time point will be generated based on number of received and expected. Compliance is defined as the actual number of assessments received for a visit divided by the expected number of assessments for that visit, the expected number of assessments per visit will be determined by subject-level study completion status.

The PRO endpoints are secondary and not part of the statistical hierarchy. Type 1 error control will not be applied to PRO data.

Key PRO endpoints

- EORTC-QLQ-C30 GHS, Physical Functioning, Fatigue, Pain subscales
- EORTC QLQ-MY20 Disease symptoms
- EQ-5D-5L utility value and VAS

Descriptive statistics (n, mean, standard deviation, median, and range) at each time point and the change from baseline will be summarized by treatment group.

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 month, treatment-by-time interaction, and stratification factors as fixed effects. A mean change between 5 and 10 points on the 1 to 100 scales of the EORTC QLQ-C30 and EORTC QLQ-MY20 has been defined as noticeable by patients and regarded as a significant change or a meaningful change (EORTC Quality of Life Group). Line plot of LS mean change from baseline, with standard error, over time may be displayed by treatment group.

For the key PRO endpoints, time to worsening and time to improvement will be derived. 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 treatment groups.

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

Time to worsening will be estimated using Kaplan-Meier methods. The hazard ratio for D-VRd relative to VRd and its associated 95% confidence interval (CI) will be calculated based on the stratified Cox proportional hazards model by the stratification factor 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. A Kaplan-Meier figure for the key PRO endpoints will be generated to show time to worsening and censored subjects.

Other PRO endpoints

These include the other scales of EORTC QLQ-C30 and QLQ-MY20.

The change from baseline at each time point may be summarized descriptively by treatment group.

Time to improvement/worsening and the mixed effect model analysis, as described for the key PRO endpoints, may be performed as appropriate.

10. MEDICAL RESOURCE UTILIZATION

Medical resource utilization (excluding study injection 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.

Additional analyzes may be conducted. Details and results of any additional analyzes will be presented in a separate report.

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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 2.5:

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 TEAE enters the sum in the nominator unweighted ($TEAE_i$ =1, otherwise $TEAE_i$ =0), and

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