Janssen Research & Development

Statistical Analysis Plan

A Phase 2 Study of Daratumumab Subcutaneous (Dara-SC) Administration in Combination with Carfilzomib and Dexamethasone (DKd) Compared with Carfilzomib and Dexamethasone (Kd) in Participants with Multiple Myeloma who have been Previously Treated with Daratumumab Intravenous (Dara-IV) to Evaluate Daratumumab Retreatment

Protocol 54767414MMY2065; Phase 2

JNJ-54767414 (DARZALEX®)

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

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

AMENDMENT HISTORY

ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ALT/SGPT	alanine aminotransferase
ANCOVA	analysis of covariance
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic Class
AUC	area under the curve
BMI	body mass index
BSA	body surface area
CBR	clinical benefit rate
CI	confidence interval
CL	total systemic clearance
Cmax	maximum concentration
CR	complete response
CRS	cytokine release syndrome
CrCL	creatinine clearance
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	Data Monitoring Committee
DOR	duration of response
DPS	Data Presentation Specifications
DRC	Data Review Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
F (%)	absolute SC bioavailability
FAS	full analysis set
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FLC	Free-light chain
IA	interim analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IQ	interquartile
IRR	infusion-related reaction
ISS	International Staging System
IVRS	interactive voice response system
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LVEF	left ventricular ejection fraction;
MedDRA	Medical Dictionary for Regulatory Activities
MR	minimal response
MRD	minimal residual disease
NAb	neutralizing antibodies
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
ORR	overall response rate
OS	overall survival

PBMC	peripheral blood mononuclear cell
PD	progressive disease
PFS	Progression-free Survival
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PP	per protocol
PR	partial response
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCR	stringent complete response
SD	standard deviation
SPEP	serum protein electrophoresis
SMQs	standardized MedDRA queries
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
Tmax	time to maximum concentration
TTP	time to disease progression
TTR	time to response
UPEP	urine protein electrophoresis
US NCI	United States National Cancer Institute
V	volume distribution
VGPR	very good partial response
Vz	volume of distribution based on terminal phase
Vz/F	apparent volume of distribution based on terminal phase after extravascular administration
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of the analysis population(s), derived variables and statistical methods for Study 54767414 MMY2065.

1.1. Trial Objectives

The primary objective is to compare the efficacy (rate of very good partial response [VGPR] or better as best response as defined by the International Myeloma Working Group [IMWG] criteria) of Dara-SC in combination with carfilzomib-dexamethasone (DKd) with the efficacy of carfilzomib-dexamethasone (Kd) in participants with relapsed refractory multiple myeloma who were previously exposed to daratumumab intravenous (Dara-IV) to evaluate daratumumab retreatment. The primary endpoint of this study is the rate of VGPR or better as defined by the IMWG criteria.

The secondary objectives of the study are:

- To further characterize the efficacy (progression-free survival (PFS), overall survival (OS), overall response rate (ORR), rate of complete response (CR)/stringent complete response (sCR)) of Dara-SC in combination with Kd
- To evaluate the minimal residual disease (MRD) negativity rate and durability of MRD negativity status
- To characterize the safety of Dara-SC in combination with Kd
- To determine time to next treatment
- To evaluate the pharmacokinetics (PK) of Dara-SC
- To determine the immunogenicity of daratumumab and recombinant human hyaluronidase PH20

The secondary endpoints are:

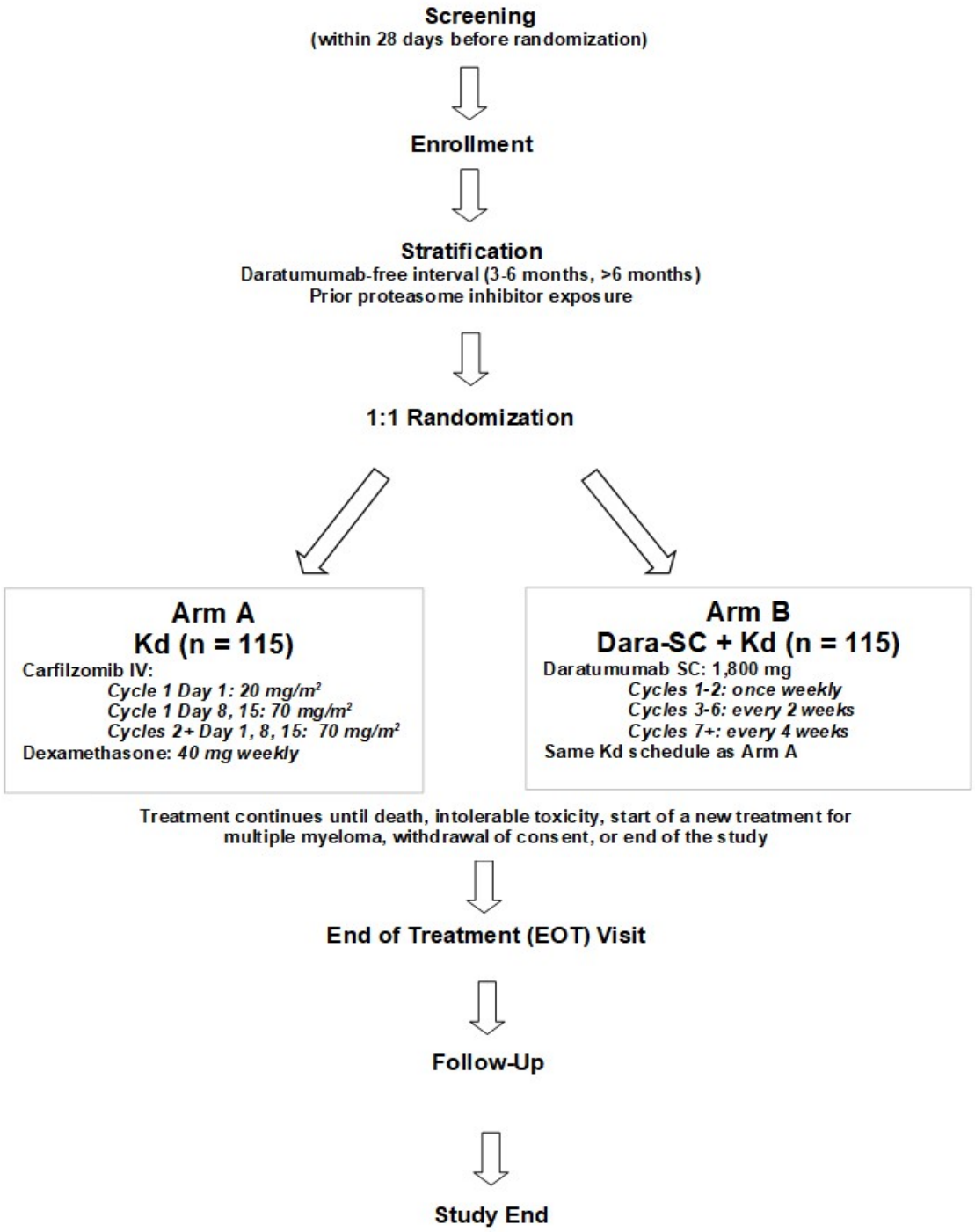
- ORR (rate of partial response, VGPR, CR, sCR)
- Rate of CR/sCR
- PFS
- OS
- MRD negativity rate
- Time to next treatment
- Serum daratumumab concentrations
- Prevalence and incidence of anti-daratumumab antibodies and anti-rHuPH20 antibodies

1.2. Trial Design

This is a Phase 2, open-label, randomized, multicenter study to determine the efficacy of DKd in adult participants with relapsed refractory multiple myeloma who had 1 or 2 prior line(s) of treatment including a line containing Dara-IV to evaluate daratumumab retreatment. Participants must have completed treatment with Dara-IV at least 3 months prior to randomization. The study will be conducted in 3 phases: Screening, Treatment, and Follow-Up. During the Treatment Phase, approximately 230 participants will be randomized in a 1:1 ratio to receive Kd or DKd, stratified by prior proteasome inhibitor exposure and daratumumab-free interval (3-6 months, >6 months). Participants in both arms will receive study intervention until confirmed progressive disease (PD), death, intolerable toxicity, start of a new treatment for multiple myeloma, withdrawal of consent, or end of the study, whichever occurs first. Follow up of participants for disease progression and survival will continue during the Follow-up Phase. A schematic overview of the study is provided below.

The primary analysis will be conducted approximately 6 months after the last participant receives the initial dose of study intervention. An interim futility analysis will occur when 40% of participants are enrolled and treated for 6 months. If the Dkd treatment group is considered ineffective at the interim analysis, the study will be terminated. The end of study is no later than 2 years after the last participant has received their initial dose of study intervention or when the sponsor decides to stop the study. A final analysis will occur at the end of the study to update PFS, overall survival, second primary malignancy and safety.

Figure 1: Schematic Overview of the Study



1.3. Statistical Hypotheses for Trial Objectives

The statistical hypothesis for the primary objective is that Dara-SC in combination with Kd will have a higher VGPR or better rate as the best response than Kd in participants who have previously received 1 or 2 prior line(s) of therapy including Dara-IV.

1.4. Sample Size Justification

Based on Study MMY1001 study data, the rate of VGPR or better as the best response was 68% for DKd participants not previously treated with daratumumab. If VGPR or better rate is assumed to be 60% for DKd and 45% for Kd in the current study, 230 participants (assigned 1:1) are needed to detect an absolute 15% increase in VGPR or better rate with 70% power using a 2-sided chi squared test at the 10% significance level.

1.5. Randomization and Blinding

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention 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 prior protease inhibitor exposure and daratumumab-free interval (3-6 months, >6 months). The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant. As this is an open-label study, blinding procedures are not applicable.

2. GENERAL ANALYSIS DEFINITIONS

Study treatment refers to combinations of the individual medications dara-SC, carfilzomib, and dexamethasone. Study drug refers to individual medications within a study treatment.

2.1. Visit Windows

Unless otherwise specified, data to be analyzed or listed over time will be presented by day and time point (as appropriate) that are recorded in the electronic case report form (eCRF).

For analyses of data by cycle, if data are collected by date (e.g., AE onset), the corresponding study evaluations will be assigned to actual sequential cycles, which are derived from the study treatment administration data. The start date of a particular cycle is defined as the date of the first scheduled dose of any component of the study treatment, and the end date of a cycle is the start date of the next cycle minus 1. For the last cycle, the end date is defined as the end of treatment visit date or the minimum of last study treatment date plus 30 days and subsequent antimyeloma therapy minus 1 day, if the end of treatment visit date is not available.

In general, if data (e.g., laboratory and vital sign etc.) are collected by cycle, the nominal cycle will be used to summarize data. However, due to possible cycle delays, assessment performed in the same cycle may not be well aligned in time scale for different subjects. 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. Analysis Sets

2.3.1. Efficacy Analysis Set(s)

- The intent-to-treat (ITT) analysis set includes all subjects who were randomized in the study. Demographics, baseline characteristics, and efficacy endpoints will be primarily analyzed based on this analysis set.

- The response-evaluable analysis set includes subjects who have a confirmed diagnosis of multiple myeloma and measurable disease at baseline or screening visit. In addition, subjects must have received at least one administration of study treatment and have adequate post-baseline disease assessments. Measurable disease is defined as follows:

  - serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL for subjects with IgG type, or ≥ 0.5 g/dL (≥ 5 g/L) for subjects with IgA, IgD, IgE, or IgM multiple myeloma or

  - urine M-protein level ≥200 mg/24 hours or

  - serum FLC multiple myeloma: involved FLC level ≥ 10 mg/dL (≥ 100 mg/L) and abnormal serum immunoglobulin kappa lambda free light chain ratio

2.3.2. Safety Analysis Set

The safety analysis set includes all subjects who received at least 1 dose of study treatment.

This analysis set will be used for safety summaries and listings.

2.3.3. Pharmacokinetics (PK) Analysis Set

The PK analysis set includes all subjects who have received at least 1 dose of dara-SC and have at least 1 post-dose pharmacokinetic sample.

This analysis set will be used for all pharmacokinetics analyses.

2.3.4. Immunogenicity Analysis Set

The immunogenicity analysis set for dara-SC includes all randomized subjects who have appropriate samples for detection of the antibodies.

Immunogenicity-evaluable analysis set for anti-rHuPH20 antibodies is defined as all subjects who receive at least one dose of Dara-SC and have appropriate plasma samples for detection of antibodies to rHuPH20 (at least 1 sample after the start of the first dose of Dara-SC).

2.3.5. Pharmacodynamics Analysis Set

NA

2.4. Definition of Subgroups

The following pre-specified subgroup (Table 1) analyses are to be performed for the primary efficacy endpoint, major secondary endpoints, and safety endpoints. Additional subgroup analyses may be performed for selected efficacy and/or safety endpoints.

Table 1: Subgroup Analyses for Efficacy and Safety Endpoints

Subgroup	Definition	Analysis Type
daratumumab-free interval (derived)	3-6 months, >6 months	Efficacy(E)
prior proteasome inhibitor exposure	Yes, No	E
Sex	Male, Female	E, Safety(S)
Age	<65, ≥65 years	E, S
Race	White, Other	S
Weight	• ≤70 kg • >70 kg	E
Baseline renal function (baseline CrCl):	• <60 mL/min • 60 to <90 mL/min • ≥90 mL/min Based on creatinine clearance (mL/min) values	S
Region	• Europe • Rest of the world	E
Baseline hepatic function	Normal, Impaired[a]	E, S
Number of prior lines of therapy	1 line, >=2 lines	E
Prior IMiD	Yes, No	E
Refractory[b] to:		
IMiD	Yes, No	E
last line of prior therapy	Yes, No	E
Type of Multiple Myeloma	IgG, Non-IgG	E
International Staging System (ISS)[c]	I, II, and III	E
cytogenetics risk group	positive for Del17P, t(4;14), t(14;16), or amplification 1q by FISH	E
ECOG performance score	0, ≥1	E

Efficacy: efficacy (VGPR or better, ORR, CR/sCR, PFS, and OS); Safety: TEAE
Keys: CrCL; ECOG; FISH; IMiD = Immunomodulatory agent;
a Includes mild, moderate and severe. mild: (total bilirubin ≤ ULN and AST > ULN) or ULN < total bilirubin ≤ 1.5×ULN; moderate: 1.5×ULN < total bilirubin ≤ 3×ULN; severe: total bilirubin > 3×ULN
b Refractory disease in this study is defined as <25% reduction in M-protein or confirmed PD by IMWG criteria during previous treatment or =< 60 days after cessation of treatment.
c Baseline ISS will be derived based on the combination of serum β2-microglobulin and albumin

2.5. Study Day and Relative Day

Study Day 1 refers to the start of the first study treatment administration. 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

There is no 'Day 0'

2.6. Baseline

Baseline measurement is defined as the last non-missing measurement prior to the start of 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. Imputation Rules for Missing Date/Time

2.7.1. 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 study treatment start
  - The day of study treatment start, if the month/year of the onset of AE is the same as month/year of the study treatment start date and month/year of the AE resolution date is different
  - The day of study treatment start or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the study treatment start date 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 study treatment start date
  - Month and day of the study treatment start date, 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 study treatment start date,
  - The AE resolution date.

- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- 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 adverse event will be set to the earlier of:
  - 00:01 as long as the onset date is after the study treatment start date
  - The time of the study treatment start if this is the same day the AE occurred.
- The missing time of resolution of an adverse event 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.

2.7.2. Concomitant Medication Start/End 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 (start date, end 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 concomitant medication was taken prior to study start, and the imputed start date is after study treatment start date, further adjust the imputed start date as the day prior to study treatment start date; if the medication was taken after study start, and the imputed start date is prior to study treatment start date, further adjust the imputed start date as study treatment start date. Also adjust the imputed medication end date so that it is on or after study treatment start date.

2.7.3. Multiple Myeloma Diagnosis Date

For partial date of original multiple myeloma diagnosis, the following imputation rules will be applied:

- If only day is missing,
    - if month and year of start of 1st line of prior multiple myeloma therapy are the same year and month of diagnosis, and day of start of the 1st line of prior multiple myeloma therapy is available, impute day with day of start of 1st line of prior multiple myeloma therapy
    - otherwise, impute day with 15
- If both month and day are missing,
    - if year of diagnosis is the same as year of start of 1st line of prior multiple myeloma therapy, and month information is available for start of the 1st line of prior multiple myeloma therapy
        - impute month with month of start of 1st line of prior multiple myeloma therapy
        - if day of start of 1st line of prior multiple myeloma therapy is available, impute diagnosis day with day of start of 1st line of prior multiple myeloma therapy; otherwise, impute diagnosis day with 15
    - otherwise, impute with June 30
- If year is missing, no imputation will be applied.

2.7.4. Prior Multiple Myeloma Therapy Start/End Date

For partially missing prior multiple myeloma therapy 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 imputed start/end date is after study treatment start date, further adjust the imputed start/end date as the day prior to study treatment start date.

2.7.5. Progressive Disease Date on Prior Multiple Myeloma Therapy

For partially missing progressive disease date on prior multiple myeloma therapy, the following imputation rules will be applied. If the date is completely missing, no imputation will be performed. Partially missing prior multiple myeloma therapy start/end dates will be imputed before imputing partially missing progressive disease date.

- If only the day is missing,
    - if the month and the year are the same as the month and the year of prior multiple myeloma therapy start date, then the day of prior multiple myeloma therapy start date will be used.
    - otherwise, 15th day of the month will be used
- If both the day and month are missing,
    - if the year is the same as the year of prior multiple myeloma therapy start date, then the month and day of prior multiple myeloma therapy start date will be used
    - otherwise, the 30th of June will be used

If the imputed progressive disease date is before the prior multiple myeloma therapy start date, further adjust the imputed progressive disease date as the prior multiple myeloma therapy start date. If the imputed progressive disease date is later than first study treatment date -1, then further adjust the imputed progressive disease date as the first study treatment date - 1.

2.7.6. Subsequent Antimyeloma Therapy Start Date

If no components of the start date are present, no imputation will be performed.

If both the month and day components are missing, the following steps apply:

- If the year is the same as the year of last study treatment end date, then the month and day of last study treatment end date + 1 day will be used.
- Otherwise, the 30th of June or the stop date of subsequent antimyeloma therapy, whichever is earlier will be used.

If only the day-component is missing, the following steps apply:

- If the month and year of the start date are the same as the month and year of the last study treatment end date, the day of last study treatment end date + 1 day is imputed.
- Otherwise, the first day of the month is imputed.

- If the imputed start date of subsequent antimyeloma therapy is after the stop date of subsequent therapy, further adjust the imputed start date of subsequent antimyeloma therapy as the stop date of subsequent therapy.

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

Note: * The first post-baseline progressive disease is based on investigator assessment (recording in disease progression CRF page).

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

One interim futility analysis is planned. The interim futility analysis will occur when 40% of participants are enrolled and treated for 6 months. The rate of VGPR or better will be the primary endpoint for the futility analysis. The criterion for futility is defined as:

- If the observed rate of VGPR or better in DKd group is no higher than the rate in the Kd group, than the null hypothesis (no treatment difference in rate of VGPR or better) will be accepted, and the study will may be terminated.

- Otherwise, the study will continue.

The criterion only serves as a statistical guidance. Assuming the rate in the Kd group is 45%, the probability of early termination is at least 53% if in fact the rate in the DKd group is no higher than 45% and is less than 8% if in fact the rate in the DKd group is at least 60%.

In addition, the rate of VGPR or better will be compared between the treatment arms using the stratified Cochran-Mantel-Haenszel test. The stratification factors are prior PI exposure and daratumumab-free interval (3-6 months, >6 months) at randomization. The Mantel-Haenszel estimate of common odds ratio, along with its 2-sided 90% confidence interval, and the nominal p-value from the CMH test will be reported for descriptive purpose. The rate of VGPR or better will also be summarized by the stratification factor.

ORR and CR or better will be analyzed using the same method as the primary endpoint. Number and percentage of subjects in the response categories below (including not evaluable (NE)) will be tabulated by treatment group. Summaries will be provided for other efficacy endpoints (sCR, PR, SD, PD, and PFS).

Other details about the conduct of these analyses can be found in a stand-alone DRC Charter and SAP.

4. SUBJECT INFORMATION

The number of subjects in each analysis set will be summarized and listed by treatment group and overall. In addition, the distribution of subjects by region, and country will be presented unless otherwise noted.

4.1. Demographics and Baseline Characteristics

Table 2 presents a list of the demographic variables that will be summarized by treatment group and overall for the ITT analysis set.

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 Mass Index (BMI) (kg/m^2)	
Body Surface Area (BSA) (m^2)	
Categorical Variables	
Age (<65, ≥65 years)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other, Not Reported)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
Baseline ECOG performance status (0, >=1)	
Weight (≤70 kg, >70 kg)	
BMI (underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese ≥30 kg/m^2)	

[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 for the ITT analysis sets.

Table 3: Baseline Characteristics Variables

Continuous Variables	**Summary Type**
Time since initial multiple myeloma diagnosis (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Selected hematology laboratory analytes (hemoglobin, platelets, absolute lymphocyte count, ~~l~~ymphocyte, 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 (Serum only, 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 diffuse myeloma-related osteopenia	
Number of extramedullary plasmacytomas [0, >=1]	
Presence of evaluable bone marrow assessment (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 and high-risk cytogenetic abnormalities (del17p, t(4;14), t(14;16), amplification 1q)	
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 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)	
Stratification factors (Prior PI exposure, dara-free interval)	

4.2. Disposition Information

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

- Subjects randomized but not treated with study medication
- Subjects received study treatment
- Subjects didn't receive study treatment and the reasons
- Subject ongoing
- Subjects completed the study treatment
- Subjects discontinued study treatment
- Reasons for discontinuation of study treatment
- Subjects completed the study

- Subjects discontinued the study participation prematurely
- Reasons for discontinuation of study

Listings of subjects will be provided for the following category:

- Subjects who discontinued study treatment
- Subjects who were randomized but never treated
- Subjects who terminated study participation prematurely

4.3. Treatment Compliance

No treatment compliance will be summarized.

4.4. Extent of Exposure

The maximum number of treatment cycles received for each subject and exposure to each of the study treatments 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 subjects with a dose modification and reasons will be summarized by treatment group and cycle.

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 drug and summarized accordingly. Additionally, the dara-SC dose intensity will be summarized for cycles 1-2, cycles 3-6, and cycles >=7.

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 infusions/medications) will be calculated for each study treatment and summarized by treatment group using descriptive statistics.

4.5. 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.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy the inclusion/exclusion criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

A list of subjects with major protocol deviations including subject ID, type of deviation, and reasons for deviation will be provided.

4.6. Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHO-DD) (September 2017) version. Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study treatment. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study treatment, including those that started before and continue on after the first dose of study treatment.

4.6.1. Prior Exposure to Multiple Myeloma Therapies

A summary of prior exposure to multiple myeloma therapies (systemic therapy, stem cell transplant, radiotherapy, or cancer-related surgery/procedure) will be provided. Specifically, the number of prior lines of therapy will be calculated and summarized by the following categories: 1, 2, >2 through frequency and descriptive statistics. Additionally, the summary of prior systemic therapies will be presented by therapy class and therapy. Summaries will be provided for time since last Dara-IV exposure to randomization, and time since last proteasome inhibitor exposure to randomization.

The therapy classes include proteasome inhibitors (PI), immunomodulatory drugs (IMiD), anti-CD38 antibody, steroids, alkylating agents and anthracyclines. Therapies included in the PI class are: bortezomib, carfilzomib, oprozomib, marizomib, and ixazomib; IMiD class: lenalidomide, pomalidomide, and thalidomide; anti-CD38 antibody class: daratumumab, and isatuximab, and steroids class: dexamethasone and prednisone, among others.

The number of subjects who had prior exposure to multiple therapy classes (e.g., PI + IMiD) or multiple therapies (e.g., bortezomib + lenalidomide) may be provided, if the number of subjects who exposed to those therapy classes or therapies is sufficient.

4.6.2. Refractory Disease

Relapsed disease is defined as an initial response to previous treatment, followed by confirmed PD by IMWG criteria >60 days after cessation of treatment.

Refractory disease is defined as <25% reduction in M-protein or confirmed PD by IMWG criteria during previous treatment or =<60 days after cessation of treatment.

Refractory status (yes, no) to a prior MM therapy class (i.e., PI/IMiD) or prior MM therapy (e.g., bortezomib, thalidomide, or Dara-IV) will be based on refractory status to each line of prior regimen, or each specific medication/therapy collected on prior systemic therapy CRF page. For each subject, refractory to each therapy class/therapy refers to refractory to his/her most recent therapy-containing line.

The number and percentage of subjects' refractory status to PI, IMiD, or anti-CD38 antibody therapy class will be summarized by the following categories: none, PI only (PI-refractory but not IMiD- and anti-CD38 antibody-refractory), IMiD only (IMiD-refractory only but not PI- and anti-CD38 antibody-refractory), anti-CD38 antibody only (anti-CD38 antibody-refractory only but not PI- and IMiD-refractory), both PI and IMiD. Refractory to specific prior multiple myeloma therapy, such as bortezomib, carfilzomib, ixazomib, lenalidomide, pomalidomide, thalidomide, daratumumab or isatuximab, and the relevant combinations of the aforementioned therapies will be provided separately.

The incidence of subjects who are refractory to their last line of therapy will be reported.

4.6.3. Concomitant Medications

Summaries of concomitant medications will be presented by therapeutic class, pharmacologic class, and drug name for each treatment group. The proportion of subjects who receive each concomitant medication will be summarized as well as the proportion of subjects who receive at least 1 concomitant medication. In addition, concomitant medications of special interest will be presented. These include pre-infusion medication, post-infusion medication, growth factor use, and systemic steroids use.

4.7. Subsequent Antimyeloma Therapy

The total number of subjects who received subsequent antimyeloma therapy will be reported for each treatment group. A summary of subsequent antimyeloma therapy will be presented by therapeutic class, pharmacologic class and drug name, coded using the WHO-DD (September 2017) version.

In addition, for subjects who received subsequent antimyeloma therapy, their best response to the first subsequent antimyeloma therapy will be summarized.

5. EFFICACY

Efficacy assessment will be performed by sponsor using a computerized algorithm, following the IMWG criteria. Detailed rules for response/PD assessment will be provided in a separate document. As a sensitivity analysis, investigator assessment of response and disease progression using the IMWG response criteria will also be summarized.

5.1. Analysis Specifications

5.1.1. Level of Significance

All statistical hypothesis tests will be based on 1-sided test at significance level of 0.05. All interval estimations will be reported using 2-sided 90% CI.

5.1.2. Data Handling Rules

5.2. Primary Endpoint(s)

The primary efficacy endpoint is VGPR or better response rate according to the IMWG criteria.

5.2.1. Definition

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

5.2.2. Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 4 components:

- Population: subjects with relapsed refractory multiple myeloma who were previously exposed to daratumumab intravenous (Dara-IV);
- Variable: VGPR or better response (see definition above);
- Intercurrent events: Subsequent anti-myeloma treatment and treatment discontinuation;
- Population-level summary: The Mantel-Haenszel estimate of common odds ratio for VGPR or better between the two treatment groups

Two strategies are used to account for the intercurrent events.

- Disease assessment after subsequent therapy will be ignored for a subject who started subsequent anti-myeloma therapy (while-on-treatment strategy).
- Treatment discontinuation will also be ignored (treatment policy strategy).

Sensitivity and supplementary analysis for the primary endpoint rate of VGPR or better are described in the analysis methods below.

5.2.3. Analysis Methods

The response rate of VGPR or better will be calculated based on a computerized algorithm for each of the treatment group. The analysis of the response rate will be based on the ITT population. The corresponding 90% exact CI will be provided.

The rate of VGPR or better will be compared between the DKd group and the Kd group using the stratified Cochran-Mantel-Haenszel(CMH) test. The stratification factors are prior PI exposure and daratumumab-free interval (3-6 months, >6 months) at randomization. The Mantel-Haenszel estimate of common odds ratio, along with its 2-sided 90% confidence interval and the p-value from the CMH test will be reported.

A sensitivity analysis, in which VGPR or better response is based on investigator assessment according to the IMWG response criteria, will be performed in a similar manner as described above.

In addition, as a supplementary analysis, both the response rate based on the computer algorithm and the response rate based on the investigator assessment will be analyzed for the response-evaluable population.

5.3. Secondary Endpoints

5.3.1. ORR

5.3.1.1. Definition

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.

5.3.1.2. Analysis Methods

ORR will be calculated for the response-evaluable population and the ITT population. ORR will be analyzed using the same mothed for the primary endpoint.

5.3.2. CR or better

5.3.2.1. 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.

5.3.2.2. Analysis Methods

The rate of CR or better will be analyzed using the same method for the primary endpoint.

In addition to VGPR or better, ORR, and CR or better, summaries for the following response categories based on the computerize algorithm will be presented by treatment group: stringent complete response (sCR), complete response (CR), very good partial response (VGPR), Clinical benefit (including sCR, CR, VGPR, PR, and MR), partial response (PR), minimal response (MR), stable disease (SD), progressive disease (PD), and not evaluable (NE). The corresponding 90% exact CI for each response category will be provided.

5.3.3. PFS

5.3.3.1. Definition

PFS is defined as the duration from the date of randomization to either progressive disease (PD) or death, whichever comes first. Disease progression will be determined according to the International Myeloma Working Group (IMWG) criteria [1, 2]. 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 without PD will be censored at the last disease assessment. 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. PFS survival is calculated in months as follows:

PFS = (date of PD/death or censoring – date of randomization + 1) / (365.25/12).

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*	• PFS event	• Date of death
• No postbaseline disease assessment	• Censored	• Date of randomization
• Other, such as: • Withdrawal of consent to study participation • Lost to follow-up	• Censored	• Date of last disease assessment prior to withdrawal of consent to study participation or lost to follow-up.

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

5.3.3.2. Analysis Methods

PFS will be calculated based on the computer algorithm and analyzed 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 90% 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.

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 90% 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 are prior PI exposure and daratumumab-free interval (3-6 months, >6 months) at randomization.

In addition, PFS rate at 12, 18 and 24 months with 90% CI will be estimated by Kaplan-Meier method and reported for each treatment group.

A sensitivity analysis of PFS, in which progressive disease is based on investigator assessment according to the IMWG response criteria, may be performed in a similar manner as described above.

5.3.4. OS

5.3.4.1. Definition

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. Overall survival is calculated in months as follows:

OS = (date of death or censoring – date of randomization + 1) / (365.25/12).

5.3.4.2. Analysis Methods

The OS will be analyzed using the same method for the PFS.

5.3.5. MRD

Bone marrow aspirates will be collected for MRD central testing (NGS) at time of suspected CR/sCR and for participants who achieve CR, have not progressed, and remain on the study, additional bone marrow aspirate will be obtained at 12, 18, and 24 months post Cycle 1 Day 1 (±1 month). For this study, three threshold values $<10^{-6}$, $<10^{-5}$, and $<10^{-4}$, will be used to evaluate MRD negativity status and its predictive value for PFS. The MRD data will be analyzed when sufficient data is available.

5.3.5.1. Definition

MRD negativity rate, defined as the proportion of subjects who have MRD negative status at 10^{-5} by bone marrow aspirate after the date of randomization and prior to progressive disease (PD) or subsequent anti-myeloma therapy. MRD positive subjects include subjects of which all tested samples were found to be MRD positive or ambiguous. Subjects with missing or unevaluable MRD status will be considered as MRD positive. Subjects who have achieved MRD negative status on or after PD or switch to subsequent anti-myeloma therapy before PD, will not be considered MRD negative in the analysis.

Durable MRD negativity rate is defined as the proportion of subjects who have achieved MRD negative status at 10^{-5} at 2 bone marrow aspirate examinations that are a minimum of 1 year apart, without any examination showing MRD positive status in between.

5.3.5.2. 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.

The overall MRD negativity rate will be calculated for each treatment group based on the ITT analysis set. The corresponding 90% 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 90% 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 are prior PI exposure and daratumumab-free interval (3-6 months, >6 months).

Durable MRD-negative rate at 10^{-5} will be similarly. MRD rate at $<10^{-6}$ and $<10^{-4}$ will be summarized as well.

5.3.6. Time to Subsequent Antimyeloma Treatment

5.3.6.1. Definition

Time to subsequent antimyeloma treatment is defined as the time from randomization to the start of subsequent antimyeloma treatment. Death due to PD without the start of any subsequent therapy will be considered as event. Subjects who withdrew consent to study or are lost to follow-up or die due to causes other than PD will be censored at the date of death or the last date known to be alive.

5.3.6.2. Analysis Methods

Analysis of time to subsequent antimyeloma treatment will be based on the ITT population. The Kaplan-Meier method will be used to estimate the distribution of time to subsequent antimyeloma treatment for the ITT population. Median time to subsequent antimyeloma treatment with 90% CI will be tabulated for each treatment group. In addition, A Kaplan-Meier curve for time to subsequent antimyeloma treatment will be plotted. The hazards ratio and its 90% CI will be obtained through a stratified Cox's regression model with treatment as the sole explanatory variable. Treatment comparison will be made using log-rank test stratified by randomization factor.

5.4. Other Endpoints

5.4.1. Clinical benefit rate

Clinical benefit rate is defined as the proportion of subjects with best response of MR or better (including sCR, CR, VGPR, PR, and MR) 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.

5.4.1.1. Analysis Methods

The corresponding 90% exact CI for clinical benefit rate will be provided for the ITT population. For durable MRD negativity rate, the 90% exact CI will be provided by treatment group for subjects who have achieved MRD negative status.

In addition, summaries for the following response categories based on the computerize algorithm will be presented by treatment group for the ITT population: stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), progressive disease (PD), and not evaluable (NE). The corresponding 90% exact CI for each response category will be provided.

5.4.2. M-Protein Response

Best M-protein response in serum and urine and best response in serum dFLC will be summarized for response-evaluable set.

6. SAFETY

All safety analyses will be based on the safety analysis set based on actual treatment received, unless otherwise specified.

For all continuous safety variables, descriptive statistics will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

6.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version (20.0).

Any AE occurring at or after the initial administration of study treatment through the day of last dose plus 30 days or prior to the start of subsequent antimyeloma therapy, whichever is earlier, or the follow-up AE (linked to an existing TEAE) with onset date and time beyond 30 days after the last dose of study treatment but prior to the start of subsequent therapy is considered to be treatment emergent. If the event occurs on the day of the initial administration of study treatment, and either event time or time of administration 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 administration of study treatment based on partial onset date or resolution date. If the event is considered drug-related (very likely, probably, or possibly related) regardless of the start date of the event; or the event that is present at baseline but worsens in toxicity grade or is subsequently considered drug-related by the investigator, then this event will be assumed to be treatment emergent.

All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summary tables will be provided for:

- TEAEs by overall and subgroup (age, sex, race, renal abnormality, hepatic abnormality)
- Toxicity Grade 3 or 4 TEAEs
- Serious TEAEs (SAEs)
- Study drug-related TEAEs and Serious TEAEs
- TEAEs leading to discontinuation of study treatment
- TEAEs by severity, toxicity grade
- TEAEs by relationship to study drug

- TEAEs leading to treatment interruption/treatment modification
- TEAEs with outcome of death
- Daratumumab infusion related reactions (DKd arm only)
- Daratumumab injection site related reactions (DKd arm only)
- Time to onset of infusion related reactions

In addition to the summary tables, listings will be provided for subjects who:

- Had TEAEs
- Had Serious TEAEs
- Had TEAEs leading to discontinuation of study drug/termination of study participation
- TEAE with outcome of death
- Had infusion related reactions or injection site related reactions
- Had TEAE grade 3 or higher

Deaths will be displayed by actual treatment received. Frequencies for the following parameters will be included in the summary table:

- Number of subjects who died
- Primary Cause of death
- Relationship to study treatment (yes/no)

Summary table will also be presented for subjects who died within 30 days of last study treatment dose and within 60 days of first study treatment dose, respectively.

A listing of subjects who died will be provided.

6.2. Adverse Events of Special Interest

6.2.1. Infections and infestations

Infections and infestations refer to adverse events with MedDRA 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. In addition, incidences of Grade 3 or 4 treatment-emergent infections and infestation will be summarized by MedDRA preferred term and treatment cycle. A summary of treatment-emergent opportunistic infections and a listing of treatment-emergent HBV reactivation will be provided as well.

6.2.2. Second Primary Malignancies

A listing of subjects who reported second primary malignancies during the study will be provided. The listing will include subject ID, treatment group, diagnosis, stud day of diagnosis, recurrence of a prior existing malignancy (yes, no) and initial diagnosis date etc. collected in new

malignancies CRF page. In addition, prior exposure to multiple myeloma therapies, treatment related to second primary malignancy, cumulative study treatment exposure, and subject survival status information will also be presented in the listing.

6.2.3. Cardiac Events

Treatment-emergent cardiac events refer to events identified by cardiac arrhythmias (SMQ), cardiac failure (SMQ), and ischemic heart disease (SMQ). A summary of number of subjects with 1 or more toxicity Grade 3 or 4 treatment-emergent cardiac events by MedDRA SMQ, preferred term and relationship to treatment will be provided. In addition, incidences of Grade 3 or 4 treatment-emergent cardiac events will be summarized by MedDRA SMQ, preferred term and treatment cycle.

6.3. Clinical Laboratory Tests

All clinical laboratory tests will be displayed for the subjects included in the safety analysis set.

Descriptive statistics will be presented for all chemistry and hematology tests at scheduled time points.

Change/percent change from baseline will be summarized for chemistry and hematology tests and displayed by treatment group.

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 summaries from baseline laboratory value to the worst on-treatment grade in chemistry and hematology tests with NCI-CTCAE, version [5.0] will be presented.

6.4. Vital Signs and Physical Examination Findings

Post baseline vital signs and physical examination findings were collected only as clinically indicated and therefore will not be summarized.

6.5. Electrocardiogram

The interpretation of the ECGs (normal, abnormal, clinically significant abnormal) as determined by a qualified physician (investigator or qualified designee) will be displayed by the number and percentage of subjects in each of the categories. Summary of the findings and shift from baseline to end of the treatment will be provided.

6.6. Cardiac Assessment/Echocardiogram or MUGA

The interpretation of the cardiac assessment (normal, abnormal, clinically significant abnormal) will be displayed by the number and percentage of subjects in each of the categories. Summary of the findings and shift from baseline to end of the treatment will be provided. Change from baseline in LVEF will be summarized over time.

6.7. Other Safety Parameters

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 and post-baseline time points. 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.

7. PHARMACOKINETICS/PHARMACODYNAMICS

Descriptive statistics (e.g., number of observations, mean, SD, median, and range) will be used to summarize pharmacokinetics data. For in-text tables, mean (SD) and N will be provided. In addition, coefficient variation (%CV) and geometric mean might be provided in the pharmacokinetic concentration summary.

7.1. Pharmacokinetics

7.1.1. Sampling Timepoints

For subjects assigned to the Kd group, blood samples to assess serum concentration of daratumumab will be obtained at Day 1 of Cycles 1 and 3. For subjects assigned to DKd, samples to assess serum concentration of dara-SC will be obtained at Day 1 of Cycles 1, 3, and 7, and Post-Treatment Week 8. On a daratumumab dosing day, blood samples need to be collected before (up to 2 hours but not after) the start of drug administration.

7.1.2. Pharmacokinetic Parameters

Descriptive statistics will be used to summarize pharmacokinetic parameters. The pharmacokinetic parameters that will be estimated include observed trough concentrations by visit and treatment.

7.1.3. Analysis Methods

Pharmacokinetic data from subjects in the pharmacokinetic analysis set will be presented at each sampling 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 dara-SC serum concentrations at each sampling time point. Line plot of mean (±SD) daratumumab serum trough concentrations over time will be provided.

7.2. Immune Response

7.2.1. Sampling Timepoints

For subjects in the Kd group, samples to assess the generation of antibodies to daratumumab (immunogenicity) will be obtained from all subjects in the Kd group at Cycle 1 Day 1. For subjects in the DKd group, samples for daratumumab immunogenicity assessments will be obtained at Day 1 of Cycles 1 and 7 predose and at Week 8 after the end of the study treatment.

For the rHuPH20 immunogenicity assessments, plasma samples will be obtained at Day 1 of Cycles 1 and 7 predose and at Week 8 after the end of the study treatment for subjects in the DKd group.

In addition, when an IRR occurs associated with the second or later daratumumab administration, 2 separate blood samples should be obtained, if possible, for determination of serum anti-daratumumab antibodies (and associated serum daratumumab concentration) and anti-rHuPH20 antibodies

7.2.2. Analysis Methods

The incidence of anti-daratumumab antibodies will be summarized by treatment group for all subjects who have appropriate samples for detection of the antibodies. The incidence of anti-rHuPH20 antibodies will be summarized for all subjects who receive at least one dose of Dara-SC and have appropriate plasma samples for detection of antibodies to rHuPH20 (at least 1 sample after the start of the first dose of Dara-SC). In addition, subjects who are positive for anti-daratumumab antibodies or anti rHuPH20 antibodies will be listed.

7.3. Pharmacodynamics

If sufficient data are available, other pharmacokinetic/pharmacodynamic (PK/PD) modeling may be performed, including exploring the relationship between serum concentrations of dara-SC and clinical efficacy/safety endpoints. If PK/PD analysis is conducted, details and results of the analysis will be presented in a separate report.

8. BIOMARKERS

Biomarker studies are designed to identify markers predictive of response (or resistance) to the study drug. 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 response rates in risk-stratified multiple myeloma subpopulations.

8.1. Minimal Residual Disease (MRD)

Bone marrow aspirates will be collected at baseline from all subjects, 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, and 3 landmark time points: 12, 18, and 24 months (within the window of +/- 1 month) after first dose of study treatment.

8.1.2. Analysis Methods

Details on MRD negativity rate analyses are described in efficacy section.

In addition, exploratory landmark analyses may be conducted to correlate MRD negativity results (as either binary or continuous values) with responses (CR or better rate) or 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.

8.2. Molecular Subtyping

8.2.1. Cytogenetic Risk Groups

A portion of the bone marrow aspirate samples collected will be utilized for translocation/mutation/genomic analysis to assess whether specific molecular subtypes having chromosomal aberrations del17p, t(4;14), t(14;16), and optionally Amplification 1q are responsive to dara-SC treatment.

8.2.2. Molecular Risk Subgroup Analysis

To determine if the study drug will lead to improved clinical responses in standard as well as high-risk molecular subgroups, the following exploratory analysis may be conducted by using the similar analysis methods specified in efficacy section.

- To evaluate VGPR or better, ORR, and PFS for subjects in high-risk molecular subgroup and subjects with the specific molecular subtypes.
- To evaluate MRD negativity rate for subjects in standard-risk and high-risk molecular subgroups.
- To evaluate PFS and OS for subjects in high-risk molecular subgroup and subjects with specific molecular subtyping.

Subgroup exploratory analysis of VGPR, ORR, and PFS by molecular risk within treatment group, as well as between molecular subgroups across treatment group may be conducted.

9. MEDICAL RESOURCE UTILIAZTION

Medical resource utilization 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, types of adverse events if involved, blood product transfusions, antibiotic use, and other concomitant medication will be calculated and tabulated

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