Janssen Research & Development

Statistical Analysis Plan

A Phase 3 Randomized, Multicenter Study of Subcutaneous Daratumumab Versus Active Monitoring in Subjects with High-risk Smoldering Multiple Myeloma

Protocol 54767414SMM3001; 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

SAP version	Issue date
Original SAP	18 April 2018
Amendment 1	November 2, 2020
Amendment 2	December 16, 2020

Summary of the major changes in SAP Amendment 2:

a) Removed interim superiority analysis per the feedback from FDA. Only interim futility analysis will be performed,

b) Revised the definition of duration of response to include death due to any cause.

c) Added a censoring rule for subjects with missing visits for PFS2 as an additional supplemental analysis

Summary of the major changes in SAP Amendment 1::

a) More details were provided for the spending function for ORR, PFS2 and OS in Section 5.1.1.

b) Description of the primary estimand was added in Section 5.2.

c) Supplemental analyses for the primary endpoint and key secondary endpoints were added in Sections 5.2.3 and 5.3.

d) ISS staging subgroups and risk category subgroups based on Mayo 2018 risk criteria were added in Section 2.4.

e) An imputation rule was added for partial subsequent anticancer therapy start date.

f) Added additional exploratory analysis to support HEMAR (Attachment 1).

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase

AST	aspartate aminotransferase
CI	Confidence interval
Cmax	maximum observed concentration
Cmin	minimum observed concentration
CR	Complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
DOR	Duration of response
DPS	data presentation specification
DRd	Daratumumab, lenalidomide, dexamethasone
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
FISH	Fluorescence in situ hybridization
IA	Interim analysis
IDMC	Independent Data Monitoring Committee
IMiD	immunomodulatory
IMWG	International Myeloma Working Group
ISS	International Staging System
ITT	intent-to-treat
IWRS	interactive web response system
LDH	lactate dehydrogenase
LLOQ	lower limits of quantification
MedDRA	Medical Dictionary for Regulatory Activities
M-protein	monoclonal protein, monoclonal paraprotein
MR	Minimal response
MRD	Minimal residual disease
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse
NGS	Next generation sequencing
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PI	proteasome inhibitor
PR	Partial response
Rd	Lenalidomide, dexamethasone
SAE	serious adverse event
SAP	statistical analysis plan
sCR	Stringent complete response
SD	Stable disease
SOC	system organ class
SPEP	serum protein electrophoresis
TEAEs	treatment-emergent adverse events
TOR	Time to response
TTP	Time to disease progression
UPEP	urine protein electrophoresis
VGPR	Very good partial response
WBC	White blood cells

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the planned analyses for study JNJ-54767414SMM3001.

1.1. Trial Objectives

The primary objective of this study is to determine whether treatment with daratumumab SC prolongs progression-free survival (PFS) compared with active monitoring in subjects with high-risk SMM.

The secondary objectives are as follows:

- To demonstrate additional clinical benefit (ORR, duration of response, OS, etc) for subjects with high-risk SMM treated with daratumumab compared with active monitoring
- To assess the safety profile of daratumumab in subjects with high-risk SMM
- To assess the clinical characteristics of symptomatic MM following progression of disease after therapy with daratumumab
- To evaluate the pharmacokinetics and immunogenicity of daratumumab administered SC in subjects with high-risk SMM
- To evaluate the immunogenicity of recombinant human hyaluronidase (rHuPH20)
- To evaluate the effect of treatment with daratumumab on patient-reported outcomes

The two exploratory objectives are as follows:

- To investigate clinical efficacy of daratumumab in high-risk subjects with genetic modifications (del17p, t(4:14), 1q gain, or other high-risk molecular subtypes)
- To explore biomarkers of response or resistance to daratumumab, including immunophenotypes and expression of MM markers (ie, CD38)

1.2. Trial Design

This is a Phase 3, randomized, open-label, 2-arm, multicenter study to evaluate the efficacy and safety of daratumumab subcutaneous (SC) administration versus active monitoring in subjects with high-risk SMM. The study population will consist of subjects at least 18 years of age with diagnosis of SMM for ≤5 years with ECOG performance status score of 0 or 1 and measurable disease, with measurable disease being defined as serum M protein ≥10 g/L or urine M protein ≥200 mg/24 hours or involved serum FLC ≥100 mg/L and abnormal serum FLC ratio. Subjects with multiple myeloma as defined by SLiM-CRAB (Ref IMWG 2014); primary systemic AL (immunoglobulin light chain) amyloidosis; prior exposure to daratumumab or other anti-CD38 therapies, approved or investigational treatments for SMM or MM, investigational drug (including investigational vaccines) or invasive investigational medical device for any indication within 4

weeks or 5 half-lives, ongoing treatment with corticosteroids with a dose >10 mg prednisone or equivalent per day at the time of randomization; or significant steroid exposure in the year prior to randomization; treatment for a malignancy (other than SMM) within 3 years will be excluded (refer to protocol for detailed inclusion/exclusion criteria).

Approximately 360 subjects will be randomized in a 1:1 ratio to either receive daratumumab SC or undergo active monitoring. The randomization will be balanced by using randomly permuted blocks and will be stratified by the number of risk factors for progression (<3 vs ≥3).

This study includes three Phases: a Screening Phase, an Active Monitoring Phase or a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 28 days before randomization. The Active Monitoring Phase and Treatment Phase will be 36 months in duration. Active monitoring cycles and treatment cycles are 4 weeks in length. The Treatment Phase, which consists of cycles of approximately 28 days, will extend from Cycle 1, Day 1 until the subject has completed 36 months of daratumumab or until confirmed PD. The Follow-up Phase will begin once a subject completes or discontinues Active Monitoring (Arm A) or study treatment (Arm B) and completes the End-of Active Monitoring Visit (Arm A) or End-of-Treatment Visit (Arm B). The Follow-up Phase for each subject will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first.

For subjects randomized to daratumumab, daratumumab will be administered weekly in Cycle 1 and 2, then every 2 weeks for Cycle 3 to Cycle 6, and every 4 weeks for Cycle 7 to Cycle 39, until confirmed PD, study treatment discontinuation or withdrawal from the study, whichever occurs first. Daratumumab 1800 mg will be administered by SC injection through a syringe by a manual push over approximately 5 minutes. Doses will be administered at alternating locations on the abdomen. Subjects will receive pre-dose and post-dose medications for prevention of infusion related reactions. All subjects in the daratumumab arm will be observed for at least 6 hours after the end of the SC injection during Cycle 1 Day 1 and, if deemed necessary by the investigator, after subsequent injections.

A schematic overview of the dosing schedule is presented as follows.

Daratumumab 1800 mg SC (for daratumumab arm):

- Cycles 1 and 2: Days 1, 8, 15, and 22 (QW)
- Cycle 3 to 6: Days 1 and 15 (Q2W)
- Cycles 7 to 39: Day 1 (Q4W)

Dose modification of daratumumab (increase or decrease) is not permitted. Dose delay is the primary method for managing daratumumab-related toxicities. Protocol-specified dose delays for daratumumab will be adjusted as necessary according to the treatment guidelines. Daratumumab may be delayed for up to 3 days, 7 days or 14 days during Cycles 1 and 2, Cycles 3 to 6 and Cycles 7+, respectively, to allow for recovery from toxicity. If daratumumab administration does not commence within the prespecified window of the scheduled administration date, then the dose will be considered a missed dose. A missed dose will not be made up. Doses of daratumumab in Cycles

7+ may be delayed up to 4 weeks. If a dose is delayed, then the dates of all subsequent doses must be adjusted. Any adverse event deemed to be related to daratumumab that requires a dose hold of more than 28 days will result in permanent discontinuation of daratumumab. Subjects missing 3 or more consecutive planned doses of daratumumab for reasons other than toxicity should be withdrawn from treatment, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon. Subjects in daratumumab treatment group will be treated until disease progression, unacceptable toxicity, or other reasons as listed in Section 10.2 of protocol.

This study will use the IMWG consensus recommendations for MM treatment response criteria (Durie 2007, Rajkumar 2011, Kumar 2016).[1,2,3] For quantitative immunoglobulin (QIg) at baseline, M-protein, and immunofixation measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory. Disease progression will be measured according to the published international uniform diagnostic criteria for MM established by the IMWG (Rajkumar 2014). Progression evaluations for the primary endpoint/final analysis will be based on IRC review, in a blinded fashion, to objectively and consistently implement the IMWG diagnostic criteria for MM.

Disease evaluation will be performed by a central laboratory until disease progression. Disease evaluation must be performed every 12 weeks on the scheduled assessment day (±7 days). If treatment has been delayed for any reason, the disease evaluation must be performed according to scheduled dates, regardless of any changes to the dosing regimen. For subjects who discontinue study treatment before disease progression, disease evaluations should continue to be performed as schedules, until confirmed disease progression, death, withdrawal of consent for study participation, or the end of study, whichever occurs first. Disease evaluations scheduled for treatment days should be collected before study treatment is administered.

Safety evaluations in this study will include adverse event monitoring, physical examinations, electrocardiogram monitoring (ECGs), SC injection-site evaluations, clinical laboratory parameters (hematology and chemistry), and Eastern Cooperative Oncology Group (ECOG) performance status. Blood pressure and temperature measurements will be collected as clinically indicated,

Blood samples will be drawn for assessment of serum concentration (pharmacokinetics) of daratumumab and the generation of antibodies to daratumumab and rHuPH20 (immunogenicity) from all subjects in the daratumumab group at Day 1 and Day 4 of Cycle 1, Day 1 and Day 4 of Cycle 3, Day 1 of Cycle 5, 7, 12 and 24, End-of-Treatment Visit, and Post-Treatment Week 8. Bone marrow aspirates will be collected to monitor minimal residual disease (MRD) in those subjects who attain a CR/sCR.

The primary endpoint is PFS. The primary analysis of PFS will be performed after approximately 165 PFS events have occurred.

There is one predetermined interim analysis. An Independent Data Monitoring Committee (IDMC) will be established to review data at the interim analysis prior to the primary endpoint analysis.

The interim analysis will occur after approximately 99 (60% of targeted events) PFS events have occurred. This is expected to occur approximately 8 months after the last subject has been randomized. In addition to the interim analysis, the IDMC will also review safety data at regular intervals during the study (i.e., after the first 60 subjects have been randomized and treated or observed for at least 8 weeks, a second safety review will occur 6 months after the first and thereafter every 12 months until primary analysis).

1.3. Statistical Hypotheses for Trial Objectives

The primary efficacy endpoint of this study is PFS. The null hypothesis is that there is no difference in PFS between daratumumab and active monitoring in subjects with high risk SMM.

The null hypotheses (H_o) of no difference between the two groups (daratumumab SC and active monitoring) will also be evaluated for the following secondary endpoints:

- ORR
- PFS2
- OS

These secondary hypotheses are to be tested in a sequential order as specified above. The details of the testing procedure are specified in Section 5.1.1.

1.4. Sample Size Justification

Approximately 360 subjects (180 per arm) will be randomized in the study. The sample size for this study is based on the alternative hypothesis of a 37.5% reduction in the risk of either progression or death (PFS). The sample size calculation assumes that the median PFS for Arm A (active monitoring) is 30 months. The longer projected median PFS compared to the published 24 months was chosen to account for the fact that ultra-high risk SMM subjects, who were included in earlier studies, are now considered to have symptomatic MM according to the updated IMWG criteria, and to account for the additional risk factors included to identify high-risk SMM for this study. Under the exponential distribution, this benefit translates to a prolongation in median PFS from 30 months to 48 months. One interim analysis for futility will take place at 60% of information. A total of 165 PFS events would provide a power of 85% to detect a reduction of 37.5% in the risk of either progression or death (hazard ratio (daratumumab vs. active monitoring) of 0.625) with a log-rank test, assuming a two-sided significance level of 5%. A 24-month accrual period and an additional 24-month follow-up are assumed.

1.5. Randomization and Blinding

Central randomization will be implemented in this study. Subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups. The randomization will be balanced by using randomly permuted blocks and will be stratified by the number of factors associated with progression to MM (<3 vs ≥ 3).

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

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

Dosing days may be adjusted to accommodate the schedule of the site or the subject, as shown in Table 1 below.

Table 1: Study Drug (Dara-SC) Administration Schedule

Cycle	Schedule	Day 1	Day 8	Day 15	Day 22
Cycle 1	Weekly	Day 1	Day 8 (±1d)	Day 15 (±1d)	Day 22 (±1d)
Cycle 2	Weekly	Day 1 (±3d)	Day 8 (±1d)	Day 15 (±1d)	Day 22 (±1d)
Cycles 3-6	Every 2 weeks	Day 1 (±3d)	–	Day 15 (±1d)	–
Cycles 7+	Every 4 weeks	Day 1 (±3d)	–	–	–

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 cycle is defined as the first scheduled dose date of the study treatment for that particular cycle, 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. If the end of treatment visit date is not available, then the end date is either the last dose date plus 28 days or subsequent anticancer therapy start date minus 1 day, whichever comes first.

In general, if data (eg, laboratory 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, the following by-week windowing rules as specified in Table 2 may be applied in the overtime data summary by study week.

Table 2: Visit Window by Week

Scheduled Study Visit	Time Interval (Week)	Time Interval (Study Day)	Target Time Point
Cycle 1 Day 1	Baseline	Day ≤ 1	1
Cycle 1 Day 8	Week 1	2 ≤ Day ≤ 9	8
Cycle 1 Day 15	Week 2	10 ≤ Day ≤ 16	15
Cycle 1 Day 22	Week 3	17 ≤ Day ≤ 23	22
Cycle 2 Day 1	Week 4	24 ≤ Day ≤ 30	29
Cycle 2 Day 8	Week 5	31 ≤ Day ≤ 37	36
Cycle 2 Day 15	Week 6	38 ≤ Day ≤ 44	43
Cycle 2 Day 22	Week 7	45 ≤ Day ≤ 51	50
Cycle 3 Day 1	Week 8	52 ≤ Day ≤ 58	57
Cycle 3 Day 15	Week 10	59 ≤ Day ≤ 72	71
Cycle 4 Day 1	Week 12	73 ≤ Day ≤ 88	85
Cycle 4 Day 15	Week 14	89 ≤ Day ≤ 100	99
Cycle 5 Day 1	Week 16	101 ≤ Day ≤ 116	113

Cycle 5 Day 15	Week 18	117 ≤ Day ≤ 128	127
Cycle 6 Day 1	Week 20	129 ≤ Day ≤ 144	141
Cycle 6 Day 15	Week 22	145 ≤ Day ≤ 156	155
Cycle 7 Day 1	Week 24	157 ≤ Day ≤ 172	169
Cycle 8 Day 1	Week 28	173 ≤ Day ≤ 200	197
Cycle 9 Day 1	Week 32	201 ≤ Day ≤ 228	225
Cycle 10 Day 1	Week 36	229 ≤ Day ≤ 256	253
… …	…	…	…
Cycle X Day 1	Week 4*(X-1)	(X-1)*28 – 23 ≤ Day ≤ (X-1)*28 + 4	(X-1)*28 + 1

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)

2.3.1.1. Primary Efficacy Analysis Set

Intent-to-treat (ITT) analysis set: defined as all subjects randomized into the study. This analysis set will be used for summary of study populations, analyses of disposition, demographic, baseline disease characteristics, and analyses of efficacy endpoints. All subjects in ITT analysis set will be analyzed according to their randomized treatment group, regardless of the actual treatment received.

2.3.2. Safety Analysis Set

Safety analysis set: defined as all randomized subjects for subjects randomized to active monitoring or all randomized subjects who received at least one dose of daratumumab for subjects randomized to daratumumab. This analysis set will be used for all safety analyses and analyses of exposure. All subjects in safety analysis set will be analyzed according to the actual treatment that they received.

2.3.3. Pharmacokinetics Analysis Set

Pharmacokinetics analysis set: defined as subjects who received at least 1 administration of daratumumab and have at least 1 pharmacokinetics sample concentration value after the first injection. All pharmacokinetic parameters will be analyzed based on the pharmacokinetics analysis set.

2.3.4. Immunogenicity Analysis Set

Immunogenicity-evaluable analysis set:

- Daratumumab immunogenicity-evaluable: Immunogenicity-evaluable analysis set for antibodies to daratumumab is defined as all subjects who receive at least one dose of Dara-SC and have appropriate serum samples for detection of anti- daratumumab antibodies.

- rHuPH20 immunogenicity-evaluable: Immunogenicity-evaluable analysis set for antibodies to rHuPH20 is defined as all subjects who receive at least one dose of Dara-SC and have appropriate plasma samples for detection of anti- rHuPH20 antibodies.

2.4. Definition of Subgroups

In general, subgroup analyses on the pre-specified subgroups in Table 3 will be performed for the primary efficacy endpoint PFS, and selected treatment-emergent adverse event (TEAE).

Table 3: Subgroup Analyses for Efficacy and Safety Endpoints

Subgroup	Definition	Analysis Type
Sex	Male, Female	E, S
Age	E: <65, ≥65 years S: < 65, 65 to < 75, and ≥ 75 years	E, S
Race	White, non-white	E, S
Region	Western EU + US, other	E, S
Weight	≤ 65 kg, > 65 to 85 kg, and >85 kg	E, S
Baseline renal function (GFR (mL/min/1.73m^2))[a]	S: Normal vs Abnormal	E, S
Baseline hepatic function	Normal, Impaired[b]	S
Risk factors associated with progression to MM[c]	< 3 vs >=3	E
ISS staging[d]	I, II, III	E
Cytogenetic risk at study entry(Yes/No)	Yes, if del(17p13), amp(1q21), t(4;14), or t(14;16) abnormality detected at baseline, No, if subjects tested for these probes but did not have any of the abnormalities	E
Mayo 2018 risk criteria[e]	Low, intermediate, or high	E
ECOG score	0 vs 1	E

E: efficacy (PFS); S: safety (TEAE)

[a] Normal: GFR (mL/min/1.73m2) ≥ 90

[b] Hepatic impairment status is classified into 4 levels per NCI Organ Dysfunction: normal (total bilirubin ≤ ULN and AST ≤ ULN); mild (total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5×ULN); moderate (1.5×ULN < total bilirubin ≤ 3×ULN); and severe (total bilirubin > 3×ULN). Impaired includes mild, moderate and severe.

[c] Risk factors: a. Serum M protein ≥30 g/L, b. IgA SMM, c. Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes (only IgA, IgM, and IgG should be considered in determination for immunoparesis; IgD

and IgE are not considered in this assessment), d. Serum involved: uninvolved FLC ratio ≥8 and <100, e. Clonal BMPCs >50% to <60% with measurable disease.
[d]ISS: Stage I: Serum beta-2 microglobulin < 3.5 mg/L and serum albumin ≥3.5 g/dL; Stage II: Not stage I or stage III; Stage III: Serum beta-2 microglobulin ≥ 5.5 mg/L
[e] Mayo 2018 risk criteria:
- Serum M protein > 2 g/dL
- I/U FLC ratio > 20
- BMPC > 20%

Patients with presence of
- 0 factors are considered as low risk
- 1 factor are considered as intermediate risk
- ⩾ 2 factors are considered as high risk

2.5. Study Day and Relative Day

Study day or relative day is defined as: date of assessment – first dosing date + 1 for any assessment done on or after first dosing date for subjects on the daratumumab arm and date of assessment – randomization date +1 for any assessment done on or after randomization for the active monitoring arm; otherwise, study day is defined as date of assessment – first dosing date/randomization date, depending on whether subject was in the daratumumab arm or the active monitoring arm. The first dose date is defined as the earliest date of non-zero dose of study drug.

2.6. Baseline

The baseline value is defined as the last non-missing measurement taken on or prior to the first dose administration of daratumumab (including time if time is available) for the treatment arm or randomization for the active monitoring arm.

2.7. Imputation of Missing Data

2.7.1. Adverse Event Start and End Date

Adverse Event Start Date

If the onset date of an adverse event is completely or partially missing, the following imputation rules will be used.

- When month and year are present, and the day is missing:
    - If the onset month and year are the same as the month and year of first dosing date, the day of first dosing or the day-component of the AE end date (possibly imputed) is imputed, whichever is earlier;
    - If the onset month and year are not the same as the month and year of first treatment with study drug, the first day of the month is imputed.
- When only a year of the onset date is present:
    - If the onset year is the same as the year of first treatment with study drug:

- If AE end date is available and is prior to first dosing date, the day and month of AE end date are imputed;
- Otherwise, the day and month of the first dosing date are imputed.

  - If the onset year is different from the year of first treatment with study drug, the 1st of January is imputed.

- If the onset date is completely missing, the first dosing date is imputed as the onset date.

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

Adverse Event End Date

If the end date of an adverse event is completely or partially missing, the following imputation rules will be used.

- If month and year are present and the day of the month is missing, the last day of the month is imputed.
- If only a year is present, the 31st of December is used.
- If date is completely missing, no imputation will be done.

After the imputation, if the imputed date is later than the date of death (if available), the date of death will be used as the imputed date.

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

2.7.2. Prior and Concomitant Medication/Therapy Start and End Date

For prior or concomitant medications/therapy, if the start or end date is completely missing, no imputation will be performed. If the start or end date is partially missing, the following imputation rules will be used.

- 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/therapy was taken prior to study start, and the imputed start date is after first dosing date, further adjust the imputed start date as the day prior to first dosing date; if the medication/therapy was taken after study start, and the imputed start date is prior to first dosing date, further adjust the imputed start date as first dosing date. Also adjust the imputed medication/therapy end date so that it is on or after first dosing date.

2.7.3. Smoldering Multiple Myeloma/First M-protein Detection Diagnosis Date

If the diagnosis date of smoldering multiple myeloma (SMM) or first M-protein detection date is completely missing, no imputation will be applied. If the diagnosis date or first M-protein detection date is partially missing, the following imputation rules will be applied:

- If only the day of the diagnosis date or first M-protein detection date is missing, impute day of diagnosis date or first M-protein detection date with 15;
- If both month and day of the diagnosis date or first M-protein detection date are missing, impute the month and day of the diagnosis date or first M-protein detection date with June 30.

2.7.4. Partial Subsequent Anticancer Therapy Start Date

If year or month of subsequent anticancer therapy start date is missing or no components of the start date are present, no imputation will be performed.

If only the day-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 last dosing date, the day of last dosing date or the day-component of the stop date of subsequent anticancer therapy is imputed, whichever is earlier.

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

After applying above adjusting method, if it results that the start date is after the subsequent anticancer therapy end date, the start date needs to be re-adjusted to be the same as the end date. No imputation will be applied for missing or partial subsequent anticancer therapy end date.

2.7.5. Partial PFS2 event date

If year or month is missing, no imputation will be applied. If year and month of progression date on subsequent Antimyeloma therapy are available and day is missing, please impute the day as 15, except,

1. If the Month & Year of Date of progression is the same as the Month & Year of the start date of first line, then the day is imputed as the day of the start date of first line.

2. If the Month & Year of Date of progression is the same as the Month & Year of start date of second line, then the day is imputed as minimum (15, (start day of the second line)).

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

There will be one interim analysis for futility which will occur when approximately 60% of the PFS events (99) have occurred. This is expected to occur approximately 8 months after the last subject has been randomized. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. The non-binding futility boundary at this interim analysis will be determined using the Kim-DeMets power spending function with parameter p=4.0. The beta spent at this analysis will be 0.0194.

4. SUBJECT INFORMATION

Analyses of subject disposition, demographic and baseline disease characteristics will be conducted on ITT analysis set. Analyses on extent of exposure will be conducted on safety analysis set. No statistical comparisons between the two treatment groups will be performed.

4.1. Demographics and Baseline Characteristics

The following subject demographics will be summarized using descriptive statistics:

- Age (continuous)
- Age category (< 65 years, 65 to < 75 years, and ≥ 75 years)
- Sex (male, female)
- Race (White, non-white)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Height (cm)
- Weight (kg) (< 45kg, ≤65 kg, > 65 kg to 85 kg, >85 kg, and > 120 kg)
- Baseline ECOG performance status (0, 1, >1)

The following baseline disease characteristics will be summarized using descriptive statistics:

- Type of myeloma by immunofixation or serum FLC assay (IgA, IgD, IgE, IgG, IgM, light chain, biclonal, or negative immunofixation)
- Type of measurable disease
- Plasma cell percentage by bone marrow aspirate or biopsy (< 10, 10 - <20, 20 - < 40, 40 - < 60, ≥ 60)
- Focal lesions
- Serum M-protein
- Serum FLC ratio
- Time from first evidence of MGUS to randomization (years)
- Time since initial diagnosis of SMM to randomization (years)
- Cytogenetic abnormality
- Renal function
- Hepatic function
- Mayo 2018 risk criteria
- ISS stage

In addition, a descriptive summary of selected hematology and chemistry laboratory analytes at baseline will be provided for each treatment group and overall. The baseline toxicity grade of selected laboratory analyte in hematology and chemistry panel will be summarized by treatment group using frequency. Central laboratory results will be used for this purpose whenever possible.

A summary of stratification factors used in the randomization (number of risk factors associated with progression to multiple myeloma) based on IWRS will be provided to evaluate whether randomization process was appropriately executed in the study.

4.2. Disposition Information

The number of subjects who enrolled, treated, and discontinued treatment with reasons of discontinuation reported on eCRF will be summarized. The number of subjects who discontinued from study with the reported reasons will also be presented.

Subject enrollment will also be summarized by country and site for intent-to-treat analysis set.

- A listing of subjects who discontinued study treatment including reasons for discontinuation will be provided. A similar listing will be provided for subjects who discontinued study participation.

4.3. Medical History

General medical history will be summarized by body system organ class and preferred term for each treatment group and overall.

4.4. Extent of Exposure

Extent of exposure to study drug will be summarized and presented on safety analysis set.

Treatment duration and the total number of treatment cycles will be summarized descriptively. The number and percentage of subjects treated within each cycle will also be summarized for the dara-SC subjects.

Treatment duration in months is derived as last non-zero daratumumab dosing date – first non-zero daratumumab dosing date + 1 and then divided by 365.25/12. The maximum number of treatment cycles for each subject is the largest cycle number in which a subject receives any non-zero dose of daratumumab.

Total dose (mg) for Dara group is defined as the sum of total dose (mg) administered and recorded on CRF at each visit. Descriptive statistics for the total daratumumab dose received and total number of injections will be provided.

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 and summarized for daratumumab treatment

group. Additionally, the daratumumab dose intensity will be summarized by Cycle during the treatment.

Relative dose intensity (%), which is defined as the ratio of total dose received and total planned dose (calculated as the planned dose level times the number of administered injections), will be calculated and summarized for each treatment group. Additionally, the relative dose intensity will be summarized by Cycle during the treatment.

The incidences of dose delays and corresponding reasons will be provided. The frequencies of actions planned prior to injection start and taken during injection will be summarized, together with reasons reported on eCRF. In addition, a summary of dose delays will also be provided by cycle during the treatment.

The treatment label identifier dispensed by each subject will be listed.
A separate listing including all daratumumab injection data will also be provided.

4.5. Protocol Deviations

Major protocol deviations will be summarized for ITT analysis set by the following types of deviation for each treatment group:

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

COVID-19 related major protocol deviations will be included in the summary as well. 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

Medications administered prior to the first dose date of study drug will be considered as prior medications. Concomitant medications are defined as those medications taken on or after the first dose date through 30 days after the last dose date, or the start date of subsequent therapy, whichever occurred first.

Prior medications will be summarized on ITT analysis set by therapeutic class, pharmacologic class, and preferred term.

Concomitant medications will be summarized on safety analysis set by therapeutic class, pharmacologic class, and preferred term.

Pre-injection medications and post-injection medications will also be summarized, respectively. Pre-injection medications will be grouped by therapeutic class, pharmacologic class, and Drug The incidence of pre-injection medications will be presented by the aforementioned groups and preferred terms. The similar summary will be provided for post-injection medications.

4.7. Subsequent Anti-myeloma Therapies

The total number of subjects who received subsequent anti-myeloma therapy for multiple myeloma will be reported for the ITT analysis set in each treatment group. A summary of subsequent anti-myeloma therapy will be presented by therapeutic class, pharmacologic class and preferred term.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

All hypotheses testing will be conducted at a 2-sided level of significance of 0.05. When required, 95% confidence intervals will be constructed.

The primary hypothesis is to be tested at the 0.05 significance level. If the primary endpoint of PFS is statistically significant at the primary analysis, the following secondary endpoints ordered below will be sequentially tested, each with an overall two-sided alpha of 0.05, by utilizing a hierarchical testing approach as proposed by Tang and Geller (1999)[5] that strongly controls Type I error rate:

- ORR
- PFS2
- OS

If the null hypothesis for any of the endpoints fails to be rejected at the primary analysis time point, then any of the subsequent endpoint(s) listed above will not be tested until the next analysis timepoint, if applicable. If the null hypothesis for an endpoint is rejected at a analysis time point, it will remain being rejected and will not be re-tested at the next analysis timepoint, if any. The significance level for each of the above secondary endpoints will be determined by the alpha-spending function specific to the endpoint. The ORR will only be tested at the primary analysis time point with a 2-sided level of significance of 0.05. For PFS2, and OS, alpha spending at the primary analysis time point and the final analysis point will be determined by a linear alpha spending function based on the observed number of the events at the time, i.e., the cumulative alpha to be spent will be the total alpha (0.05) multiplied by the proportion of the observed number of the events out of the total expected number of the events. For example, if 59% targeted PFS2 events are observed at the primary analysis, the corresponding alpha level will be 0.0295(2-sided)). A total of 134 PFS2 events and a total 107 OS events are expected at the final analysis.

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 of this study is PFS as assessed by the independent review committee (IRC), defined as the duration from the date of randomization to either progression to multiple myeloma, according to the IMWG diagnostic criteria for MM, or death due to any cause, whichever occurs first. Progression evaluations for the primary endpoint/final analysis were based on IRC review, in a blinded fashion, to objectively and consistently implement the IMWG diagnostic criteria for MM. Data from the central laboratory, local clonal plasma cell assessment and images performed at the study site (or designated facility) assessed by independent radiological review were provided to IRC for progressive disease identification. Subjects who start anti-cancer therapies for multiple myeloma without disease progression will be censored at the last disease assessment before the start of subsequent therapies. Subjects who withdraw consent from the study before disease progression will be censored at the last disease assessment before withdrawal of consent to study. Subjects who are lost to follow-up will be censored at the last disease assessment before the subjects were lost to follow-up. Subjects who have not progressed and are still alive at the clinical cut-off date for analysis will be censored at the last disease assessment. Subjects without any post-baseline disease assessment will be censored at 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	Date of Progression or Censoring	Outcome
No postbaseline disease assessment	Randomization	Censored
Disease progression prior to start of anti-cancer therapy for multiple myeloma	Earliest date that indicates disease progression	PFS event
Death prior to start of anti-cancer therapy for multiple myeloma	Date of death	PFS event
Other, such as: o Withdrawal of consent to study participation, o Lost to follow-up o Start of subsequent anti-cancer therapy prior to disease progression or death	Date of last disease assessment on or prior to withdrawal of consent to study participation, lost to follow-up, or start of subsequent anti-cancer therapy	Censored

Note, Subjects who were already diagnosed multiple myeloma per baseline central imaging review will be censored at randomization.

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 high-risk SMM;
- Variable: PFS (see definition above);
- Intercurrent events: 1) start of subsequent anti-myeloma treatment prior to disease progression or death, 2) treatment discontinuation, 3) study discontinuation;
- Population-level summary: Hazard ratio between the two treatment groups.

The strategies to account for the intercurrent events are,

- subjects will be censored at the last disease assessment prior to start of subsequent therapy (while on treatment strategy),
- Treatment discontinuation will be ignored (treatment policy strategy),
- Subjects will be censored at the last disease assessment prior to study discontinuation (hypothetical strategy).

5.2.3. Analysis Methods

Analysis of PFS(IRC) will be performed 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. The Kaplan-Meier curve for PFS will also be plotted by treatment group.

The PFS(IRC) distributions between the 2 treatment groups will be compared using the stratified log-rank test. The p-value from a stratified log-rank test will be reported. The treatment effect (hazard ratio) and its 2-sided 95% CI will be estimated using a stratified Cox regression model with treatment as the sole explanatory variable. The stratification factor used in the analyses will be the number of risk factors associated with progression to multiple myeloma (<3 vs ≥ 3).

In addition, landmark PFS rate with 95% CI will be estimated by Kaplan-Meier method and reported for each treatment group.

Sensitivity analyses for PFS(IRC) will include PFS(investigator), in which disease progression is determined based on investigator assessment per the IMWG criteria, and PFS(algorithm), in which disease progression is determined based on a validated computer algorithm adapted based on the 2014 IMWG diagnostic criteria for multiple myeloma (Rajkumar 2014)[4]. Details of the computerized algorithm is described in a separate document. Both PFS(investigator) and PFS(algorithm) will be analyzed in a similar manner as PFS(IRC).

Supplemental analyses for PFS(IRC) will include,

1) subjects who die due to COVID-19 will be censored, i.e. deaths due to COVID prior to start of subsequent anti-cancer therapy for MM will not be counted as PFS events;

2) subjects who start subsequent anti-cancer therapy for MM prior to disease progression or death will not be censored;

3) If the PFS event date and the latest date of scheduled disease evaluation immediately preceding the event differs more than 2.5 times the disease evaluation intervals (i.e. 30 weeks), which indicates that subject missed at least 2 consecutively scheduled disease evaluation (include hemoglobin, Creatinine, Creatinine clearance, serum FLC assessment, and corrected calcium only), then the event will not be considered as a PFS event in this sensitivity analysis. Instead, the subject will be censored at the date of last disease evaluation prior to the PFS event.

Additional analyses may be performed to assess the impact of COVID-19 as needed.

5.3. Secondary Endpoints

5.3.1. Time to Biochemical or SLiM-CRAB Progression (BOD-PFS)

5.3.1.1. Definition

Biochemical or SLiM-CRAB (BOD) progression is assessed based on the validated algorithm according to the definition of biochemical progression per the protocol and the IMWG criteria for diagnostic progression, i.e. either biochemical progression or PFS(algorithm) event. Time to biochemical or SLiM-CRAB (BOD) progression is defined as the time between the date of randomization and the date of first documented evidence of confirmed BOD progression, or death (due to any cause, prior to subsequent MM therapy), whichever occurs first. Subjects who have no postbaseline disease assessment, withdraw consent to study participation, start subsequent anti-cancer therapy prior to BOD progression or death, or who are lost to follow-up, will be censored. In addition, subjects who were already diagnosed multiple myeloma per baseline central imaging review will be censored at randomization.

5.3.1.2. Analysis Methods

The analysis of BOD-PFS will be similar to the analysis of the primary endpoint PFS described above.

5.3.2. Overall Response Rate (ORR)

5.3.2.1. Definition

Overall response rate (ORR) is defined as the proportion of subjects with a PR or better response based on the computerized algorithm, per the IMWG response criteria, before the start of subsequent anti-myeloma therapy.

5.3.2.2. Analysis Methods

The analysis of ORR will be performed on the ITT analysis set. The number and percentage of subjects in the following response categories will be tabulated by treatment group: sCR, CR, VGPR, PR, stable disease (SD), progressive disease (PD), and not evaluable (NE). The overall response (including sCR, CR, VGPR, or PR), VGPR or better (sCR, CR, or VGPR), and CR or better (sCR, or CR) will also be summarized. For each of the above categories, two-sided 95% Clopper-Pearson exact confidence interval (CI) will also be presented by treatment group.

Stratified CMH test will be used to test treatment difference in the proportion of subjects who achieved an overall response. The CMH estimate of odds ratio and its 95% confidence interval and p-value for testing treatment difference will be reported. The analysis will be stratified by number of risk factors associated with progression to multiple myeloma (<3 vs ≥3).

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

5.3.3. Complete Response Rate

5.3.3.1. Definition

Complete response (CR) rate is defined as, the proportion of subjects with a CR or sCR as defined by the IMWG response criteria.

5.3.3.2. Analysis Methods

The analysis of the response rate of CR or better will be similar to the analysis of ORR described above.

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

5.3.4. Time to first-line treatment for MM

5.3.4.1. Definition

Time to first-line treatment for MM is defined as, the time from the date of randomization to the start date of the first-line treatment for MM. Death due to PD without start of first-line treatment for MM will be considered as event. Subjects who withdraw consent to study or are lost to follow-

up or die due to causes other than disease progression or subjects without receiving subsequent anti-cancer therapy will be censored at date of death or the last date known to be alive. Subjects who were already diagnosed multiple myeloma per baseline central imaging review will be censored at randomization.

5.3.4.2. Analysis Methods

The analysis of the time to first-line treatment of MM will be similar to the analysis of primary endpoint PFS described above.

5.3.5. Progression-free Survival on First-line Therapy for MM

5.3.5.1. Definition

Progression-free survival on first-line therapy (PFS2) is defined as the time from randomization to progression on first-line therapy or death, whichever comes first. Disease progression will be based on investigator assessment. Any deaths are considered as PFS2 events. Subjects who start first-line therapy without disease progression on study treatment will be censored at the last disease assessment on or before starting first-line therapy. Subjects who start first-line therapy after progression on study treatment, are still alive and not yet progress on first-line therapy, will be censored at the last date of follow-up or the day before the start date of 2nd line of next therapy, whichever comes first. Subjects without any post-baseline follow-up will be censored at the randomization. Subjects who were already diagnosed multiple myeloma per baseline central imaging review will be censored at randomization.

Determination of dates of PFS2 event and dates for censoring is summarized in Table 5 as follows.

Table 5: PFS2 Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
No post-baseline disease assessment	Randomization	Censored
Alive and no disease progression on study treatment	Date of last disease assessment on or prior to start of 1st line of next therapy	Censored
Disease progression on study treatment and progress on the 1st line of next therapy or any death	Minimum of earliest date that indicates progression on the 1st line of next therapy and date of death	PFS2 event
Other	Minimum of start date of 2nd line of next therapy minus 1 and last date of follow-up	Censored

5.3.5.2. Analysis Methods

The analysis of progression-free survival on first-line therapy for MM will be similar to the analysis of primary endpoint PFS described above. Two supplementary analyses will be performed, 1) subjects who die due to COVID-19 will be censored at the last disease assessment prior to the death; and 2) subject who missed at least 2 consecutively scheduled visit prior to the PFS2 event will be censored. Visit schedule is every 6 months after initial PD. Subject will be censored at the date of last visit prior to the PFS2 event if the PFS2 event date and the latest date

of scheduled visit immediately preceding the event differs more than 2.5 times the disease evaluation intervals (i.e. 15 months), which indicates that subject missed at least 2 consecutively scheduled visit. .

5.3.5.3. Best Response on first-line Therapy for MM

Subject's best response while on first-line therapy is determined based on investigator assessment per the IMWG response criteria. The number and percentage of subjects in the following response categories will be tabulated by treatment group: sCR, CR, VGPR, PR, stable disease (SD), progressive disease (PD), and not evaluable (NE). The overall response (including sCR, CR, VGPR, or PR), VGPR or better (sCR, CR, or VGPR), and CR or better (sCR, or CR) will also be summarized. For each of the above categories, two-sided 95% Clopper-Pearson exact confidence interval (CI) will also be presented by treatment group.

5.3.6. Overall Survival

5.3.6.1. Definition

Overall survival is measured from the date of randomization to the date of death due to any cause. Subjects who are lost to follow-up will be censored at the last known alive date. Subjects who died after consent withdrawal will be considered as having an OS event. Subjects who are still alive at the clinical cut-off date for the analysis or the survival status is unknown will be censored at the last known alive date. The date of last known alive will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

5.3.6.2. Analysis Methods

The analysis of overall survival will be similar to the analysis of primary endpoint PFS described above. As a supplementary analysis, OS will be analyzed with subjects who die due to COVID-19 censored, i.e. deaths due to COVID-19 will not be counted as OS events.

5.3.7. Incidence of MM with adverse prognostic factors

5.3.7.1. Definition

Incidence of MM with adverse prognostic factors is defined as progression to International Staging System (ISS) III MM (based on β2-microglobulin), MM with adverse cytogenetic characteristics (FISH findings of del(17p), t(4;14), t(14;16) or amp(1q21)), or r-ISS III MM (based on β2-microglobulin, LDH and adverse cytogenetic characteristics).

5.3.7.2. Analysis Methods

Proportions of subjects who progress to MM with adverse prognostic factors will be tabulated and two-sided 95% Clopper-Pearson exact confidence intervals (CI) will be presented by treatment group.

5.3.8. Duration of Response

5.3.8.1. Definition

Duration of response(DOR) is calculated from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progression to MM based on the computerized algorithm, according to IMWG criteria or death due to any cause, whichever occurs first.

Subjects who start subsequent anti-cancer therapies without PD will be censored at the date of the last disease assessment prior to the start of subsequent anti-cancer therapies. Subjects who have not progressed or subjects who die due to causes other than disease progression will be censored at the last disease assessment date.

5.3.8.2. Analysis Methods

Analysis of DOR will be based on subjects who achieved a response of PR or better. Median DOR with 95% CI will be estimated based on the Kaplan-Meier method for each treatment group. The Kaplan-Meier curve for DOR will be plotted by treatment group.

No formal statistical comparison of DOR between the treatment groups will be made.

5.3.9. Time to Response

5.3.9.1. Definition

Time to response (i.e., time to first response) is defined as the time from the date of randomization to the date of initial documentation of a response of PR or better based on the computerized algorithm, according to IMWG response criteria.

5.3.9.2. Analysis Methods

For subjects who achieve a response of PR or better, descriptive statistics (n, mean, standard deviation, median, and range) will be provided to summarize TTR for the responders in each treatment group.

6. SAFETY

Analysis of safety data will be provided on the safety analysis set. All subjects will be analyzed according to the actual treatment they received.

The safety assessments to be evaluated include AEs, deaths, clinical laboratory tests (hematology, chemistry), electrocardiogram (ECG) and ECOG performance scores.

6.1. Adverse Events

AEs will be recorded in standard medical terminology and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. For AE reporting, the verbatim term used in the CRF by investigators to identify adverse events will be

coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

The relationships to study medication will be recorded as not related, doubtful, possible, probable, or very likely on eCRF for all the AEs. Adverse events will be categorized and summarized according to their highest relationship to study medication. An adverse event is considered as related to study medication if the relationship is recorded as possible, probable or very likely.

For subjects treated with daratumumab, treatment-emergent adverse events (TEAEs) are defined as any AE with onset date and time on or after that of the first dose through 30 days after the last study drug administration, or the day prior to start of subsequent 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 study agent administration but prior to the start of subsequent therapy; or any AE that is considered related to (very likely, probably, or possibly related) study medication regardless of the start date of the event. AEs with missing or partial onset date and time will be considered as treatment-emergent unless the onset date and time of an AE can be determined as earlier than that of the first dose, or later than 30 days after last study drug administration. For subjects on active monitoring, treatment-emergent adverse events will be defined as AEs that occur after randomization and prior to start of subsequent therapy, or prior to discontinuation from the study or if the subject continues on study for 3 years, then up to 30 days after that, whichever is earlier.

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 1 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.

6.1.1. Overview of TEAEs

An overview of TEAEs reported through the study will be provided for each treatment group. Overall summary of TEAE will include the subjects with TEAEs, serious TEAEs, TEAEs related to study treatment, TEAEs of maximum toxicity grade of 1 to 5, TEAEs leading to treatment discontinuation, TEAEs leading to dose modification (delay within cycle, cycle delay, or dose skipped), and TEAEs with fatal outcome.

A similar overview of TEAEs will be presented by treatment cycle.

6.1.2. All TEAEs

The following summaries will be provided for all TEAEs:

- TEAEs by system organ class (SOC) and preferred term (PT)
- Most common (≥10%) TEAEs by SOC and PT
- Most common (≥10%) TEAEs by PT

6.1.3. Toxicity Grade 3 or 4 TEAEs

The following grade 3 or 4 TEAEs will be summarized:

- Grade 3 or 4 TEAEs by SOC and PT
- Most commonly reported (≥5%) grade 3 or 4 TEAE by SOC and PT

A similar summary of grade 3 or 4 TEAEs will be presented by SOC, PT and by study week.

In addition, a listing of grade 3 or 4 TEAEs will also be provided.

6.1.4. Treatment-related TEAEs

The following TEAEs will be summarized by relationship to study treatment:

- TEAEs by SOC, PT, and relationship
- Grade 3 or 4 TEAEs by SOC, PT and relationship

6.1.5. Serious TEAEs

The incidence of serious TEAEs will be summarized as below:

- Serious TEAEs by SOC and PT
- Serious TEAEs by SOC, PT and relationship to study treatment
- Most commonly reported (≥2%) serious TEAEs by SOC and PT

A similar summary of serious TEAEs will be presented by SOC, PT and study week.

In addition, a listing of serious TEAEs will be provided.

6.1.6. TEAEs Leading to Treatment Discontinuation

The TEAEs leading to permanent treatment discontinuation will be summarized by SOC, PT and grade 3/4 for those subjects indicated as having discontinued study treatment due to an adverse event on the eCRF “End of Treatment” page.

A listing for subjects who discontinued study treatment due to AE will be provided.

6.1.7. TEAEs Leading to Dose Modification

Incidence of TEAEs leading to dose modification (delay within cycle, cycle delay, or dose skipped) will be summarized by SOC, PT and grade 3/4 for each treatment.

6.1.8. TEAEs with Fatal Outcome

The TEAEs with fatal outcome will be summarized by PT and relationship to study treatment for each treatment group. A listing of TEAEs with fatal outcome will also be provided.

6.2. Deaths

The number of subjects who died during the study and the primary causes of death will be summarized for the ITT analysis set. In addition, the similar summaries will be presented for all deaths and death within 30 days of last dose or active monitoring completion respectively.

A listing of subjects who died during the study will be provided.

6.3. Adverse Events of Clinical Interest

6.3.1. Summary of Infusion/Injection-related Reactions (IRR)

The incidence of infusion/injection-related reactions (IRRs), as recorded on eCRF, will be presented by SOC, PT, and toxicity grade 3/4. In addition, the total number of subjects with IRR in more than 1 infusion/injection will be presented. The timing of IRR will also be evaluated through a summary of IRR by event onset time.

A listing of infusion/injection-related reactions will be provided.

6.3.2. Injection-site Reactions

For the Dara-SC treatment group, injection-site reactions will be recorded on eCRF. The incidence of injection-site reactions will be summarized by SOC, PT, and toxicity grade 3/4. A listing of injection-site reactions will be provided.

6.3.3. Infections and Infestations

Infections and infestations refer to the adverse events with SOC of infections and infestations. The grade 3 or 4 treatment-emergent infections and infestations will be summarized by preferred term and relationship to treatment.

6.3.4. 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.

6.3.5. Second Primary Malignancies

A listing of subjects who reported second primary malignancies during the study will be provided. This listing will include diagnosis, study day of diagnosis, recurrence of a prior existing malignancy (yes, no) and pathology diagnosis (biopsy, aspirate etc.) information whenever a second primary malignancy is observed. In addition, treatment related to second

primary malignancy, cumulative study treatment exposure, and whether or not subjects received subsequent anti-cancer therapy (yes, no) information will also be presented in the listing.

6.3.6. Adverse Events by Subgroups

The subgroup analysis for the following TEAEs will be performed based on the subgroups specified in Section 2.4:

- Overview of TEAEs
- Summary of all TEAEs
- Grade 3 or 4 TEAEs
- Serious TEAEs

6.4. Clinical Laboratory Tests

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

- Hematology Panel:
  - hemoglobin
  - white blood cell (WBC) count, absolute neutrophil count, and absolute lymphocyte count
  - platelet count

- Serum Chemistry Panel:
  - AST
  - ALT
  - total bilirubin
  - glucose
  - creatinine
  - alkaline phosphatase
  - sodium
  - blood urea nitrogen (BUN) or urea
  - serum calcium corrected for albumin
  - potassium

Descriptive statistics for values and changes from baseline at each scheduled visit for hematology and chemistry laboratory parameters will be provided. 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/GFR.

In addition, the worst toxicity grade in hematology and chemistry during the treatment will be summarized by treatment group and toxicity grade. Shifts tables from baseline to the worst toxicity grade during treatment will be generated.

A listing of subjects with any laboratory results outside the reference ranges will be provided.

6.5. Vital Signs and Physical Examination Findings

Vital signs will be monitored as clinically necessary. Only abnormal vital signs and physical examination will be recorded in the eCRF, as part of AE reporting in the AE reporting page. No summary of vital signs and physical examination will be provided..

6.6. Electrocardiogram

The ECG data will be collected at Screening, visits as clinically indicated during treatment, and End-of-Treatment visit.

The number and percentage of subjects with normal and abnormal either clinically significant or not clinically significant ECG results will be summarized for each treatment group. A listing of subjects who experienced clinically significant abnormal ECGs in either baseline or post-baseline will be produced.

6.7. ECOG Performance Status

ECOG performance status, which evaluates the effect of the disease status on the activities of daily living, will be assessed at Screening, every 6 months during the treatment/active monitoring period, end-of-treatment/active monitoring visit and at PD. The shift summaries of ECOG performance status from baseline to each post baseline time points will be provided for each treatment group. The shift summary from baseline to the worst performance score during treatment/active monitoring will also be presented.

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1. Pharmacokinetics

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.

The pharmacokinetic parameters are defined as:

- C_{min} - Minimum observed concentration: defined as the concentration observed immediately before the injection
- C_{max} - Maximum observed concentration: defined as the first concentration observed after the end of the injection

The C_{min}, and C_{max} will be determined based on the assigned collection timepoints. If there are sufficient data, population pharmacokinetic analysis of serum concentration-time data of daratumumab may be performed using nonlinear mixed effects modeling and may include data from other clinical studies. If performed, details will be provided in a population pharmacokinetic analysis plan and results of the analysis will be presented in a separate report.

Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point specified in protocol. Plot of mean (±SD) daratumumab serum peak and trough concentrations over time will be provided.

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

7.2. Immunogenicity

The incidence of anti-daratumumab antibodies along with the titer and incidence of neutralizing antibodies will be summarized for all subjects who receive at least 1 dose of Dara-SC and have appropriate samples for detection of antibodies to daratumumab (ie, subjects with at least 1 sample obtained after the first dose of daratumumab).

The incidence of anti-rHuPH20 antibodies along with the titer and incidence of neutralizing antibodies will be summarized for all subjects who receive a dose of Dara-SC and have appropriate samples for detection of antibodies to rHuPH20.

A listing of subjects who are positive for anti-daratumumab or anti-rHuPH20 antibodies will be provided.

7.3. Pharmacokinetic/Pharmacodynamic Relationships

Pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of daratumumab and endpoints of clinical efficacy and safety. If performed, details and results of the analysis will be presented in a separate report.

8. BIOMARKERS

Biomarker studies are designed to evaluate if there are any differences in depth of response, cytogenetic risk factors and immune-phenotypes in high risk SMM patients. Samples for biomarker evaluations will be collected as specified in the protocol Time and Events Schedule for bone marrow aspirate samples and whole blood samples.

With the emergence of highly effective drug regimens for multiple myeloma that effectively eliminate malignant plasma cells, the utility of assessing minimal residual disease (MRD) has gained greater importance in determining the depth of response to therapy. For this study, three threshold values, 10^{-4}, 10^{-5} and 10^{-6}, may be used to evaluate MRD negativity status and its predictive value for PFS and OS. The MRD negative rate will be calculated for the Daratumumab treatment group and the corresponding 95% exact CI will be provided.

A portion of the bone marrow aspirate samples collected, as specified in the Time and Events Schedule, will be utilized for translocation/mutation/genomic analysis (DNA/RNA) to assess whether specific molecular subgroups are responsive to daratumumab treatment. The high risk molecular subgroup is defined as subjects who have either del17p, t(4;14), t(14; 16), amp1q or a combination of these. This definition of high risk may evolve with emerging data from the scientific community. The standard-risk molecular subgroup includes subjects who had molecular test results by bone marrow aspirate, but do not meet molecular high-risk criteria. Analyses will evaluate ORR, PFS and OS as it relates to risk within each arm to see if they have similar outcomes to standard risk patients.

Biomarker studies are designed to identify markers predictive of response (or resistance) to daratumumab. Exploratory analyses, stratified by clinical covariates or molecular subgroups, may

be performed using the appropriate statistical methods (eg, parametric or non-parametric, univariate or multivariate, analysis of variance, or survival analysis, depending on the endpoint).

Subjects may be grouped by cohort, dose schedule, or clinical response. As this is an open-label study with an active monitoring control arm, statistical analyses will be done to aid in the understanding of the results.

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

9. PATIENT-REPORTED OUTCOMES

Patient-reported outcomes (PROs) will be evaluated in this study through the following 3 instruments: EORTC QLQ-C30, EORTC QLQ-MY20, and the EQ-5D-5L. The EORTC QLQ-C30, EORTC QLQ-MY20, and the EQ-5D-5L 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 resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The recall period is 1 week (the past week). A higher score represents a higher (“better”) level of functioning, or a higher (“worse”) level of symptoms. The EORTC QLQ-MY20 is a disease-specific module administered with the EORTC QLQ-C30 in patients with multiple myeloma. From the EORTC QLQ-MY20, 9 items were administered resulting in the disease symptom scale and the future perspective scale. The recall period, response options, and score interpretation are the same as the EORTC QLQ-C30.

The EQ-5D-5L is a generic measure of health status. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale rating “health today” with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the 5 separate questions are categorical and cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual (but scoring by the UK algorithm allows for values less than 0).

Analysis of PRO data will be performed on 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.

At each time point for analysis, the number and percentage of PRO instrument assessment forms that are expected, received, and missing will be tabulated by treatment group. The missing PRO assessments are defined as the expected number of assessments for a visit minus the actual number of assessments received for that visit, the expected number of assessments per visit will be determined by subject-level study completion status.

9.1. Patient Reported Outcome Endpoints

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

9.1.1.1. Definition

Key PRO Endpoints

- EORTC QLQ-C30: global health status (GHS); emotional functioning
- EORTC QLQ-MY20: Future perspective
- EQ-5D-5L: utility values and visual analog scale (VAS)

9.1.1.2. Analysis Method

Descriptive statistics (n, mean, standard deviation, median, and range) will be provided for all PRO endpoints at each time point, by treatment group.

A repeated measures mixed effects model analysis will be conducted estimating change from baseline at each time point between two treatment groups. ITT subjects who have a baseline value and at least one post-baseline value are included in the analysis. Change from baseline will be fitted to a mixed effects model including subjects as a random effect, and baseline value, treatment group, time in month, treatment-by-time interaction, and the stratification factor as fixed effects. Line plot of LS mean change from baseline, with standard error, over time may be displayed by treatment group.

9.1.2. Time to worsening/improvement

9.1.2.1. Definition

For the key PRO endpoints, time to worsening and time to improvement will be derived. A distribution based method will be used to define worsening/improvement in scores, i.e., half standard deviation away from the mean score at baseline combining both treatment groups.

9.1.2.2. Analysis Method

Time to worsening will be estimated using Kaplan-Meier methods. The hazard ratio for daratumumab relative to active monitoring and its associated 95% confidence interval (CI) will be calculated based on the stratified Cox proportional hazards model by the stratification factor at the 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.

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

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ATTACHMENT 1: ADDITIONAL EXPLORATORY ANALYSIS TO SUPPORT HEMAR

1. DEFINITION OF SUBGROUPS

Subgroup analyses will be performed for the ITT population, pre-defined subgroups as defined in section 2.4, 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 achieved a PR or better
- For subjects who achieved MRD negativity (10^{-4}, 10^{-5} and 10^{-6})
- Baseline ECOG performance status (0 or 1)
- Baseline risk factors (grouped) for progression to MM (<3 vs ≥ 3)
- Baseline risk factors (Stand-alone) for progression to MM:
    - Serum M protein ≥30g/L
    - IgA SMM
    - Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes (only IgA, IgM and IgG)
    - Serum involved : uninvolved FLC ratio ≥8 and <100
    - Clonal BMPCs>50% to <60% with measurable disease
    - Serum M protein > 2 g/dL
    - I/U FLC ratio > 20
    - BMPC > 20%

Subgroup analyses will be performed if data warrants.

2. ENDPOINTS FOR SUBGROUP ANALYZES

As described in Sections 5.2 (Primary Efficacy Endpoints), 5.3 (Secondary Endpoints) and 9.1 (Patient-Reported Outcomes), the following endpoints will be evaluated by subgroups as defined in Section 1, Appendix:

- PFS
- Time to Biochemical or SLiM-CRAB progression
- ORR
- Time to first-line treatment for MM
- PFS2
- OS
- Duration of response
- Time to Response
- EORTC QLQ-C30, EORTC QLQ-MY20, EQ-5D-5L (Section 9.1.1.1)
- PRO: Time to worsening/improvement (Section 9.1.1.2)
- Time to progression
- Incidence of MM with adverse prognostic features

2. EXPOSURE ADJUSTED INCIDENCE RATES (EAIR)

2.1. 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.

2.2. 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.

2.3. 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:

$$EAIR_i = \frac{1}{t_i}.$$

2.4. Average EAIR

The *EAIR* averaged over all patients is

$$EAIR = \frac{\sum_{i=1}^{n} TEAE_i}{\sum_{i=1}^{n} t_i},$$

whereby

a) a TEAE enters the sum in the nominator unweighted ($TEAE_i$ =1, otherwise $TEAE_i$ =0), and
b) the duration of exposure enters the denominator as described before: $t_i = \begin{cases} time\ of\ TEAE \text{ if occurring (non-censored data)} \\ total\ duration\ of\ treatment \text{ if no event occurs (censored data)} \end{cases}$.

2.5. EAIRs on the level of a SOC and on the global level on a 'per-PT' basis

2.5.1. 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.

2.5.2. 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).

2.5.3. 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.

2.6. Second analyses

2.6.1. 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.

2.6.2. 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*.

2.6.3. 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))

3. 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

3. 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.