Janssen Research & Development

Statistical Analysis Plan

A Phase 3 Randomized, Multicenter Study of Subcutaneous vs. Intravenous Administration of Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma

Protocol 54767414MMY3012; Phase 3

Amendment 1

JNJ-54767414 (daratumumab)

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AMENDMENT HISTORY

SAP Version	Issue Date
Original SAP	6 February 2018
Amendment 1	12 February 2019

The following is a summary of the major changes from the original version of the SAP:

1. Updates on the data cutoff and primary analysis strategy according to the Protocol Amendment 2 to allow Japan to enroll beyond the initially planned 480 subjects;
2. Updated and clarified on the Statistical Hypotheses Section 1.3 and Efficacy Section 5, added a new Section 1.4 of Non-inferiority Margins Justification to address FDA's comments on alpha level, estimand and non-inferiority margins;
3. Refined the parameters for the biomarker analysis;
4. Added exploratory endpoint and analyses for PFS2 (Section 5.4.2);
5. Added attachments of IMWG computerized algorithm and additional exploratory analysis to support HEMAR.

ABBREVIATIONS

AE	adverse event
ALB	albumin
ALKY	alkylating agent
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
B2MG	beta2 microglobulin
BUN	blood urea nitrogen
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CR	complete response
CT	cancer therapy
CTSQ	Cancer Therapy Satisfaction Questionnaire
Dara IV	daratumumab for intravenous infusion
Dara SC	daratumumab administered subcutaneously
DMC	Data Monitoring Committee
DOR	duration of response
DPS	Data Presentation Specifications
ECG	electrocardiograms
ECOG	European Cooperative Oncology Group
eCRF	electronic case report form
FLC	free light chain
FM	Farrington-Manning
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GM	geometric mean
HLT	high level term
ICH	International Conference on Harmonization
LDH	lactic acid dehydrogenase
LLN	lower limit normal
IMiD	immunomodulatory drug
IMWG	International Multiple Myeloma Working Group
IRR	infusion-related reaction
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous
IWRS	Interactive Web Response System
MDSCs	myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities

MM	multiple myeloma
MR	minimal response
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression free survival
PI	proteasome inhibitor
PK	pharmacokinetic
PP	per-protocol
PR	partial response
PT	preferred term
rHuPH20	recombinant human hyaluronidase
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCR	stringent complete response
SD	stable disease
SMQ	standardized MedDRA queries
SOC	system organ class
SWT	satisfaction with therapy
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TNT	time to next therapy
TTR	time to response
ULN	upper limit normal
VGPR	very good partial response
WBC	white blood cell

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of the analysis set(s), derived variables and statistical methods for the primary analysis of the open-label, active-controlled, multicenter, Phase 3 study to demonstrate that the efficacy and pharmacokinetics for Dara SC are not inferior to those for Dara IV in subjects with relapsed or refractory multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or whose disease is double refractory to both a PI and an IMiD.

1.1. Trial Objectives

Primary Objectives

- To show that subcutaneous (SC) administration of daratumumab co-formulated with recombinant human hyaluronidase PH20 (Dara SC) is non-inferior to intravenous administration of daratumumab (Dara IV) in terms of the overall response rate (ORR)
- To show that Dara SC is non-inferior to Dara IV in terms of the maximum trough concentration (C_{trough})

Secondary Objectives

- To assess the pharmacokinetics and immunogenicity of Dara SC and Dara IV
- To evaluate the safety of Dara SC and Dara IV
- To evaluate the clinical benefit of Dara SC and Dara IV
- To evaluate the immunogenicity of rHuPH20 following Dara SC administration
- To evaluate patient-reported satisfaction with Dara SC and Dara IV

1.2. Trial Design

This is a phase 3, randomized (1:1), open-label, active-controlled, multicenter study to demonstrate that the efficacy and pharmacokinetics for Dara SC are not inferior to those for Dara IV in subjects with relapsed or refractory multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or whose disease is double refractory to both a PI and an IMiD. Approximately 480 subjects will be assigned randomly to the Dara SC group or the Dara IV group in a 1:1 ratio. The randomization will be stratified by body weight at baseline (≤65 kg, 66 kg to 85 kg, >85 kg), number of prior lines of therapy (≤4 prior lines versus >4 prior lines), and type of myeloma (IgG versus non-IgG).

The study consists of 3 phases: Screening Phase, Treatment Phase, and Follow-up Phase. The Screening Phase will be up to 28 days before randomization. The Treatment Phase will extend from randomization until discontinuation of treatment with study drug. Each subject will be treated until the sponsor confirms that disease progression has occurred for that subject, the subject has unacceptable toxicity, or other reasons. The Follow-up Phase begins immediately

following the End-of-Treatment Visit, and will continue until death, loss to follow up, consent withdrawal for study participation, or study end, whichever occurs first.

Treatment cycles are 28 days in length. The dosing schedule for both groups will be weekly for Cycles 1 and 2, every 2 weeks for Cycles 3 to 6, and every 4 weeks thereafter. Subjects who are assigned to the Dara SC group will receive a fixed dose of Dara SC 1800 mg (daratumumab 1800 mg co-formulated with rHuPH20 2000 IU/ml). Dara SC will be delivered by SC injection in the abdominal wall in left/right locations, alternating between individual doses. All subjects in the Dara SC group 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 consecutive injections. Subjects who are assigned to the Dara IV group will receive Dara IV 16 mg/kg by IV infusion pump.

Assessment of disease response will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria using a computerized algorithm. The primary analysis will occur approximately 6 months after the planned 480 subjects have been randomized. However, to support local submission in Japan, the study extended the local enrollment to reach the targeted number of Japanese subjects after the planned 480 subjects were all randomized. Additional subgroup analysis for Japanese subjects may be conducted approximately 6 months after the last Japanese subject has been randomized. The study is considered completed approximately 18 months after the last subject is randomized. At the end of the study, subjects who are benefiting from study treatment with daratumumab can continue to receive treatment after the end of the study.

1.3. Statistical Hypotheses for Trial Objectives

The clinical and pharmacokinetic hypotheses are that the ORR and maximum C_{trough} for Dara SC 1800 mg are not inferior to the ORR and maximum C_{trough}, respectively, for Dara IV 16 mg/kg in subjects with multiple myeloma who have received at least 3 prior lines of therapy including a PI and an IMiD, or whose disease is refractory to both a PI and an IMiD. Both the null hypotheses for clinical and PK need to be rejected to declare non-inferiority.

1.3.1.1. Statistical Hypotheses for ORR

For this study, the clinical non-inferiority of Dara SC relative to Dara IV is defined using 60% retention of the ORR (i.e., a non-inferiority margin of 40%). The non-inferiority hypothesis for ORR can be stated as:

H_0: $ORR_{SC} / ORR_{IV} < 60\%$

H_1: $ORR_{SC} / ORR_{IV} \geq 60\%$ (non-inferiority)

The primary analysis will use the non-inferiority test for non-unity null according to Farrington and Manning (1990)[1]. The relative risk and its two-sided 95% CI will be provided. In order to

declare non-inferiority, the lower bound of the two-sided 95% CI of the relative risk needs to be ≥ 60%.

1. If the lower bound of the two-sided 95% CI of the relative risk is ≥100%, superiority of Dara SC relative to Dara IV will be concluded.

1.3.1.2. Statistical Hypotheses for Maximum C_{trough}

For the co-primary endpoint of maximum C_{trough}, which is defined as the concentration at pre-dose on Cycle 3 Day 1, non-inferiority of Dara SC relative to Dara IV is defined using a non-inferiority margin of at least 80% of the ratio of geometric mean (GM) of maximum C_{trough}. The non-inferiority hypothesis for maximum C_{trough} can be stated as:

H_0: $GM_{SC} / GM_{IV} < 80\%$

H_1: $GM_{SC} / GM_{IV} \geq 80\%$ (non-inferiority)

Dara SC will be considered non-inferior to Dara IV on maximum C_{trough} if the lower bound of the 90% CI for the ratio of the geometric means is at least 80%.

1.4. Non-inferiority Margins Justification

The clinical non-inferiority of Dara SC relative to Dara IV in the current study is defined using a 60% retention of ORR from previous clinical Study MMY2002, a study of 106 subjects with relapsed or refractory multiple myeloma who had received at least 3 prior therapies and who were treated with Dara IV 16 mg/kg, an ORR of 29.2% (95% CI: 20.8%, 38.9%) was observed. There is no established standard of care for the targeted population, and the recent approvals were based on single-arm studies with ORR as the primary endpoint.

The 60% retention will result in minimal loss of benefit in terms of observed ORR. For example, if the observed ORR for Dara IV is 30%, then an ORR of at least 25% needs to be observed for Dara SC. The clinical relevance of the 60% retention of ORR was justified based on the benefit/risk of Dara SC and a strong indication of similar efficacy from early efficacy and pharmacokinetics data. Subjects enrolled into MMY2002 had a median of 5 prior lines of therapy. Outcomes for this population of patients generally are measured in months. Due to prior therapies, these patients also tend to be more frail, with lower organ reserves, compared with subjects with newly diagnosed multiple myeloma. A shorter infusion time would reduce time spent in a healthcare setting and a lower incidence of IRRs could enable them to stay on therapy longer. In addition, in the daratumumab Study MMY1004 Part 1, the ORR was 38% for 45 subjects receiving Dara-MD 1800 mg, and the maximum C_{trough} was similar or higher compared to Dara IV, strongly suggesting similar efficacy with Dara SC.

For the co-primary endpoint of maximum C_{trough}, the non-inferiority of Dara SC relative to Dara IV is defined using a non-inferiority margin of at least 80% of the ratio of geometric mean (GM) of maximum C_{trough}. Since this is a PK endpoint, the selection of non-inferiority margin and the choice of alpha level follow the convention for bioequivalence studies.

1.5. Sample Size Justification

There is no established standard of care for the targeted population, and the recent approvals were based on single-arm studies with ORR as the primary endpoint. In a previous clinical study (MMY2002), of 106 subjects with relapsed or refractory multiple myeloma who had received at least 3 prior therapies and who were treated with Dara IV 16 mg/kg, an ORR of 29.2% (95% CI: 20.8%, 38.9%) was observed.

Non-inferiority of Dara SC to Dara IV in the current study is defined using a 60% retention of the lower bound (20.8%) of the 95% CI from Study MMY2002. The clinical relevance of the 60% retention of ORR was justified based on the benefit/risk of Dara SC and a strong indication of similar efficacy from early efficacy and pharmacokinetics data. The 60% retention will result in minimal loss of benefit in terms of observed ORR.

With a planned 1:1 randomization, 480 subjects (n=240 in the Dara SC group and n=240 in the Dara IV group) will be needed to demonstrate non-inferiority with a power of 80% and a one-sided alpha=0.025, assuming that the true ORR is the same for both groups. The sample size calculation is based on the methodology for the non-inferiority test for non-unity null, as described by Farrington and Manning (1990)[1].

The study is also designed to establish comparability of maximum C_{trough} between Dara SC and Dara IV. The 2 formulations of daratumumab will be considered similar if the lower bound of the 90% CI for the ratio of the geometric means of C_{trough} on Cycle 3 Day 1 is at least 80% (non-inferiority margin of 20%). A one-sided test is selected based on previous analyses that demonstrated a strong relationship between maximum C_{trough} and efficacy. However, there is no apparent relationship between drug exposure in the therapeutic dose range and adverse events of interest. With a planned 1:1 randomization, 480 subjects and a one-sided alpha=0.05, the power will be >95%. This assumes a true ratio of the C_{trough} of 1, a non-inferiority margin of at least 80% of the geometric mean ratio, a coefficient of variation of 0.6.

1.6. Randomization and Blinding

Central randomization will be implemented in this study. Subjects will be assigned randomly to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by body weight at baseline (≤65 kg, 66 kg to 85 kg, >85 kg), number of prior lines of therapy (≤4 prior lines versus >4 prior lines), and type of myeloma (IgG versus non-IgG). An interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject.

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

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

For analyses of data by cycle, if data are collected by date (e.g., AE onset), the corresponding study evaluations will be assigned to actual sequential cycles, which are derived from the study drug administration data. The start date of a cycle is defined as the first scheduled dose date of the study drug 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 or the minimum of last dose date plus 30 days or subsequent anticancer 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 summary by study week.

2.2. Pooling Algorithm for Analysis Centers

Data from all study centers will be pooled for analyses.

2.3. Study Drug

In this study, study drug refers to Dara SC or Dara IV. In the Dara SC group, Dara SC will be administered by SC injection at a fixed dose of 1800 mg. In the Dara IV group, Dara IV 16 mg/kg will be administered by IV infusion. Each subject's dose in the Dara IV group will be calculated based on the subject's weight rounded to the nearest kilogram, but does not need to be recalculated for weight changes that are <10% from baseline.

Dose reduction or increase of Dara IV or Dara SC is not permitted. Dose delay or dose skip is the primary method for managing daratumumab-related toxicities.

The first dose date is defined as the earliest date of non-zero dose of study drug. The last dose date is defined as the latest date of non-zero dose of study drug.

A subject is considered as treated in a cycle if he/she receives any non-zero dose of study drug in that cycle.

2.4. Baseline Definitions

The baseline value is defined as the last non-missing measurement taken on or prior to the first dose administration of study drug (including time if time is available).

Study day is defined as date of assessment – first dosing date + 1 for any assessment done on or after first dosing date; otherwise, study day is defined as date of assessment – first dosing date. The first dose date is defined as the earliest date of non-zero dose of study drug.

2.5. Unique Lab Value

In general, in instances when there are multiple records at a given visit date for lab parameters associated with disease assessment, the following rules will be applied to select the unique lab value for analysis: a.) multiple records from both central and local lab, central lab value always takes precedence over local lab value; b) multiple records from central lab, select the latest value as the unique lab value; c.) multiple records from local lab, select the latest lab value as the unique lab value.

2.6. Analysis Sets

The analysis sets for the study are:

- 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 including time-to-event endpoints. All subjects in ITT analysis set will be analyzed according to their randomized treatment group, regardless of the actual treatment received.

- Safety analysis set: defined as all randomized subjects who receive at least 1 dose of study drug (Dara SC or Dara IV). 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.

- Per-protocol (PP) analysis set: defined as all treated subjects who have measurable disease at baseline and have no major protocol deviations with respect to eligibility. The per-protocol analysis set will be used for critical sensitivity analyses of ORR in the context of the non-inferiority design.

- Response-evaluable analysis set: defined as subjects who have a confirmed diagnosis of multiple myeloma and measurable disease at baseline or screening visit. In addition, subjects must have received at least 1 administration of study drug and have at least 1 post baseline disease assessment. Measurable disease at baseline is defined in section 2.9.1. This analysis set will be used as sensitivity analyses for selective response-related endpoints such as ORR, VGPR or better rate, and CR or better rate.

- Pharmacokinetics analysis set: defined as subjects who received at least 1 administration of study drug and have at least 1 pharmacokinetics sample concentration value after the first dose administration. All pharmacokinetic parameters except for maximum C_{trough} will be analyzed based on the pharmacokinetics analysis set.

- Pharmacokinetics-evaluable analysis set: defined as subjects who received all 8 weekly full doses of Dara IV or Dara SC in Cycle 1 and Cycle 2 within the dosing time window according to the Time and Events Schedule in protocol and provided a pre-dose pharmacokinetic sample on Cycle 3 Day 1 within the sampling window of 8 hours prior to

the start of dose administration. The Pharmacokinetics-evaluable analysis set will be used to summarize the maximum C_{trough}.

- Immunogenicity-evaluable analysis set:

    - Daratumumab immunogenicity-evaluable: Immunogenicity-evaluable analysis set for antibodies to daratumumab is defined as all subjects who receive at least 1 dose of Dara SC or Dara IV and have appropriate serum samples for detection of anti-daratumumab antibodies to daratumumab (at least 1 sample after the start of the first dose of daratumumab).

    - rHuPH20 immunogenicity-evaluable: Immunogenicity-evaluable analysis set for anti-rHuPH20 antibodies is defined as all subjects who receive at least 1 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).

2.7. Imputation of Missing Data

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

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.

After the imputation, if the imputed date is later than the date of death (if available) after imputation, 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. Multiple Myeloma Diagnosis Date

If the diagnosis date of multiple myeloma (MM) is completely missing, no imputation will be applied. If the diagnosis date is partially missing, the following imputation rules will be applied:

- If only the day of the diagnosis date is missing:
    - If the month and year of the diagnosis date are the same as the month and year of the start date of the first line of prior MM therapy, and day of the start date of the first

line of prior MM therapy is available, impute day of the diagnosis date with the day of the start date of the first line of prior MM therapy;

- Otherwise, impute day of diagnosis date with 15;

- If both month and day of the diagnosis date are missing:
  - If the year of the diagnosis date is the same as the year of the start date of the first line of prior MM therapy, and the month of the start date of the first line of prior MM therapy is available:
    - if both month and day of the start date of the first line of prior MM therapy are available, impute diagnosis month and day with the month and day of the start date of the first line of prior MM therapy;
    - if only the month of the start date of the first line of prior MM therapy is available, impute the month of diagnosis date with the month of the start date of the first line of prior MM therapy and the day of the diagnosis date with 15;
    - Otherwise, impute the month and day of the diagnosis date with June 30.

2.7.4. First Subsequent Anticancer Therapy Start Date

If the start date of the first subsequent anticancer therapy is completely missing or the month is missing, no imputation will be performed. If only the day of the first subsequent therapy start date is missing, the following imputation rules will be applied:

- If the month and year of the start date are the same as the month and year of the last dosing date, the day of last dosing date +1 or the day-component of the stop date of subsequent anticancer therapy will be imputed, whichever is earlier.
- If the month and year of the start date are not the same as the month and year of last dosing date, the first day of the month will be imputed.

2.8. General Analysis Method

In general, continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median and range. Categorical variables will be summarized using frequency and percentage. For time-to-event variables, which is defined as from the date of randomization to the date of the event, the Kaplan-Meier method will be used for descriptive summaries. For the calculation of time-to-event and duration-of-event variables, the difference between the start date and the end date plus 1 day will be used.

2.9. Other General Definitions

2.9.1. Measurable Disease of Multiple Myeloma at Baseline and Measurable Type

Measurable disease at baseline is defined by any of the following:

- IgG multiple myeloma: Serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
- IgA, IgD, IgE, IgM multiple myeloma: serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or
- Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin free light chain (FLC) ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio.

If a subject meets the criteria for serum M-protein, the measurable disease type is serum; otherwise, if a subject meets the criteria for urine M-protein, the measurable disease type is urine; otherwise if a subject meets the criteria for FLC, the measurable disease type is FLC. If a subject meets both of the criteria for serum M-protein and urine M-protein, then the measurable disease type is "serum and urine".

2.9.2. Type of Multiple Myeloma

Type of myeloma for a subject is determined by serum heavy chain or serum FLC or urinary FLC. Serum heavy chain refers to serum immunoglobulin of IgG, IgA, IgM, IgD, or IgE. Serum and urine FLC refers to kappa or lambda type.

A subject will be classified as IgG type of myeloma if any reported result contains serum heavy chain 'IgG' regardless of FLC reported, similarly for IgA, IgM, IgD and IgE type. A subject will be classified as the light chain type of myeloma if any reported result is either 'Lambda light chains' or 'Kappa light chains' but without heavy chain reported. A subject will be reported as 'biclonal' if the distinct test results contain different heavy chain values or different FLC values. A subject will be classified as "Negative immunofixation" if the reported result is "Not Detected" and with no serum heavy chain, serum light chain and urine light chain reported.

2.9.3. International Staging System (ISS)

ISS staging is based on the combination of serum β2-microglobulin (B2MG) and serum albumin (ALB) at baseline.

- Stage I: β2-microglobulin<3.5 mg/L and serum albumin≥ 35 g/L
- Stage III: β2-microglobulin ≥ 5.5 mg/L
- Stage II: Neither stage I nor stage III
- (β2-microglobulin<3.5 mg/L but serum albumin< 35 g/L, or β2-microglobulin
- ≥3.5 mg/L to 5.5 mg/L irrespective of the serum albumin level)

2.9.4. Hepatic Function

Hepatic impairment is classified into 4 levels per NCI organ dysfunction criteria, using baseline total bilirubin and Aspartate Aminotransferase (AST):

- 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
- Severe: total bilirubin > 3×ULN

2.9.5. Relapsed Disease

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

2.9.6. Refractory Disease

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.

2.9.7. High Risk/Standard Risk Cytogenetics

The high risk and standard risk cytogenetics are defined as follows:

- High risk: subjects that are positive for any of del17p, t(14;16), t(4;14) by FISH/Karyotype
- Standard risk: subjects with sufficient cytogenetic testing to rule out presence of deletion of del17p, t(14:16), and t(4:14)

A subject will be classified as "Undetermined" if a subject had either no cytogenetic testing performed or had cytogenetic testing performed but risk categorization could not be determined.

2.9.8. Time since Initial Multiple Myeloma Diagnosis

Time since initial multiple myeloma diagnosis to randomization in years is calculated as date of randomization – date of initial MM diagnosis + 1, divided by 365.25.

2.9.9. End of Follow-up and Duration of Follow-up

The end of follow-up is defined as the maximum date of the following study evaluations: labs (hematology, chemistry, immunology), adverse events, vital signs, ECOG performance status, PRO assessment, bone marrow cytogenetics, lytic bone lesions, extra-medullary plasmacytomas, study drug administration, ECG, pre-dose medications, post-dose medications, concomitant medications, subsequent therapy, medical encounters, clinical events/disease response per investigator and date of last known to be alive. For subjects who died on study, the end of follow-up is the date of death. For subjects who died after the end of study, the end of follow-up will be set to the maximum date derived above.

Duration of follow-up (in months) = the date of end of follow-up - the date of randomization + 1, divided by 365.25/12.

2.10. Definition of Subgroups

In general, subgroup analyses on the pre-specified subgroups in Table 1 will be performed for the primary efficacy endpoint ORR, major secondary endpoint of rate of infusion-related reactions (IRRs), and safety endpoints treatment-emergent adverse event (TEAE). Additional exploratory 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
Sex	Male, Female	E, S
Age	E: <75, ≥75 years S: < 65, 65 to < 75, and ≥ 75 years	E, S
Race	White, Other	E, S
Region	Asia/Pacific, Other	E, S
Baseline weight	≤ 65 kg, >65 to 85 kg, and >85 kg	E, S
Baseline renal function (Glomerular filtration rate [GFR] [mL/min/1.73m^2])	E: ≤60, >60 (mL/min/1.73m^2) S: <30, 30 to <60, 60 to <90, and ≥90 (mL/min/1.73m^2)	E, S
Baseline hepatic function	Normal, Impaired[a]	S
ISS staging	I, II, and III	E
Number of prior lines of therapy	≤ 4 lines, >4 lines	E
Type of myeloma	IgG, non-IgG	E
Cytogenetic risk	High risk, Standard risk	E
ECOG performance score	0, ≥1	E

E: efficacy (ORR); S: safety (TEAEs).
[a] Includes mild, moderate and severe.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

No interim analysis is planned for this study.

An independent Data Monitoring Committee (DMC), consisting of 2 clinicians and 1 statistician, will be established to review safety data periodically during the study. The DMC will review comprehensive safety data and provide recommendations concerning the conduct of the study. The details will be provided in a separate DMC charter.

The statistical analysis plan for the DMC will be provided in a separate DMC SAP.

4. SUBJECT AND TREATMENT 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. Subject Disposition

The number of subjects who are randomized, treated, ongoing, 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. The number of subjects who discontinued treatment by cycle with the reported reasons will also be provided.

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

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

4.2. 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, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and Not reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Height (cm)
- Weight (kg) (≤65 kg, >65 kg to 85 kg, >85 kg)
- Baseline ECOG performance status (0, 1, 2)

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

- Type of myeloma (IgA, IgD, IgE, IgG, IgM, light chain, biclonal, or negative immunofixation)
- Type of measurable disease (serum and urine, serum, urine, FLC)
- ISS staging (I, II, III)
- standard-risk and high-risk cytogenetic abnormalities (del17p, t(4;14), t(14;16))
- Time since initial diagnosis to randomization (years)
- Number of lytic bone lesions (None, 1-3, 4-10, more than 10)
- Presence of diffuse myeloma-related osteopenia (Yes, No)
- Presence of extramedullary plasmacytomas (Yes, No)
- Bone marrow % plasma cells (<10, 10 – 30, > 30)

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.

In addition, a summary of stratification factors used in the randomization (body weight at baseline, number of prior lines of therapy, and type of myeloma) based on IWRS will be provided to evaluate whether or not randomization process was appropriately executed in the study.

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. Prior Therapies

4.4.1. Prior Multiple Myeloma Therapies

The number and percentage of subjects who had prior exposure to multiple myeloma therapies (systemic therapy, autologous stem cell transplant [ASCT], radiotherapy, cancer-related surgery) will be summarized by treatment group. Specifically, for prior systemic therapies, the number of prior lines of therapy will be summarized descriptively and summarized by the following categories: ≤ 4 and > 4.

The summary of prior systemic therapies will be presented by therapy class and therapy. The therapy classes include proteasome inhibitors (PI), immunomodulatory drugs (IMiD), steroids, alkylating agents and anthracyclines.

- PI therapy class includes: bortezomib, carfilzomib, oprozomib, ixazomib, and marizomib;
- IMiD therapy class includes: lenalidomide, pomalidomide, and thalidomide;
- Steroids therapy class includes: dexamethasone and prednisone, among others.

Further update of the above lists will be specified in the Data Presentation Specifications (DPS). 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 class or therapies is sufficient.

Additionally, the prior systemic therapy will be summarized by therapeutic class, pharmacologic class and preferred term.

4.4.2. Refractory Status to Prior Systemic Therapy

Refractory status (yes, no) to a particular prior systemic therapy class (i.e., PI/IMiD) or prior systemic therapy (e.g., bortezomib or thalidomide) will be based on refractory status to each line of therapy, or each specific 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 the most recent PI or IMiD therapy class will be summarized by the following 4 categories: none (neither PI-refractory nor IMiD-

refractory), PI only (PI-refractory but not IMiD-refractory), IMiD only (IMiD-refractory only but not PI-refractory), both PI and IMiD. Refractory to specific prior therapy, such as bortezomib, carfilzomib, ixazomib, lenalidomide, pomalidomide, or thalidomide 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.

4.5. 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.

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. Similar summaries will be provided for subjects who received concomitant growth factor support, systemic steroids, antiviral systemic use, and prophylactic antiviral medications during the study, respectively.

Pre-dose medications and post-dose medications will also be summarized by therapeutic class, pharmacologic class, and preferred term, respectively.

4.6. Subsequent Anticancer Therapies

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

In addition, for subjects who received subsequent anticancer therapy for multiple myeloma, the best response to the first subsequent anticancer therapy will be summarized.

4.7. 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 by treatment group.

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.

In addition, duration of daratumumab administration in minutes is derived for each visit separately. It includes both interruption time and actual dose administration time, and is calculated as maximum dose administration end time – minimum dose administration start time. Duration of daratumumab administration in minutes will be summarized by first dose administration, second dose administration, and subsequent dose administrations.

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 each treatment group. Dose intensity will be summarized for both treatment groups in both units of mg/cycle and mg/kg/cycle. Additionally, the daratumumab dose intensity will be summarized by Cycles 1-2, Cycles 3-6, and Cycle 7+ during the treatment.

Relative dose intensity (%), which is defined as the ratio of total dose received and total planned dose, will be calculated and summarized for each treatment group. Additionally, the relative dose intensity will be summarized by Cycles 1-2, Cycles 3-6, and Cycle 7+ during the treatment.

The incidences of treatment cycle delays, dose delays, dose skip and corresponding reasons will be provided. The frequencies of actions planned prior to infusion or injection start and taken during infusion or injection will be summarized, together with reasons reported on eCRF. In addition, a summary of treatment modifications will also be provided by Cycles 1-2, Cycles 3-6, and Cycle 7+ during the treatment.

A separate listing including all daratumumab dose administration data will be provided.

4.8. 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 criteria
- Developed withdrawal criteria but not withdrawn
- Received wrong treatment or incorrect dose
- Received a disallowed concomitant treatment
- Other

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

5. EFFICACY

Assessment of disease will be conducted in accordance with the IMWG response criteria. Efficacy evaluations will include the following: measurements of myeloma proteins, bone marrow examinations, skeletal surveys and other imaging studies, and serum calcium corrected for albumin.

5.1. Analysis Specifications

5.1.1. Level of Significance

For the co-primary endpoint of ORR, the hypothesis tests will be based on one-sided test at significance level of alpha=0.025 to demonstrate the non-inferiority of Dara SC relative to Dara IV. If the non-inferiority of the Dara SC relative to Dara IV is claimed and the lower bound of the two-sided 95% CI of the relative risk is ≥100%, the superiority of Dara SC relative to Dara IV will be concluded.

For the co-primary endpoint of maximum C_{trough}, one-sided test at significance level of alpha=0.05 is selected to demonstrate the non-inferiority of Dara SC relative to Dara IV in terms of the maximum trough concentration.

Non-inferiority of Dara SC relative to Dara IV will be claimed only if both endpoints of ORR and maximum C_{trough} meet their criteria. Therefore, the overall type I error will be strictly controlled at level of alpha=0.025 (one-sided). In addition, since maximum C_{trough} is a pharmacokinetic endpoint, the conventional choice of alpha=0.05 (one-sided) is selected.

Once the non-inferiority null hypothesis is rejected for both the ORR and maximum C_{trough}, the following major secondary endpoints ordered below will be sequentially testing for superiority by utilizing a hierarchical procedure to control familywise Type I error rate at a two-sided significance level of 0.05. The major secondary endpoints will be sequentially tested in the following order:

1) Rate of infusion-related reactions
2) Progression-free survival
3) Rate of VGPR or better
4) Overall Survival

5.1.2. Computerized Algorithm

A validated computerized algorithm (Attachment 2), which is based on the IMWG response criteria (Durie 2006, Rajkumar 2011)[2,3] and has been used and validated by an independent review committee in study MMY2002, also used in MMY3003, MMY3004, MMY3007, and MMY3008 will be used to determine response and disease progression for each subject. Unless specified otherwise, relapse from CR by positive immunofixation or trace amount (defined as less than 0.5 g/dl) of M protein is not considered to be progressive disease in the IMWG response criteria.

The primary efficacy analyses will be based on the computerized algorithm assessments. Analyses for the primary endpoint ORR and selected major secondary efficacy endpoints based on investigator assessments using the IMWG response criteria will also be performed as sensitivity analyses.

5.1.3. Data Handling Rules

There is no imputation planned for missing efficacy endpoint values.

5.2. Primary Efficacy Endpoint(s)

5.2.1. Definition

The co-primary endpoint of this study for efficacy is overall response rate, which is defined as the proportion of subjects who achieve partial response (PR) or better according to the IMWG response criteria, including the subjects with either complete response (including stringent complete response [sCR]) or partial response (including VGPR), during or after treatment with study drug but at or prior to the start of subsequent anticancer therapy. Subjects with overall responses achieved after the start of subsequent anticancer therapy will not be considered as responders.

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 or refractory multiple myeloma who have received at least 3 prior lines of therapy including a PI and an IMiD, or whose disease is double refractory to both a PI and an IMiD;
- Variable: overall response, which is defined as response if the best response is PR or better assessed at or prior to the start of subsequent anticancer therapy and non-response otherwise;
- Intercurrent event: Treatment discontinuation is considered as an intercurrent event for overall response and treatment policy strategy will be implement, i.e., disease assessments ignoring the treatment discontinuation will be implemented.
- Population-level summary: relative risk of overall response between two treatment groups.

5.2.3. Analysis Methods

The primary 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, minimal response (MR), stable disease (SD), progressive disease (PD), and not evaluable (NE). The overall response (including sCR + CR + VGPR + PR), VGPR or better (sCR + CR + VGPR), and CR or better (sCR + 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.

Farrington-Manning (FM) test will be used to test the overall response rate. The FM estimate of relative risk with its 2-sided 95% confidence interval and p-value will be reported. If the lower bound of the 95% CI is $\geq$ 60%, the non-inferiority of Dara SC relative to Dara IV will be concluded. If non-inferiority in ORR is established and the lower limit of the 95% CI of the relative risk is $\geq$100%, the superiority of Dara SC relative to Dara IV will be concluded.

A sensitivity analysis of ORR based on the per-protocol and response-evaluable analysis sets will be performed in a similar manner as described above.

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

A supplementary analysis of ORR based on the first 480 randomized subjects in intent-to-treat analysis set will also be performed in a similar manner.

5.3. Major Secondary Endpoints

The major secondary efficacy endpoints include progression-free survival (PFS), response rate of VGPR or better, response rate of CR or better, time to next therapy (TNT), overall survival (OS), duration of response (DOR), and time to response (TTR).

5.3.1. Progression-free Survival

5.3.1.1. Definition

PFS is defined as the duration from the date of randomization to either progressive disease, according to the IMWG response criteria, or death due to any cause, whichever occurs first.

Subjects who start subsequent anticancer therapies for multiple myeloma without disease progression will be censored at the last disease assessment before the start of subsequent therapies. Subjects who withdrew consent from the study before disease progression will be censored at the last disease assessment before withdrawal of consent to study. Subjects who are lost to follow-up will be censored at the last disease assessment before 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 2 as follows.

Table 2: PFS Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
No postbaseline disease assessment	Randomization	Censored
Disease progression at or prior to start of subsequent anticancer therapy	Earliest date that indicates disease progression	PFS event
Death at or prior to start of subsequent anticancer therapy	Date of death	PFS event
Other, such as: Withdrawal of consent to study participation, Lost to follow-up Start of subsequent anticancer therapy prior to disease progression or death	Date of last disease assessment prior to withdrawal of consent to study participation, lost to follow-up, or start of subsequent anticancer therapy	Censored

5.3.1.2. Analysis Methods

Analysis of PFS 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 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. Stratification factors used in the analyses include body weight at baseline (≤65 kg, 66 kg to 85 kg, >85 kg), number of prior lines of therapy (≤4 prior lines versus >4 prior lines), and type of myeloma (IgG versus non-IgG).

In addition, the number and percentage of subjects who had a PFS event or were censored will be reported. The reasons for progressive disease and censoring of PFS will also be summarized for ITT analysis set.

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

5.3.2. Response Rate of VGPR or Better

5.3.2.1. Definition

Response rate of VGPR or better is defined as the proportion of subjects with a response of VGPR or better (VGPR, CR or sCR) according to IMWG response criteria, during or after treatment with study drug but at or prior to the start of subsequent anticancer therapy.

5.3.2.2. Analysis Methods

The response rate of VGPR or better will be calculated for each treatment group on both ITT and response-evaluable analysis sets. The corresponding 95% Clopper-Pearson exact CI will be provided.

Stratified CMH test will be used to test the proportion of subjects who achieved a VGPR or better response. The CMH estimate of odds ratio and its 95% confidence interval and p-value will be reported. Stratification factors used in the analysis include body weight at baseline (≤65 kg, 66 kg to 85 kg, >85 kg), number of prior lines of therapy (≤4 prior lines versus >4 prior lines), and type of myeloma (IgG versus non-IgG).

A sensitivity analysis of response rate of VGPR 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.

5.3.3. Response Rate of CR or Better

5.3.3.1. Definition

Response rate of CR or better is defined as the proportion of subjects with a response of a CR or better (CR or sCR) according to IMWG response criteria, during or after treatment with study drug but at or prior to the start of subsequent anticancer therapy.

5.3.3.2. Analysis Methods

The response rate of CR or better will be calculated for each treatment group on both ITT and response-evaluable analysis sets. The corresponding 95% Clopper-Pearson exact CI will be provided.

An 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 Next Therapy

5.3.4.1. Definition

Time to next therapy is defined as the time from randomization to the start of subsequent anticancer therapy for multiple myeloma. Death due to PD without start of subsequent anticancer therapy will be considered as event. Subjects who withdrew consent to study or are lost to

follow, or die due to causes other than disease progression or subjects without receiving subsequent anticancer therapy will be censored at date of death or the last date known to be alive.

5.3.4.2. Analysis Methods

TNT will be analyzed using similar statistical methods as described in Section 5.3.1.2 for PFS analysis.

5.3.5. Overall Survival

5.3.5.1. Definition

Overall survival is defined as the time from the date of randomization to the date of the subject's death due to any cause. Death after end of study will also be considered as an OS event.

Subjects who are lost to follow-up will be censored at the time of lost to follow-up. Subject who is still alive at the clinical cut-off date for the analysis will be censored at the date of last known to be alive. The date of last known to be alive will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

5.3.5.2. Analysis Methods

OS will be analyzed using similar statistical methods as described in Section 5.3.1.2 for PFS analysis.

A summary of reasons for censoring of overall survival will be provided.

5.3.6. Time to Response

5.3.6.1. 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 for patients who had PR or better as their best response.

5.3.6.2. Analysis Methods

For the 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.

The similar analyses will be conducted for time to response of VGPR or better and time to response of CR or better.

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

5.3.7. Duration of Response

5.3.7.1. Definition

Duration of response is calculated from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease as defined according to IMWG criteria or death due to PD, whichever occurs first, for the subjects who had achieved a response of PR or better.

Subjects who start subsequent anticancer therapies without PD will be censored at the date of the last disease assessment prior to the start of subsequent anticancer 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.

5.3.7.2. 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.

5.4. Other Efficacy Endpoints/Variables

Other efficacy endpoints include the proportion of subjects with best M-protein response for subjects with measurable disease in serum or urine, and the proportion of subjects with maximal reduction of ≥90% and ≥50% from baseline in the difference between involved and uninvolved serum FLC (dFLC) for subjects with measurable disease of FLC only, and exploratory efficacy endpoint of progression-free survival on next line of therapy (PFS2).

5.4.1. Best M-protein/dFLC Response

5.4.1.1. Definition

Serum/urine M-protein or FLC reduction, defined as the percent change from baseline at each post-baseline assessment visit in the quantitation of the corresponding serum/urine M-protein or FLC, according to the measurable type at baseline.

Best M-protein response is defined as the maximal percent reduction or the lowest percent increase from baseline in serum M-protein for subjects with measurable heavy chain at baseline or urine M-protein for subjects without measurable heavy chain, but with measurable light chain disease at baseline.

For subjects without measurable heavy chain and light chain disease at baseline, best response in serum dFLC is defined as the maximal percent reduction or the lowest percent increase from baseline in the difference between involved and uninvolved serum FLC level.

5.4.1.2. Analysis Methods

The number and percentage of subjects in each response category, along with presentation of ≥90% reduction and ≥50% reduction, will be tabulated for each treatment group.

5.4.2. Progression-free Survival on Next Line of Therapy (PFS2)

5.4.2.1. Definition

Progression-free survival on next line of therapy (PFS2) is defined as the time from randomization to progression on next line of therapy or death, whichever comes first. Any deaths are considered as PFS2 events, including the deaths after end of study.

Subjects who start next line of therapy without disease progression on study treatment will be censored at the last disease assessment before starting next line of therapy. For subjects who start next line of therapy after progression on study treatment, are still alive and not yet progress on next line of therapy, they will be censored on the last date of follow-up. Subjects without any post-baseline follow-up will be censored at the randomization.

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

Table 3: PFS2 Event and Censoring Method

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

5.4.2.2. Analysis Methods

PFS2 based on investigator assessment on ITT analysis set will be analyzed using similar statistical methods as described in Section 5.3.1.2 for PFS analysis.

5.5. Subgroup Analysis for Efficacy Endpoints

For assessment of internal consistency and investigation of homogeneity of the treatment effect across subgroups, a subgroup analysis of the primary efficacy endpoint of ORR based on pre-specified subgroups defined in Section 2.10 will be conducted.

A forest plot of subgroup analysis on ORR will be generated.

Additional exploratory subgroup analyses may be performed for selected efficacy and/or safety endpoints.

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), vital signs, 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.

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; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered drug-related by the investigator. 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.

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 of maximum toxicity grade of 1 to 5, and TEAEs leading to treatment discontinuation.

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 (e.g., ≥10%) TEAEs by SOC and PT
- TEAEs by SOC, PT, and maximum toxicity grade

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 (e.g., ≥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 treatment cycle.

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 drug:

- 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 drug
- Most commonly reported (e.g., ≥2%) serious TEAEs by SOC and PT

A similar summary of serious TEAEs will be presented by SOC, PT and treatment cycle.

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 treatment with study drug due to an adverse event on the eCRF "End of Treatment" page.

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

6.1.7. TEAEs Leading to Treatment Modifications

Incidence of TEAEs leading to treatment modifications (i.e., cycle delay, dose delays, or dose skip) will be summarized by SOC, PT and grade 3/4 for each treatment group.

6.1.8. TEAEs with Fatal Outcome

The TEAEs with fatal outcome will be summarized by PT and relationship to study drug 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 within 30 days of last dose and deaths within 60 days of first dose, respectively.

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

6.3. Adverse Events of Clinical Interest

6.3.1. Infusion-related Reactions

6.3.1.1. Rate of Infusion-related Reactions

For the major secondary endpoint of rate of IRRs, the proportion of subjects who have an IRR along with its 95% Clopper-Pearson exact CI will be calculated for each treatment group on the safety analysis set.

Stratified CMH test will be used to test the IRR rate. The CMH estimate of odds ratio and its 2-sided 95% confidence interval and p-value will be reported. Stratification factors used in the analysis include body weight at baseline (≤65 kg, 66 kg to 85 kg, >85 kg), number of prior lines of therapy (≤4 prior lines versus >4 prior lines), and type of myeloma (IgG versus non-IgG).

A subgroup analysis on rate of IRRs will be conducted for the subgroups of race and baseline weight defined in Section 2.10. A forest plot of the subgroup analysis on rate of IRRs will be generated.

6.3.1.2. Summary of Infusion-related Reactions

The incidence of infusion-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 will be presented. Time to onset of IRR will be summarized descriptively. The timing of IRR will also be evaluated through a summary of IRR by event onset time.

A listing of infusion-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. Treatment-emergent infections and infestations may also be summarized by preferred term and treatment cycles.

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. Tumor Lysis Syndrome

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

6.3.6. Second Primary Malignancies

The second primary malignancies during the study will be summarized by cancer type and preferred term. A listing of subjects who reported second primary malignancies during the study will also be provided. This listing will include diagnosis, study day of diagnosis, recurrence of a prior existing malignancy (yes, no) and pathology diagnosis (biopsy, aspirate etc.) information whenever a second primary malignancy is observed. In addition, cumulative study drug exposure, the treatment for second primary malignancy and the outcome information will also be presented in the listing.

6.3.7. Adverse Events by Subgroups

The subgroup analysis for the following TEAEs will be performed based on the subgroups specified in Section 2.10:

- 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
  - sodium
  - alkaline phosphatase
  - uric acid
  - blood urea nitrogen (BUN) or urea
  - calcium and albumin-adjusted calcium
  - lactic acid dehydrogenase (LDH)
  - 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, and creatinine.

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.

6.5. Vital Signs and Physical Examination Findings

Descriptive statistics will be provided for values and changes from baseline over time for vital signs (pulse, temperature, systolic and diastolic blood pressure) at each scheduled visit. Similar analysis may be performed for weight at Day 1 of each treatment cycle.

Clinically significant physical examination findings occurred at post-baseline were collected as AEs, and therefore will not be summarized.

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, Day 1 of each treatment cycle and end-of-treatment visit. The shift summaries of ECOG performance status from baseline to each scheduled visit, including Day 1 of each treatment cycle and end-of-treatment visit, will be provided for each treatment group. The shift summary from baseline to the worst performance score during treatment will also be presented.

7. PHARMACOKINETICS/IMMUNOGENICITY/PHARMACODYNAMICS

Unless specified otherwise, descriptive statistics will be used to summarize pharmacokinetics and pharmacodynamics data. In addition, coefficient variation and geometric mean will be provided in the pharmacokinetic concentration summary.

7.1. Pharmacokinetics

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:

- Maximum C_{trough} - Serum pre-dose concentration of daratumumab on Cycle 3 Day 1
- C_{min} - Minimum observed concentration
- C_{max} - Maximum observed concentration

The Maximum C_{trough}, 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.

7.1.1. Maximum C_{trough}

For the co-primary endpoint maximum C_{trough}, which is defined as the concentration at pre-dose on Cycle 3 Day 1, the summary statistics such as the geometric mean, coefficient of variation, median, and range will be provided by treatment group. The ratio of the geometric means and the

corresponding 90% confidence interval utilizing logarithmic transformation of C_{trough} values will be provided. If the lower bound of the 90% CI for the ratio of the geometric means of maximum C_{trough} is ≥ 80% (non-inferiority margin of 20%), Dara SC will be considered non-inferior to Dara IV.

Box plot of maximum C_{trough} will be provided.

The analyses of maximum C_{trough} will be performed on the pharmacokinetics-evaluable analysis set.

7.1.2. Other Pharmacokinetic Parameters

The following pharmacokinetic parameters will also be summarized on the pharmacokinetics analysis set:

- Minimum observed concentration (C_{min}): defined as the concentration observed immediately before dose administration;
- Maximum observed concentration (C_{max}): defined as the concentration observed after the end of dose administration.

The C_{min} and C_{max} will be determined based on assigned collection timepoint. Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point specified in protocol. Plot of mean (±standard deviation) daratumumab serum peak and trough concentrations over time will be provided.

A scatter plot of daratumumab serum concentration over time will also 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 or Dara IV and have appropriate samples for detection of anti-daratumumab antibodies (i.e., subjects with at least 1 sample obtained after their first dose of daratumumab).

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

Subjects who are positive for anti-daratumumab or anti-rHuPH20 antibodies will be listed. A listing of subject status of anti-daratumumab or anti-rHuPH20 antibodies at any time during the study with daratumumab concentrations at the time of each immunogenicity sample will also be provided.

7.3. Pharmacokinetic/Pharmacodynamics Analyses

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. BIOMARKER

Biomarker studies are designed to evaluate if there are any differences with Dara SC and Dara IV on biomarkers for daratumumab pharmacodynamics and mechanism of action. Samples for biomarker evaluations will be collected as specified in the protocol Time and Events Schedule.

The immunophenotyping analyses including the assessments of natural killer (NK) cells, T cells, and B cells in peripheral blood will be performed. The analyses for CD38+ myeloid-derived suppressor cells (MDSCs) and CD38+ regulatory T cells will also be performed.

Descriptive statistics for values and changes from baseline at each scheduled visit for absolute counts (cells/µl) of total NK cells and percent total NK cells (as a percentage of lymphocytes) in peripheral blood will be provided. The plots of absolute counts of total NK cells and percent NK cells in blood over time will also be provided. Similar analyses will be performed for CD8+ T cells, activated CD8+ T cells, CD3+ T cells, B cells, CD38+ myeloid-derived suppressor cells, and CD38+ regulatory T cells as well.

Further analysis of other biomarkers may be performed and the results may be presented in a separate report.

9. PATIENT-REPORTED OUTCOMES

The modified Cancer Therapy Satisfaction Questionnaire (modified-CTSQ) is a patient-reported outcome (PRO) measure to assess patient satisfaction of Dara SC compared with Dara IV in support of market access and payer request for patient-reported outcomes data.

The modified-CTSQ was adapted, with approval from the instrument developer, to contain 9 items specific to satisfaction with therapy and for comparison of IV with SC mode of administration. Each item asks about the most recent cancer therapy using a 5-point verbal rating scale (see Attachment 3). The modified-CTSQ asks about previous administration of daratumumab, not the current visit administration. To achieve unbiased assessments, the modified-CTSQ should be administered before the subject's clinical examination, the subject receives any tests or test results, and the subject's health, health data, or emotions are discussed.

The modified-CTSQ is a secondary endpoint, not part of the statistical hierarchy. Non-inferiority will not be analyzed for this endpoint. Type I error control was not applied to patient-reported outcome data.

9.1. Modified-CTSQ Scoring

For this study, the modified-CTSQ contains 1 multi-item domain (Satisfaction with Therapy [SWT]) and 2 single items (Thoughts about Cancer Therapy) as summarized in Table 4, each item has 5 response options coded as 1-5.

Table 4: Modified-CTSQ Domain Structure and Scoring Information

Modified-CTSQ Domain	Description of Items in Domain	Total # of Items	Minimum # of Completed Items Required to Score
Thoughts about Cancer Therapy (CT)	Q1: Worth taking even with side effects Q2: Think about stopping CT	2	No summary score
Satisfaction with Therapy	Q3: How worthwhile was CT Q4: Taking CT as difficult as expected Q5: Benefits meet expectations Q6: Were side effects as expected Q7: Satisfied with form of CT Q8: Satisfied with most recent CT Q9: Would you take this CT again	7	5

For most of the items, a higher coded number indicates a more positive response (e.g., 5 is the most positive response indicator and 1 is the least positive response indicator). However, for items Q2 (think about stopping CT) and Q4 (taking CT as difficult as expected), a higher coded number indicates a more negative response. For the analysis purpose, to ensure that a higher domain score is associated with a better response outcome and a lower domain score is associated with a worse response outcome, we need to reverse-code the response values for these two items Q2 and Q4. This is done by subtracting the initial (raw) response value from 6 for each of these 2 items. For example, we create 2 new variables Q2R and Q4R which contain reverse-coded response values for items Q2 and Q4:

$$Q2R = 6 - Q2;$$

$$Q4R = 6 - Q4;$$

To calculate the domain score for Satisfaction with Therapy (SWT), the minimum number of completed items is required, as shown in Table 4. If the number of completed items is greater than or equal to the minimum number of completed items required, the domain score is calculated using the following formula in general:

Domain score = [(Sum of completed item responses/Number of completed items) - 1] × 100 / (Maximum possible item response value – Minimum possible item response value)

However, if fewer items are completed than the minimum number indicated in Table 4, then the domain is not scored (i.e. a missing value is assigned).

Since the maximum possible item response value is 5 and the minimum possible response value is 1 for all modified-CTSQ items, a simpler way to represent the above formula for the modified-CTSQ SWT domain is: SWT domain score = (Mean of completed item responses – 1) × 25. For Q4 item, the reverse-coded response value Q4R is used in calculating SWT domain score.

For the modified-CTSQ SWT domain, a higher calculated domain score on a scale of 0 to 100 is a more positive indicator.

9.2. Analysis Method

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 scheduled assessment, and others will be unscheduled assessments.

At each time point for analysis, the number and percentage of modified-CTSQ 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 particular 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.

For each modified-CTSQ item score and SWT domain score, descriptive statistics (n, mean, standard deviation, median, and range) will be provided for each time point by treatment group. The mean difference (with its 95% CI) of SWT domain score will be calculated and compared between treatment groups at each time point.

Line plot of mean scores with standard error over time will be displayed by treatment group for each individual item score and SWT domain score.

10. MEDICAL RESOURCE UTILIZATION

Medical resource utilization data associated with medical encounters due to IRRs or injection site reactions, primarily hospitalizations, outpatient visits and emergency room visits, will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study.

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 will be tabulated. The treatment-emergent adverse events leading to the hospitalization/outpatient visits and leading to on-study transfusions will also be summarized.

REFERENCE

1. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med. 1990;9:1447-1454.
2. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467–1473. Corrigenda/Erratum in: Leukemia. 2007; 21:1134-1135.
3. Rajkumar SV, Harousseau J-L, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011; 4691-4695.

ATTACHMENT 1: ADDITIONAL EXPLORATORY ANALYSIS TO SUPPORT HEMAR

1. DEFINITION OF SUBGROUPS

Subgroup analyses will be performed using listed below to determine whether the treatment effect is consistent among subgroups. Analyses will be conducted for the ITT population and for the following subgroups:

- For subjects who reached CR/sCR as their best response
- For subjects who reached VGPR as their best response
- For subjects who reached PR as their best response
- For subjects who reached MR/SD as their best response
- For subjects who reached PD as their best response
- For subjects who reached MR or better as their best response (i.e. subjects with clinical benefit)
- For subjects who reached PR or better as their best response
- For subjects who reached VGPR or better as their best response

2. SUBGROUP ANALYZES

Kaplan-Meier estimates will be used to estimate distribution of time to event by treatment arm based on all ITT population. Data will be calculated and summarized with descriptive statistics. The following time-to-event endpoints will be analyzed by pre-defined subgroups as defined in section 2.10 and in section 1, Appendix:

- PFS
- TNT
- OS
- DOR
- PFS2

In addition, as described in Sections 5.3.6 (TTR), 6.3.1 (IRR) and 9.2 (PRO), the following endpoints will be evaluated by pre-defined subgroups as defined in section 2.10 and in section 1, Appendix:

- TTR
- IRRs
- modified-CTSQ

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ATTACHMENT 3: MODIFIED CANCER THERAPY SATISFACTION QUESTIONNAIRE

Modified Cancer Therapy Satisfaction Questionnaire
US English

The following pages ask some questions about your cancer therapy (IV/SC). Within this questionnaire, "Cancer therapy (IV/SC)" refers to your current or most recent cancer therapy (including: IV therapy and subcutaneous therapy (SC)). Please read each question and answer as honestly as you can without the help of anyone. There are no right or wrong answers; the answers should be based on your own personal experiences.

Your Thoughts about Cancer Therapy (IV/SC)

The following statements ask you to share your **thoughts about cancer therapy (IV/SC)**. Please answer each question below by *checking the box* that best represents your opinion (check only one box per question).

In general, in the last four weeks, how *often did you feel*:	**Always**	**Most of the time**	**Some-times**	**Rarely**	**Never**
1. That cancer therapy (IV/SC) was worth taking even with the side effects?	☐5	☐4	☐3	☐2	☐1

2. In general, **in the last four weeks**, how often did you think about stopping your cancer therapy (IV/SC)?

☐5	☐4	☐3	☐2	☐1
Always	Most of the time	Sometimes	Rarely	Never

Satisfaction with Cancer Therapy (IV/SC)

The following statements are about your satisfaction with your **most recent cancer therapy (IV/SC)**. Please answer each question below by *checking the box* that best describes your level of satisfaction (check only one box per question).

3. **Overall**, how worthwhile was your cancer therapy (IV/SC)?

☐5	☐4	☐3	☐2	☐1
Very worthwhile	Quite worthwhile	Moderately worthwhile	A little worthwhile	Not worthwhile at all

4. **Overall**, was taking cancer therapy (IV/SC) as difficult as you expected?

☐5	☐4	☐3	☐2	☐1
Much more difficult than I thought it would be	Somewhat more difficult than I thought it would be	As difficult as I thought it would be	Somewhat easier than I thought it would be	Much easier than I thought it would be

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5. **Overall,** how well did the **benefits** of cancer therapy (IV/SC) meet your expectations?

☐5	☐4	☐3	☐2	☐1
Much better than my expectations	Somewhat better than my expectations	Met my expectations	Somewhat worse than my expectations	Much worse than my expectations

6. **Overall,** were the **side effects** of cancer therapy (IV/SC) as you expected?

☐5	☐4	☐3	☐2	☐1
Much better than I expected	Somewhat better than I expected	Exactly as I expected	Somewhat worse than I expected	Much worse than I expected

7. How satisfied were you with the **form** of your cancer therapy (IV/SC)?

☐5	☐4	☐3	☐2	☐1
Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

8. **Overall,** how satisfied were you with your most recent cancer therapy (IV/SC)?

☐5	☐4	☐3	☐2	☐1
Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

9. Taking everything into consideration, if given the choice again, would you decide to take this cancer therapy treatment?

☐5	☐4	☐3	☐2	☐1
Yes, definitely	Probably Yes	I don't know	Probably not	Definitely not

Thank you.

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