Janssen Research & Development

Statistical Analysis Plan
Report for Primary Analysis

An Open label, International, Multicenter, Dose Escalating Phase 1/2 Trial Investigating the Safety of Daratumumab in Combination with Lenalidomide and Dexamethasone in Patients with Relapsed or Relapsed and Refractory Multiple Myeloma

Protocol GEN503 Amendment 7

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

None

ABBREVIATIONS

AE	Adverse Event
CAE	Critical Adverse Event
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
DLT	Dose-Limiting Toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic(s)
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation

1. INTRODUCTION

This is an open-label, dose-escalation, multicenter, Phase 1/2 safety study of daratumumab in combination with lenalidomide and dexamethasone (Len/Dex) in the treatment of subjects with relapsed or relapsed and refractory multiple myeloma. The dose escalation portion of the study (Phase 1) will be a standard 3 + 3 design and will evaluate daratumumab, at doses from 2 mg/kg up to a maximum of 16 mg/kg, in combination with Len/Dex in 28-day treatment cycles. A recommended Phase 2 dose (RP2D) will be determined during Phase 1. The Phase 2 will open to further explore the safety and efficacy of the RP2D in approximately 30 subjects.

This document serves as the statistical analysis plan for the primary analysis, covering both Phase 1 and Phase 2 of the study. As of Amendment 7, the primary analysis will be achieved. All subjects in the study have either received at least 12 months of study drug or have discontinued. Ongoing subjects may continue treatment with study drug with a limited schedule of assessments. The study treatment of daratumumab, lenalidomide or dexamethasone is referred to as the "study drug" throughout.

1.1. Trial Objectives

Primary Objective

The primary objective is to establish the safety profile of daratumumab when given in combination with Len/Dex in subjects with relapsed or relapsed and refractory multiple myeloma.

Secondary Objectives

- To evaluate the efficacy of daratumumab when given in combination with Len/Dex in subjects with relapsed or relapsed and refractory multiple myeloma.
- To evaluate the pharmacokinetic (PK) profile of daratumumab when given in combination with Len/Dex in subjects with relapsed or relapsed and refractory multiple myeloma.
- To assess the immunogenicity of daratumumab.

1.2. Trial Design

This is an open-label, dose-escalation, multicenter Phase 1/2 safety study of daratumumab in combination with Len/Dex in the treatment of subjects with relapsed or relapsed and refractory multiple myeloma. The dose escalation portion of the study (Phase 1) will be a standard 3 + 3 design and will evaluate daratumumab, at doses from 2 mg/kg up to a maximum of 16 mg/kg, in combination with Len/Dex in 28-day treatment cycles. The standard "3 + 3" rules for dose escalation will be applied, However, if the study sites have identified 4 eligible subjects to start a new dose level, all 4 subjects may be enrolled. The maximum tolerated dose (MTD) will be defined as the highest dose of the combination regimen at which less than 33% of subjects experience dose-limiting toxicity (DLT). A recommended Phase 2 dose (RP2D) will be determined during Phase 1. The MTD or any dose evaluated in the range of 2 to 16 mg/kg of daratumumab may be considered as the RP2D based on available safety, PK/pharmacodynamic, and efficacy data from Phase 1. The RP2D could be selected before escalation to or completion

of the 16 mg/kg cohort. Once the RP2D is determined, the expansion (Phase 2) will open to further explore the safety and efficacy of the RP2D in approximately 30 subjects.

For Phase 1 and Phase 2 of the study there will be a Screening Period followed by the first 2 treatment cycles and will consist of weekly daratumumab infusions, totaling 4 infusions during each 28-day cycle. Cycles 3 through 6 will consist of daratumumab infusions administered every other week; Cycle 7 and all subsequent cycles will consist of monthly daratumumab infusions. The combination treatment may continue until the subject experiences disease progression or unacceptable toxicity, whichever comes first. For Phase 1 only, to minimize the risk of cytokine release syndrome, the first infusion of the first cycle will be preceded by a predose infusion the day before the scheduled full-dose infusion. The predose infusion will be 10% of the full dose, but will never be more than 10 mg in total dose. Further measures to prevent cytokine release syndrome will include premedication with antihistamines, acetaminophen, and dexamethasone before each daratumumab infusion (both predose and full dose).

For Phase 1 and Phase 2, lenalidomide will be administered at a dose of 25 mg orally (PO) on Days 1 through 21 of each 28-day cycle, and dexamethasone will be administered at a total dose of 40 mg weekly. As of Amendment 6, subjects older than 75 years or underweight (body mass index [BMI] <18.5), the dexamethasone dose may be administered at a dose of 20 mg weekly. On weeks when daratumumab is administered the 20 mg dose should be administered as the pre-medication per protocol. Details on the dosing regimens for Len/Dex are provided in protocol.

During Phase 1, decisions to escalate the dose of daratumumab for the next cohort will be based on the safety data obtained from the 3 (+ 3) subjects in the previous cohort during their first treatment cycle (28 days). The Independent Data Monitoring Committee (IDMC) will evaluate all safety data (including SAEs, AEs, and laboratory data) after each cohort completes Cycle 1. The third subject in the cohort must have received all 4 full doses of daratumumab, and data from an observation period of 6 days after the last infusion must be available for the IDMC to review. Based on the results presented in these safety profiles, the IDMC will recommend to the sponsor if it appears safe to escalate the dose. The recommendation will be discussed and confirmed by the sponsor, who will ultimately decide if dose escalation will occur. Subjects who discontinue the study during the first cycle for reasons other than a DLT will be replaced.

The IDMC and sponsor may decide to implement intermediate doses to ensure subject safety and better define the RP2D. The RP2D, as defined by the IDMC and sponsor, or the maximum dose tested will be the dose level at which subjects will be treated in Phase 2 of the study.

In both phases of the study, investigational product will be administered per schedule up to disease progression, intolerability, withdrawal, death, or unless otherwise indicated by IDMC. Daratumumab may be continued until investigator's or sponsor's recommendation of discontinuation, the subject's decision to discontinue for any reason, or disease progression.

1.3. Statistical Hypotheses for Trial Objectives

For both two phases, the primary endpoint is adverse event; therefore, no formal statistical hypothesis testing is planned.

1.4. Sample Size Justification

No formal sample size determination was performed for Phase 1 of this study because a standard dose escalation study design of 3 + 3 subjects in each cohort was chosen for Phase 1.
For Phase 2, it is assumed that lenalidomide + dexamethasone would achieve an overall response rate (ORR) of 50% in the targeted population. With a two-sided alpha of 0.10 and assuming that the addition of daratumumab improves the ORR to 75%, a sample size of approximately 30 subjects would achieve 89% power to detect such a difference. If the addition of daratumumab can improve the ORR to 80%, this sample size would achieve 97% power to detect such a difference.

1.5. Randomization and Blinding

Not applicable.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

The baseline value is defined as the closest non-missing value taken on or prior to the first dosing date (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.

Day 1 is the first dosing date.

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

However, assessment performed in the same cycle may not be well aligned in time scale for different subjects due to possible cycle delays. To address this, the following by-week windowing rule will be used.

Time Interval (Week)	Time Interval (Study Day)	Target Time Point
Baseline	Day ≤ 1	1
Week 1	2 ≤ Day ≤ 11	8
Week 2	12 ≤ Day ≤ 18	15
Week 3	19 ≤ Day ≤ 25	22
Week 4	26 ≤ Day ≤ 32	29
Week 5	33 ≤ Day ≤ 39	36
Week 6	40 ≤ Day ≤ 46	43
Week 7	47 ≤ Day ≤ 53	50
Week 8	54 ≤ Day ≤ 63	57
Week 10	64 ≤ Day ≤ 77	71
Week 12	78 ≤ Day ≤ 91	85
Week 14	92 ≤ Day ≤ 105	99
Week 16	106 ≤ Day ≤ 119	113
Week 18	120 ≤ Day ≤ 133	127
Week 20	134 ≤ Day ≤ 147	141
Week 22	148 ≤ Day ≤ 161	155

Week 24	162 ≤ Day ≤ 182	169
Week 28	183 ≤ Day ≤ 210	197
Week 32	211 ≤ Day ≤ 238	225
Week 36	239 ≤ Day ≤ 266	253
…	…	…
Week 4*(X-1)	(X-1)*28 – 13 ≤ Day ≤ (X-1)*28 + 14	(X-1)*28 + 1
…	…	…

If more than 1 assessment falls within the same time window, the one closest to the target day will be considered as scheduled and others as unscheduled #1, #2, etc., achieving 1 assessment per time interval.

2.2. Pooling Algorithm for Analysis Centers

Not applicable.

2.3. Analysis Sets

2.3.1. Efficacy Analysis Set(s)

The following efficacy populations will be used for Phase 2.

Intent-to-Treat (ITT) population: all enrolled patients who signed the informed consent during Phase 2. This is the analysis population for all efficacy endpoints.

Per-protocol (PP) population: all ITT patients who met all entry criteria and did not have any major protocol deviations that would significantly impact efficacy evaluation during Phase 2. The PP population will be used as sensitively analyses for the selected efficacy endpoints.

2.3.2. All Treated Analysis Set

All treated analysis set includes all enrolled patients who received at least one non-zero dose of any study drug during Phase 1. This population will be used for all efficacy and safety analyses in Phase 1.

2.3.3. Safety Analysis Set

The safety analysis set includes all enrolled patients who received at least one non-zero dose of any study drug during Phase 2. This population will be used for all safety analyses in Phase 2.

2.3.4. QT Evaluable Analysis Set

QT evaluable analysis set in each phase consists of all enrolled patients who had at least one non-zero dose of daratumumab, and had a baseline Electrocardiogram (QT) evaluation and a post-baseline QT evaluation.

2.4. Definition of Subgroups

Not applicable for Phase 1.

For Phase 2, exploratory subgroup analyses may be performed for selected efficacy endpoints:

Subgroup	Category	Analysis Type
Age	18- < 65, 65- <75, ≥ 75	E,S
Sex	Female, Male	E,S
Race	White, Other (excluding unreported)	E
ISS staging	I, II, III	E
Number of prior lines of therapy	1 line, 2-3 lines, >3 lines	E
Refractory to PI	Yes	E
Refractory to last line of prior therapy	Yes	E
Prior exposure to lenalidomide	Yes, No	E
Type of myeloma	IgG vs. non-IgG	E
Renal function	Creatinine clearance: <30, 30- <60, ≥ 60 mL/min	E
Bone marrow % plasma cells	≤30, 30<- ≤60, >60	E

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

2.5. Imputation of Missing Data

2.5.1. Adverse Event Start/End Date

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

- When month and year are present and the day is missing. If the onset month and year are the same as the month and year of first dose date, the day of first dose 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 dose, the first day of the month is imputed.
- When only a year is present or no components of the onset date are present. If the onset year is the same as the year of first dose, if AE end date is available and is prior to first dose date, the day and month of AE end date are imputed. Otherwise, the day and month of the first dose date are imputed. If the onset year is different from the year of first dose, the 1st of January is imputed.
- If the onset date is completely missing, the first dose date is imputed as the onset date.
- No imputation will be done for partial or missing AE onset time.

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

- If month and year are present and the day of the month is missing, the last day of the month is imputed.
- If only a year is present, the 31st of December is used.
- If 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.

2.5.2. Concomitant Medication Start/End Date

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

- If the date is completely missing, no imputation will be performed.
- Otherwise, the following rules will be applied to impute partially missing dates (start date, stop date). If only the day is missing, the 15th day of the month will be used. If both the day and month are missing, the 30th of June will be used.

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

2.6. Other General Definitions

2.6.1. Measurable Multiple Myeloma and Measurable Type

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

- Serum monoclonal paraprotein (M-protein) level ≥ 1.0 g/dL or urine M-protein level ≥ 200 mg/24 hours; or
- IgA multiple myeloma: Serum M-protein level greater than or equal to 0.5 g/dL or urine M-protein level ≥ 200 mg/24 hours; or
- Light chain multiple myeloma: Serum immunoglobulin free light chain (FLC) ≥ 10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.

If a patient meets criteria for serum M-protein, the measurable disease type is serum; otherwise, if a patient meets criteria for urine M-protein, the measurable disease type is urine; otherwise if a patient meets criteria for FLC, the measurable disease type is FLC.

2.6.2. Type of Multiple Myeloma

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

A patient 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 patient 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 patient will be classified as 'Serum free light chain only' if all reported results are 'Not Detected'. A patient will be reported as 'biclonal' if the distinct test results contain different heavy chain values or different FLC values.

2.6.3. ISS Staging

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

- Stage I: B2MG < 3.5 mg/L and ALB ≥ 3.5 g/dL (≥35 g/L)
- Stage III: B2MG ≥ 5.5 mg/L
- Stage II: neither I nor III.

2.6.4. Refractory Disease

Refractory myeloma is defined as disease that is nonresponsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have achieved minimal response (MR) or better before progressing. The following refractory disease categories are derived: refractory to PI only, refractory to IMiD only, refractory to PI + IMiD, refractory to the last line of prior therapy, refractory to alkylating agents (ALKY), or refractory to PI + IMiD + ALKY, In addition, refractoriness to bortezomib, carfilzomib, lenalidomide, pomalidomide, thalidomide or combinations will also be derived.

2.6.5. Month and Year

One year equals to 365.25 days. One month equals to 365.25/12 days.

2.6.6. Years since Initial Multiple Myeloma Diagnosis

This is calculated as date of first dose – date of initial MM diagnosis +1, divided by 365.25.

2.6.7. Total Dose Received

Total dose of daratumumab is the sum of administered doses recorded on the infusion forms at all visits, which is calculated in mg/kg.

2.6.8. Duration of Treatment/Infusion

Duration of study drug in months is derived as last dose date – first dose date + 1, divided by 365.25/12, separately for daratumumab, lenalidomide and dexamethasone.

Duration of daratumumab infusion in hours is derived for each infusion. It includes actual infusion time and interruption time if any.

2.6.9. Duration of Follow-up

The end of follow-up is the date of death for subjects who died; for subjects who are still alive, 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,

bone marrow cytogenetics, lytic bone lesions, extra-medullary plasmacytomas, study drug administration, ECG, disposition, concomitant medications, subsequent therapy, clinical events/disease response per investigator and date of last known to be alive.

Duration of follow-up (in months) equals the end of follow-up minus the first dosing date plus 1, divided by 365.25/12.

2.6.10. Relative Dose Intensity

The relative dose intensity (%) is the ratio of total dose received (mg/kg) and total planned dose (mg/kg), calculated as the planned dose level times the number of administered infusions.

2.6.11. Relationship of Adverse Events to Study Drug

For each adverse event, its relationship to study drug is determined by investigator and recorded on the eCRF. An adverse event is considered as related to study drug if the relationship is possible or probable.

2.6.12. Treatment Emergent Adverse Events

Treatment emergent adverse events (TEAEs) are defined as any AE with onset date and time on or after that of the first dose of study drug infusion through 30 days after the last dose of study drug or the day prior to start of subsequent therapy, whichever is earlier; or any AE that is considered related to (probably, or possibly related) study drug 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 infusion .

2.6.13. Linking of Treatment Emergent Adverse 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.

2.7. General Analysis Specifications

Categorical variables are to be summarized using frequency counts and percentages. Continuous variables are to be summarized by the following descriptive statistics: mean, standard deviation, median and range (minimum and maximum).

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

No formal interim analysis is planned. However, this interim data cut intends to support the BLA submission.

An independent data monitoring committee (IDMC) is used to make the RP2D dose recommendation based on the safety data in Phase 1. The IDMC and sponsor may decide to implement intermediate doses to ensure subject safety and better define the RP2D. The RP2D, as defined by the IDMC and sponsor, or the maximum dose tested will be the dose level at which subjects will be treated in Phase 2 of the study.

In both phases of the study, investigational product will be administered per schedule up to disease progression, intolerability, withdrawal, death, or unless otherwise indicated by IDMC.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Subject eligibility will be summarized for all subjects with a non-missing informed consent date. Number of subjects who did not meet all inclusion/exclusion criteria will be summarized, together with the specific non-met criterion. A listing of subjects who didn't meet all inclusion/exclusion criteria will be produced.

Patient enrollment will be summarized by country and site.

The following demographic and baseline characteristic panels will be summarized by dose group (2, 4, 8, or 16 mg/kg) and overall for Phase 1, and for the safety population for Phase 2:

- Demographics: age (continuous), age category (18 to < 65 years, 65 to < 75 years, and ≥ 75 years), sex (male, female), race (White, Black, Asian, Other, Not reported), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported), height (cm), weight (kg), baseline ECOG performance status (0, 1, 2).

- Baseline disease characteristics: type of myeloma (IgA, IgD, IgE, IgG, IgM, light chain, biclonal, other), ISS Staging (I, II, III), time since initial MM diagnosis (years), number of lytic bone lesions (None, 1-3, 4-10 more than 10), and bone marrow % plasma cells < 5, ≥5 – ≤ 10, >10 – ≤ 30, > 30).

- Disease related laboratory values: hemoglobin (g/L), hemoglobin category (< 80 g/L, 80 – 100 g/L, >100 g/L), platelets (giga/L), platelets category (< 75 giga/L, ≥ 75 giga/L), calcium (mmol/L), calcium category (>ULN, ≤ULN), corrected calcium (mmol/L), corrected calcium category ((>ULN, ≤ULN)， creatinine (umol/L), creatinine category (> ULN, ≤ ULN), (mg/L), creatinine clearance (mL/min), creatinine clearance category (≥ 90, 60 - < 90, 30 - < 60, 15 - < 30, < 15 mg/L), albumin (g/L), and albumin category (< 35 g/L, ≥ 35 g/L).

- Renal impairment using baseline creatinine clearance: Stage 1: ≥ 90 ml/min; Stage 2: 60 – <90 mL/min; Stage 3: 30 – <60 mL/min; Stage 4: 15 – <30 mL/min; Stage 5: < 15 mL/min

In addition, two panels of baseline laboratory tests will be summarized: hematology and serum chemistry.

The frequencies of CTC toxicity grade for these laboratory parameters at baseline will also be provided.

General medical history (including past and current conditions) will be summarized separately by body system and preferred term. Listing will be generated for abnormal medical history and prior surgeries.

Vital signs, including temperature, pulse, systolic and diastolic blood pressure at baseline will be summarized.

ECG results at baseline will be summarized by overall interpretation: normal, abnormal and clinically significant, abnormal and not clinically significant.

4.2. Disposition Information

The number of patients, who were screened, enrolled and failed screening will be summarized overall. The reasons for screening failure will also be provided.

The number of patients who withdraw from study treatment (end of treatment information), including the reason for withdrawal from treatment, will also be summarized by dose group and overall for all treated subjects in Phase 1 and for the safety population in Phase 2.

All disposition and withdrawal data will also be listed.

4.3. Treatment Compliance

See Section 4.4.

4.4. Extent of Exposure

Descriptive statistics will be provided by dose group and overall for total number of pre-dose (Phase 1 only) and full daratumumab infusions, treatment duration (the interval between date of first infusion and date of last infusion), total dose (mg) received from pre-dose and full infusions, and relative dose intensity (calculated for each full-infusion as the ratio of dose intensity (mg/kg) and the planned dose level (mg/kg)).

The number and percent of patients with incomplete daratumumab infusions (i.e. total volume of infusion not administered) and reason for incomplete infusion will be summarized by dose group, visit and overall.

The duration of daratumumab infusions (hours) will also be summarized.

All infusions will be listed by patient and visit. For Phase 1, both pre-dose and full infusions will be listed.

Exposure to lenalidomide and dexamethasone (dose and duration) will be also summarized separately by dose group, visit and overall.

4.5. Protocol Deviations

Number of patients who did not meet all inclusion/exclusion criteria will be summarized, together with the specific non-met criterion. A listing of major protocol deviation will be provided.

4.6. Prior and Concomitant Medications

Only prior medications collected in this trial are the prior MM therapies as recorded on the CRF.

The number of lines of prior MM therapy will be summarized descriptively as well as by the following categories: 1, 2-3, >3. Frequency will also be presented for subjects with the following types of prior therapies: PI, IMiD, radiotherapy, steroids, lenalidomide, pomalidomide, thalidomide, bortezomib, carfilzomib, dexamethasone, prednisone, chemotherapy, alkylating agents, anthracyclines, and ASCT.

The incidence of refractory status to the most recent IMiD or PI will be provided (none, PI only, IMiD only, both PI and IMiD). The incidence of subjects that are refractory to the last line of therapy, alkylating agents, bortezomib, carfilzomib, lenalidomide, pomalidomide, and thalidomide will be provided separately.

In addition, a listing will be provided, including all prior multiple myeloma therapy.

Use of concomitant therapies and concomitant steroids therapy will be provided separately by therapeutic class, pharmacologic class, and preferred term. Additionally, a listing will be generated for all concomitant medications.

Pre-infusion medications will be grouped by analgesics, antihistamines, corticosteroids (long-acting, intermediate-acting), and other. Post-infusion medications will be grouped by analgesics, antihistamines, corticosteroids (long-acting, intermediate-acting). The incidence of pre-infusion and post-infusion medications will be presented by the aforementioned groups and preferred terms.

In addition, subsequent anticancer therapy will be summarized and listed similarly.

5. EFFICACY

5.1. Analysis Specifications

For Phase 1, all treated population will be used for all efficacy analyses.

For Phase 2, ITT/PP population will be used for efficacy analyses.

All categorical data will be presented as frequencies and percentages. The total number of patients in the population (N) will be used as the denominator for percentage calculations, unless stated otherwise in the table shell. Percentages will not be calculated for zero frequencies.

All continuous data will be summarized by using number of patients with available data to be summarized (n); mean; standard deviation (SD); median; minimum and maximum. In general, the minimum and maximum will be presented to the same number of decimal places as the raw data; the mean and median will be presented to 1 more decimal place than the raw data; the SD will be presented to 2 more decimal places than the raw data.

5.1.1. Level of Significance

No formal statistical test will be conducted.

5.1.2. Data Handling Rules

Efficacy assessment will be performed by sponsor per International Multiple Myeloma Working Group (IMWG) guidelines (Durie 2006, Rajkumar 2011). Response will be assessed by a computerized algorithm. An efficacy data listing will be generated to show the components for the response assessments.

Detailed data handling rules for efficacy assessment are provided in a separate computerized algorithm document: Disease Progression and Response Assessment.

5.2. Primary Efficacy Endpoint

Definition

Overall response rate (ORR) is defined as the proportion of patients with either complete response (CR, including stringent complete response [sCR]) or partial response (PR, including very good partial response [VGPR]).

The objective response according to the International uniform response criteria for MM as defined by Rajkumar et al [(1)], will be determined the category of response (sCR; CR; VGPR; PR; SD) for each patient.

The definition of each response is given below.

Response subcategory		Response criteria
Stringent complete Response	Scr	• CR as defined below, *plus* • Normal FLC ratio, *and* • Absence of clonal PCs by immunohistochemistry or 2- to 4-color flow cytometry
Complete Response	CR[a]	• Negative immunofixation of serum (or negative endogenous M-protein*)and urine, *and* • Disappearance of any soft tissue plasmacytomas, *and* • < 5% PCs in bone marrow *daratumumab interference test
Very Good Partial Response	VGPR[a]	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or* • ≥ 90% reduction in serum M-component plus urine M-component < 100 mg/24 hours
Partial Response	PR	• ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours • If serum and urine M-protein are not measurable, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is require in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light chain assay is also not measurable, ≥ 50% reduction in bone marrow PCs is required in place of M-protein, provided baseline percentage was ≥ 30% • In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.
Minimal Response	MR[b]	• In patients with relapsed refractory myeloma adopted from the EBMT criteria: • ≥ 25% but ≤ 49% reduction of serum M-protein *and* reduction in 24-hour urine M-protein by 50% to 89% • In addition to the above criteria, if present at baseline, 25% to 49% reduction in the size of soft tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
Stable Disease	SD	Not meeting criteria for CR, VGPR, PR, or progressive disease

Key: CR = complete response; EBMT = European Group for Blood and Marrow Transplantation; FLC = free light chain; MR = minimal response; PC = plasma cell; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.

[a] Clarifications to the criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.

[b] MR in patients with relapsed refractory myeloma.

Analysis Methods

ORR will be analyzed for all treated subjects in Phase 1, and for ITT and PP populations in Phase 2.

The number and percentage of patients in the following response categories will be tabulated by dose group and overall: sCR, CR, sCR + CR, VGPR, VGPR or better, PR, ORR, MR, ORR + MR, stable disease (SD), progressive disease (PD), and not evaluable (NE). For each of the above categories, two-sided 95% exact confidence interval (CI) will also be presented.

Subgroup analyses as specified in Section 2.4 will also be performed..

5.3. Major Secondary Endpoints

5.3.1. Time to Progression

Definition

Time to progression (TTP) is defined as the number of days from the date of first dose (Day 1) to the date of first record of disease progression. Relapse from CR is not considered as disease progression. Deaths due to disease progression will be treated as an event on the date of death, unless disease progression is documented before death. Patients who start subsequent therapy for MM will be censored at the last disease assessment prior to the start of subsequent therapies (inclusive). Patients, who are lost to follow-up, withdraw consent, withdraw from study without disease progression, or die due to causes other than disease progression will be censored at the last disease assessment date.

A diagnosis of PD must be confirmed by 2 consecutive assessments.

Criteria for progression of disease, adapted from International Myeloma Workshop Consensus Panel 1
Increase of ≥ 25% from lowest response value in any of the following:
- Serum M-component (absolute increase must be ≥ 0.5 g/dl), and/or
- Urine M-component (absolute increase must be ≥ 200 mg/24 h), and/or
- Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL).
- Only in patients without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow Serum cell percentage (absolute percentage must be ≥ 10%)
- Definite development of new bone lesions or soft tissue Serumcytomas or definite increase in the size of existing bone lesions or Serumcytomas
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to Serum cell proliferative disorder.

Notes:
Response criteria adapted from Rajkumar et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Work shop Consensus Panel 1
a) Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels; “25% increase” refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue Serumcytomas, or hypercalcemia and the “lowest response value” does not need to be a confirmed value.

Analysis Methods

TTP will only be analyzed for Phase 2.

Median time to progression will be estimated using the Kaplan-Meier method for the ITT population. No inferential analysis will be performed.

The Kaplan-Meier estimates will be plotted to produce a survival curve.

As an exploratory analysis, same TTP analyses are repeated based on investigator assessment, where PD was determined by study investigators.

5.3.2. Duration of Response

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 in the IMWG

criteria. Relapse from CR is not considered as disease progression. Deaths due to disease progression will be treated as an event on the date of death, unless disease progression is documented before death. Patients who start subsequent therapy for MM will be censored at the last disease assessment prior to the start of subsequent therapies (inclusive). Patients, who are lost to follow-up, withdraw consent, withdraw from study without disease progression, or die due to causes other than disease progression will be censored at the last disease assessment date.

Analysis Methods

Duration of response will only be analyzed for Phase 2.

Duration of response will be estimated using the Kaplan-Meier method for the responders in ITT population. The same analysis will be repeated for the PP population as the sensitivity analysis.

No inferential statistics will be provided. A swim lane plot for responders will also be produced.

5.3.3. Progression-Free Survival

Definition

Progression free survival (PFS) is defined as the time between the date of first dose of daratumumab and either disease progression or death, whichever occurs first. Relapse from CR is not considered as disease progression. Subjects who start subsequent therapies for multiple myeloma will be censored at the last disease assessment that is not later than the start of subsequent therapies. Subjects who withdraw from the study before disease progression will be censored at the last disease assessment. Subjects who complete the study, have not progressed, and are still alive at the cut-off date of the analysis will be censored at the last disease assessment. All subjects who were lost to follow-up before the end of the study will be censored at the time of the last disease assessment. Patients with no post baseline disease assessment will be censored on Day 1.

Analysis Methods

PFS will only be analyzed for Phase 2.

PFS will be estimated using the Kaplan-Meier method for the ITT population. No inferential analysis will be performed.

The Kaplan-Meier estimates will be plotted to produce a survival curve.

As an exploratory analysis, same PFS analyses are repeated based on investigator assessment, where PD was determined by study investigators.

Kaplan-Meier estimates will also be plotted to produce the survival curves for responder vs. non-responder based on computerized algorithm.

5.3.4. Time to Response

Definition

Time to first response is defined as the time from the date of first dose of daratumumab to the date of initial documentation of a response (PR or better). Those subjects without response will be censored either at PD, or in the absence of PD, at the last disease assessment before the start of subsequent therapy. Patients with no post baseline disease assessment will be censored on Day 1.

Time to best response is defined as the time between the date of first dose of daratumumab and the date of the initial evaluation of the best response (PR or better) to treatment. Subjects without response will be censored either at PD, or in the absence of PD, at the last disease assessment before the start of subsequent therapy. Patients with no post baseline disease assessment will be censored on Day 1.

Analysis Methods

The Kaplan-Meier method will be used to estimate the distribution of time to response and time to best response for each dose group for all treated subjects in Phase 1, and for ITT population in Phase 2.

In addition, descriptive statistics (mean, standard deviation, median, and range) will be provided to summarize time to first response and time to best response for responders in each treatment group.

5.3.5. Overall Survival

Definition

Overall Survival (OS) is defined as the number of days from administration of the first dose (Day 1) to date of death.

Data for patients who are alive at the date of last contact or have unknown status will be censored at the date of the last contact. Those patients who have withdrawn will be considered to be alive and censored at the date of withdrawal.

Analysis Methods

OS will only be analyzed for Phase 2.

OS will be estimated using the Kaplan-Meier method for the ITT population. No inferential analysis will be performed.

The Kaplan-Meier estimates will be plotted to produce a survival curve.

Kaplan-Meier estimates will also be plotted to produce the survival curves for responder vs. non-responder based on computerized algorithm.

5.4. Other Efficacy Variable(s)

5.4.1. Serum/Urine M-Protein or FLC Reduction

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.

Analysis Methods

Waterfall plot will be generated for maximum percent reduction from baseline in serum/urine M-protein or FLC, based on the measurable type at baseline for all treated subjects in Phase 1, and for ITT population in Phase 2.

5.4.2. Change in Bone Marrow % Plasma Cells

Definition

Bone marrow % plasma cell is based on results from either biopsy or aspirate.

Analysis Methods

Among responders, a shift table of bone marrow % plasma cells (< 5, $\geq 5 - \leq 10$, $>10 - \leq 30$, > 30) from baseline value to first post-baseline value will be provided. In addition, a figure will be generated to display the corresponding numeric change in bone marrow % plasma cells for responders.

6. SAFETY

For all treated subjects in Phase 1, and for safety population in Phase 2, the safety profiles of daratumumab or combination with Len/Dex will be evaluated by the incidence of adverse events (AEs), death, laboratory results, vital signs, physical examination findings, and ECG results.

Safety evaluations will be made by treatment actually received. The severity of AEs and the toxicity of laboratory parameters will be assessed using NCI CTC version 4.03. Adverse events are coded using MedDRA version 17.0.

6.1. Adverse Events

Unless otherwise specified, only treatment-emergent adverse events (TEAEs) will be summarized.

6.1.1. Treatment Emergent Adverse Events

The following summaries will be provided for all TEAEs:

- An overview of TEAE will be provided, including the incidence of TEAE, serious TEAE, maximal severity of TEAE, treatment discontinuation due to TEAE, TEAE leading to treatment interruption, and death due toTEAE.
- An overview of TEAE by subgroups specified in Section 2.4
- Separate listings for each category above.

In addition, the following summaries will be generated:

- TEAEs by system organ class (SOC) and preferred term (PT)
- Most common (at least 5%) TEAEs by system organ class (SOC) and preferred term (PT)
- TEAEs by SOC, PT, and grade 3 or 4.
- TEAEs by SOC, PT, and worst toxicity grade
- TEAEs by SOC, PT, and relationship to study medication
- Most common (at least 10%) TEAEs by system organ class (SOC), preferred term (PT), and grade 3 or 4.
- TEAEs by SOC, PT, and grade 3/4 by subgroups specified in Section 2.4
- Serious TEAEs by SOC and PT
- Serious TEAEs by SOC, PT, and worst toxicity grade
- Serious TEAEs by SOC, PT, and relationship to study medication
- Most common (at least 1%) serious TEAEs by system organ class (SOC) and preferred term (PT)
- Grade 3 or 4 TEAEs by SOC and PT
- Grade 3 or 4 TEAEs by SOC, PT, and relationship to study drug

The following summaries for TEAEs leading to treatment modifications will be provided:

- TEAEs leading to infusion interrupted by PT, and relationship to study drug
- TEAEs leading to infusion prolonged by PT, and relationship to study drug.
- TEAE leading to hospitalization or prolonged hospitalization by SOC and PT.
- Treatment discontinuation due to TEAEs by PT and relationship to study drug
- Study discontinuation due to TEAEs by PT and relationship to study drug
- Death due to TEAEs by PT and relationship to study drug.

6.1.2. Adverse Events of Clinical Interest

6.1.2.1. Infusion Related Reactions

For each phase, the infusion related reactions (IRRs) will be clinically reviewed and identified. The incidence of IRRs will be presented by SOC, PT, and toxicity grade (any grade and grade 3 or 4). The incidence of IRRs will also be presented by type of pre-infusion steroids.

The time to onset of infusion related reaction will be summarized.

All infusion related reactions will be also listed.

6.1.2.2. Infections/Infestations

For each phase, TEAEs in the SOC of infections/infestations will be summarized by PT and event onset time (≤ 8 weeks, 8 – ≤ 16 weeks, 16 – ≤ 24 weeks, > 24 weeks). Kaplan-Meier plot of time to first onset of infections/infestations event will also be provided.

6.1.2.3. Neutropenia

For each phase, TEAEs in the PT of neutropenia will be summarized by event onset time (≤ 8 weeks, 8 – ≤ 16 weeks, 16 – ≤ 24 weeks, > 24 weeks). A listing of grade 3 or 4 neutropenia will also be provided.

6.2. Deaths

For each phase, number of patients who died during the study and the primary cause of death will be summarized. In addition, all deaths within 30 days of last study drug will be summarized.

A listing will be generated for all patients who died during the study.

6.3. Clinical Laboratory Tests

For each phase, treatment-emergent worsening worst toxicity grade during treatment will be tabulated for applicable laboratory parameters. Descriptive statistics for values and changes from baseline for these laboratory parameters will be provided. In addition, shifts from baseline toxicity grade to worst toxicity grade during treatment will be generated.

Shifts from baseline during treatment will be summarized for natural killer cells also.

6.4. Vital Signs and Physical Examination Findings

For each phase, descriptive statistics will be provided for values and changes from baseline over time for vital signs, together with minimal, maximal, last value on study, and their changes from baseline.

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

6.5. Electrocardiogram

Frequencies of overall interpretation of ECG results (normal, abnormal and clinically significant, abnormal and not clinically significant) over time will be provided.

All the ECG results and the change from baseline overtime will be listed. QTcB/QTcF intervals and the change from baseline overtime will be summarized for each phase using the QT evaluable analysis set.

6.6. Other Safety Parameters

6.6.1. ECOG Performance Status

For each phase, frequencies of ECOG performance status (0, 1, 2, >2) over time will be summarized. Shifts from baseline ECOG performance status to the best scoring during treatment will be generated. All ECOG performance status for each patient will be listed.

7. PHARMACOKINETICS/PHARMACODYNAMICS/IMMUNOGENICITY

7.1. Pharmacokinetics

PK analyses will be performed on the pharmacokinetic-evaluable population, defined as all treated subjects whose PK profiles allow accurate calculation of at least one of the PK parameters.

For Phase 1, descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point and for each PK pharmacokinetic parameter. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. Mean (SD) serum daratumumab concentrations-time profiles will be plotted for the first full-dose administration and separately for peak and trough serum concentrations throughout treatment.

For Phase 2, Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics.

If sufficient data are available, population pharmacokinetic analysis of serum concentration-time data of daratumumab will be performed using nonlinear mixed-effects modeling. If the population pharmacokinetic analysis is conducted, details will be provided in a population pharmacokinetic analysis plan, and results of the analysis will be presented in a separate report.

7.2. Immunogenicity

Immunogenicity/immune response (human antihuman antibody - HAHA) is defined as the antibody response to daratumumab and will be assessed based on available data. Sample and subject status will be provided by the bioanalytical group. Subjects with ADA positive samples at baseline are classified as “positive” if titer increases at least 2-fold following treatment. If titer remains the same after treatment or if ADA titer reduces/ or ADA disappear, the subject is classified as “negative”. Patients with unevaluable status following treatment will be classified as “subjects with baseline samples only”.

The anti-daratumumab antibodies summarization and analysis will be based on the observed data therefore no imputation of missing data will be performed. Incidence of antibody (positive, negative, unevaluable) status will be summarized. In addition, a listings of subject positive for anti-daratumumab antibodies will be presented. A listing of sample anti-daratumumab antibody results and concurrent daratumumab serum concentration may also be provided.

7.3. Pharmacodynamics

Not applicable.

7.4. Pharmacokinetic/Pharmacodynamic Relationships

If sufficient data are available, pharmacokinetic/pharmacodynamic modeling of daratumumab, including examining the relationship between paired serum concentration of daratumumab and changes in other relevant biomarkers and efficacy may be planned and performed in a separate statistical analysis plan and study report.

8. BIOMARKER ANALYSES

Biomarker analyses will be focused on over time performance of total natural killer cells, and the percent of natural killer cells change from baseline to last value on treatment. The corresponding summaries and figures will be provided.

REFERENCES

1. Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al., Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011 May 5;117 (18):4691-

ATTACHMENTS

None