DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

MEDI4736-MM-005

MULTICENTER, SINGLE-ARM, PHASE 2 STUDY TO DETERMINE THE EFFICACY FOR THE COMBINATION OF DARATUMUMAB (DARA) PLUS DURVALUMAB (DURVA) (D^2) IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA (RRMM) WHO HAVE PROGRESSED ON DARA WHILE ON A DARA-CONTAINING REGIMEN AS THE MOST RECENT MULTIPLE MYELOMA THERAPY. "FUSION MM-005"

The information contained in the attached report is the property of Celgene and should not be shared or used for any purpose other than that for which it was provided.

Celgene is committed to providing information about its clinical trials to researchers and patients with the goal of furthering science and enhancing healthcare worldwide. Laws and regulations require, however, that Celgene protects patient privacy. The company may further have legal or contractual obligations not to disclose commercial or technical information provided by or related to certain partner companies or vendors.

The attached report is presented in its original format, but certain information has been redacted in order to comply with the aforementioned obligations or to protect Celgene's confidential commercial information. The redactions are based on the following principles:

- Redacted information has been replaced by grey space, maintaining original spacing and pagination.
- Any information that might allow the identification of individuals has been redacted for anonymization.
- Attachments to this report that contain confidential information are not made available. Such attachments include those that contain identifiable patient information, such as subject listings, narratives, and profiles. They also may contain confidential commercial information such as methodologies, and hypothesis generating and exploratory analyses.
- Cross-references to these attachments (such as links to subject listings in Section 16.2) are not redacted from the body of the report. However, the hyperlinks in the electronic document are no longer functional.
- Information about Celgene vendors and their services are redacted because many contracts prohibit disclosure of that information. Further, laws and regulations prevent us from disclosing certain information about our vendors or their services because it is protected by copyright.

Information about Celgene's redaction policies and the availability of additional data from this report may be found at http://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/.

STATISTICAL ANALYSIS PLAN

MULTICENTER, SINGLE-ARM, PHASE 2 STUDY TO DETERMINE THE EFFICACY FOR THE COMBINATION OF DARATUMUMAB (DARA) PLUS DURVALUMAB (DURVA) (D^2) IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA (RRMM) WHO HAVE PROGRESSED ON DARA WHILE ON A DARA-CONTAINING REGIMEN AS THE MOST RECENT MULTIPLE MYELOMA THERAPY.

"FUSION MM-005"

STUDY DRUG(S): MEDI4736

PROTOCOL NUMBER: MEDI4736-MM-005

DATE FINAL: 09 Nov 2017

Prepared by:

CCI [redacted] On behalf of

Celgene International II Sàrl

Rue des Moulins 4

2108 Couvet

Switzerland

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN (SAP) AND SAP AMENDMENT APPROVAL SIGNATURE PAGE	
SAP TITLE	MEDI4736-MM-005 Statistical Analysis Plan
SAP VERSION, DATE	Final Version 1.0, 09 Nov 2017
SAP AUTHOR	PPD Printed Name and Title PPD Signature and Date
PROTOCOL TITLE	MULTICENTER, SINGLE-ARM, PHASE 2 STUDY TO DETERMINE THE EFFICACY FOR THE COMBINATION OF DARATUMUMAB (DARA) PLUS DURVALUMAB (DURVA) (D^2) IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA (RRMM) WHO HAVE PROGRESSED ON DARA WHILE ON A DARA-CONTAINING REGIMEN AS THE MOST RECENT MULTIPLE MYELOMA THERAPY. "FUSION MM-005"
INVESTIGATIONAL PRODUCT(S)	MEDI4736
PROTOCOL NUMBER	MEDI4736-MM-005
PROTOCOL VERSION, DATE	Final Version 1.0, 03 Oct 2016
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.

Statistical Therapeutic Area Head

Signature _____

Printed Name PPD Date _____

Lead Clinical Research Physician / Clinical Research Physician

Signature _____

Printed Name PPD Date _____

Lead Product Safety Physician

Signature _____

Printed Name PPD Date _____

SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN (SAP) AND SAP AMENDMENT APPROVAL SIGNATURE PAGE	
SAP TITLE	MEDI4736-MM-005 Statistical Analysis Plan
SAP VERSION, DATE	Final Version 1.0, 09 Nov 2017
SAP AUTHOR	PPD Printed Name and Title Signature and Date
PROTOCOL TITLE	MULTICENTER, SINGLE-ARM, PHASE 2 STUDY TO DETERMINE THE EFFICACY FOR THE COMBINATION OF DARATUMUMAB (DARA) PLUS DURVALUMAB (DURVA) (D^2) IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA (RRMM) WHO HAVE PROGRESSED ON DARA WHILE ON A DARA-CONTAINING REGIMEN AS THE MOST RECENT MULTIPLE MYELOMA THERAPY. "FUSION MM-005"
INVESTIGATIONAL PRODUCT(S)	MEDI4736
PROTOCOL NUMBER	MEDI4736-MM-005
PROTOCOL VERSION, DATE	Final Version 1.0, 03 Oct 2016
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.

Statistical Therapeutic Area Head

Signature PPD

Printed Name PPD Date PPD

Lead Clinical Research Physician / Clinical Research Physician

Signature

Printed Name PPD Date

Lead Product Safety Physician

Signature

Printed Name PPD Date

SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN (SAP) AND SAP AMENDMENT APPROVAL SIGNATURE PAGE	
SAP TITLE	MEDI4736-MM-005 Statistical Analysis Plan
SAP VERSION, DATE	Final Version 1.0, 09 Nov 2017
SAP AUTHOR	PPD Printed Name and Title Signature and Date
PROTOCOL TITLE	MULTICENTER, SINGLE-ARM, PHASE 2 STUDY TO DETERMINE THE EFFICACY FOR THE COMBINATION OF DARATUMUMAB (DARA) PLUS DURVALUMAB (DURVA) (D^2) IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA (RRMM) WHO HAVE PROGRESSED ON DARA WHILE ON A DARA-CONTAINING REGIMEN AS THE MOST RECENT MULTIPLE MYELOMA THERAPY. "FUSION MM-005"
INVESTIGATIONAL PRODUCT(S)	MEDI4736
PROTOCOL NUMBER	MEDI4736-MM-005
PROTOCOL VERSION, DATE	Final Version 1.0, 03 Oct 2016
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.

Statistical Therapeutic Area Head

Signature _____

Printed Name PPD Date _____

Lead Clinical Research Physician / Clinical Research Physician

Signature PPD

Printed Name _____ Date PPD

Lead Product Safety Physician

Signature _____

Printed Name PPD Date _____

SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN (SAP) AND SAP AMENDMENT APPROVAL SIGNATURE PAGE	
SAP TITLE	MEDI4736-MM-005 Statistical Analysis Plan
SAP VERSION, DATE	Final Version 1.0, 09 Nov 2017
SAP AUTHOR	PPD Printed Name and Title Signature and Date
PROTOCOL TITLE	MULTICENTER, SINGLE-ARM, PHASE 2 STUDY TO DETERMINE THE EFFICACY FOR THE COMBINATION OF DARATUMUMAB (DARA) PLUS DURVALUMAB (DURVA) (D^2) IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA (RRMM) WHO HAVE PROGRESSED ON DARA WHILE ON A DARA-CONTAINING REGIMEN AS THE MOST RECENT MULTIPLE MYELOMA THERAPY. "FUSION MM-005"
INVESTIGATIONAL PRODUCT(S)	MEDI4736
PROTOCOL NUMBER	MEDI4736-MM-005
PROTOCOL VERSION, DATE	Final Version 1.0, 03 Oct 2016
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.

Statistical Therapeutic Area Head

Signature _____

Printed Name PPD Date _____

Lead Clinical Research Physician / Clinical Research Physician

Signature _____

Printed Name PPD Date _____

Lead Product Safety Physician PPD

Signature PPD

Printed Name _____ Date PPD

1. LIST OF ABBREVIATIONS

Table 1: Table of Abbreviations

Abbreviation or Specialist Term	Explanation
ADaM	Analysis data model
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the curve
BMI	Body mass index
CIs	Confidence intervals
CL/F	Clearance
Cmax	Maximum observed concentration
CR	Complete response
CRF	Case report/record form
CTCAE	Common Terminology Criteria for Adverse Events
D^2	Daratumumab (DARA) plus durvalumab (DURVA)
DARA	Daratumumab
DURVA	Durvalumab
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
DRT	Dose Review Team
EBMT	European Group for Blood and Marrow Transplantation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EE	Efficacy Evaluable (population)
EOT	End of treatment
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Council for Harmonisation

IMWG	International Myeloma Working Group
IP	Investigational product
IRAC	Independent Response Adjudication Committee
IV	Intravenous
IVRS	Interactive voice response system
KM	Kaplan-Meier
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MM	Multiple myeloma
CCI	[redacted]
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
CCI	[redacted]
PE	Pulmonary embolism
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PS	Performance status
PT	Preferred term
QW	Weekly
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RNA	Ribonucleic acid
RRMM	Relapsed and refractory multiple myeloma
SAP	Statistical analysis plan
SAS	Statistical analysis system
sCR	Stringent complete response
SD	Stable disease
SOC	System organ class
StdDev	Standard Deviation

TEAE	Treatment-emergent adverse event
T_{max}/ t_{max}	Time to peak plasma concentration
$t_{1/2}$	Terminal elimination half-life
TTP	Time to progression
TTR	Time to response
US	United States
VGPR	Very good partial response
VTE	Venous thromboembolism
V_z/F	Volume of distribution
WHO	World health organization

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations to be performed for Celgene's protocol MEDI4376-MM-005 *Multicenter, single-arm, Phase 2 study to determine the efficacy for the combination of daratumumab (DARA) plus durvalumab (DURVA) (D^2) in subjects with relapsed and refractory multiple myeloma (RRMM) who have progressed on DARA while on a DARA-containing regimen as the most recent MM therapy. "Fusion MM-005"* which was issued on 03 Oct 2016. This study will also determine the safety and evaluate the pharmacokinetics (PK) of D^2. Throughout this SAP, treatment group will be referred to as D^2 arm. This document contains definitions for the analysis populations, derived variables, and the statistical methods to be employed for the analysis of efficacy, safety, and PK.

Two interim analyses for futility and a final analysis are planned and will be conducted in this study. The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock and any data analysis for the interim/final analysis. The SAP also provides a description of the strategy, rationale, and statistical techniques to be used to achieve the objectives of Stage 1 and Stage 2 of Part 1 and Part 2 (expansion) of this study. This SAP will be finalized and signed prior to the clinical database lock for the final analysis. All statistical analyses detailed in this SAP will be conducted using Statistical Analysis System (SAS®) Version 9.2 or higher.

3. STUDY OBJECTIVES

3.1. Primary Objective

To determine the efficacy of D^2 in subjects with RRMM who have progressed on a current treatment regimen containing DARA.

3.2. Secondary Objectives

- Determine the safety of D^2 in subjects with RRMM who have progressed on a current treatment regimen containing DARA.
- Evaluate additional measures of efficacy of D^2 in subjects with RRMM who have progressed on a current treatment regimen containing DARA.
- Evaluate the pharmacokinetics (PK) of D^2 in subjects with RRMM who have progressed on a current treatment regimen containing DARA.

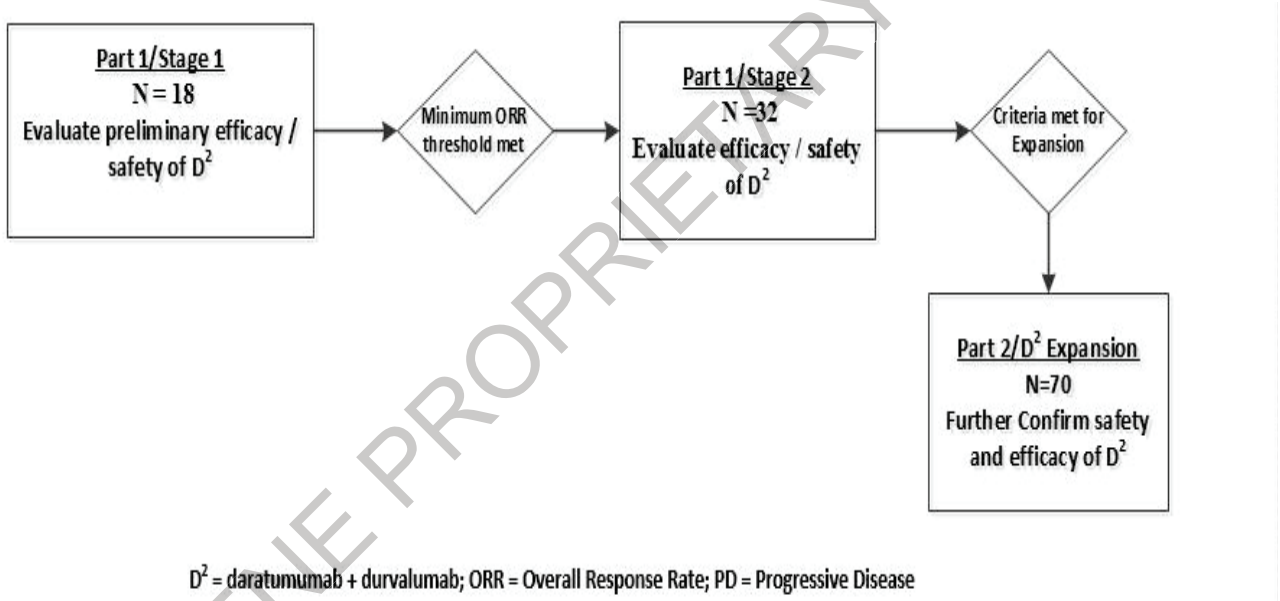
CCI [redacted]

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a single-arm, multicenter, Phase 2 study to evaluate the efficacy and safety of the combination regimen of D^2. The study will consist of 2 parts; Part 1 has a 2-stage design while Part 2 consists of an expansion phase (see Figure 1) Subjects will receive intravenous (IV) DARA at 16 mg/kg on the same dosing schedule (weekly [QW], every 2 weeks [Q2W] or every 4 weeks [Q4W] of each 28-day cycle) received on their last prior therapy containing DARA. The dosing schedule for DARA may be adjusted during the course of the study. Subjects will also receive IV DURVA at 1500 mg on Day 2 (Cycle 1) and on Day 1 (Cycles ≥ 2) of each 28-day treatment cycle. The dosing schedule is outlined in Table 2.

Figure 1: Overall Study Design



D^2 = daratumumab + durvalumab; ORR = Overall Response Rate; PD = Progressive Disease

Table 2: Dosing Schedules

IV DURVA (Dose: 1500 mg)	IV DARA (Dose: 16 mg/kg)
Cycle 1: Day 2 / 28-day cycle Cycle ≥ 2: Day 1 / 28-day cycle	Subjects should start study treatment on the same dosing schedule as their last DARA-containing regimen (QW, Q2W, or Q4W) The dosing schedule should be modified, during the course of the study, as shown below, provided that the subject has a response of stable disease (SD) or better: QW frequency (Days 1, 8, 15, and 22/ 28-day cycle): Weeks 1 to 8, then Q2W from Weeks 9 to 24, then Q4W from Weeks 25 and onward Q2W frequency (Days 1, 15/ 28-day cycle): Weeks 1 to 16, then Q4W from Weeks 17 and onward Q4W frequency (Day 1/28-day cycle): Week 1 onwards until disease progression

DARA = daratumumab; DURVA = durvalumab; IV = intravenously; QW = weekly; Q2W = every 2 weeks; Q4W = every 4 weeks.

An Independent Response Adjudication Committee (IRAC) will be set up for this trial to review study data. The IRAC will determine tumor response to therapy and will confirm the time of progressive disease (PD) (if disease progressed) at scheduled or unscheduled visits for each subject.

The safety and efficacy of the study will be monitored by an independent Data Monitoring Committee (DMC) who is not involved in the trial conduct. The DMC will meet and review study data at pre-specified intervals throughout the trial.

Safety data will be monitored by the Celgene Medical Monitor and Safety Physician on an ongoing basis throughout the study. Should a significant safety issue be identified, the DMC will be convened to make a recommendation as to the future conduct of the study.

The decision to discontinue a subject, which will not be delayed or refused by the Sponsor, remains the responsibility of the treating physician. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

The study will be conducted in compliance with the International Council for Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

4.1.1. Part 1: 2-Stage Design

4.1.1.1. Stage 1

A cohort of 18 subjects will be enrolled to determine the preliminary efficacy of D^2. Once the 18 subjects have been enrolled and the last subject has completed at least 3 cycles of treatment, an interim analysis for futility purpose will be conducted to determine if the study can proceed to Stage 2.

4.1.1.1.1. Early Safety Monitoring

Once 6 subjects have been enrolled and completed the first treatment cycle in Stage 1 of this study, the enrollment continuity would depend on the availability of safety data from the ongoing Phase 2 study (MEDI4736-MM-003) of DARA and DURVA in previously DARA-naïve patients. At the time of the development of this SAP document, MEDI4736-MM-003 safety data was available, and the Dose Review Team tolerability profile of D^2 has been determined by the MEDI4736-MM-003 Dose Review Team to be adequate; thus to allow for enrollment of additional patients. Hence, enrollment in MEDI 4736-MM-005 continued as planned in Stage 1, without any pause in enrollment to support an early safety monitoring review of the data.

4.1.1.2. Stage 2

If 3 or more subjects achieved a response (partial response [PR] or better) out of the 18 subjects at the end of Stage 1, then an additional 32 subjects will be enrolled to evaluate the safety and efficacy of D^2.

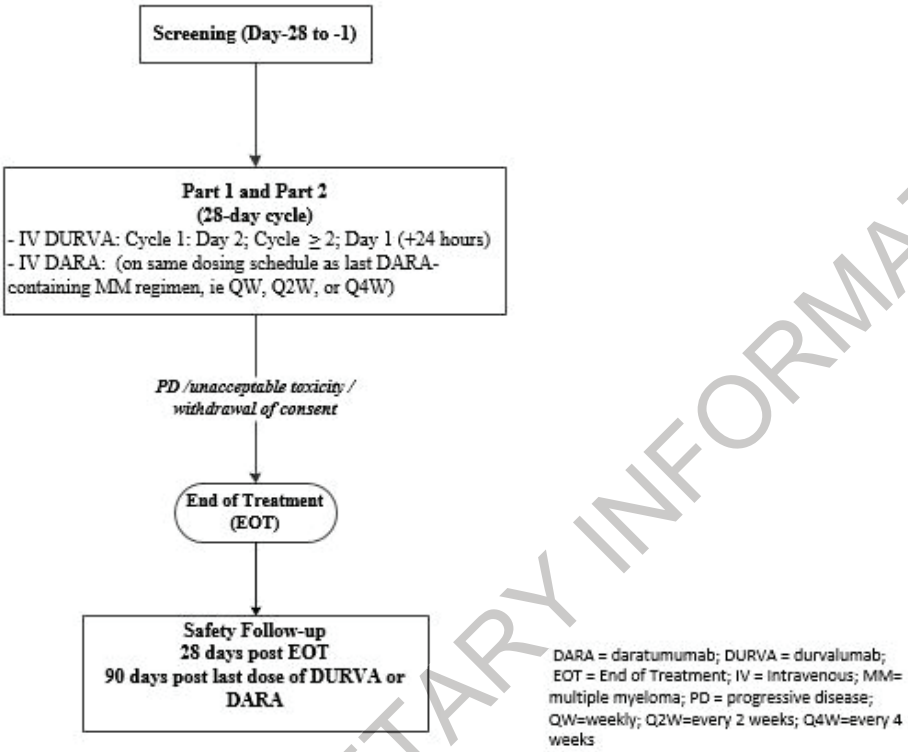
4.1.2. Part 2: Expansion

Upon completion of Part 1, if at least 9 subjects achieve a response (PR or better) out of a total of 50 subjects and it is determined to further confirm the efficacy and safety of D^2, an additional 70 subjects may be enrolled.

4.2. Study Duration for Subjects

The study will consist of the following consecutive phases: Screening, Treatment, and Follow-up. The Screening Phase may not exceed a 28-day window prior to start of study treatment (Cycle 1 Day 1). Subjects may continue on study treatment until PD or unacceptable toxicity. All subjects will have an End of Treatment (EOT) visit within 7 days after discontinuation of all study treatment. Subjects are to return to the study site 28 (+3) days after the EOT visit and 90 (+3) days after the last dose of DURVA or DARA for safety follow-up visits (see Figure 2).

Figure 2: Study Schematic



4.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre specified in the protocol, whichever is the later date.

4.4. Study Endpoints

Table 3: Study Endpoints

Endpoint	Name	Description
Primary	Overall response rate (ORR)	Myeloma response rate (partial response [PR] or better),according to the International Myeloma Working Group (IMWG) Uniform Response Criteria (Rajkumar, 2011).
Secondary	Safety	Type, frequency, seriousness and severity of adverse events (AEs), and relationship of AEs to study treatment
Secondary	Time-to-response (TTR)	Time from treatment initiation to the first documentation of response (Partial Response [PR] or greater)
Secondary	Duration of response (DOR)	Time from the first documentation of response (PR or better) to the first documentation of PD or death, whichever is earlier, based on the investigator assessment according to the IMWG Uniform Response Criteria
	Progression-free survival (PFS)	Time from treatment initiation to the first documentation of PD or death from any cause during study, whichever occurs earlier
	Time to progression (TTP)	Time from treatment initiation to the first documentation of PD
	Overall survival (OS)	Time from treatment initiation to death due to any cause
Secondary	Pharmacokinetic (PK) parameters	Typical serum/plasma PK parameters for DURVA and DARA, such as maximum observed concentration (C_{max}), area under the concentration-time curve (AUC), time to maximum concentration (T_{max}), terminal elimination half-life ($t_{1/2}$), clearance (CL/F), and volume of distribution (V_z/F)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

Endpoint	Name	Description
	[redacted]	CCI [redacted]
	[redacted]	[redacted]

4.5. Sample Size and Power Considerations

The study consists of 2 parts. In Part 1, a two-stage design with one interim analysis for futility at the end of Stage 1 is used. PASS software, Version 13.03 has been used to calculate the sample sizes. Setting the Type I error rate at 0.05, a total sample size of 50 subjects provides a power of at least 80% to reject the null hypothesis of overall response rate (ORR) less than 10% with a target response rate of 25%. In Stage 1, 18 subjects will be enrolled and if there are at least 3 subjects out of 18 who achieved a response (PR or above) by end of cycle 3, the study will continue to Stage 2. If there are 2 or less subjects who achieved a response out of 18 subjects in Stage 1, the study will be terminated for futility and will not proceed to Stage 2. In Stage 2, an additional 32 subjects will be enrolled. If there are at least 9 subjects who achieved a response out of a total of 50 subjects from Stages 1 and Stage 2, the null hypothesis will be rejected. If it is determined at the end of Part 1 to further evaluate the efficacy and safety of the combination regimen of D^2, then up to an additional 70 subjects will be enrolled in Part 2. This will bring the total number of subjects treated during the study up to approximately 120. The additional subjects will add to the certainty about the efficacy and safety of this combination therapy. Table 4 shows the exact 95% confidence intervals (CIs) around the response rates observed based on different scenarios. For example, if the observed ORR is 25%, the lower limit of the 95% CI will be 17.5%. If the observed ORR is 30%, the lower limit of the 95% CI will be 22.0%.

Table 4: Estimated Overall Response Rate and 95% Confidence Interval Out of 120 Subjects

Number of Responders in 120 Subjects	Overall Response Rate	95% Confidence Interval
30	25.0 %	17.5, 33.7
31	25.8 %	18.3, 34.6
32	26.7 %	19.0, 35.5
33	27.5 %	19.7, 36.4
34	28.3 %	20.5, 37.3
35	29.2 %	21.2, 38.2
36	30.0 %	22.0, 39.0
37	30.8 %	22.7, 39.9
38	31.7 %	23.5, 40.8
39	32.5 %	24.2, 41.7
40	33.3 %	25.0, 42.5

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

- Data from all study centers will be combined for analysis;
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.0000 will be presented as '> 0.9999';
- Confidence intervals will be presented as 2-sided 95% CIs unless specified differently in specific analysis;
- Summary statistics will consist of the number and percentage of subjects (or cycles, if appropriate) in each category for discrete variables, and the sample size, mean, median, standard deviation (StdDev), minimum (Min), and maximum (Max) for continuous variables;
- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value;
- All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses;
- All listings will be sorted for presentation in order of cohort, study center, subject, and date of procedure or event, unless otherwise specified;
- All analysis and summary tables will have the analysis population sample size (ie, number of subjects);
- The day of the first dose of any study drug will be defined as Day 1;
- Baseline value will be defined as the last value on or before the first dose of study drug is administered. For subjects who were not treated, baseline will be the assessment value taken on the visit of Cycle 1 Day 1 if available; otherwise, the value on or prior to enrollment date will be used.

5.2. Analysis Populations

5.2.1. Full Analysis Set Population

The Full Analysis Set Population (FAS) will include all enrolled subjects. The primary efficacy analysis will be performed on the FAS population.

5.2.2. Safety Population

The Safety Population will include all subjects who take at least one dose of DURVA or DARA. All safety analyses will be based on this population.

5.2.3. Efficacy Evaluable Population

The supportive efficacy analyses will be performed on the Efficacy Evaluable (EE) Population, which will include all enrolled subjects who take at least one dose of DURVA or DARA and who have measurable disease at baseline and at least one post-baseline efficacy measurement.

5.2.4. Pharmacokinetic Population

The PK Population will include all subjects who receive at least one dose of study treatment and who have at least one measureable plasma concentration. For subjects who are determined to be noncompliant with respect to administration of investigational product (IP), or for subjects with incomplete data, a decision as to their inclusion in the population will be made on a case-by-case basis prior to the analysis.

6. SUBJECT DISPOSITION

A summary of subjects enrolled by country and site will be provided for the FAS.

The total number of subjects who failed screening ("screen failures") will be summarized for all screened subjects.

A summary of subjects in each analysis population (Section 5.2) will be reported.

Subject disposition (analysis population allocation, entered, completed, discontinued, along with primary reason for discontinuation) will be summarized for the FAS using frequency and percentage.

Individual subject listings will be provided to support the summary tables.

Reasons for subject discontinuation during screening will be summarized for the following categories:

- Screen failure
- Death
- Adverse event (AE)
- Pregnancy
- Withdrawal by subject
- Withdrawal by parent/guardian
- Study terminated by sponsor
- Protocol violation
- Physician decision
- Other (to be specified on the case report form [CRF])

Reasons for treatment discontinuation or the discontinuation from the investigational product(s) will be summarized for the following categories:

- Death
- Adverse event
- Pregnancy
- Progressive disease
- Lack of efficacy
- Recovery
- Withdrawal by subject
- Withdrawal by parent/guardian
- Noncompliance with study drug

- Lost to follow-up
- Study terminated by sponsor
- Protocol violation
- Physician decision
- Disease relapse
- Transition to commercially available treatment
- Other (to be specified on the CRF)

Reasons for discontinuation from study follow-up will be summarized for the following categories:

- Completed
- Death
- Adverse event
- Pregnancy
- Progressive Disease
- Withdrawal by subject
- Withdrawal by parent/guardian
- Lost to follow-up
- Study terminated by sponsor
- Protocol violation
- Physician decision
- Disease relapse
- Transition to commercially available treatment
- Other (to be specified on the CRF)

7. PROTOCOL DEVIATIONS/VIOLATIONS

Protocol deviations/violations will be identified and assessed by the clinical research physician or designee following company standard operational procedure. Protocol deviations/violations will be summarized for the FAS.

A listing of subjects with protocol deviations/violations in the FAS will be provided.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized for the FAS, Safety Population, and EE population. Individual subject listings will be provided to support the summary tables.

8.1. Demographics

Age (years), height (cm), weight (kg), body mass index (BMI) (weight [kg] / height [m^2]) at baseline will be summarized descriptively (eg, mean, StdDev, median, Min, and Max). Sex, race, and ethnicity will be summarized by frequency tabulations.

Age will be calculated as follows: age = Integer ≤ [(Date of consent – Date of birth + 1) / 365.25]. If the date of birth is incomplete, age as captured on the electronic CRF (eCRF) will be used.

8.2. Baseline Characteristics

Categorical baseline characteristics like Eastern Cooperative Oncology Group (ECOG) performance status (PS), baseline electrocardiogram (ECG), disease diagnosis, prior disease therapies, baseline symptoms, cytogenetics at initial MM diagnosis, bone lesion assessments, bone marrow biopsy/aspirates, non-measurable plasmacytoma assessments, and M-protein free light chain will be summarized using frequency count and percentages.

Continuous baseline variables such as temperature (°C), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (beats/min), measurable plasmacytoma assessments and laboratory data at baseline will be summarized by descriptive statistics in the same way as continuous demographic variables.

A listing of baseline characteristics will also be provided.

8.3. Medical History

A summary of medical history will be presented by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities® (MedDRA) Version 19.0 or higher for the FAS. A similar summary will be generated only for MH with a currently active diagnosis. Specific medical history of interest will be summarized by pre-specified terms using counts and percentages.

A listing of medical history and specific medical history of interest will also be provided.

8.4. Prior Cancer History

Prior cancer history and prior diagnostic history will be summarized using counts and percentages and listed separately.

8.5. Prior Antimyeloma Therapy

Whether subjects had prior radiation or prior antimyeloma therapy, this information will be summarized with frequency counts and percentages. The number of prior regimens of MM

therapy will be summarized descriptively. The number of prior regimens of MM therapy (eg, 1, 2, ≥ 3) will also be summarized by frequency tabulations.

A listing of prior therapies for this disease will also be provided.

8.6. Prior and Concomitant Procedures/Surgeries

8.6.1. Prior Procedures/Surgeries

Prior cancer surgeries for the disease under study and prior procedures/surgeries not related to cancer will be summarized using counts and percentages and listed separately.

8.6.2. Concomitant Procedures/Surgeries

The Concomitant Procedures/Surgeries CRF records date of procedure/surgery, indication, and the type of procedure/surgery, and the type of procedure/surgery will be coded using MedDRA Version 19.0 or higher. Concomitant procedure/surgeries will be summarized in frequency tabulations by SOC and PT.

A listing of concomitant procedures/surgeries together with prior procedures/surgeries will be provided as well.

8.7. Prior and Concomitant Medications

Medications initiated prior to the start of study treatment and which were continued after the start of study treatment will be counted as both prior and concomitant medications according to World Health Organization (WHO) therapeutic drug class and generic drug name for the FAS.

8.7.1. Prior Medications

Prior medications are defined as medications that were started before the start of study treatment and either ended before the start of study treatment or continued during the study treatment. A summary showing the number and percentage of subjects who took prior medications will be presented by World Health Organization (WHO) therapeutic drug class and generic drug name for the FAS.

A listing of prior medications together with concomitant medications will also be provided.

8.7.2. Concomitant Medications

Concomitant medications are defined as medications that were either initiated before the first dose of study drug and continued during the study treatment, or initiated on/after the date of the first dose of study drug till the end of last dose of study drug plus 90 days.

A summary showing the number and percentage of subjects who took concomitant medications will be presented by WHO therapeutic drug class and generic drug name for the FAS.

A listing of concomitant medications together with prior medications will also be provided.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Study treatment and extent of exposure summaries will be provided and will be based on the Safety Population. Descriptive statistics will be provided for treatment duration, the number of cycles, cumulative dose, dose intensity, and compliance, and relative dose intensity also will be summarized by treatment and overall treatment arm (D^2) .

A listing of dosing records will be listed by cycles for the Safety Population.

9.1. Treatment Duration

The treatment duration (in weeks) of DURVA or DARA for each subject in a cycle is defined as the actual length of each cycle (Refer to Section 16.1.2 for the definition of cycle length); in particular, the treatment duration of the last cycle is defined as:

(Dosing period end date of last cycle – Date of Day 1 in last cycle + 1) / 7 (in weeks)

Dosing period end date of last cycle = Min [death date, date of Day 1 in last cycle + 28 - 1].

The overall treatment duration (in weeks) of DURVA or DARA for each subject is defined as:

(Dosing period end date of last cycle – First dose date of study treatment in the first cycle + 1) / 7 (in weeks).

In addition to treatment duration, the number of cycles received will also be summarized.

9.2. Cumulative Dose

Cumulative dose is defined as the sum of all doses taken across the treatment period in milligrams. Cumulative dose will be calculated separately for each drug.

Cumulative dose for DURVA- = Sum of (administered dose of each visit [mg])

Cumulative dose for DARA = Sum of (administered dose of each visit [mg/kg])

9.3. Dose Exposure

Dose exposure is defined as the total number of days on the study drug during the treatment phase (excluding the periods of dose break per protocol or dose interruptions). Dose exposure will be calculated separately for each drug.

9.4. Average Daily Dose

Average daily dose is defined as the cumulative dose divided by dose exposure (mg/day). Average daily dose will be calculated separately for each drug. For DARA the average daily dose will be calculated in mg/kg/day, using the first recorded weight in each cycle to define the weight used in the denominator.

9.5. Dose Intensity

Dose intensity during treatment is defined as the cumulative dose divided by the treatment duration: dose intensity (mg/day) = cumulative dose (mg) / treatment duration (days).

Dose intensity will be calculated separately for each drug. For DARA dose intensity will be calculated in mg/kg/day, using the first recorded weight in each cycle to define the weight used in the denominator.

9.6. Relative Dose Intensity

Relative dose intensity is defined as the dose intensity for the given period divided by planned dose intensity for the same period, expressed as a percentage, i.e., relative dose intensity (%) = (dose intensity / planned dose intensity)*100.

- For DURVA the planned dose intensity is (dose level) / per 28 days, with dose level of 1500 mg.
- For DARA, the planned dose intensity with dose level of 16 mg/kg are provided as follows:
  - For patients with QW frequency for DARA in their last DARA-containing regimen prior to enrollment in to this study:
    - 4*(dose level) / per 28 days, for week 1 to 8;
    - 2*(dose level) / per 28 days, for week 9 to 24
    - 1*(dose level)/per 28 days, for week ≥25
  - For patients with Q2W frequency for DARA in their last DARA-containing regimen prior to enrollment in to this study:
    - 2*(dose level) / per 28 days, for week 1 to 16;
    - 1*(dose level) / per 28 days, for week ≥17
  - For patients with Q4W frequency for DARA in their last DARA-containing regimen prior to enrollment in to this study:
    - 1*(dose level) / per 28 days, from week 1 until disease progression

9.7. Dose Reduction/Interruption/Delay

Dose reduction/interruption/delay will be summarized separately for each drug. The number of subjects who have at least one dose reduction/interruption/delay, number of dose reductions/interruptions/delays per subject, and reason for dose reduction/interruption/delay will be summarized.

10. EFFICACY ANALYSIS

Primary efficacy analyses will be performed on the FAS population. Supportive efficacy analyses will also be performed using the EE Population.

All analyses will use descriptive statistics.

Tumor response, including PD, will be assessed by the investigators and the IRAC using the International Myeloma Working Group (IMWG) uniform response criteria.

10.1. Overall Response Rate

The primary efficacy endpoint will be based on tumor responses as assessed by an IRAC using the IMWG Uniform Response Criteria. The ORR will be calculated as the number of responders (PR or better), divided by the number of subjects in the FAS population. The ORR together with the proportions in each category based on the IMWG criteria (ie, stringent complete response [sCR], complete response [CR], very good partial response [VGPR], PR, stable disease [SD], and PD. Refer Table 6) will be tabulated, together with the 2-sided exact 95% CI.

Listings of lab assessments for efficacy parameters will also be provided.

10.2. Time to Response

The time to response (TTR) (for responders only, per IMWG uniform response criteria) is calculated as the time from treatment initiation of the study treatment to the first date of documented response (PR or better). Time to response will be summarized using descriptive statistics.

10.3. Duration of Response

Duration of response (DOR; for responders only, per IMWG Uniform Response Criteria) is defined as the time from the earliest date of documented response (PR or better) to the first documentation of PD or death, whichever is earlier. Duration of response will be analyzed using the KM method. Median DOR along with the two-sided CI will be provided. Censoring for DOR will follow the same rules for Progression-free survival (see Table 5).

10.4. Progression-free survival

Progression-free survival (PFS) is defined as the time from treatment initiation to the first date of documented PD or death from any cause during the study whichever occurs earlier.

Subjects who do not have a PFS event will be censored on the last adequate assessment date. Progression-free survival will be summarized for the FAS using Kaplan-Meier (KM) statistics.

Subjects who had PD prior to receiving other antimyeloma therapy will be considered to have the event on the date of PD. Subjects who died without documented PD and without receiving other antimyeloma therapy will be considered to have an event on the date of death. Subjects who did not have disease progression at the time of the data cut-off date will be censored on the date of their last adequate response assessment on or prior to the cut-off date. For subjects with PD documented between scheduled assessments, the event will be considered to have occurred

on the date of last scheduled adequate assessments with no progression. The censoring rules for PFS are provided in Table 5. These rules are based on the United States Food and Drug Administration (US FDA) guidance for cancer trial endpoints (FDA Guidance, 2007).

Table 5: Censoring Rules for Progression-free Survival

Situation	Date of Progression or Censoring	Situation Outcome
Death within the first two scheduled assessments without disease progression	Date of death	Event
Progression	If the first PD is a scheduled assessment, then Date of first PD; If the first PD is an unscheduled assessment and no previous assessment, then Date of PD; If the first PD is an unscheduled assessment and has previous assessment, then Date of previous assessment (regardless of the response type)	Event
Death between scheduled assessments	Date of death	Event
No progression	Date of last adequate assessment with evidence of no progression	Censored
Death or progression after two or more missed scheduled assessments	Date of last adequate assessment with evidence of no progression	Censored
New antimyeloma / non-protocol cancer treatment started prior to progression or death due to any reason	Date of last adequate assessment with evidence of no progression before the start of new treatment	Censored

PD = progressive disease.
Source: United States Food and Drug Administration (US FDA) guidance for cancer trial endpoints for the approval of cancer drugs and biologics (FDA Guidance, 2007).

10.5. Time to Progression

Time to progression (TTP) is defined as time from treatment initiation to the first documented progression, confirmed by IRAC. Censoring rules for TTP are similar as for PFS (see Table 5), however Death within the first two scheduled assessments without disease progression and Death between scheduled assessments will be censored at the date of death. The TTP will be analyzed using the KM method. Median TTP and the corresponding 95% CI will be provided.

10.6. Overall Survival

Overall survival (OS) is defined as time from treatment initiation to death due to any cause. Subjects who died will be considered as having events on the date of death. Subjects who are

alive or lost to follow-up will be censored on the last-known-alive date. The OS will be analyzed using the KM method. Median OS and the corresponding 95% CI will be provided.

11. SAFETY ANALYSIS

The purpose of this section is to define the safety parameters for the study. The safety variables for this study include AEs, clinical laboratory evaluations, 12-lead ECGs, physical examinations, vital signs, pregnancy testing for females of childbearing potential and concomitant medications and procedures. All summaries of safety data will be conducted using the Safety Population unless otherwise specified.

Individual subject listings will be provided for the FAS to support the tables.

11.1. Adverse Events

Adverse events will be analyzed in terms of treatment-emergent AEs (TEAEs) which are defined as any AEs that begin or worsen on or after the start of study drug through 90 days after the last dose of DURVA or DARA, whichever is later. All AEs will be coded using the MedDRA Version 19.0 or higher.

A treatment-related TEAE is defined as a TEAE which is considered to be related to the study drug.

If a subject experiences the same AE more than once with different toxicity grade, then the event with the highest grade will be tabulated in "by grade" tables. If a subject experiences multiple AEs under the same PT (SOC), then the subject will be counted only once for that PT (SOC). In addition, AEs with a missing intensity will be presented in the summary table as an intensity category of "Missing."

The incidence of TEAEs will be summarized by MedDRA SOC and PT. The intensity of AEs will be graded 1 to 5 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 or higher. For all other AEs not described in the CTCAE criteria, the intensity will be assessed by the investigator as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4) or death (Grade 5). Tables summarizing the incidence of TEAEs will be generated for each of the following:

- All TEAEs;
- All TEAEs by decreasing frequency of PT
- TEAEs by cycle;
- TEAEs for the first cycle;
- All TEAE with NCI CTCAE Grade 1-2;
- All TEAE with NCI CTCAE Grade 3-4;
- All TEAE with NCI CTCAE Grade 5;
- TEAEs reported as treatment-related;
- Treatment-related TEAEs with NCI CTCAE Grade 1-2;
- Treatment-related TEAEs with NCI CTCAE Grade 3-4;
- Treatment-related TEAEs with NCI CTCAE Grade 5;

- Serious TEAE;
- Treatment-related serious TEAEs;
- TEAEs leading to permanent discontinuation of study drug;
- Treatment-related TEAEs leading to permanent discontinuation of study drug;
- TEAEs leading to study drug dose delay/interruption/infusion interruption;
- TEAEs leading to death;
- Overall deaths;
- Deaths within 28/60/90 days of the last dose of study drug;
- Deaths within first 60 days from Cycle 1 Day 1.

Listings for the corresponding summary tables will be presented separately. A listing for non-treatment-emergent AEs will also be provided.

11.2. Adverse Events of Special Interest

The following TEAEs of special interest (AESI) will be summarized by SOC and PT:

- Diarrhea / Colitis
- Pneumonitis / Interstitial lung disease (ILD)
- Hepatitis and increases in transaminases
- Endocrinopathies (adrenal insufficiency, hyperthyroidism, hypothyroidism, hypophysitis / hypopituitarism, and Type I diabetes mellitus)
- Dermatitis / rash and pruritis
- Nephritis and increases in serum creatinine
- Neuromuscular toxicity (e.g. Guillain-Barré and myasthenia gravis)
- Pancreatitis (or labs suggestive of pancreatitis – increased serum lipase or increased serum amylase)
- Infusion Reactions
- Hypersensitivity Reactions

11.3. Clinical Laboratory Evaluations

Clinical laboratory values from the central laboratories (hematology and chemistry) will be graded according to NCI CTCAE Version 4.03 or higher for applicable tests. The worst grade during the treatment period will be summarized. Frequency distributions for shift from baseline to the worst grade during the treatment period will be presented.

Clinical laboratory values from the central laboratories will also be summarized descriptively (N, mean, StdDev, median, Min, and Max).

Listings of clinical laboratory data from the central laboratory and also from the local laboratory (hematology, chemistry, coagulation, thyroid function tests, renal function assessment) with abnormal flags will be provided by subjects and tests.

11.4. Vital Sign Measurements

For vital signs, the shift from baseline to worst during the treatment in below, within, and above the normal ranges will be displayed in cross–tabulations for each treatment. Summary statistics (N, mean, StdDev, median, Min, and Max) of observed values and change from baseline values will be presented.

11.5. Electrocardiograms

The overall ECG interpretation will be summarized by presenting the number and percentage of subjects with 'Normal', 'Abnormal, not clinically significant', and 'Abnormal, clinically significant' by treatment arm. The shift from baseline to worst during treatment in the overall ECG interpretation will be displayed in cross-tabulations.

11.6. Eastern Cooperative Oncology Group Performance Status

A shift table from baseline to best post baseline ECOG PS score will be displayed in cross-tabulations. A listing of ECOG PS scores will also be provided.

11.7. Other Assessments

Categorical characteristics like non-measurable plasmacytoma assessment will be summarized using frequency counts and percentages for the Full Analysis Set Population, by visit.

Continuous variables like measurable plasmacytoma assessment will be summarized by descriptive statistics for observed values and the change from baseline (mean, StdDev, median, Min, and Max).

11.8. Pharmacokinetic Analysis

Pharmacokinetic analysis will be based on the PK population. Non-compartmental PK parameters such as time to maximum concentration (Tmax), maximum observed concentration (Cmax), area under the curve (AUC), terminal elimination half-life (t1/2), clearance (CL/F), and volume of distribution (Vz/F) will be estimated from the plasma concentration-time profile for DURVA. For DARA, typical serum PK parameters, such as C_{max}, AUC, T_{max}, $t_{1/2}$,CL/F and V_z/F will be summarized. All concentration data and PK parameters will be summarized descriptively.

CCI

13. INTERIM ANALYSIS

This study will be conducted in 2 parts with two interim analyses being planned.

The first interim analysis will be conducted at the end of Stage 1 of Part 1, when the first 18 subjects enrolled have completed at least 3 cycles of treatment. If at least 3 subjects out of 18 achieve a response (PR or better), the study will continue to Stage 2. The second interim analysis will be conducted at the end of Stage 2. If at least 9 subjects achieve a response (PR or better) out of a total of 50 subjects and it is determined by the Sponsor to further confirm the efficacy and safety of D^2, an additional 70 subjects may be enrolled.

14. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

Not applicable.

15. REFERENCES

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, FDA/CDER/CBER May 2007.

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;117(18):4691-5.

16. APPENDICES

16.1. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (ie, the Date9. datetime format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- **Procedure Dates** are the dates on which given protocol-specified procedure are performed. They include the dates of laboratory testing, physical examinations, tumor scans, etc. They should be present whenever data for a protocol-specified procedure are present and should only be missing when a procedure are marked as NOT DONE in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in CRF data logs. Specifically, they are the start and end dates for adverse events and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix 16.2 (eg, for duration or cycle assignment, etc). However, in listings, log dates will be shown as recorded without imputation.
- **Milestone Dates** are dates of protocol milestones such as randomization, study drug start date, study drug termination date, study closure date, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.
- **Outcome Dates** are dates corresponding to study endpoints such as survival, progression, etc. In most cases they are derived either from a milestone (eg, the survival date is derived from the death date), or a procedure date (eg, the progression date is derived from the date of the tumor scan that was used to determine progression). They may be subject to endpoint-specific censoring rules if the outcome did not occur, but are not otherwise subject to imputation.
- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules.

Dates recorded in comment fields will not be imputed or reported in any specific format.

16.1.1. Calculation Using Dates

Calculations using dates (eg, subject's age or relative day after the first dose of study drug) will adhere to the following conventions:

- Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study drug (eg, durvalumab) plus 1 day. The generalized calculation algorithm for relative day is the following:

- If TARGET DATE ≥ DSTART then STUDY DAY = (TARGET DATE – DSTART) + 1;
- Else use STUDY DAY = TARGET DATE – DSTART.

  Note that Study Day 1 is the first day of treatment of study drug. Negative study days are reflective of observations obtained during the baseline/screening period. Note: Partial dates for the first study drug are not imputed in general. All effort should be made to avoid incomplete study drug start dates.

- Age (expressed in days) is calculated: AGE = CONSENT – DATE of BIRTH + 1. In practice, age will be transformed to years by dividing the difference by 365.25 days, then truncating.
  - Preference is for using calculated age from clinical database. When not available, calculated age from CRF or interactive voice response system (IVRS) may be used. If only a partial birth date is given then the age as reported in the CRF will be used.
  - Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:

    WEEKS = DAYS /7
  - Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:

    MONTHS = DAYS /30.4167

16.1.2. Calculation of Cycles

The start date of each treatment cycle will be calculated based on study drug exposure records for each subject. The start date of the first cycle will be the date when the subject receives any dose of study drug.

Once the start dates, eg, S_1, S_2, S_3… are calculated, the end date of each cycle is calculated as the day before the start date of the following cycle, ie, $E_i = S_{i+1} - 1$. For the last cycle, the end date will be calculated as the start date plus prescribed cycle length, or the treatment discontinuation date, or the death date, whichever is earlier. If a date is on or after S_i and before S_{i+1}, the corresponding cycle number will be i.

16.2. Date Imputation Guideline

16.2.1. Impute Missing Adverse Events / Prior or Concomitant Medications

Incomplete Start Date:

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first doing date will be assigned to the missing fields.

- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first doing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.

Missing day, month, and year

No imputation is needed; the corresponding AE will be included as TEAE.

Incomplete Start Date: If the imputed start date is after the stop date, then the start date will be imputed by the stop date

Incomplete Stop Date: If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day.

16.2.2. Adverse Events

Partially missing AE start dates will be imputed in the analysis data model (ADaM) dataset for AEs, but partially missing AE end dates will not be imputed in the same dataset. If the AE end date is complete with no missing year, month, or day, and the partially missing start date imputed by the rules below is after the AE end date, then the start date will be imputed by the AE end date.

16.2.3. Prior/Concomitant Medications/Procedures

Partially missing start/stop dates for prior/concomitant medications and partially missing start dates for prior/concomitant procedures will be imputed in the ADaM dataset for prior/concomitant medications/procedures. For prior/concomitant medications, if the stop date is complete with no missing year, month, or day, and the partially missing start date imputed by the rule below is after the stop date, then the start date will be imputed by the stop date.

Partially missing prior/concomitant medication/procedure start dates will be imputed by the earliest possible date given the non-missing field(s) of the date.

Partially missing prior/concomitant medication stop dates will be imputed by the latest possible date given the non-missing field(s) of the date.

16.3. International Myeloma Working Group Uniform Response Criteria

Table 6: International Myeloma Working Group Uniform Response Criteria

Response Category	Response Criteria
Stringent Complete Response (sCR)	CR as defined below, *plus* Normal serum free light chain (FLC) ratio *and* Absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry
Complete Response (CR)	Negative immunofixation of serum and urine *and* Disappearance of any soft tissue plasmacytomas *and* $\leq$ 5% plasma cells in bone marrow 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.

Table 6: International Myeloma Working Group Uniform Response Criteria (Continued)

Response Category	Response Criteria
Very Good Partial Response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis *or* 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hours. In patients in whom the only measurable disease is by serum FLC levels: VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.
Partial Response (PR)	≥ 50% reduction of serum M-Protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours If the serum and urine M-protein are not measurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable, and the serum free light chain assay is also unmeasurable, a ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%. In addition to the above, if present at baseline a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.
Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR, or PD
Progressive disease (PD)	**Requires only one of the following:** 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 plasma cell percentage (absolute percentage must be ≥ 10%) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

Table 6: International Myeloma Working Group Uniform Response Criteria (Continued)

Response Category	Response Criteria
Additional Response Criteria	
Molecular Complete Response	CR plus negative allele-specific oligonucleotide polymerase chain reaction (ASO-PCR), sensitivity 10^{-5}
Immuno-phenotypic Complete Response	Stringent CR *plus* Absence of phenotypically aberrant plasma cells (clonal) in BM with a minimum of 1 million total BM cells analyzed by multi-parametric flow cytometry (with > 4 colors)
Minimal Response (MR) in patients with relapsed refractory myeloma adopted from the European Group for Blood and Marrow Transplantation (EBMT) criteria	≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50%-89% In addition to the above criteria, if present at baseline, 25%-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)

BM = bone marrow; FLC = free light chain.

a All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if the starting M-component is ≥5 g/dL.

Source: Adapted from Rajkumar, 2011.