Official Title of Study:

A PHASE2, RANDOMIZED, OPEN LABEL TRIAL OF

LENALIDOMIDE/DEXAMETHASONE WITH OR WITHOUT ELOTUZUMAB IN

SUBJECTS WITH PREVIOUSLY UNTREATED MULTIPLE MYELOMA IN JAPAN

NCT Number: NCT02272803

Document Date (Date in which document was last revised): April 2, 2017

STATISTICAL ANALYSIS PLAN
FOR CSR

A PHASE2, RANDOMIZED, OPEN LABEL TRIAL OF LENALIDOMIDE/DEXAMETHASONE WITH OR WITHOUT ELOTUZUMAB IN SUBJECTS WITH PREVIOUSLY UNTREATED MULTIPLE MYELOMA IN JAPAN

PROTOCOL(S) CA204116

VERSION # 2.0

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Research Hypothesis:

Elotuzumab + lenalidomide/dexamethasone will demonstrate Objective Response Rate (ORR) of > 71% when given to subjects with newly diagnosed, previously untreated MM.

Schedule of Analyses:

The primary endpoint of ORR will be performed at least 6 months after last subject's first treatment for the purpose of the CSR, which will contain all of the analyses specified in this Statistical Analysis Plan (SAP). Additional analyses may be performed, which depend on the timing of regulatory authority filing. The final analysis may be performed at the timing of the study discontinuation.

2   STUDY DESCRIPTION

2.1   Study Design

This is a Phase 2, randomized, open-label, multi-center trial investigating lenalidomide/dexamethasone with and without elotuzumab in subjects with newly diagnosed, previously untreated multiple myeloma who are ineligible for high-dose therapy plus stem-cell transplantation (SCT) because of age ($\geq$ 65 years) or coexisting conditions.

The primary objective of this study is to estimate the ORR of elotuzumab + lenalidomide/dexamethasone in subjects with newly diagnosed, previously untreated MM.

Eligible subjects will be randomized in a 1:1 ratio to receive either elotuzumab/lenalidomide/dexamethasone (ELd) [Investigational Arm] or lenalidomide/dexamethasone (Ld) [Control Arm]. The randomization will be stratified by International Staging System (ISS) stage (1 - 2 versus 3). Approximately eighty subjects in total will be randomized to either arm.

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                    ┌─────────────────────────────────────────┐
                    │     Investigational Arm (ELd Arm)        │
                    │              Elotuzumab                  │
                    │  Cycles 1 & 2: 10 mg/kg IV Day 1, 8, 15, 22│
                    │  Cycles 3 to 18: 10 mg/kg IV Day 1, 15   │
                    │  Cycles 19 and beyond: 20 mg/kg IV Day 1 │
                    │                                          │
                    │             Lenalidomide                 │
                    │  Days 1 - 21 of each cycle: 25 mg PO     │
                    │                                          │
                    │            Dexamethasone                 │
                    │  Day 1, 8, 15, and 22 of each cycle:     │
                    │  - Weeks with Elo: 8 mg IV + 28 mg PO    │
                    │  - Weeks without Elo: 40 mg PO           │
                    │                                          │
                    │             28 DAY Cycle                 │
                    │  Disease Assessments every 4 weeks       │
                    └─────────────────────────────────────────┘
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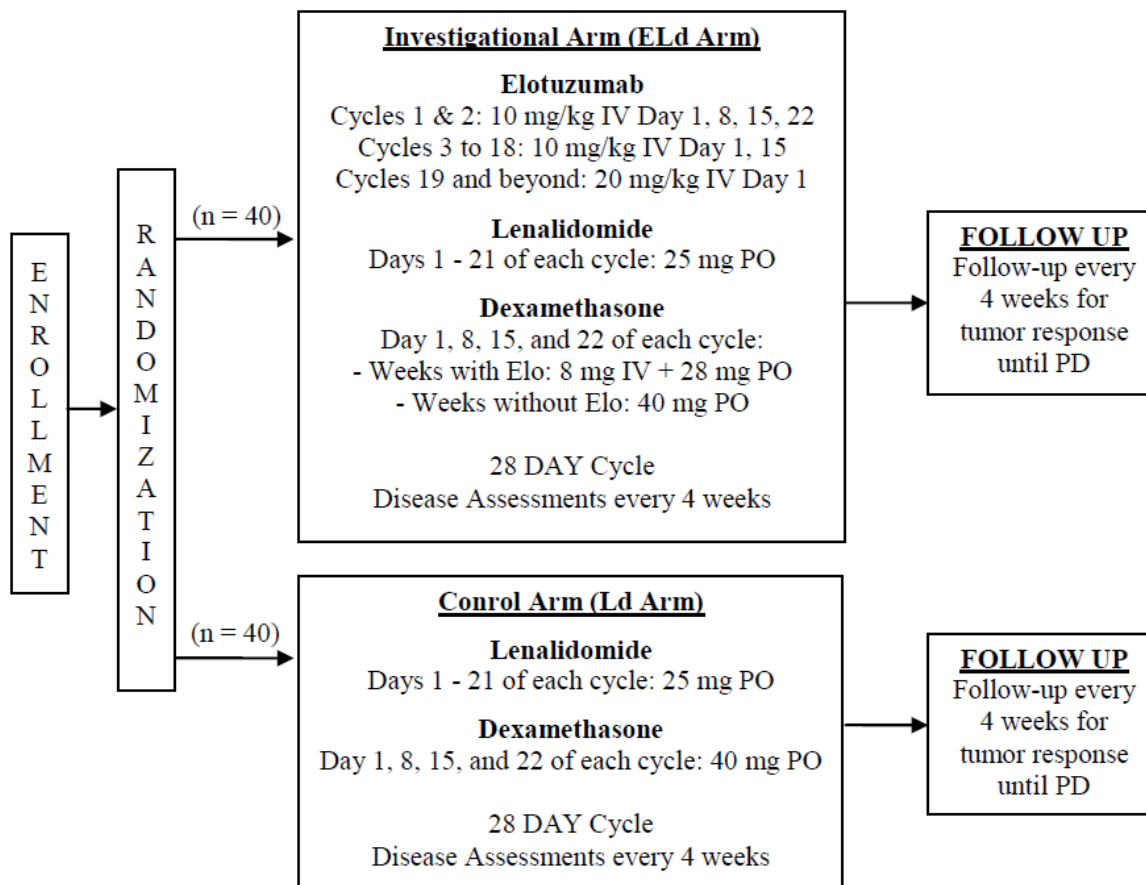
A cycle is defined as 28 days. Treatment with study drug continues until disease progression (PD), unacceptable toxicity or subject meets other criteria for discontinuation of study drug.

Disease assessments, based on the International Myeloma Working Group (IMWG) response criteria, will be conducted every 4 weeks relative to the first dose of study medication until disease progression. Response and progression assessment will be investigator-based and no central lab or independent review is planned.

For the subject who does not have documented disease progression at time of study drug discontinuation, tumor assessments should still be performed according to the same schedule until disease progression even if a subsequent anti-myeloma treatment is initiated prior to disease progression.

Blood samples for pharmacokinetic (PK) and immunogenicity analysis will be collected in all subjects who received elotuzumab, prior to elotuzumab infusion on Day 1 of Cycles 1 through 4, 6, 9, 12, 15 and 18, as well as at the end of the study or discontinuation of treatment, and 30-day and 60-day follow-up visits. In addition, serial PK samples including two hours post end of infusion will be drawn in Cycles 1, 2 and 3.

For full details of the schedule and timing of assessments see Protocol Section 5.

2.2 Treatment Assignment

Eligible subjects will be randomized in a 1:1 ratio to receive either ELd Arm [Investigational Arm] or Ld Arm [Control Arm].

The randomization will be stratified by ISS stage (1 -2 versus 3) and will be carried out via permuted blocks within the stratum.

2.3 Blinding and Unblinding

This is an open label trial.**Protocol Amendments**

Amendment 01 20-Nov-2014	The purpose of this amendment is to change and clarify the handling of Investigational Products, the dosage of premedication prior to elotuzumab infusion and the process of laboratory assessments. This amendment includes three changes: 1) Lenalidomide has to be stored at 15° - 25°C because it is provided as Investigational Product, 2) The dosage of Acetaminophen as a premedication prior to elotuzumab infusion is allowed from 300 mg to 1,000 mg according to the package insert in Japan, and 3) The cytgenetic assessments will be performed at the local central laboratory designated by the sponsor because they require fresh bone marrow samples, and also these results will be collected using the eCRF.

3 OBJECTIVES

3.1 Primary Objectives

To estimate the ORR of elotuzumab + lenalidomide/dexamethasone in subjects with newly diagnosed, previously untreated MM.

3.2 Secondary Objective

- To estimate the difference in ORR between elotuzumab + lenalidomide/dexamethasone (ELd) and lenalidomide/dexamethasone (Ld).

- To assess Progression Free Survival (PFS) in each arm;

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4   ENDPOINTS

4.1   Endpoint Definitions

The primary and secondary endpoints are Objective Response Rates (ORR) based on investigator tumor assessments using IMWG criteria.

4.1.1   Objective Response Rate (ORR)

The primary and secondary endpoints of Objective Response Rate (ORR) are defined as the proportion of randomized subjects who achieve a partial response (PR) or better, i.e. stringent complete response (sCR), complete response (CR), very good partial response (VGPR) and PR, according to the IMWG criteria. Response assessment will be evaluated by the investigator using the IMWG criteria during the trial for all randomized subjects.

4.1.2   Progression-Free Survival

4.1.2.1   Definition of an Adequate Tumor Assessment

In the analysis of PFS, subjects who do not progress are censored. A non-progressing subject can be censored on the date of a tumor assessment only if there is sufficient information to rule out progression. An "adequate" tumor assessment visit for ruling out progression will require the following information:

- Serum monoclonal paraprotein results, if measurable at baseline, and
- Urine monoclonal paraprotein results, if measurable at baseline.
- Serum free light chain results, if measurable at baseline. This is only relevant for subjects who do not have measurable serum and urine monoclonal paraprotein results.

4.1.2.2   Date of Progression or Censoring When Different Components of a Per Time Point Tumor Assessment Conducted at Different Times

As different tumor measurements may be conducted on different days, for instance, the blood draw for serum M-protein may be on a different date than 24-hour urine, the investigators were instructed to report the earliest date of the measurements associated with that time point for progression. In contrast, if tumor measurements are done on different dates and the subject is being censored, instructions were to report latest date of the measurements associated with that time point.

4.1.2.3   Primary Definition of Progression-Free Survival (PFS)

Primary Definition of PFS: PFS, under the primary definition, is the time from randomization to the date of the first documented tumor progression, as determined by the investigator using the IMWG criteria, or to death due to any cause, provided, progression or death does not occur more than 10 weeks (two or more assessment visits) after the last adequate tumor assessment. Clinical deterioration will not be considered progression.

The following censoring rules will be applied to the primary definition of PFS:

- Subjects who receive subsequent systemic secondary anti-myeloma therapy prior to documented progression will be censored at the date of the last adequate tumor assessment prior to or on the initiation of the new therapy.

- Subjects who have an event (documented progression or death) > 10 weeks (2 assessment visits) after their last tumor assessment will be censored at their last adequate tumor assessment prior to the event.

- Subjects who neither receive subsequent therapy prior to progression nor have a progression event will be censored at their last adequate tumor assessment.

- In addition, subjects who do not have any post-baseline tumor assessments and who do not die within 10 weeks of randomization will be censored on the date of randomization.

In all cases, if there are no adequate assessments for censoring then the subject is censored on the date of randomization

4.1.2.4   Secondary Definition of Progression-Free Survival – ITT Definition

Intent-to-Treat (ITT) Definition of PFS: PFS will also be analyzed applying an ITT definition that utilizes all of the data on each randomly assigned subject at the time of the PFS analysis. PFS under the ITT definition will be defined as the time from randomization to the date of the first documented tumor progression or death due to any cause. Clinical deterioration will not be considered progression. A subject who neither progresses nor dies will be censored on the date of their last adequate tumor assessment. A subject who does not have any post-baseline tumor assessments and who has not died will be censored on the date at which they were randomized.

4.1.3   Duration of Response

Duration of response will be measured for subjects whose best response is PR or better, from the time that the criteria for objective response are first met until the date of a progression event (according to the primary definition of PFS). A subject with objective response who does not have a progression event will be censored at the same time they were censored under the primary definition of PFS.

4.1.4   Time to Tumor Response

Time to response is defined as the time from randomization to the first objective documentation of PR or better. Time to response is restricted to the population of subjects who achieved a best response of PR or better.

The duration of all the above endpoints will be measured in months.

5   SAMPLE SIZE AND POWER

The number of subjects in the investigational arm (ELd arm) is based on the primary objective of assessment in objective response rate in ELd arm. The design will test the null hypothesis that the response rate $\leq 71\%$ versus the alternative that the true response rate $> 71\%$. The test will have a significance level of 15% (one-sided) and will have 80% power to reject the null hypothesis if the true response rate is 85%. If there are 32 or more responders out of 40 subjects in the ELd arm, the null hypothesis will be rejected. The study design requires 40 subjects in ELd arm.

The control arm (Ld arm) is designed to evaluate add-on efficacy clinically for Elotuzumab with 40 subjects. The randomized ratio of ELd to Ld is 1:1.

This is a randomized study and the results from both treatment arms will help assess the effect of elotuzumab addition to Ld in the treatment of Japanese subjects with newly diagnosed MM, and put into the right perspective. However, no formal comparisons between treatment arms are planned since a formal comparative study would require a prohibitively large sample size. The efficacy of adding elotuzumab to Ld therapy in the treatment of subjects with newly diagnosed, previously untreated MM will be confirmed on the basis of the large global pivotal study CA204-006, results of which will be used in conjunction with results from the current study to support the JNDA submission.

6   STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1   Study Periods

There are three periods in this study: screening, on-treatment and post-treatment follow-up.

Screening: Most screening procedures must be done no more than 14 days prior to randomization. Some exceptions include efficacy assessments, ECGs and concomitant medications, which can be done up to 28 days or 21 days prior to randomization. See Section 5 of the Protocol for full details of study procedures and timings. For analyses purposes, data collected within 60 days of randomization and prior to first dose will fall into the screening/baseline period. Site personnel should make every effort to initiate study drug treatment within three days after randomization.

On-Treatment Period: The on-treatment period has three phases: the first two cycles, cycles 3-18, and cycle 19 and beyond. All cycles are 28 days in duration. The first two cycles are characterized by weekly visits, safety assessments, and, in the experimental arm, elotuzumab infusions. Cycles 3-18 are characterized by fortnightly visits, safety assessments and, in the experimental arm, elotuzumab infusions. Cycles 19 and beyond, are characterized by once every 4 weeks visit, safety

assessments and in the experimental arm, elotuzumab infusions. Subjects should have myeloma urine and serum laboratory assessments every four weeks while on treatment until they progress and should have imaging for extramedullary plasmacytomas, if indicated, and at the time of CR/sCR assessment. The timing of the tumor assessments will be independent of dosing. Study treatment ends when the subject progresses, experiences unacceptable toxicity, or withdraws consent.

<u>Follow-up Period:</u> Subjects who discontinue study therapy prior to progression must continue to undergo tumor assessments on the same schedule used in the on-treatment period, regardless of whether they are receiving new anti-myeloma therapy. The only exception to this is if the subject withdraws consent for all study procedures or loses the ability to consent freely.

6.2   Treatment Regimens

Subjects will be randomized to one of two treatment arms, ELd or Ld. Subjects will receive these treatments in 28-day cycles until disease progression, unacceptable toxicity or withdrawal of consent.

On ELd arm subjects receive:

- Elotuzumab: 10mg/kg intravenous (IV) on Days 1, 8, 15 and 22 of the cycle during Cycles 1 and 2; Days 1 and 15 during Cycles 3-18 and 20mg/kg intravenous (IV) on Day 1 of the cycle during subsequent cycles.

- Lenalidomide: 25mg orally (po) on Days 1-21 of each cycle.

- Dexamethasone: Administered on Days 1, 8, 15 and 22 of cycle. 28mg po + 8mg IV whenever given prior to elotuzumab; 40mg po on weeks on which no elotuzumab is given.

On Ld arm subjects receive:

- Lenalidomide: 25mg po on Days 1-21 of each cycle.

- Dexamethasone: 40mg po on Days 1, 8, 15 and 22 of each cycle.

6.3   Populations for Analyses

The following subject populations will be used for the statistical analysis:

- Enrolled subjects: all subjects who signed informed consent
- Randomized subjects: all subjects who were randomized to either treatment group
- Treated subjects: all randomized subjects who received at least one dose of study treatment.

Analyses of baseline characteristics, including demography, and efficacy will be carried out on all randomized subjects. Analyses of safety will be based on all treated subjects.

7 STATISTICAL ANALYSES

7.1 General Methods

Continuous variables will be summarized using descriptive statistics; i.e. number of non-missing observations (n), mean, standard deviation (STD), median, minimum, maximum, first quartile and third quartile. Categorical variables will be summarized by frequencies and percentages. The Kaplan-Meier (KM) product limit method will be used to estimate the distribution and median of each time-to-event endpoint in which censoring is involved. The Brookmeyer and Crowley method[17] will be used to compute a 95% confidence interval (CI) for the median of each time-to-event endpoint.

The analyses of tumor response and progression-free survival will be conducted using the best overall response, date of response, and date of progression assigned by the Investigator.

Laboratory results, adverse events, and other symptoms will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0, except where CTCAE grades are not available. Individual laboratory values will be presented in both the conventional US units and the International System of Units (SI). Adverse events will be categorized using the most current version of Medical Dictionary for Regulatory Activities (MedDRA), by system organ class and preferred term. Prior therapies will be summarized using the most current version of the World Health Organization (WHO) drug dictionary.

Statistical analyses will be carried out in SAS (Statistical Analysis System, SAS Institute, North Carolina, USA), unless otherwise indicated.

7.2 Study Conduct

7.2.1 Accrual Patterns

Tables summarizing accrual by site number, overall and by treatment group will be generated.

7.2.2 Protocol Violations

A relevant protocol deviation is defined as a deviation from the protocol which is programmed in the database and which could potentially affect the interpretability of the study results.

The number and percentage of subjects with any relevant protocol deviation and each specific deviation will be presented overall and by treatment group.

The following eligibility deviations are considered relevant in this study and will be summarized for all randomized subjects:

1. Any prior systemic anti-myeloma therapy

2. Non-measurable disease. This occurs when none of the following three conditions are met:
    1. IgG, IgA, or IgM M-protein $\geq$ 0.5 g/dL

2. M-protein $\geq$ 200 mg in 24-hour urine.

3. Serum free light chain (sFLC) assay showing involved FLC level >= 10 mg/dL (>=100 mg/l) provided the serum FLC ratio is abnormal

3. No baseline tumor assessment. This occurs when there are no tumor assessments at all (laboratory assessments) on or prior to first day of dosing. See section 4.1.2.1, for definition of adequate tumor assessment.

Also, the following on-treatment deviations are considered relevant in this study and will be summarized for all treated subjects:

4. Non-protocol specified systemic anti-myeloma therapy prior to discontinuation of study therapy

5. Received non-assigned treatment regimen throughout the study.

6. Subjects continuing to receive study therapy after 10 weeks of first documented progression per investigator (as progression should be confirmed).

If assessments based on the central laboratory is unavailable, but the local laboratory results are available, then those will be used for evaluating deviations 2 and 3.

A by subject listing of relevant protocol deviations will be provided.

7.3 Study Population

7.3.1 Subject Disposition

A frequency table of enrolled subjects, broken down by whether or not they were randomized, and the reasons for not being randomized, will be produced.

Subject disposition during the treatment period will be summarized, overall and by treatment group. The number and percentage of subjects randomized, treated, still on treatment and discontinued from the treatment will be presented.

By-subject listings will also be produced to accompany the tables on enrollment and the subject disposition table.

In addition, a by-subject listing indicating whether the subject was included in each of the analysis populations will be provided.

7.3.2 Demographic and Subject Characteristics

Demographic and baseline characteristics will be summarized, overall and by treatment group. The following parameters will be summarized; age at the time of informed consent (years), age category at time of informed consent (<65 years, $\geq$65 years), and (<75 years, $\geq$75 years), gender (Male, Female), weight (kg) and ECOG performance status (0,1,2) .

An accompanying by-subject listing of demographic and subject characteristics will be presented.

7.3.3 Disease Characteristics at Baseline

Baseline disease characteristics will be summarized, overall and by treatment group. The following parameters will be presented to summarize baseline disease:

- Serum M-protein (g/dL)

- Urine M-protein (mg/24 hours)

- Myeloma type (IgG, IgA, IgM, Light chain disease)

- Number of lytic bone lesions (0, 1-3, >3)

- Myeloma[18] Risk Categories

  - High risk: ISS stage II or III **and** t(4;14) or del(17p) abnormality
  - Low risk: ISS stage I or II **and** absence of t(4;14), del(17p) and 1q21 abnormalities and age < 55 years
  - Standard risk: any subjects not meeting the definition of high or low risk.
  - Not Evaluable: Subjects having missing data preventing the classification in the other 3 categories

- Individual FISH/Cytogenetic abnormalities (del 17p, 1 q21 amplification, t(14; 16), t(4; 14), del 13, 1p32.3, 1q21, t(14;20), hypodiploidy)

- β2 microglobulin (mg/L) (<3.5, ≥3.5-<5.5, >=5.5)

- Albumin (g/L) (<3.5, ≥3.5)

- LDH (<300 IU/L, ≥300 IU/L)

- Creatinine Clearance (mL/sec) (<0.5, 0.5 -<1, 1-<1.5, >=1.5)

- Soft tissue plasmacytomas (Yes, No)

- ISS Stage at randomization (I, II, III)

- Time from disease diagnosis to randomization (months)

An accompanying by-subject listing of disease characteristics at baseline will be presented.

7.3.4 General Medical History

The number and percentage of subjects with any relevant medical history and by body system will be presented, overall and by treatment group.

By subject listings of medical history will be provided. A by subject listing of pregnancy test data will also be provided.

7.3.5   Baseline Safety Laboratory Tests

Baseline safety laboratory evaluations will be the last available samples taken on or before Cycle 1, Day 1 and within 60 days before randomization.

Baseline safety laboratory values will be presented by CTC severity grade, by treatment group. Separate tables will be generated for hematology (hemoglobin, WBC, ANC [neutrophils plus bands], ALC [absolute lymphocyte count] and platelets), liver function (ALT, AST, alkaline phosphatase, albumin, and total bilirubin) and renal function/electrolytes (sodium, potassium, bicarbonate, chloride, calcium, glucose, and creatinine, creatinine clearance < 60 ml/min, ≥ 60 ml/min). Sodium, potassium, chloride, calcium, and glucose will be presented separately, based on their high and low values.

7.4   Extent of Exposure

7.4.1   Study Therapy

Lenalidomide, oral dexamethasone and IV dexamethasone are given at fixed doses and are not adjusted for body surface area or weight. The elotuzumab dose, in contrast, is adjusted for weight. Throughout this SAP, a subject's elotuzumab dose level at a particular time point will refer to the actual dose, in mg/kg, rather than their planned dose. A subject's actual elotuzumab dose level will be computed by dividing their total dose delivered, in mg, as recorded on the "Record of Study Medication" eCRF page, by their latest pre-dose weight, in kg, on Day 1 of that cycle.

7.4.1.1   Duration of Study Therapy

The number of cycles of treatment received by subjects will be summarized (using n, mean, STD, median, min, max, q1 and q3) by treatment group. A summary of the number of subjects taking each drug in each cycle will also be presented by treatment group.

The duration of each treatment (elotuzumab, dexamethasone [oral, IV, and oral and IV combined] and lenalidomide), in months, will be calculated as:

$$(date\ of\ last\ dose\ of\ the\ drug - date\ of\ first\ dose\ of\ the\ drug + 1)/30.4375$$

Duration of each of the study treatments will be summarized by treatment group.

7.4.1.2   Dose Modifications

Elotuzumab

- **Dose Reduction**

Reduction of Elotuzumab dosing is not permitted as per the protocol.

- **Dose Delay**

A delay for Elotuzumab will be computed based on records from the dosing CRF page. A delay in Elotuzumab dosing will be defined as the number of days from the start date of the previous infusion to the start date of the current infusion being > 8 days and ≤10 days (if in cycles 1, 2 or first infusion of cycle 3) or > 15 days and ≤ 21 days (from cycle 3, second infusion of cycle 3 - cycle 19) or > 29 days and ≤ 35 days (from cycle 20 onwards).

For courses with a delay of Elotuzumab infusion, the time of delay in infusion will be summarized in the categories: 2- 3 days, 4 - 7 days.

The number and percentage of subjects with any dose delay, with 1, 2, 3, or ≥ 4 reported delays will be summarized. For subjects with a delay, their reason for delay (from the dose change page of the CRF) will be summarized in the groups: "hematologic toxicity", "non-hematologic toxicity", "AE", "dosing error" and "other". For subjects without an available reason for delay, the category "unknown" will be used.

A by-subject listing for dose delay will be presented for all treated subjects. This listing will include all reported delays per CRF, regardless of whether the subject had a computed delay based on the actual dosing dates.

- **Dose Omission**

An omission for Elotuzumab will be calculated based on records from the study medication CRF page. If the interval between the two dosing dates for Elotuzumab is >10 days (in cycles 1, 2 or first infusion of cycle 3) or >21 days (from the second infusion of cycles 3-18), or > 35 days from cycle 19 and beyond, the dose will be considered to have been omitted.

For courses with an omission of Elotuzumab infusion, the time between the previous and current infusion will be summarized in the categories: 11 - 14, 15 - 21, 22 - 27, 28 - 35, ≥36 days.

The number and percentage of subjects with a dose omission, and with 1, 2, 3, or ≥4 omissions will be summarized. For subjects with an omission, their reason for omission (from the dose modification page of the CRF) will be summarized in the groups: "hematologic toxicity", "non-hematologic toxicity", "AE", "dosing error" and "other". For subjects without an available reason for omission, the category "unknown" will be used.

A by-subject listing for dose omission will be presented for all treated subjects. This listing will include all reported omissions per CRF, regardless of whether the subject had a computed omission based on the actual dosing dates.

- **Dose Interruption**

The number and percentage of subjects with any interruption in their elotuzumab infusion, with 1, 2, 3, or ≥ 4 interruptions, with an interruption due to "infusion reaction", "infusion administration issues" and "other" will be presented. In addition, duration of interruptions (in minutes) will be summarized via descriptive statistics.

A by subject listing will be generated for elotuzumab IV interruptions. This listing will include reason for interruption, whether the infusion was resumed, and duration of the interruption.

- **IV Rate Reduction**

The number and percentage of subjects with any elotuzumab IV rate reduction, with 1, 2, 3, or ≥ 4 rate reductions, and with rate reductions due to "infusion reaction," "infusion administration issues," and "other" will be presented.

A by subject listing will be generated for elotuzumab IV rate reductions.

Lenalidomide

- **Dose Reduction**

Reduction of Lenalidomide will be computed based on the actual dose received. In any study day (excluding, cycle 1, day 1), the drug will have a calculated <u>reduction</u> compared to the previous day, if the actual level of the administered dose is below the actual level of the administered dose in the previous instance. The information for this analysis will be derived programmatically, using the total daily dose on the "Record of Study Medication - lenalidomide" eCRF page.

The daily dose levels are defined as follows:

Dose level 0 or full dose (25 mg): ≥ 20.0

Dose level -1 (15 mg): 12.5 mg to < 20.0

Dose level -2 or starting dose for moderate renal impairment (10 mg): 8.75 to < 12.5 mg

Dose level -3 for subjects with severe renal impairment (15 mg every 48 hours): 6.25 to < 8.75 mg

Dose level -4 for subjects with End Stage Renal Disease (ESRD) (5 mg): < 6.25 mg

The number and percentage of subjects with a dose reduction, and the lowest dose level achieved per subject (-1, -2, -3, ≤ -4), will be presented by treatment group. This table will be broken out by whether the subject started at the standard dose level or at the 10 mg dose level.

The reason for dose reduction as reported by the investigator will be tabulated for all instances with a calculated reduction based on the dose modification for Lenalidomide page. A category "unknown" will be defined for all calculated reductions with no reason reported by the investigator.

A by-subject listing of dose reductions will be generated. This will include all reported reductions per investigator, regardless of whether it met the requirements for a calculated reduction.

- **Dose Interruption**

In any cycle, the Lenalidomide dose will be considered as interrupted if there is a gap of two or more days between two dosing dates within that cycle where the subject did not receive the study drug. This will be calculated based on the information from the dose modification CRF for Lenalidomide.

The number and percentage of subjects with dose interruption, with 1, 2, 3, or ≥ 4 reported interruptions will be presented. For subjects with a computed interruption, their reason for

interruption will be summarized from the dose modification CRF. For subjects without an available reason for interruption, the category "unknown" will be used.

Dexamethasone (IV) and Oral

For IV dexamethasone the following summaries will be provided:

- The number of subjects with any dose delay, with 1, 2, 3, or ≥ 4 reported delays, and with a reason for delay of "hematologic toxicity", "non-hematologic toxicity", "AE", "dosing error" and "other".

- The number of subjects with any reported dose omission, with 1, 2, 3, or ≥ 4 reported omissions, and with a reported reason for omission of "hematologic toxicity", "non-hematologic toxicity", "AE", "dosing error" and "other".

- The number of subjects with any reduction in the dose of the drug, and with a reason for the reduction of "hematologic toxicity", "non-hematologic toxicity", "AE", "dosing error", and "other").

For PO dexamethasone the following summaries will be produced:

- The number of subjects with any dose modification, with 1, 2, 3, or ≥ 4 reported modifications, and with a reason for the modification of "hematologic toxicity", "non-hematologic toxicity", "AE", "dosing error" and "other").

By subject listings of record of study medication for each of IV dexamethasone and PO dexamethasone will be provided.

7.4.1.3   Cumulative Dose, Dose Intensity, and Relative Dose Intensity

A subject's cumulative dose of lenalidomide is defined as the sum of each dose they took, as recorded in their medication diary. In order to compute the cumulative dose of dexamethasone, IV dexamethasone will have to be converted to its equivalent oral dose. This will be done by treating each mg of IV dexamethasone as 1.32 mg of oral dexamethasone, i.e. making use of the fact that the mean bioavailability of oral dexamethasone was estimated to be 0.76. A subject's cumulative dose of dexamethasone will be defined as the sum of all dexamethasone doses, oral and IV, converted to oral equivalent. The cumulative dose administered will be summarized for each of these drugs, by treatment group.

Elotuzumab:

A subject's cumulative dose of elotuzumab is measured in mg/kg, and is defined as the sum of their elotuzumab doses (mg/kg) (actual, not planned) over all infusions.

Elotuzumab dose intensity (mg/kg/week) and relative dose intensity per subject will be calculated separately for Cycles 1 and 2, and Cycles 3 and beyond cycle 18, since elotuzumab planned dose intensity in Cycles 1 and 2 differs from that in Cycles 3 and beyond.

Cycle 1 and 2

$$7 \times \left(\frac{cumulative\ dose\ of\ elotuzumab\ during\ the\ first\ 2\ cycles}{\binom{\min(date\ of\ first\ dose\ of\ elotuzumab\ in\ the\ last\ cycle\ among\ the\ first\ 2\ cycles+28,\ death\ date)-}{date\ of\ first\ dose\ of\ elotuzumab\ in\ Cycle\ 1}} \right)$$

Cycle 3 and beyond

$$7 \times \left(\frac{cumulative\ dose\ of\ elotuzumab\ starting\ from\ Cycle\ 3}{\binom{\min(date\ of\ first\ dose\ of\ elotuzumab\ in\ last\ cycle\ +\ 28,\ death\ date)\ -}{date\ of\ first\ dose\ of\ elotuzumab\ in\ Cycle\ 3}} \right)$$

The relative dose intensity will be calculated as

Dose Intensity/Planned Dose Intensity(PDI)

Planned dose per week for elotuzumab is 10mg/kg/week for the first 2 cycles, 5mg/kg/week for cycles 3 and beyond. The PDI per subject for elotuzumab will be computed by averaging the planned doses per week over the treatment duration e.g., elotuzumab PDI for a subject whose last dose was the first dose of third cycle would have the PDI computed as

$$Elotuzumab\ PDI\ ((mg/kg/wk) = \frac{4 \times 10 + 4 \times 10 + 4 \times 5}{12}$$

Dose intensity and relative dose intensity of elotuzumab will be summarized for the E-Ld group only.

Lenalidomide:

A subject's cumulative dose of lenalidomide is defined as the sum of each dose taken, as recorded in their medication diary.

Dose intensity and relative dose intensity for lenalidomide (mg/week) will be calculated separately for subjects who began the study at the standard daily dose, 25mg/day and those who, because of moderate renal impairment, began the study at < 25mg/day (at 10mg/day dose will be assumed when computing the RDI as this is the recommended dose for subject with moderate renal disease per protocol).

The lenalidomide dose intensity, per subject, will be calculated as:

$$7 \times \left(\frac{cumulative\ dose\ of\ lenalidomide}{\binom{\min(date\ of\ 1st\ dose\ of\ lenalidomide\ in\ last\ cycle\ in\ which\ lenalidomide\ was\ administered)}{+28,death\ date)-date\ of\ first\ dose\ of\ lenalidomide}} \right)$$

$$7 \times \left(\frac{cumulative\ dose\ of\ lenalidomide}{\binom{start\ date\ of\ last\ cycle\ in\ which\ lenalidomide\ was\ administered\ -}{date\ of\ first\ dose\ of\ lenalidomide}+28} \right)$$

The relative dose intensity of lenalidomide is the dose intensity per week divided by the planned dose intensity per week, 131.25mg (or 52.5mg for subjects who begin therapy at <25mg/day(10mg/day per protocol)).

Dexamethasone:

The dose intensity (mg/week) of dexamethasone, per subject, will be calculated separately for the period encompassing Cycles 1 and 2, Cycle 3-18 and Cycle 19 and beyond since dexamethasone dosing is different in these 3 periods.

Cycle 1 and 2:

$$7 \times \left(\frac{\text{cumulative dose of dexamethasone during the first two cycles}}{\left(\begin{array}{c} \min(\text{date of first dose of dexamethasone in last cycle among first 2 cycles} + 28, \text{death date}) - \\ \text{date of first dose of dexamethasone in first cycle} \end{array} \right)} \right)$$

Cycle 3-18:

$$7 \times \left(\frac{\text{cumulative dose of dexamethasone during Cycle 3} - \text{Cycle 18}}{\left(\begin{array}{c} \min(\text{date of first dose of dexamethasone in last cycle among 18 cycles} + 28, \text{death date}) - \\ \text{date of first dose of dexamethasone in Cycle 3} \end{array} \right)} \right)$$

Cycle 19 and beyond:

$$7 \times \left(\frac{\text{cumulative dose of dexamethasone starting from Cycle 19}}{\left(\begin{array}{c} \min(\text{date of first dose of dexamethasone in last cycle } + 28, \text{death date}) - \\ \text{date of first dose of dexamethasone in Cycle 19} \end{array} \right)} \right)$$

The relative dose intensity of dexamethasone is the dose intensity per week divided by the planned dose intensity per week. The planned dose of dexamethasone in the experimental arm on elotuzumab dosing days, 8mg IV dexamethasone plus 28mg oral dexamethasone, is equivalent to 38.5mg of oral dexamethasone. The planned dose in the experimental arm when dexamethasone is not being administered with elotuzumab is 40mg. Thus, the planned weekly dose of dexamethasone in the experimental arm for Cycles 1 and 2 will be equivalent to 38.5mg oral dexamethasone, the planned weekly dose of dexamethasone in the experimental arm for Cycle 3 - Cycle 18 , during which IV dexamethasone is given on Days 1 and 15 only, will be equivalent to 39.25mg of oral dexamethasone and the planned weekly dose of dexamethasone in the experimental arm for Cycle 19 and beyond, during which IV dexamethasone is given on Days 1 only, will be equivalent to 39.64mg of oral dexamethasone . The planned weekly dose of dexamethasone in the control arm is 40mg for all cycles.

In the dose intensity formulas, if the patient took a dose on his death date then 1 day will be added to the denominator.

Descriptive statistics (n, mean, STD, median, min, max, q1 and q3) will be presented for the cumulative dose, and dose intensity of each agent, by treatment group. The number and percentage of subjects whose relative dose intensity falls into the following categories will be presented, by treatment group: $\geq 90\ \%$, 80% to < 90%, 70% to < 80%, 60% to < 70%, < 60%.

7.4.2 Premedication Other than Dexamethasone for Hypersensitivity Reactions

A by-subject listing of pre-medication for elotuzumab, other than dexamethasone, will be provided. This listing will be generated from the "Pre-medication for Elotuzumab (other than Dexamethasone)" eCRF module and pre-medications will be coded using the BMS WHO drug dictionary.

7.4.3 Concomitant Medication

Concomitant medications are medications, other than study medication or pre-medications for elotuzumab recorded on the "Pre

-medication for Elotuzumab" eCRF page, which are taken by subjects any time on-study, no earlier than the first day of study drug and no later than 60 days after the last dose of study drug. Concomitant medications will be coded using the BMS WHO drug dictionary. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior only.

The number and percentage of subjects taking any concomitant medication and each medication (Anatomical Therapeutic Chemical [ATC] classification system drug name) will be summarized, overall and by treatment group.

A by subject listing of concomitant medication will be provided.

7.4.4 Discontinuation of Study Therapy

The number and percentage of subjects who have discontinued all study treatment and reason for discontinuation will be summarized by treatment group and overall using subject status eCRF page from end of treatment. This summary, unlike other safety analyses, will include all randomized subjects and will be grouped by treatment group as randomized. This is done in order to give a full accounting of all subjects who are off study treatment, including those who were randomized but never treated.

In addition, for subjects in the Elotuzumab arm, who discontinued one drug, while continuing at least one of the other two study drugs, their reason for treatment discontinuation will be summarized based on the dose modification CRF. Subjects will be counted in this summary if there is evidence from the dosing CRF that the subject received the combination therapy in at least one cycle, followed by additional cycles, where one of the drugs in the combination was discontinued.

7.4.5 Subsequent Anti-Myeloma Therapy

A by-subject listing of all subsequent surgery, all subsequent radiation therapy, and all subsequent systemic anti-myeloma therapy will be provided using the BMS WHO drug dictionary.

7.5   Efficacy

Efficacy analyses (ORR and PFS) will be conducted on the population of all randomized subjects.

All analyses of ORR and PFS will be based on the investigator evaluation. Unless stated otherwise, whenever a stratified analysis is specified, the stratifications factor will be those used in the randomization, that is:

- Stage of disease (ISS 1 – 2 versus 3)

CIs will be at the two-sided 70% level and at the two-sided 95% level for ORR analysis as primary endpoint, and the other analyses, respectively.

7.5.1   Analyses of Objective Response

Analysis for Primary objective:
The response rate and its corresponding exact two-sided 70% confidence interval (Clopper and Pearson[19]) will be calculated in the ELd arm.
The number and percentage of subjects in each category of best overall response per Investigator (complete response [CR], and whether CR was stringent CR [sCR], PR and whether PR was very good partial response [VGPR], stable disease [SD], progressive disease [PD], or unable to determine [UD]) will be presented, by treatment group.

Analysis for Secondary objective:

An estimate of the response rate and an associated exact two-sided 95% CI will be presented, by treatment group.

The difference in ORR between two treatment arms along with two-sided 95% CI will be estimated using the method of DerSimonian and Laird adjusted by stage of disease (ISS stage 1- 2 versus 3). In addition, the response rate and its corresponding exact two-sided 95% confidence interval will be calculated in both arms.

7.5.2   Analysis of Progression-Free Survival

The PFS analyses will be conducted using both the primary and the ITT definitions of PFS.

The PFS function for each treatment arm will be estimated using the KM product limit method and will be displayed graphically. A two-sided 95% CI for median PFS in each arm will be computed via the Brookmeyer Crowley method. Estimates for one-year and two-year PFS if last patient is followed for at least 1 or 2 years correspondingly, will be presented along with their associated 95% CIs. These estimates will be come from the KM curve and their standard errors (SEs), for use in constructing CIs, will be computed using Greenwood's formula[20].

The estimate of the PFS hazard ratio, of ELd to Ld, will be calculated using a Cox proportional hazards model, with stage of disease (ISS 1 – 2 versus 3) as the stratification factor and treatment

as the sole covariate. Ties will be handled using the Breslow method[2122]. A two-sided, 95% CI for the hazard ratio will also be presented.

A by-subject listing will be presented including treatment arm, PFS duration under the primary definition, PFS duration on the ITT definition, whether the subject was censored under the primary definition, and if censored, the reason, and whether the subject was censored under the ITT definition, and if censored, the reason.

7.5.3 Time to Tumor Response, and Duration of Response

The distributions of duration of response will be estimated, by arm, using the KM product limit method. The KM estimates will be presented graphically and tables will be produced presenting number of events, number of subjects involved, medians, and 95% CIs for the medians.

Time to tumor response, which does not involve censoring, will be summarized by treatment group, using descriptive statistics.

A by-subject listing will be presented including treatment arm, and, duration of response, whether the subject was censored for duration of response, and, if so, the reason.

7.5.4 Efficacy Laboratory Tests

A by subject listing of efficacy will be provided to present the following:

- Percent change in serum and urine M-protein, from baseline and nadir.
- Serum free light chain kappa and lambda concentrations and the kappa/lambda ratio.
- Serum and urine immunofixation test results.
- Corrected Calcium results
- Results of bone marrow analysis, including plasma cells (%) and clonality of plasma cells.
- Radiologic evaluation of extramedullary plasmacytoma and lytic bone lesions

7.6 Safety

Safety summaries will be based on the treated subject population, grouped by treatment regimen received. All subject's treatment regimen received will equal the arm to which they were assigned at randomization as long as they did not receive the wrong regimen at every administration.

7.6.1 Adverse Events

AEs will be categorized using the most recent version of the MedDRA, by system organ class (SOC) and preferred term (PT). The severity of AEs will be graded using the NCI CTCAE (v 3.0).

On-study AEs are defined as non-serious and serious AEs with an onset date on or after the first dose until 60 days after the last dose. See Section 8.4, Imputing AE Onset Dates, for a discussion of imputation rules for incomplete or missing AE onset dates. If the relationship to study drug is missing, then the AE will be assumed to be related to study drug.

Unless specified otherwise, AEs will be counted only once within each SOC and PT, according to their worst CTC grade.

Tables will be sorted by SOC and PT, with SOCs ordered by decreasing frequency overall and then alphabetically. PTs will be sorted within SOCs by descending frequency overall and then alphabetically. The sorting will be done based on the total column when arms are presented side-by-side.

Frequency tables of the worst grade of on-study AE will be presented. One summary table will present AEs broken out by individual grade, 1, 2, 3, 4 or 5 along with an Any Grade category. Another one will present AEs by grouped grades as follows "Any, Grade 3-4 and Grade 5." The summary of combined grades will be repeated for on-study drug-related AEs.

A by-subject listing all AEs will be presented.

In addition the following will be presented by treatment arm:

- Frequency of AE before and after cycle 19 for subjects on the Elotuzumab arm

- Exposure-adjusted AE incidence rates (including multiple occurrences of unique events) will be calculated for each SOC and PT.

Exposure-adjusted incidence rate per 100 person-years will be used and will be calculated as:

$$100 \times \frac{Total\ number\ of\ unique\ AEs}{\left(\frac{subject\ date\ of\ last\ dose\ of\ study\ drug-\ subject\ date\ of\ first\ dose\ of\ study\ drug+60+1}{365.25}\right)}$$

and will be displayed along with a count of events.

7.6.2   Serious Adverse Events and Adverse Event Leading to Discontinuation

Summaries of worst grade of on-study SAE, both by individual grade (1, 2, 3, 4, or 5, along with an Any Grade category) and by grade grouped as "Any, Grade 3-4 and Grade 5" will also be presented. This last summary will be repeated for:

- On-study drug-related SAEs

- On-study AEs leading to discontinuation.

- Drug related AEs leading to discontinuation

By-subject listings of SAEs and AEs leading to study drug discontinuation will be produced.

7.6.3   Adverse Events of Special Interest

Infusion reaction is a known elotuzumab toxicity. It will be based on investigator assessment and will be defined as any non-serious or serious adverse event judged by the investigator to be infusion related and which also occurs on the day of or the day after the elotuzumab infusion. These summaries will be presented:

- Frequency tables of the worst grade of on-study investigator infusion reaction (any grade and grade 1 through 5) by treatment group.

- Frequency of infusion reaction by infusion rate.

- Frequency of infusion reaction by cycle.

By subject listings of infusion reactions will be produced.

7.6.4 Second Primary Malignancies

By-subject listings of second primary malignancies (SPM) will be provided. Information on SPM will be obtained from the "Survival Status" eCRF page.

7.6.5 Deaths

The number and percentage of deaths and the investigator-reported cause of death will be presented, by treatment group and overall. This will be summarized for all deaths, and for those reported on study treatment or within 60 days of discontinuing study treatment.

7.6.6 Clinical Laboratory Evaluations

On-treatment laboratory tests for safety are defined as those that occur after first dose of any study therapy until 60 days after last dose of any study therapy.

The number and percentage of subjects with each worst severity grade for on-study hematology parameters (hemoglobin, Leukocytes, Lymphocytes (absolute), Absolute neutrophil count and platelet count) will be presented, by treatment group. Grades will be categorized as Grade 1, Grade 2, Grade 3, Grade 4, Any Grade and Grade 3-4. Subjects will be counted only once for each parameter, according to their worst post baseline CTC grade. The percentage of subjects with each worst severity grade will be calculated out of the number of subjects with a post-baseline (on-study) assessment for each lab parameter. Subjects with no on treatment assessment for a lab parameter will be reported in the "Not Reported" category.

This summary will be repeated for:

- Liver parameters (Alanine Aminotransferase, Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Total Bilirubin) with available CTC grades

- Renal/electrolyte parameters (sodium, potassium, bicarbonate, calcium, glucose, and creatinine) with available CTC grades. Sodium, potassium, chloride, calcium, and glucose will be presented separately, based on their high and low values.

For blood urea nitrogen (BUN), direct bilirubin, and total protein, the worst category on-treatment will be presented. Results will be categorized as; below upper normal limits, above upper normal limits or not reported.

For reporting purposes, urea will be converted to BUN, using the conversion factor: urea (mmol/L) / 0.357 = BUN (mg/dL).

Subjects experiencing any potential drug induced liver injury (DILI) will be summarized by treatment group as follows:

- A summary of the number and percentage of subjects with (AST or ALT > 3 × upper limit of normal (ULN)) and (Total bilirubin > 2 × ULN and ALP < 2 × ULN) will be presented.

If any potential cases of DILI are identified then clinical review will be conducted to ensure no other immediate apparent possible causes of AT elevation and hyperbilirubinemia are present, including but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drugs known to be hepatotoxic.

Note: The timing for total bilirubin rising to >2xULN needs to be concomitant with or within

30 days after ALT or AST rising to >3xULN. ALP needs to be <2xULN at the time of or within 2 weeks before ALT or AST rising to > 3xULN or TBILI>2xULN. This normal ALP value (<= 2xULN) must be present within 2 weeks of either the ALT/AST criteria or the TBILI criteria.

A by subject listing of all laboratory data will be provided. A separate listing will be provided for all subjects potentially experiencing DILI.

7.6.7 Echocardiogram, MUGA Scan and Electrocardiograms

A by subject listing of echocardiogram and multi gated acquisition (MUGA) scan data collected at screening will be presented. A separate by subject listing of electrocardiogram (ECG) data collected at screening will also be presented.

7.6.8 Vital Signs, Physical Measurements and Physical Examination

Vital signs parameters (body temperature, respiratory rate, seated diastolic and systolic blood pressure and heart rate) will be presented by visit and time point in a subject listing.

Physical measurements (weight and ECOG Performance Status) will be presented by visit and timepoint in a subject listing.

7.7 Pharmacokinetic Analysis

Elotuzumab concentrations taken pre (elotuzumab) dose, at each scheduled visit, will be summarized, by cycle and day, for subjects in the elotuzumab arm only. In addition to the standard summary statistics, the geometric mean will also be presented.

A by subject listing of elotuzumab concentrations will be provided.

Elotuzumab concentrations will be combined with concentration data from other studies and will be analyzed using population pharmacokinetic (PPK) analysis. Results of the PPK analysis may also be used to explore the relationship between elotuzumab and efficacy/safety endpoints. Results of the PPK analysis and potential exploratory exposure response analysis will be reported separately.

7.8   Anti-drug Antibody Analysis

ADA status of a sample:

- Baseline ADA positive sample: ADA is detected in the last sample prior to the first dosing date/time of elotuzumab.

- On study ADA positive sample: after the first dosing date/time of elotuzumab:
    - ADA is detected in a subject whose baseline is negative

- ADA is detected and ADA titer is at least 9-fold or greater ($\geq$) than the baseline positive ADA titers

- On study ADA negative sample: after the first dosing date/time of elotuzumab, no ADA detected relative to baseline.

Anti drug antibody (ADA) will be summarized for elotuzumab arm only with the following categories:

- <u>Baseline ADA Positive Subject:</u> A subject with Baseline ADA Positive Sample

- <u>ADA Positive Subject:</u> A subject with at least one ADA positive sample after the first elotuzumab dose relative to baseline.
    - *Persistent Positive:* ADA positive sample at 2 or more sequential timepoints at least 3 months apart
    - *Only the Last Sample Positive:* ADA positive sample only in the last sampling timepoint.
    - *Other Positive*: not persistent positive with ADA negative sample in the last sampling
    - *Neutralizing Positive:* At least one ADA Positive Sample with neutralizing antibodies detected.

- <u>ADA Negative Subject:</u> A subject with no ADA positive sample after the first elotuzumab dose relative to baseline.

A by subject listing of all ADA data at each time-point will be provided along with corresponding elotuzumab concentration values measured as a part of pharmacokinetic assessments.

8   CONVENTIONS

8.1   Baseline Definition

Baseline evaluations will be those performed within 60 days before randomization and prior to first dosing date. When an assessment is repeated multiple times within the screening evaluation period, the baseline evaluation will be the one closest to the first dosing date.

Laboratory tests and procedures (ECG, physical measurement and 2D echocardiogram MUGA, skeletal survey and plasmacytoma) done on the first date of dosing will be assumed to have occurred prior to dosing and therefore baseline evaluation for those parameters will be those prior or on the first dosing date.

8.2   Age Definition

Age (years) will be calculated as:

$$\frac{date\ of\ informed\ consent - date\ of\ birth + 1}{365.25}$$

8.3   Duration and Study Day Definition

In instances in which study period between two dates are to be calculated (for example, duration of response and PFS), the convention to be used is as follows: later date – earlier date + 1 day.

Study day is calculated as assessment date – first dose date + 1 day, if the assessment is taken on or after the first dose day. If the assessment is taken prior to the first dose day, study day will be calculated as assessment date – first dose date. Date of first dose is defined as Study Day 1.

8.4   Day Conversion of Date Imputation

Conversion from days to months or years:

- 1 year = 365.25 days
- 1 month = 30.4375 days

Imputation for partial or missing progression dates:

- If only the day is missing, the 1st of the month will be used to replace the missing day.
- If the day and month are missing or a date is completely missing, the date of progression will be moved back to the last complete tumor assessment date.

In both the cases given above, the imputed date will still be considered an event.

Imputation for partial or missing death dates:

- If only the day is missing, the later of the last known alive date and the 1st of the month will be used to replace the missing day.

- If both the day and the month are missing, the later of the last know alive date and Jan 1st will be used to replace the missing information.

In both the cases given above, the imputed date will still be considered an event.

For partial dates of start of subsequent anti-myeloma therapy, the following conventions will be used:

- When the day is missing, the alternative therapy will be assumed to start on the first day of the given month if this day is later than the last dosing date. Otherwise the alternative therapy will be assumed to start on the day following the last dosing date.

- When the day and the month are missing, the alternative therapy will be assumed to start on the first day of the given year if this day is later than the last dosing date. Otherwise the alternative therapy will be assumed to start on the day following the last dosing date.

8.5   AE, Laboratory Results and Concomitant Medication

Safety data will be handled according to the BMS safety data conventions (described in "Analysis of Safety Data - Reference to CT SOP 109"). This document includes descriptions on how to analyze AE data as well as how to handle partial dates, missing dates, and unknown end dates when analyzing safety data.

The following dictionaries will be used to code medical terms and to derive toxicity grades:

- Adverse events and other symptoms will be graded according to the NCI CTC Version 3.0 and categorized according to the latest version of MedDRA at the time of the database lock.
- Laboratory results will be classified according to the CTC Version 3.0 grading system.
- All medications will be coded as per the latest version of the WHO Drug dictionary at the time of analysis.
- Tables and listings for laboratory results will be available in SI and US units.

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APPENDIX 1   LIST OF ABBREVIATIONS

ADA	Anti-Drug Antibody
ADCC	antibody dependent cell-mediated cytotoxicity
AE	Adverse Event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMS	Bristol Myers Squibb
CI(s)	Confidence Interval(s)
CR	Complete Response
CRF	Case Report Form

CSR	Clinical Study Report
CS1	CD-2 subset 1
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug induced liver injury
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ESRD	End Stage Renal Disease
FISH	Fluorescence in situ hybridization
IHC	immunohistochemistry
IMiDs	induction, and bortezomib or immune modulatory drugs
IMWG	International Myeloma Working Group
ISS	International Staging System
ITT	Intent-to-Treat
IV	Intravenous
JNDA	Japan New Drug Application
KM	Kaplan-Meier
Ld	Lenalidomide, (low-dose) Dexamethasone
LdE	Lenalidomide, (low-dose) Dexamethasone, Elotuzumab
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labor and Welfare
MM	Multiple Myeloma
M-proteins	Monoclonal immunoglobulin
MUGA	Multi Gated Acquisition
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PBMCs	peripheral blood mononuclear cells

PD	Progression
PFS	Progression-Free Survival
PK	Pharmacokinetic
PO	Oral
PPK	Population Pharmacokinetics
PR	Partial Response
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCID	severe combined immunodeficient
sCR	Stringent Complete Response
SCT	stem-cell transplantation
SD	Stable Disease
SE	Standard Error
sFLC	Serum free light chain
SI	International System of Units (SI)
██████	████████████████████████████
SOC	System Organ Class
SOP	Standard Operating Procedure
STD	Standard Deviation
TBILI	total bilirubin
UD	Unable to Determine
ULN	Upper Limit of Normal
VGPR	Very Good Partial Response
WHO	World Health Organization