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CLINICAL PROTOCOL CA204116

A Phase 2, Randomized, Open Label Trial of Lenalidomide/dexamethasone With or Without Elotuzumab in Subjects with Previously Untreated Multiple Myeloma in Japan

Revised Protocol Number: 03
Incorporates amendment(s) 03 and administrative letter 05

Study Director

[redacted]

Medical Monitor
Su Tien Nguyen

[redacted]

protocol may apply to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

SYNOPSIS

Clinical Protocol CA204116

Protocol Title: A Phase 2, Randomized, Open Label Trial of Lenalidomide/dexamethasone With or Without Elotuzumab in Subjects with Previously Untreated Multiple Myeloma in Japan

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

Investigational Arm:

- Elotuzumab
  - Cycle 1 - 2: 10 mg/kg IV, Days 1, 8, 15, 22
  - Cycle 3 - 18: 10 mg/kg IV, Days 1 and 15
  - Cycle 19 and beyond: 20 mg/kg IV, Day 1
- Lenalidomide: 25 mg po QD, Days 1 - 21 of each cycle
- Dexamethasone administered on Days 1, 8, 15, and 22 of each cycle:
  - On weeks when elotuzumab is administered:
    - 28 mg po (3 - 24 hours prior to start of elotuzumab infusion) AND
    - 8 mg IV (at least 45 minutes prior to elotuzumab administration)
  - On weeks when elotuzumab is NOT administered:
    - 40 mg po

Control Arm:

- Lenalidomide: 25 mg po QD, Days 1 - 21 of each cycle
- Dexamethasone: 40 mg po, Days 1, 8, 15, and 22 of each cycle

A cycle is defined as 28 days. Treatment with study drug continues until disease progression, unacceptable toxicity or subject meets other criteria for discontinuation of study drug outlined in Section 3.5.

Study Phase: 2

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

Objectives:

Primary Objective

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

Secondary Objectives

- To estimate the difference in ORR between elotuzumab + lenalidomide/dexamethasone (ELd) and lenalidomide/dexamethasone (Ld);
- To assess Progression Free Survival (PFS) in each arm.

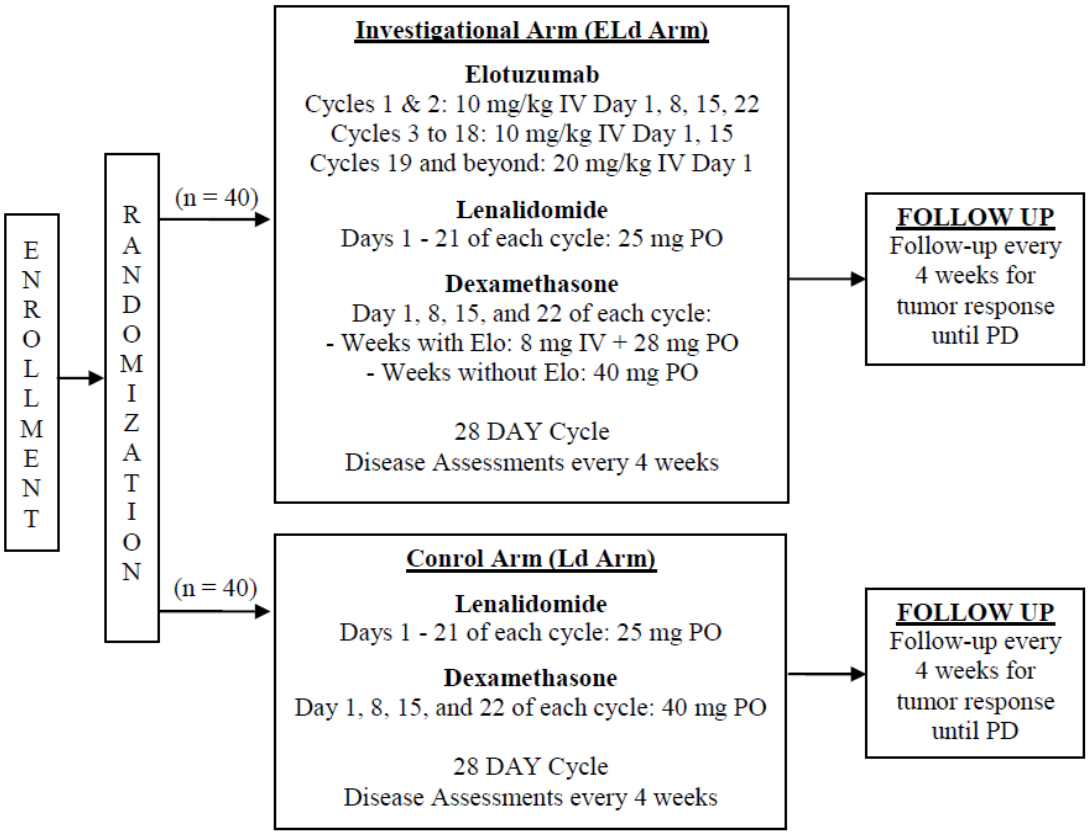
[redacted]

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.

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

Figure 1: **Study Design Schematic**



A cycle is defined as 28 days. Treatment with study drug continues until disease progression, 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.

Study Population:

Subjects who are newly diagnosed with symptomatic Multiple Myeloma and who:

- have not received any prior systemic anti-myeloma therapy AND
- have measurable disease AND
- are not candidates for high-dose therapy plus stem-cell transplantation because of age (≥ 65 years) or coexisting conditions.

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for CA204116

Medication	Potency	IP/Non-IP
Elotuzumab Powder for Solution for Infusion	400 mg/vial	IP
Lenalidomide (Revlimid®) capsule	5 mg, 10 mg, 15 mg and 25 mg	IP
Dexamethasone Tablets	2 mg and 4 mg & various strengths	Non-IP
Dexamethasone Solution	4 mg/ml, 8 mg/ml & various strengths	Non-IP

Elotuzumab and lenalidomide will be supplied by the BMS.
Dexamethasone tablets and solution for IV infusion will be obtained by the investigating site's standard prescribing procedures.

Study Assessments:

Tumor response assessment will be evaluated by the investigator using the IMWG criteria during the trial for all treated subjects. Objective Response Rate (ORR) is defined as stringent complete response (sCR), complete response (CR), very good partial response (VGPR) and partial response (PR) according to the IMWG criteria.

Statistical Considerations:

Sample Size: The number of subjects in 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 ≤ 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%. The study design requires 40 subjects in ELd arm.

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

Endpoints: The primary and secondary endpoint of Objective Response Rate (ORR) is defined as the proportion of treated 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

Analyses:

Primary Endpoint:

The response rate and its corresponding exact one-sided 85% confidence interval will be calculated in the ELd arm. In addition, the two-sided 95% confidence interval will be computed for the ELd arm.

Secondary Endpoints:

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 the Ld arm.

The PFS analyses will be conducted using both the primary and the ITT definitions of PFS. The PFS functions for each randomized arm will be estimated using the Kaplan-Meier product-limit method. Two-sided, 95% confidence intervals for median PFS and the first and third quartiles will be computed by treatment arm. PFS rates at 1, 2, and 3 years will be estimated from the KM curve. Each analysis will be performed after all subjects have been followed for the appropriate time.

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1.2 Research Hypothesis

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

1.3 Objectives(s)

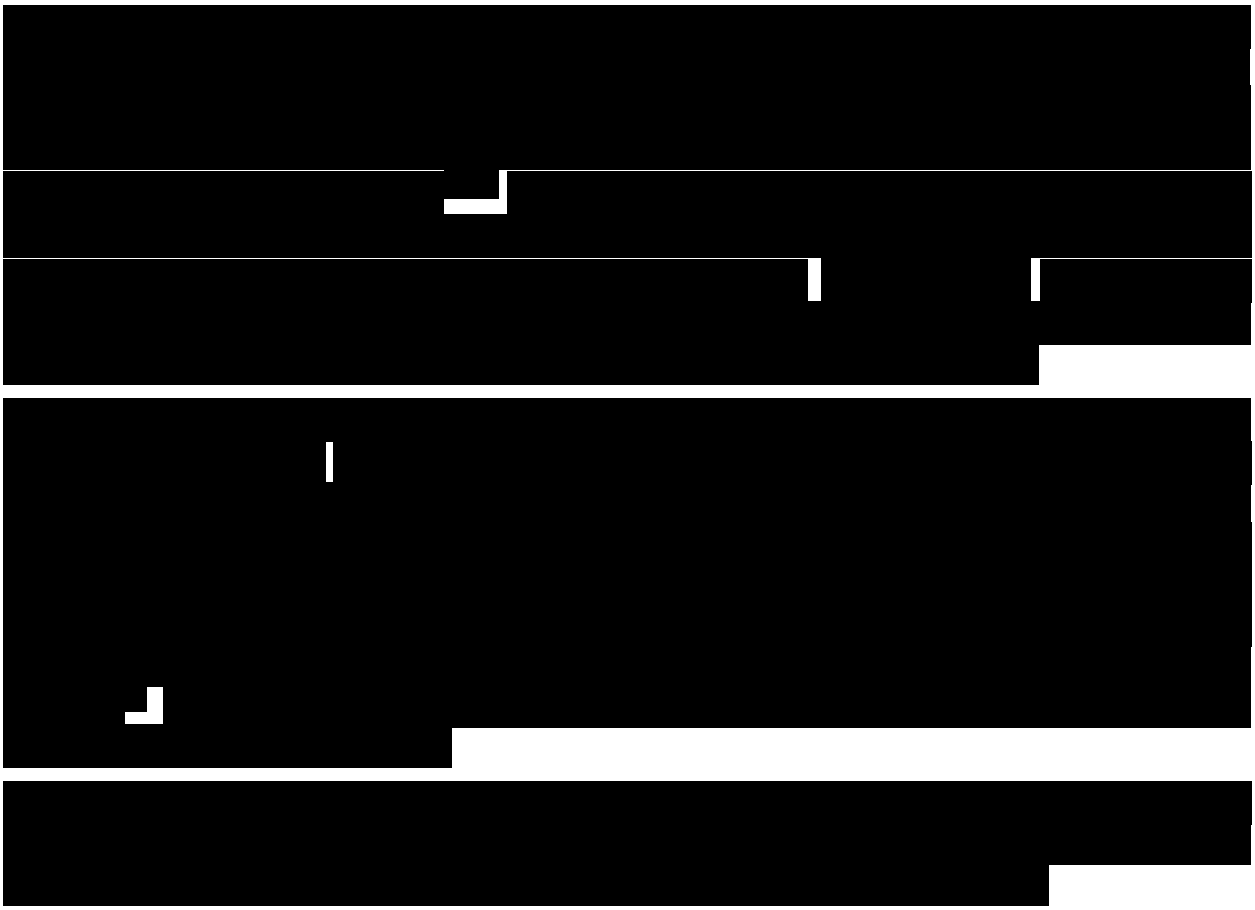
1.3.1 Primary Objectives

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

1.3.2 Secondary Objectives

- To estimate the difference in ORR between elotuzumab + lenalidomide/dexamethasone (ELd) and lenalidomide/dexamethasone (Ld);
- To assess Progression Free Survival (PFS) in each arm.

[redacted]



2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with the standards specified by Article 14 Paragraph 3 and Article 80-2 of the Pharmaceutical Affairs Law (PAL) in Japan, and Good Clinical Practice (J-GCP), as defined by the International Conference on Harmonisation (ICH) and the Ministerial Ordinance Concerning the Standards for the Implementation of Clinical Studies on Pharmaceutical Products and concerning notifications in Japan, and in accordance with the ethical principles underlying European Union Directive 2001/20/EC, the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) and J-GCP. article 1.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board (IRB) approval prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board

Before study initiation, BMS and the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects, which are submitted to by BMS via the head of the study sites. BMS should also provide the IRB via the head of the study site with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB via the head of the study site with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB’s written approval of the written informed consent form and any other information to be provided to the subjects, via the head of the study site, prior to the beginning of the study, and after any revisions are completed for new information.

5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the head of the study site, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, and the subjects' signed ICF.

The consent form must also include a statement that BMS, the IRB, and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

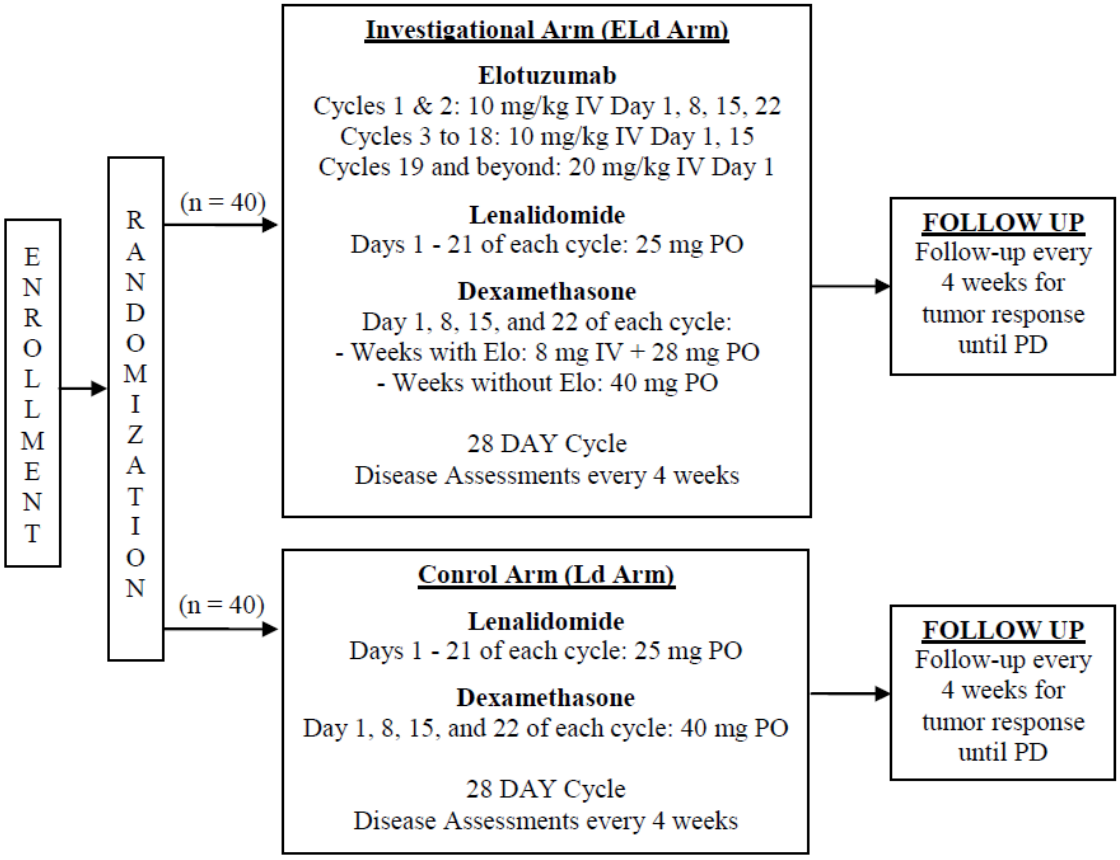
3.1 Study Design and Duration

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 (≥ 65 years) or coexisting conditions.

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.

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



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 outlined in Section 3.5.

Disease assessments, based on the 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.

3.2 Post Study Access to Study

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug up to 12 months after the approval of investigational product by the responsible health authority or until the investigational product becomes commercially available within the country, whichever occurs sooner. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health

authorities and ethics committee, or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to study drug if any of the following occur: a) the marketing application is rejected by the responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subject is, in the investigator's opinion, willing and able to comply with the protocol requirements.

b) Subject has given voluntary written informed consent before performance of any study related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to their future medical care.

2. Target Population

a) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.

b) Life-expectancy > 3 months.

c) Newly diagnosed, untreated, symptomatic, documented myeloma AND;

i) Who are not candidates for high-dose therapy plus SCT because of age (≥ 65 years) or coexisting conditions. Refusal to undergo high dose therapy with SCT is NOT sufficient for entry onto CA204116 for a subject < 65 years old. There must be a comorbidity that prevents SCT for a subject < 65 years old, AND;

ii) Measureable disease (patient must meet one of these criteria)

(a) serum IgG M-protein ≥ 0.5 g/dL OR

(b) serum IgA M-protein ≥ 0.5 g/dL OR

(c) serum IgM M-protein ≥ 0.5 g/dL OR

(d) Urine M-protein ≥ 200 mg/24-hour OR

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

d) Subject Re-enrollment: This study does not permit the re-enrollment of a subject that has discontinued the study as a pre-treatment failure.

3. Age and Reproductive Status

a) Males and Females, ages ≥ 20 years, inclusive

b) Subjects must be willing to refrain from blood donations during study drug therapy and for 90 days after therapy.

c) Women of childbearing potential (WOCBP) and men must be using 2 acceptable methods of contraception to avoid pregnancy throughout the study for a period of at least 1 month (4 weeks) before study treatment and women for up to 120 days, men for up to 180 days after the last dose of study drug in such a manner that the risk of pregnancy is minimized. See Section 3.3.3 for the definition of WOCBP and also refer to the Revlimid risk management plan guidelines.

d) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) The first should be performed within 10 - 14 days and the second within 24 hours prior to the start of study drug. A prescription for lenalidomide for a female of childbearing potential must not be issued by the prescriber until negative pregnancy tests have been verified by the prescriber.

e) Women must not be breastfeeding.

f) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s), elotuzumab in combination with lenalidomide/dexamethasone, plus the time to washout (90 days) plus 30 days (duration of ovulatory cycle) for a total of 120 days post-treatment completion.

g) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s), elotuzumab in combination with lenalidomide/dexamethasone, plus the time to washout (90 days) plus 90 days (duration of sperm turnover) for a total of 180 days post-treatment completion.

h) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Progestogen only hormonal contraception associated with inhibition of ovulation.
- Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
- Nonhormonal IUDs, such as ParaGard®
- Bilateral tubal occlusion
- Vasectomised partner with documented azoospermia 90 days after procedure
    - ♦ Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
- Intrauterine hormone-releasing system (IUS)
- Complete Abstinence
    - ♦ Complete abstinence is defined as the complete avoidance of heterosexual intercourse (refer to Glossary of Terms)
    - ♦ Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus the washout time of the investigational drug plus 30 days).
    - ♦ It is not necessary to use any other method of contraception when complete abstinence is elected.
    - ♦ Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 6.4.
    - ♦ Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
    - ♦ The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge with spermicide
- Male or female condom with or without spermicide*
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

  * A male and female condom must not be used together

UNACCEPTABLE METHODS OF CONTRACEPTION

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactation amenorrhea method (LAM)

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Subjects with non-secretory myeloma.

b) Smoldering MM, defined as asymptomatic MM with absence of lytic bone lesions.

c) Monoclonal Gammopathy of Undetermined Significance (MGUS) defined by all of the following: serum M protein < 3 g/dL, absence of lytic bone lesions, anemia, hypercalcemia and renal insufficiency related to monoclonal protein and (if determined) proportion of plasma cells in the bone marrow of 10% or less.

d) Diagnosis of Waldenstrom's disease or other conditions in which IgM M protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions.

e) Plasma cell leukemia (defined as either ≥ 20% of peripheral WBC comprised of plasma/CD138$^+$ cells or an absolute count of ≥ 2 x 10^9/L).

2. Medical History and Concurrent Diseases

a) POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

b) Significant cardiac disease as determined by the investigator including:

i) Known or suspected cardiac amyloidosis;

ii) Congestive heart failure of Class III or IV of the NYHA classification;

iii) Uncontrolled angina, hypertension or arrhythmia;

iv) Myocardial infarction in past 6 months;

v) Any uncontrolled or severe cardiovascular disease.

c) Prior cerebrovascular event with persistent neurologic deficit.

d) Known HIV infection or active hepatitis A, B, or C.

e) Any medical conditions that, in the investigator's opinion, would impose excessive risk to the subject. Examples of such conditions include:

i) Any uncontrolled disease, such as pulmonary disease, infection, seizure disorder;

ii) Active infection that requires parenteral anti-infective treatment;

iii) Any altered mental status or any psychiatric condition that would interfere with the understanding of the informed consent.

f) Prior or concurrent malignancy, except for the following:

i) Adequately treated basal cell or squamous cell skin cancer;

ii) Or any other cancer from which the subject has been disease-free for > 5 years.

g) Unable to tolerate thromboembolic prophylaxis including, aspirin, Coumadin (warfarin) or low-molecular weight heparin as clinically indicated.

3. Physical and Laboratory Test Findings

a) Corrected serum calcium ≥ 11.5 mg/dl within 2 weeks of randomization (despite appropriate measure such a short course of steroids, bisphosphonates, hydration, calcitonin).

b) Absolute neutrophil count < 1000 cells/mm^3. No granulocyte colony stimulating factors (G-CSF or GM-CSF) allowed within 1 week of randomization. No pegylated granulocyte colony stimulating factors allowed within 3 weeks of randomization.

c) Platelets < 75,000 cell/mm^3 (75 x 10^9/L). Qualifying laboratory value must occur at most recent measurement prior to randomization and must be no more than 14 days prior to randomization. No transfusions are allowed within 72 hours prior to qualifying laboratory value.

d) Hemoglobin < 8 g/dL. Qualifying laboratory value must occur at most recent measurement prior to randomization and must be no more than 14 days prior to randomization. No transfusions are allowed within 72 hours prior to qualifying laboratory value.

e) Total bilirubin ≥ 2 x ULN or direct bilirubin ≥ 2.0 mg/dL.

f) AST or ALT ≥ 3 x ULN.

g) Creatinine clearance (CrCl) < 30 mL/min measured by 24-hour urine collection or estimated by the Cockcroft and Gault formula:

Female CrCl = (140 - age in years) x weight in kg x 0.85 / 72 x serum creatinine in mg/dL

Male CrCl = (140 - age in years) x weight in kg x 1.00 / 72 x serum creatinine in mg/dL

4. Prior Therapy or Surgery

a) Administration of systemic chemotherapy, biologics, immunotherapy, clarithromycin or any investigational agent (therapeutic or diagnostic) for multiple myeloma except bisphosphonate therapy within 3 weeks prior to randomization.

b) Treatment with plasmapheresis within 4 weeks prior to randomization.

c) Steroids within 3 weeks of randomization, except:

i) short course (of ≤ 4 days) of 40 mg dexamethasone or equivalent for emergency use (baseline M proteins must be drawn after this short course and prior to randomization);

ii) ≤ 10 mg prednisone or equivalent per day;

iii) Steroid with little to no systemic absorption (ie, topical or inhaled steroids).

d) Major surgery within 4 weeks prior to randomization (kyphoplasty is not considered major surgery); subjects should have been fully recovered from any surgical related toxicities.

5. Allergies and Adverse Drug Reaction

a) Known hypersensitivity to lenalidomide, dexamethasone, any excipients in the elotuzumab formulation or recombinant protein.

6. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 24 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal :

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

3.4 Concomitant Treatments

3.4.1 Required

Subjects must receive thrombo-embolic prophylaxis, per institutional guidelines or PI discretion. Examples of commonly used thrombo-embolic prophylaxis medications include aspirin, low molecular weight heparin, and vitamin K antagonists.

Subjects must receive pre-medications (Sections 4.5.1.1 and 4.5.1.2) prior to each dose of elotuzumab.

3.4.2 Permitted at Investigator's Discretion

- IV corticosteroids, diphenhydramine, or hydroxyzine, acetaminophen/paracetamol, H2 inhibitors (ie, cimetidine), leukotriene inhibitors (montelukast sodium) for the management of infusion reactions. Additional supportive measures should be provided as indicated including:
- oxygen inhalation
- epinephrine
- bronchodilators
- oral antiviral and antimicrobial prophylaxis
- anti-emetics
- and bisphosphonates.

Per the ASCO 2007 Clinical Practice Guidelines, [39] bisphosphonate therapy should be administered for a period of 2 years. At 2 years, the investigator should seriously consider discontinuing bisphosphonates in subjects with at least stable disease, although further use is at the discretion of the investigator.

Routine clinical practice for monitoring and prevention of osteonecrosis of the jaw (ie, comprehensive dental exam, treating active oral infections, eliminating sites of high risks for oral infection, excellent oral hygiene and avoiding invasive dental procedures while on treatment) must be followed.

- Erythropoietin (EPO) or darbepoetin (prior and ongoing use according to the package insert and institutional guidelines)
- Red blood cell or platelet transfusion
- Prophylactic administration of G-CSF in a subject who is experiencing recurrent difficulties with neutropenia, or therapeutic use in subjects with serious neutropenic complications (such as tissue infection, sepsis syndrome or fungal infection) may be considered at the investigator's discretion, consistent with American Society of Clinical Oncology guidelines (American Society of Clinical Oncology 2006).

3.4.3 Prohibited and/or Restricted Treatments

Any systemic, anti-myeloma therapy other than lenalidomide, dexamethasone and elotuzumab are prohibited while on study. Concomitant steroids, other than weekly dexamethasone (Section 4.5.1) or steroids allowed (as defined in eligibility criteria) are prohibited unless used to treat an adverse event. Guidelines for selection and use of other concomitant medications should be derived from the lenalidomide and dexamethasone prescribing information. Other than study medications, administration of any therapeutic or diagnostic investigational agent (for any indication) is prohibited while on study without prior Sponsor approval.

3.4.4 Surgery and Radiation

Use of radiotherapy or surgical intervention must be recorded on the Case Report Form.

Localized radiation therapy to a site of pre-existing disease may be permitted while on study. Following approval by the medical monitor, the patient may initiate or continue with protocol therapy without interruption during the course of palliative radiation therapy if the investigator believes that the risk of excessive bone marrow suppression or other toxicity is acceptable, and it is in the best interest of the patient to do so.

If the subject develops a definite increase in the size of existing bone lesions or soft tissue plasmacytomas that meets the criteria for disease progression, treatment must be discontinued for progressive disease regardless of whether radiation therapy is initiated.

Kyphoplasty, vertebroplasty or emergency orthopedic surgery is permitted.

3.5 Discontinuation of Subjects followings any Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy (Subject must discontinue elotuzumab and lenalidomide).
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Progressive Disease (see Section 5.5.4 for definition of disease progression).
- Subjects who receive any non-protocol specified systemic anti-myeloma therapy prior to documented progression will be discontinued from all study treatment (including lenalidomide/dexamethasone), however, tumor assessments must continue at 4 week intervals until documented progression.
- Subjects experiencing a Grade 4 infusion reaction must discontinue elotuzumab. Subjects may continue lenalidomide and dexamethasone treatment. Refer to Section 4.5.2.2.

- Subjects experiencing angioedema, Grade 4 rash, exfoliative or bullous rash, Stevens Johnson syndrome, or toxic epidermal necrolysis related to lenalidomide must discontinue lenalidomide. Subjects in the elotuzumab arm may continue elotuzumab and dexamethasone.
- Subjects experiencing a 28-day delay in all study drugs lenalidomide, dexamethasone, and elotuzumab due to an adverse event(s) related to study treatment must be discontinued from study drug. Subjects experiencing delays unrelated to study therapy, for example due to radiation therapy may delay study treatment up to 42 days. Delays greater than 28 days must be discussed with the medical monitor.

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Study Follow up

Subjects who discontinue study drug may continue to be followed as out lined in Section 5.

Subjects should be encouraged to continue participation in the trial until the protocol definition of disease progression is met (Section 5.5.4). Subjects who discontinue study therapy before progression (eg, due to toxicity) should be encouraged to allow the necessary laboratory results (eg, M-protein data, radiologic data, calcium results) to be collected until progression criteria are

fulfilled, even if the subject is on subsequent therapy. These data can be obtained by the subject's local health care provider or the site staff and then analyzed and entered into the CRF/database by the central or local lab.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as

to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

All protocol-specified investigational product and non- investigational products are considered study drug. See Table 4-1 for product description of elotuzumab, lenalidomide and dexamethasone.

Table 4-1: Study Drugs for CA204116 Treatment Period

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Elotuzumab Powder for Solution for Infusion	400 mg/vial	IP	Open Label	20 mL Vial/ Sterile, white to off-white, preservative-free, lyophilized cake	Store at 2° - 8 °C
Lenalidomide (Revlimid®)capsule	5 mg, 10 mg, 15 mg and 25 mg	IP	Open Label	21 capsules per bottle	Store at 15° - 25°C.
Dexamethasone Tablets	2 mg and 4 mg & various strengths	Non-IMP	NA	Various	Refer to label on container or package insert/summary of product characteristics
Dexamethasone Solution	4 mg/mL, 8 mg/mL & various strengths	Non-IMP	NA	Various	Refer to label on container or package insert/summary of product characteristics

Elotuzumab and lenalidomide will be supplied by the BMS. Dexamethasone tablets and solution for IV infusion will be obtained by the investigating site's standard prescribing procedures.

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product(s) is/are: Elotuzumab powder for solution for infusion, lenalidomide (Revlimid®) capsules 5 mg, 10 mg, 15 mg, and 25 mg.

4.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

In this protocol, non-investigational product(s) are: dexamethasone tablets and concentrate for solution for IV infusion, diphenhydramine (or equivalent H1 blocker), ranitidine (or equivalent H2 blocker), acetaminophen, thrombo-embolic prophylaxis medications include aspirin, low molecular weight heparin, and vitamin K antagonists.

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

4.3.1 Elotuzumab

The lyophilized elotuzumab drug product should be stored at 2° to 8°C. Prior to administration the drug product must be reconstituted with Sterile Water for Injection, and then further diluted in 0.9% sodium chloride normal saline, as per the instructions in Appendix 3. After the dose is diluted in normal saline, the elotuzumab infusion must be administered within 8 hours if stored at room temperature. If a delay is anticipated, the prepared dose may be refrigerated at 2° to 8°C for up to 24 hours. If stored under refrigerated conditions, the prepared study drug solution should be equilibrated to room temperature (process takes 2 - 2.5 hours) and the container must be

gently inverted to mix well before administration. Do not use the accelerated warming method. If administration is delayed beyond the specified time, the prepared dose solution must be discarded, and the reason documented by the pharmacist in study drug accountability records. The dose of elotuzumab to be administered to a subject will be calculated by multiplying the subject's weight (kg) by 10 mg/kg (20 mg/kg for Cycle 19 and beyond). The subject's predose weight on Day 1 of each cycle will be used to calculate the dose for each cycle. Subjects will receive a dose of elotuzumab IV on Days 1, 8, 15, and 22 of the first 2 cycles and on Days 1 and 15 of subsequent cycles (Day 1 only for Cycle 19 and beyond). Each dose should be infused as per instructions in Appendix 3.

4.3.2 Lenalidomide

Lenalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Females should be advised to avoid pregnancy while taking lenalidomide (Revlimid®) and for up to 8 weeks after the last dose of lenalidomide. Furthermore, subjects taking lenalidomide should refrain from donating blood until at least 8 weeks or sperm until at least 116 days after last dose of lenalidomide.

Because of this potential toxicity and to avoid fetal exposure to lenalidomide, lenalidomide is only available under a special restricted distribution program. This program is called the Revlimid Risk Management Plan and provided from the sponsor separately for this study. Under this program, only prescribers and pharmacists registered with the program can prescribe and dispense the product. In addition, lenalidomide must only be dispensed to subjects who are registered and meet all the conditions of the Revlimid Risk Management Plan. Subjects who have the potential of pregnancy in the Revlimid Risk Management Plan must be instructed about contraception and undergo the scheduled pregnancy tests.

4.4 Method of Assigning Subject Identification

When the investigator obtained informed consent from a subject, the site staff will fax the enrollment form to the enrollment center or enter subject information into an enrollment form on a website which was generated by the enrollment center, and receive Patient Identification number (PID) via a fax or web site. Once the investigator confirm that the subject met the eligibility criteria determined in the protocol, the site staff will send the registration form with the result of subject eligibility to the enrollment center via a fax or web site, and then receive the confirmation sheet from the enrollment center. 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).

4.5 Selection and Timing of Dose for Each Subject

4.5.1 Study Drug Administration

Dexamethasone

On weeks without elotuzumab (including the control arm), administer the weekly dose of 40 mg dexamethasone on Day 1, 8, 15, and 22 (-1 to +3 days). At the investigator's discretion, the oral dexamethasone may be given as a split dose over 2 consecutive days each week.

On weeks of elotuzumab infusion, administer dexamethasone as a split dose of:

- 28 mg po (between 3 - 24 hours prior to the start of elotuzumab infusion) AND
- 8 mg IV (on the day of elotuzumab infusion at least 45 min prior to the start of infusion).
- At the discretion of the investigator, the oral dexamethasone component may be given as a split dose 12 - 24 and 3 hours prior to elotuzumab.

Elotuzumab

Elotuzumab will be administered intravenously at a dose of 10 mg/kg weekly (Days 1, 8, 15, and 22 of a 4-week cycle) of the first 2 cycles and every 2 weeks (Day 1 and Day 15) for Cycles 3 through 18, then at a dose of 20 mg/kg every 4 weeks Cycle 19 (Day 1) and beyond. A window of -1 to + 3 days is permitted in Cycles 1 and 2.

In Cycle 1 and 2, an elotuzumab dose that falls outside of the pre-specified window must be skipped.

In Cycles 3 and beyond, elotuzumab dosing may be delayed for up to 1 week as clinically indicated. The reason for the delay must be recorded on the CRF. If unable to administer within 1 week, then the dose should be skipped and resumption of the elotuzumab continues per the protocol defined schedule.

In addition, the following must also be administered 30 - 90 min prior to any elotuzumab:

- H1 blocker: diphenhydramine (25 - 50 mg po or IV) or equivalent
- H2 blocker: ranitidine (50 mg IV) or equivalent
- Acetaminophen (300 - 1000 mg po).

See Appendix 3 for elotuzumab dosing instructions.

Lenalidomide

Lenalidomide will be taken orally 25 mg once daily for the first 3 weeks of a 4-week cycle. On the days of elotuzumab administration, the dose of lenalidomide is to be administered at least 2 hours after completion of elotuzumab dosing. Subjects should not break, chew or open the capsules.

Table 4.5.1-1: Treatment Schedule

Investigational Arm (ELd Arm)												
Cycle #	**1 - 2**				**3 - 18**				**19 +**			
Day # (-1/+3 days)[a]	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Dexamethasone - PO	28 mg	28 mg	28 mg	28 mg	28 mg	40 mg	28 mg	40 mg	28mg	40 mg	40 mg	40 mg
Dexamethasone - IV	8 mg	8 mg	8 mg	8 mg	8 mg	-	8 mg	-	8 mg	-	-	-
Elotuzumab - IV	10 mg/kg	10 mg/kg	10 mg/kg	10 mg/kg	10 mg/kg	-	10 mg/kg	-	20 mg/kg	-	-	-
Lenalidomide - PO	25 mg Days 1 - 21				25 mg Days 1 - 21				25 mg Days 1 - 21			
Control Arm (Ld Arm)												
Cycle #	**1 - 2**				**3 - 18**				**19 +**			
Day # (-1/+3 days)	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Dexamethasone - PO	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg
Lenalidomide - PO	25 mg Days 1 - 21				25 mg Days 1 - 21				25 mg Days 1 - 21			

[a] For elotuzumab and dexamethasone dosing, a window -1 to +3 days is permitted. In Cycles 3 and beyond, elotuzumab dosing may be delayed for up to 1 week as clinically indicated.

4.5.1.1 Premedication Regimen in Subjects Without a Prior Infusion Reaction

Consult the Sponsor for further guidance regarding premedication management eg, alternative medications for subjects allergic or intolerant to any premedication or to determine if locally used equivalent medications are acceptable.

On weeks of elotuzumab infusion, the weekly dexamethasone will be split into a po and IV administration (described in Section 4.5.1) which will also serve as premedication for elotuzumab.

Intravenous and po dexamethasone doses are calculated to prevent an imbalance in dexamethasone exposure between the investigational and control arms (Refer to Section 4.5.1.2 for premedication in subjects with prior infusion reaction).

In addition, the following must also be administered 30 - 90 minutes prior to elotuzumab:

- H1 blocker: diphenhydramine (25 - 50 mg po or IV) or equivalent
- H2 blocker: ranitidine (50 mg IV) or equivalent
- Acetaminophen (300 - 1000 mg po).

4.5.1.2 Premedication Regimen in Subjects With a Prior Infusion Reaction

To be re-treated with elotuzumab, subjects with prior infusion reaction must receive H1, H2 blockers and acetaminophen at maximum doses specified (ie, 50 mg diphenhydramine, 50 mg ranitidine, and 1000 mg acetaminophen).

To prevent imbalance in dexamethasone exposure between the two arms in the study, doses of intravenous dexamethasone above 10 mg require a decrease in the po dexamethasone. Recommended dexamethasone dosing is summarized below and in Table 4.5.1.2-1. Decisions to use more aggressive premedication schemes in subjects with only prior Grade 1 or only one prior Grade 2 infusion reaction must be approved by the Sponsor or designee.

- For subjects with prior Grade 1 infusion reaction, the same dexamethasone premedication regime as in Section 4.5.1 may be used.
- For subjects with prior Grade 2 infusion reaction, administer 10 mg IV dexamethasone (instead of 8 mg) as the premedication steroid at least 45 minutes prior to elotuzumab. Subjects should still take 28 mg oral dexamethasone either as a single dose or split dose (16 mg 12 - 24 hours AND 12 mg at least 3 hours prior to elotuzumab).
- For subjects with Grade 3 or recurrent Grade 2 elotuzumab infusion reactions, consultation with the Sponsor or designee is recommended. For these subjects, administer 18 mg IV dexamethasone as the premedication steroid at least 45 minutes prior to elotuzumab. To prevent imbalance in dexamethasone exposure between the two arms in the study, on the weeks that subjects receive 18 mg IV dexamethasone, they must only receive a total of 16 mg oral dexamethasone (8 mg 12 - 24 hours AND 8 mg at least 3 hours prior to elotuzumab). Eighteen mg of IV dexamethasone has similar exposure to approximately 24 mg oral dexamethasone.

Table 4.5.1.2-1: Corticosteroid Premedication[a]

Prior Infusion Reaction	Corticosteroid Premedication[b] Prior to Elotuzumab
None or Only Grade 1 infusion reaction[c]	28 mg po dexamethasone (3 - 24 hrs prior to elotuzumab) AND 8 mg IV dexamethasone at least 45 min prior to elotuzumab
Prior Grade 2 infusion reaction[d]	28 mg po dexamethasone (3 - 24 hrs prior to elotuzumab) AND 10 mg IV dexamethasone at least 45 min prior to elotuzumab
Prior Grade 3 or recurrent Grade 2 infusion reaction	8 mg oral dexamethasone (12 - 24 hrs prior to elotuzumab) AND 8 mg oral dexamethasone (at least 3 hrs prior to elotuzumab) AND 18 mg IV dexamethasone at least 45 min prior to elotuzumab

[a] For prior infusion reactions, use maximum doses H1, H2 blockers and acetaminophen as described in Section 4.5.1.2.

[b] At the discretion of the investigator, the oral dexamethasone component may be given as a split dose 12 - 24 and 3 hours prior to elotuzumab.

[c] Subjects with prior Grade 1 infusion reaction may be premedicated as per Grade 2 infusion reactions.

[d] Subjects with prior Grade 2 infusion reaction may be premedicated as per Grade 3 infusion reactions.

If a subject with a prior Grade 2 - 3 infusion reaction also requires dose reduction of dexamethasone, the weekly dexamethasone on the days of elotuzumab infusion should be no lower than 8 mg IV (on the day of elotuzumab infusion at least 45 minutes prior to elotuzumab).

The oral portion of dexamethasone may be split between the day prior and day of infusion as this may further reduce the incidence of infusion reactions. For example, for subjects with only a prior Grade 1 infusion reaction, the following split dose may be given: 12 mg dexamethasone po (12 - 24 hours prior to elotuzumab) AND 16 mg dexamethasone po (at least 3 hours prior to elotuzumab) AND 8 mg IV dexamethasone at least 60 minutes prior to elotuzumab.

Subjects with Grade 4 infusion reaction are not eligible to receive additional elotuzumab. These subjects should still continue to receive lenalidomide and dexamethasone.

4.5.2 Guidelines for Elotuzumab Infusion in Subjects with Infusion Reactions

4.5.2.1 Grade 1 Infusion Reaction

Grade 1 elotuzumab infusion-related reactions by definition, require,no intervention; however, increased monitoring is recommended.

4.5.2.2 Grade ≥ 2 Infusion Reaction

Infusion reactions during the elotuzumab infusion: For a Grade ≥ 2 elotuzumab infusion related reaction, the infusion must be interrupted. The subject should be treated as clinically indicated with one or more of the following medications or interventions: antiemetics, antihistamines, analgesics, corticosteroids, leukotriene inhibitors, oxygen inhalation, epinephrine, bronchodilators, or other supportive measures as indicated. Subjects with a Grade 4 elotuzumab

infusion reaction must have elotuzumab permanently discontinued. These subjects should continue to receive lenalidomide and dexamethasone per protocol.

Once the elotuzumab infusion-related reaction has resolved to Grade ≤ 1, the infusion can be restarted at 0.5 mL/minute. If symptoms do not recur after 30 minutes, the infusion rate may be increased in a stepwise fashion starting at a rate per investigator's discretion, and increasing up to a rate per investigator's discretion, up to a maximum of 5.0 mL/minute.

Subjects who experience an infusion reaction require vital signs to be monitored every 30 minutes for 2 hours after the end of the elotuzumab infusion. If the elotuzumab infusion reaction recurs, the infusion must be stopped and not restarted on that day. Appropriate therapy should be administered to address the subject's signs and symptoms. The infusion can be reattempted at the next protocol defined infusion time point at the investigator's discretion with additional premedication as described in Table 4.5.1.2-1.

Infusion reactions after the completion of elotuzumab infusion: Should a Grade ≥ 2 infusion reaction occur following completion of an elotuzumab infusion, the subject should be treated as clinically indicated with 1 or more of the following medications or interventions: diphenhydramine, acetaminophen, hydrocortisone, H2 inhibitor, leukotriene inhibitor, oxygen inhalation, epinephrine, bronchodilators, or other supportive measures as indicated.

Elotuzumab infusions on subsequent weeks after a prior Grade ≥ 2 infusion reaction: Subjects with prior Grade 2 or higher infusion reactions should have the next infusion started at 0.5 mL/min and then escalated in a stepwise fashion (0.5 mL/minute every 30 minutes to a maximum of 5.0 mL/min). If no Grade ≥ 2 infusion reaction occurs, the next infusion may be increased in a stepwise fashion starting at a rate per investigator's discretion, and up to a maximum of 5.0 mL/minute. If tolerated, all subsequent infusions may start at a rate per investigator's discretion, up to a maximum rate of 5.0 mL/minute.

4.5.3 Dose Delay or Interruption

If the dose of one drug in the regimen (ie, lenalidomide, dexamethasone or elotuzumab) is delayed or interrupted, the treatment with the other drugs may continue as scheduled. Subjects experiencing a 28-day delay in all study drugs lenalidomide, dexamethasone, and elotuzumab due to an adverse event(s) related to study treatment must be discontinued from study drug. Subjects experiencing delays unrelated to study therapy, for example due to radiation therapy may delay study treatment up to 42 days. Delays greater than 28 days must be discussed with the medical monitor.

Each cycle is 28 days. While dose delays or interruptions are permitted, the start of each cycle cannot be delayed and is fixed relative to Cycle 1 Day 1. Adjustments to the Cycle 1 Day 1 anchored schedule should not be performed. Missed doses should be skipped, not delayed, if not given within the allowed window.

Subjects may continue on study therapy even if components of the study therapy must be discontinued. For example, a subject on lenalidomide and dexamethasone may continue on study therapy even if dexamethasone must be discontinued for an adverse event. Likewise, a subject on

the investigational arm may continue on study therapy if elotuzumab must be discontinued for an adverse event or other reason. Patients are considered still on study therapy even if they continue solely on lenalidomide.

Please consult the BMS medical monitor or any questions regarding dose interruption or study therapy discontinuation.

4.5.3.1 Elotuzumab

In Cycle 1 and 2, an elotuzumab dose that falls outside of the pre-specified window (-1 to +3 days) must be skipped.

In Cycles 3 and beyond, elotuzumab dosing may be delayed for up to 1 week. If unable to administer within 1 week, then the dose should be skipped and resumption of the elotuzumab continues per the protocol defined schedule.

4.5.3.2 Dexamethasone

Dexamethasone delay should be performed as clinically indicated at the discretion of the investigator.

For subjects receiving elotuzumab, the weekly dexamethasone dose that coincides with or is temporally closest to the elotuzumab dosing must be administered as part of the premedication for elotuzumab per the guidance in Section 4.5.1.

4.5.3.3 Lenalidomide

Lenalidomide delay should be performed as clinically indicated at the discretion of the investigator.

Subjects should be instructed that if a dose of lenalidomide has been missed and it has been less than 12 hours since the subject's regular dosing time, to take lenalidomide as soon as the subject remembers. If it has been more than 12 hours, the dose must be skipped. Subjects should not take 2 doses at the same time.

4.5.4 Recommended Dose Reductions

The criteria presented in this section for dose modification are meant as general guidelines, and they are based on current US standards of clinical practice. Local standards may differ and may be followed. Dose modification may occur in the setting of lower grade toxicity if the investigator, in consultation with the Medical Monitor/Sponsor, believes that it is in the interest of subject safety.

4.5.4.1 Elotuzumab

No dose reduction is allowed for elotuzumab.

4.5.4.2 Dexamethasone

Dexamethasone dose reductions for toxicity must be performed as clinically indicated. Recommended management is described in Table 4.5.4.2-1 and Table 4.5.4.2-2. Deviations to the recommended dose reductions are allowed based on the clinical judgment of the investigator.

Table 4.5.4.2-1: Dexamethasone Dose Reductions

CTC AE CATEGORY	ADVERSE EVENT	TREATMENT ADJUSTMENT
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1 - 2 (requiring medical management)	Treat with a proton pump inhibitor. If symptoms persist despite above measures, decrease by one dose level.
	≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Reduce by one dose level and resume along with concurrent therapy with a proton pump inhibitor. If symptoms persist despite above measures, reduce to dose level -3.
	Acute pancreatitis	Reduce to dose level -3.
Cardiovascular	Edema ≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	Use diuretics as needed, and decrease dexamethasone by one dose level. If edema persists despite above measures, decrease by another dose level.
Neurology	Confusion or Mood alteration ≥ Grade 2 (interfering with function ± interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Decrease by one dose level and resume. If symptoms persist despite above measures, decrease by another dose level.
Musculoskeletal	Muscle weakness ≥ Grade 2 (symptomatic and interfering with function ± interfering with activities of daily living)	Hold dose until muscle weakness is ≤ Grade 1. Decrease dexamethasone by 1 dose level and resume. If weakness persists despite above measures, decrease by another dose level.
Metabolic	Hyperglycemia ≥ Grade 3 or higher	Treat with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease by one dose level until levels are satisfactory.
Constitutional	Insomnia ≥ Grade 2	Decrease by one dose level and resume.

Dose reduction for persistent Grade 2 or Grade ≥ 3 AEs believed to be related to dexamethasone and not listed above are permitted. Dose reductions should follow guidance in Table 4.5.4.2-1 and Table 4.5.4.2-2.

For subjects receiving elotuzumab, regardless of dexamethasone dose reduction, at least 8 mg of the weekly dexamethasone dose must be administered IV as part of the premedication for elotuzumab with the remainder of the weekly dexamethasone dose administered orally as described in Section 4.5.1. Contact the medical monitor to discuss dexamethasone IV premedication for subjects in the investigational arm who reach dose level -3 and must discontinue oral dexamethasone due to dose limiting toxicity.

On weeks without elotuzumab, no IV dexamethasone should be administered.

Table 4.5.4.2-2: Dexamethasone Dose Levels

Dose Level	Weeks with Elotuzumab		Weeks without Elotuzumab	
	PO	IV	PO	IV
0	28 mg	8 mg	40 mg	0 mg
-1	12 mg	8 mg	20 mg	0 mg
-2	0 mg	8 mg	12 mg	0 mg
-3	0 mg	contact Medical Monitor	0 mg	0 mg

4.5.4.3 Lenalidomide

Dose adjustments, as summarized below, are recommended for the management of NCI CTCAE Grade 3 and 4 toxicities for thrombocytopenia, neutropenia or other toxicities that are judged by the investigator to be related to lenalidomide. Information in Table 4.5.4.3-1 and Table 4.5.4.3-2 is based on current standard of clinical practice.

Table 4.5.4.3-1: Treating Thrombocytopenia Related to Lenalidomide

When Platelet Counts:	Recommended Course
Fall to < 30,000/mm^3	Interrupt lenalidomide treatment; follow complete blood counts weekly.
Return to ≥ 30,000/ mm^3	Resume lenalidomide at 15 mg, Days 1 - 21, once daily.
For each subsequent drop < 30,000/ mm^3	Interrupt lenalidomide treatment.
Return to ≥ 30,000/ mm^3	Resume lenalidomide at 5 mg less than previous dose, Days 1 - 21, once daily. Do not dose below 5 mg.

Table 4.5.4.3-2: Treating Neutropenia Related to Lenalidomide

When Neutrophil Counts:	Recommended Course
Fall to < 1000/ mm^3	Interrupt lenalidomide treatment, add G CSF;[a] follow complete blood counts weekly.
Return to ≥ 1000/ mm^3 and neutropenia is the only toxicity	Resume lenalidomide at 25 mg, Days 1 - 21, once daily.
Return to ≥ 1000/mm^3 and if other toxicity	Resume lenalidomide at 15 mg, Days 1 - 21, once daily.
For each subsequent drop < 1000/ mm^3	Interrupt lenalidomide treatment.
Return to ≥ 1000/ mm^3	Resume lenalidomide at 5 mg less than previous dose, Days 1 - 21, once daily. Do not dose below 5 mg.

In case of neutropenia, consider the use of growth factors in subject management.

[a] G-CSF = Granulocyte Colony-Stimulating Factor

Lenalidomide Dose Adjustments in Subjects with Renal Impairment

Since lenalidomide is primarily excreted via the kidney, adjustments to the dose of lenalidomide are provided based on the lenalidomide country prescribing information. The regimen of 21-day dosing every 28 days remains the same despite the dose reductions described below.

Table 4.5.4.3-3: Lenalidomide Dose Adjustments in Subjects with Renal Impairment

Creatinine Clearance (CrCl):	Recommended Course
Moderate renal impairment (30 ≤ CrCl < 60 mL/min)	10 mg, every 24 hours
Severe renal impairment (CrCl < 30 mL/min, not requiring dialysis)	15 mg every 48 hours
End Stage Renal Disease (CrCl < 30 mL/min, requiring dialysis)	5 mg once daily. On dialysis days, dose should be administered following dialysis

Source: Lenalidomide USPI

Dose Adjustments During Treatment for Other Grade 3 and 4 Toxicities

Angioedema, Grade 4 rash, exfoliative or bullous rash, Stevens-Johnson syndrome or toxic epidermal necrolysis requires permanent discontinuation of lenalidomide. For Grade 2 - 3 skin rash judged to be related to lenalidomide interruption or discontinuation should be considered.

For other Grade 3 and 4 toxicities judged to be related to lenalidomide, hold treatment and restart lenalidomide at the next lower dose level when toxicity has resolved to ≤ Grade 2.

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Starting at Cycle 1 Day 1, all treated patients will be assessed for drug compliance of all treatments administered during the course of the study. Treatment compliance will be monitored by drug accountability and recorded in the subject's medical record. For those medications taken at home (lenalidomide and dexamethasone), subjects will be provided with a medication diary in which to record study drug doses and will be instructed to bring this diary and study drug containers (lenalidomide and oral dexamethasone) to clinic visits.

4.8 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

It is the study drug storage manager's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

It is the study drug storage manager's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

Arrangements for the return of study drug will be made by the responsible Study Monitor.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CA204116)

Procedure	Screening Visit (-28 to -1 days of randomization)	Notes
Eligibility Assessments		
Informed Consent	X	Prior to any screening procedures
Inclusion/Exclusion Criteria	X	Within 14 days of randomization
Medical History	X	Includes date of diagnosis MM, Med Hx should be completed within 28 days of randomization
Safety Assessments		
Physical Examination	X	Include height and weight (Section 5.4.1) within 14 days of randomization
Vital Signs	X	Temperature, BP, HR, RR (Section 5.4.1) within 14 days of randomization
Performance Status (ECOG)	X	Within 14 days of randomization
Serious Adverse Events Assessment	X	Collected from the time of informed consent
Second Primary Malignancy	X	Collected from the time of informed consent (Section 6.7)
Concomitant Medications	X	Within 21 days of randomization
2-D Echocardiogram or MUGA	X	Within 28 days of randomization (Section 5.4.3)
ECG	X	Within 28 days of randomization (Section 5.4.3)
Laboratory Assessment for Safety		
CBC, differential, platelets	X	Within 14 days of randomization (Section 5.4.4)
Serum Chemistry	X	Within 14 days of randomization (Section 5.4.4)
Serum β2-microgloblin	X	Within 14 days of randomization (assessment of ISS stage)
Serum Albumin	X	Within 14 days of randomization (assessment of ISS stage)

Table 5.1-1: Screening Procedural Outline (CA204116)

Procedure	Screening Visit (-28 to -1 days of randomization)	Notes
Urinalysis	X	Within 14 days of randomization (Section 5.4.4)
Pregnancy Test	X	For WOCBP only. 2 pregnancy tests, one 10 - 14 days prior to start of study drug and one within 24 hours prior to start of study drug. Urine tests must have a sensitivity of at least 25 IU/L.
Efficacy Assessments		
Myeloma Urine and Serum Lab tests	X	Within 28 days of randomization. Central lab analysis. (Section 5.5.2)
Bone Marrow Aspiration/Biopsy	X	Within 28 days of randomization. Bone marrow aspirate is mandatory. Bone marrow biopsy is optional. (Section 5.5.2)
Cytogenetic analysis and FISH	X	Within 28 days of randomization. Local Central lab analysis. (Section 5.5.2 and 5.7.2)
Skeletal Survey	X	Within 28 days of randomization
CT/MRI assessment for extramedullary soft tissue plasmacytoma	X	Within 28 days of randomization, if clinically indicated.
Study Drug		
Randomize	X	First dose of study drug must occur within 3 days of randomization
Dispense Study Drug	X	Those supplied by BMS or sourced by the investigator

Table 5.1-2: Short-term Procedural Outline (CA204116) Cycles 1 & 2

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 - 28[a]	Notes
Safety Assessments						
Targeted Physical Examination	X					Perform up to 3 days prior to dosing, include weight (Section 5.4.1)
Vital Signs	X	X	X	X		Measure vital signs prior to pre-medication, pre-elotuzumab infusion, 30 minutes after the start of elotuzumab infusion, at the end of infusion, and 30 and 120 minutes after the completion of infusion. Control arm measure vital signs once at each visit.
Performance Status (ECOG)	X					Evaluate prior to dosing
Serious Adverse Event Assessment	X	X	X	X		Evaluate prior to dosing
Adverse Events Assessment	X	X	X	X		Evaluate prior to dosing
Second Primary Malignancy	X					Section 6.7
Concomitant Medications	X	X	X	X		Evaluate prior to dosing
Laboratory Test for Safety						
CBC, differential, platelets	X	X	X	X		Can be drawn up to 3 days prior to study visit. (Section 5.4.4)
Serum Chemistry	X					Can be drawn up to 3 days prior to study visit. (Section 5.4.4) **Serum calcium and albumin every 4 weeks from date of first dose of study drug until disease progression, even if subject is on subsequent therapy**
Pregnancy Test	X	X	X	X		For WOCBP only. Urine tests must have a sensitivity of at least 25 IU/L. Weekly test within 24 hours of study medication.

Table 5.1-2: Short-term Procedural Outline (CA204116) Cycles 1 & 2

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 - 28[a]	Notes
Efficacy Assessments						
Myeloma Urine and Serum Lab Tests	**Every 4 weeks from date of first dose of study drug until progression, regardless of whether patient is on study therapy or subsequent therapy.**					**Day 1 of each cycle (except Cycle 1 - refer to Screening visit for defined window) until disease progression.** 24-hour urine sample can be collected within ± 7 days of visit, and must be obtained with each cycle in all subjects who have measurable UPEP M protein (≥ 200 mg/24 hours) at baseline. Subjects without measurable urine M protein at baseline and at next two subsequent cycles do not have to submit q4 week urine samples with each cycle (but must submit q12 week urine samples) until SPEP M protein becomes undetectable. In order to full fill CR/sCR criteria, both serum and urine immunofixation must be performed and be negative on two consecutive assessment. Therefore, at the time SPEP becomes undetectable, UPEP sample collection must promptly resume for these subjects, and also continue q4 weeks until SPEP becomes detectable. Central lab analysis. (Section 5.5.2)
Bone Marrow Aspiration/Biopsy	For confirmation of CR/sCR if applicable or, if clinically indicated at time of suspected disease progression					Bone marrow aspirate is mandatory. Bone marrow biopsy is optional. Bone marrow samples must be assessed for clonal cells at the local lab by immunohistochemistry of the biopsy or immunoflourescence (flow cytometry) of the aspirate. Plasma cell percentage and light chain restriction assessments are required. (Section 5.5.2)
Skeletal Survey	If clinically indicated					Section 5.5.3.1
CT/MRI assessment for extramedullary soft tissue plasmacytoma	As clinically indicated and at the time of CR/sCR assessments					Section 5.5.3.2

Table 5.1-2: Short-term Procedural Outline (CA204116) Cycles 1 & 2

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 - 28[a]	Notes
Response per IMWG based criteria	**Every 4 weeks from date of first dose of study drug until progression, regardless of whether patient is on study therapy or subsequent therapy.**					Investigator assessment All response categories require two consecutive assessments. (Section 5.5.4)
Serum PK (Investigational arm only)	←	—	—	→		Refer to Section 5.6 for specific time points
Anti-Drug Antibody (ADA) (Investigational arm only)	←	—	—	→		Refer to Section 5.6 for specific time points
[redacted]	←	—	—	→		Refer to Section 5.7.1 for specific time points
Study Drug						
Premedication for Elotuzumab (Investigational arm only)	X	X	X	X		
Elotuzumab Infusion (Investigational arm only)	X	X	X	X		In Cycles 1 and 2, an elotuzumab dose that falls outside of the pre-specified window (-1 to +3 days) must be skipped.
Lenalidomide Administration	Day 1 - 21 of each cycle					
Dexamethasone Administration	X	X	X	X		
Dispense Lenalidomide	X					Dispense lenalidomide on Day 1 of cycle per the Revlimid Risk Management Plan

[a] For the patients who discontinue in Cycle 1 or 2, the procedure of "End of Treatment" and "Post End of Treatment" in Table 5.1-3 must be applied.

Table 5.1-3: Long-term Procedural Outline (CA204116) Cycles 3 and Beyond

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Day 23 - 28	End of Treatment	Days 30 & 60 Post End of Treatment[a]	Notes
Safety Assessments								
Targeted Physical Examination	X					X		Perform up to 3 days prior to dosing, include weight (Section 5.4.1)
Vital Signs	X		X*			X		Measure vital signs prior to administration of premedication, pre-elotuzumab infusion, 30 minutes after the start of elotuzumab infusion, at the end of infusion, and 30 minutes after the completion of elotuzumab infusion. Control arm measure vital signs once at each visit. *Not required in Cycles 19 and beyond
Performance Status (ECOG)	X					X		Evaluate prior to dosing
Serious Adverse Events Assessment	X		X*			X	X	Evaluate prior to dosing *Not required in Cycles 19 and beyond All SAEs must be collected that occur within 60 days of discontinuation of dosing
Adverse Events Assessment	X		X*			X	X	Evaluate prior to dosing *Not required in Cycles 19 and beyond
Second Primary Malignancy	X					X	X	Section 6.7 Performed at 30 and 60 day ± 1 week EOT follow up visits.
Concomitant Medications	X		X*			X	X	Evaluate prior to dosing *Not required in Cycles 19 and beyond

Table 5.1-3: Long-term Procedural Outline (CA204116) Cycles 3 and Beyond

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Day 23 - 28	End of Treatment	Days 30 & 60 Post End of Treatment[a]	Notes
Laboratory Test for Safety								
CBC, differential, platelets	X					X		Can be drawn up to 3 days prior to study visit. (Section 5.4.4)
Serum Chemistry	X					X		Can be drawn up to 3 days prior to study visit. (Section 5.4.4) **Serum calcium and albumin every 4 weeks from date of first dose of study drug until disease progression, even if subject is on subsequent therapy.**
Pregnancy Test	X		X*			X	X	For WOCBP only. Urine tests must have a sensitivity of at least 25 IU/L. Test must be completed on Day 1 and Day 15 within 24 hours prior to dosing. **WOCBP must perform a pregnancy test 90 days off treatment. This test may be performed locally if the patient is unable to return to your center.** *Not required in Cycles 19 and beyond. However, patients with irregular menstrual cycles must have a pregnancy test every two weeks.

Table 5.1-3: Long-term Procedural Outline (CA204116) Cycles 3 and Beyond

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Day 23 - 28	End of Treatment	Days 30 & 60 Post End of Treatment[a]	Notes
Efficacy Assessments								
Myeloma Urine and Serum Lab Tests	**Every 4 weeks from date of the first dose of study drug until progression, regardless of whether patient is on study therapy or subsequent therapy.**							**Day 1 of each cycle until disease progression.** 24-hour urine sample can be collected within ± 7 days of visit, and must be obtained with each cycle in all subjects who have measurable UPEP M protein (≥ 200 mg/24 hours) at baseline. Subjects without measurable urine M protein at baseline and at next two subsequent cycles do not have to submit q4 week urine samples with each cycle (but must submit q12 week urine samples) until SPEP M protein becomes undetectable. In order to full fill CR/sCR criteria, both serum and urine immunofixation must be performed and be negative on two consecutive assessment. Therefore, at the time SPEP becomes undetectable, UPEP sample collection must promptly resume for these subjects, and also continue q4 weeks until SPEP becomes detectable. Central lab analysis. (Section 5.5.2)
Bone Marrow Aspiration/Biopsy	For confirmation of CR/sCR if applicable or, if clinically indicated at time of suspected disease progression							Bone marrow aspirate is mandatory. Bone marrow biopsy is optional. Bone marrow samples must be assessed for clonal cells at the local lab by immunohistochemistry of the biopsy or immunoflourescence (flow cytometry) of the aspirate. Plasma cell percentage and light chain restriction assessments are required. (Section 5.5.2)

Table 5.1-3: Long-term Procedural Outline (CA204116) Cycles 3 and Beyond

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Day 23 - 28	End of Treatment	Days 30 & 60 Post End of Treatment[a]	Notes
Skeletal Survey	If clinically indicated							Section 5.5.3.1
CT/MRI assessment for extramedullary soft tissue plasmacytoma	As clinically indicated and at the time of CR/sCR assessments							Section 5.5.3.2
Response per IMWG based criteria	**Every 4 weeks from date of first dose of study drug until progression, regardless of whether patient is on study therapy or subsequent therapy.**							Investigator assessment All response categories require two consecutive assessments. (Section 5.5.4)
Serum PK (Investigational arm only)	←						→	Refer to Section 5.6 for specific time points
Anti-Drug Antibody (ADA) (Investigational arm only)	←						→	Refer to Section 5.6 for specific time points
[redacted]	X							Cycle 3 Day 1 only Refer to Section 5.7.1 for specific time points
Study Drug								
Premedication for Elotuzumab (Investigational arm only)	X		X*					*Not required in Cycles 19 and beyond
Elotuzumab Infusion (Investigational arm only)	X		X*					In Cycles 3 and beyond, elotuzumab dosing may be delayed for up to 1 week. If unable to administer within 1 week, then the dose should be skipped and resumption of the elotuzumab continues per the protocol defined schedule. *Not required in Cycles 19 and beyond. Elotuzumab dose will be 20 mg/kg at Cycle 19 and beyond as the subject will receive elotuzumab at only Day 1 of each cycle.

Table 5.1-3: Long-term Procedural Outline (CA204116) Cycles 3 and Beyond

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Day 23 - 28	End of Treatment	Days 30 & 60 Post End of Treatment[a]	Notes
Lenalidomide Administration	Day 1 - 21 of each cycle							
Dexamethasone Administration	X	X	X	X				
Dispense Lenalidomide	X							Dispense lenalidomide on Day 1 of cycle per the Revlimid Risk Management Plan

[a] **For subjects who discontinue study therapy before progression (eg, due to toxicity), the necessary laboratory results must be collected and the efficacy assessments must be performed until progression is confirmed even if it is beyond 60 days post end of treatment.**

5.2 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments during the Screening or Lead-in period will not be permitted (this does not include parameters that require a confirmatory result).

Any new result will override the previous result (i.e., the most current result prior to Registration) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

5.3 Study Materials

The following will be distributed to sites for use in this study:

- Registration Forms
- NCI CTCAE booklets version 3.0
- Elotuzumab Investigator Brochure
- Lenalidomide (Revlimid®) Package Insert
- Drug Preparation Guidelines
- Subject Dosing Diary
- Laboratory Manuals
- CRFs (electronic)
- Pregnancy Surveillance Forms
- Revlimid Risk Management Plan.

5.4 Safety Assessments

All subjects who receive study drug will be evaluated for safety parameters. Additionally, any occurrence of an SAE from the time of consent forward will be documented.

Safety assessment will be performed prior to study drug dosing at dosing visits, unless otherwise specified.

Safety will be evaluated for all treated subjects using the NCI CTCAE version 3.0. Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests.

Additional procedures and assessments may be performed as part of standard of care however data for these assessments should remain in the subject's medical record and should not be provided to BMS, unless specifically requested by the sponsor. If additional safety assessments are performed for adverse events, then results should be submitted on the CRF.

5.4.1 Vital Signs, Physical Measurements, and Physical Examination

Vital signs (body temperature, respiratory rate, seated blood pressure and heart rate) will be recorded as outlined in Table 5.1-1, Table 5.1-2, and Table 5.1-3. Blood pressure, respiratory rate and heart rate should be measured after the subject has been seated quietly for at least 5 minutes prior to measurement. Subjects in the control arm will have vital signs measured once

at each visit. Subjects randomized to the investigational arm will have additional vital signs as follows:

- Prior to pre-medication administration
- Prior to the start of the elotuzumab infusion
- Thirty minutes after the start of infusion
- At the end of the infusion
- Thirty and 120 minutes post completion of the elotuzumab infusion for Cycle 1 and 2
- Cycle 3 and beyond post infusion vital signs will be measured at 30 minutes
- Subjects who experience a Grade ≥ 2 infusion reaction require vital signs to be monitored every 30 minutes for 2 hours after the end of the elotuzumab infusion.

Height will be recorded at screening. Weight will be measured at study visits as indicated in Table 5.1-1, Table 5.1-2, and Table 5.1-3.

A full physical examination will be performed at the screening visit, whereas a targeted exam will occur at Day 1 and during on-treatment up to 3 days prior to dosing and post-treatment visits. A targeted physical examination may be performed by a qualified professional guided by the examiner's observations and/or subject complaints on new or changed conditions, symptoms, or concerns. Targeted physical exam includes assessment of heart, lung, and abdomen.

5.4.2 Performance Status

Performance assessment will be performed at Screening, on-treatment Day 1 of each cycle and at End of Treatment visit using ECOG performance scale and criteria as described in Appendix 2. The assessment should be completed prior to any study-related procedures, treatment or clinician assessment.

5.4.3 Echocardiogram or MUGA scan and Electrocardiogram

A MUGA scan or 2-dimensional echocardiogram and electrocardiogram (ECG) will be performed at screening within 28 days of randomization.

5.4.4 Laboratory Assessments for Safety

All safety laboratory assessments indicated in Table 5.4.4-1 should be done at a local laboratory.

Table 5.4.4-1: Safety Laboratory Assessments (may be drawn up to three days prior to visit)

	Screening as outlined in Table 5.1-1 within 14 days of randomization	Study Visits as outlined in Table 5.1-2 and Table 5.1-3
Hematology		
CBC	X	X
Differential	X	X
Platelets	X	X
Chemistry		
Sodium	X	X
Potassium	X	X
Chloride	X	X
Carbon Dioxide or Bicarbonate[a]	X	X
Albumin	X	X
Alkaline Phosphatase	X	X
ALT (SGPT)	X	X
AST (SGOT)	X	X
Total Bilirubin	X	X
Direct Bilirubin (if total billirubin is abnormal)	X	X
Lactate Dehydrogenase	X	X
BUN (or Urea)	X	X
Creatinine and Creatinine Clearance[b]	X	X
Glucose	X	X
Calcium	X	X
Total Protein	X	X
Coagulation Test		
PT	X	X[c]
PTT	X	
INR	X	X[c]
Pregnancy Test		
Urine or Serum Pregnancy	X (2 tests: one 10 - 14 days prior to the start of study drug and one within 24 hours prior to the start of study drug)	X

Table 5.4.4-1: Safety Laboratory Assessments (may be drawn up to three days prior to visit)

	Screening as outlined in Table 5.1-1 within 14 days of randomization	Study Visits as outlined in Table 5.1-2 and Table 5.1-3
Urinalysis		
Protein	X	
Glucose	X	
Urobilinogen	X	

[a] To be done in sites where this is a standard part of the chemistry panel. In sites where testing for CO_2/HCO_3 is not standard, the test is optional.

[b] To be measured by 24-hour urine collection or estimated by the Cockcroft and Gault formula in sites.

[c] To be done if subject is being treated with warfarin for thromboembolic prophylaxis. Subjects who are not on vitamin K antagonists do not require coagulation tests after screening

5.5 Efficacy Assessments

Efficacy endpoints will be based on serum and urine protein electrophoresis (SPEP and UPEP), corrected calcium (serum calcium and serum albumin), and bone marrow assessments at predefined intervals as specified in Table 5.1-1, Table 5.1-2, and Table 5.1-3. Assessments for SPEP and UPEP will be based on central lab results, whereas assessments of bone marrow, bone lesions, extramedullary plasmacytomas, and corrected calcium will be based on local analysis at the site. Serum β2 microglobulin will be performed locally at screening. If SPEP and UPEP M protein are performed at a local laboratory, results must be recorded in the CRF/eCRF.

5.5.1 Primary and Secondary Efficacy Assessment

Response assessments according to the international diagnostic criteria of the International Myeloma Working Group (IMWG criteria)[21] will be used for the primary analysis. For the purposes of this study, all subjects' tumor assessments by SPEP M protein and UPEP M protein quantification, corrected calcium (calcium and albumin), and serum free light chain (when indicated for CR assessment), should be re-evaluated per the protocol-stated frequency relative to the date of first dose of study drug until disease progression based on the IMWG criteria, irrespective of dose delays or treatment cycle. **If subject does not have documented disease progression at time of study drug discontinuation, then tumor assessments should still be performed according to the same schedule described above until disease progression even if a subsequent anti-myeloma treatment is initiated prior to disease progression.**

All efficacy laboratory assessments should be done through the central laboratory, except corrected calcium, and bone marrow assessments for plasma cell percentage and light chain restriction (clonality by Immunohistochemistry or flow cytometry). All bone marrow aspirate and core biopsy samples should be assessed locally. For any SPEP or UPEP assessment performed locally, in lieu of a central lab assessment, (ie, if the subject cannot complete a visit at

the study site), M protein quantification must be performed. Any laboratory samples analyzed locally, including for efficacy, must be entered on the appropriate CRF.

5.5.2 Laboratory Assessments for Myeloma

All serum and urine lab tests must be sent to the central lab, except serum calcium and albumin which are performed locally, until disease progression or withdrawal of consent, even if the subject is discontinued from study therapy and has started new myeloma therapy.

Twenty-four-hour urine sample can be collected within ± 7 days of visit, and must be obtained with each cycle in all subjects who have measurable UPEP M protein (≥ 200 mg/24 hours) at baseline. Subjects who have urine M protein of < 200 mg/24 hours at baseline and at next 2 subsequent assessments do not have to submit q4 week urine samples with each cycle (but must submit q12 week urine samples) until SPEP M protein values becomes undetectable. In order to full fill CR/sCR criteria, both serum and urine immunofixation must be performed and be negative on two consecutive assessment. Therefore, at the time SPEP becomes undetectable, 24-hr UPEP collection should promptly resume and continue q4 weeks until SPEP becomes detectable. Any local serum and urine myeloma lab tests that may also have been performed must also be reported in the CRF.

1) **Serum:** serum protein electrophoresis (SPEP) for M protein quantification, total serum protein, immunofixation, and quantitative immunoglobulin assay.
   a) **Immunofixation:** Immunofixation of serum is required at baseline and to confirm CR regardless of whether measurable M-protein was present at baseline.
   b) **Serum free light chain:** Serum should be collected at screening and time of CR for serum free light chain analysis. This measurement is required to document sCR.
   c) **Other:** All other serum tests will be followed at each tumor assessment.
2) **Urine:** 24-hour urine collection electrophoresis for M protein quantification, urinary light chains, and immunofixation. 24-hour urine must be collected with each cycle for all subjects, except for those subjects with no measurable M protein in the urine at baseline and at next two subsequent time points.
   a) Immunofixation of urine is required at baseline and to confirm CR regardless of whether measurable M-protein was present at baseline.
   b) All other urine tests will be followed at each tumor assessment.
3) **Bone marrow aspiration/biopsy:** Assessment of bone marrow for percentage plasma cells is required within 28 days of randomization and while on study to confirm CR (ie, subjects who become immunofixation negative) or, if clinically indicated, at time of suspected disease progression (a second confirmation bone marrow analysis for CR is not needed). The percentage $CD138^{+}$ cells and clonality (based on kappa/lambda ratio) will also be assessed to confirm stringent CR (sCR). Flow cytometry will be performed only to confirm CR. In addition, biomarker tests must also be performed on the fresh bone marrow sample obtained at screening (if applicable; refer to Section 5.7.2).

Table 5.5.2-1: Bone marrow samples

Bone marrow sample	Local Laboratory	Local Central Laboratory
Aspirate[a]	Samples required at the following times to evaluate percentage plasma cells: • Screening (within 28 days of randomization) • When subject is immunofixation negative in both serum and urine (second bone marrow sample not required for confirmation) In addition, evaluate flow cytometry to assess plasma cell clonality (i.e., lambda and kappa IHC or flow cytometry to assess light chain restriction). • At time of suspected disease progression, if needed (see Section 5.5.4) to assess progression in subjects who's myeloma become nonsecretory	Screening (within 28 days of randomization) • send for genetic assessments (karyotype and FISH)[b]
Biopsy	Not required by protocol unless an aspirate sample (at any time point above) is not available due to a dry tap or due to laboratory preferences of the local pathologist. IHC of biopsy for clonality by local lab if aspirate is not available.	

[a] Should be replaced by core biopsy sample only if: 1) aspirate is not available at any time point due to a dry tap or 2) subject is immunofixation negative in serum and urine and flow cytometry is not available at the site.

[b] Genetic assessments (karyotype and FISH) should be performed at the local central laboratory designated by the Sponsor on a fresh bone marrow sample. However, if a new bone marrow sample collection is not feasible and if this assessment was performed locally within the 28 days of randomization, the local results must be entered into the eCRF.

4) **Serum corrected calcium:** Serum corrected calcium should be collected with each cycle for all subjects until disease progression.

5.5.3 Imaging Assessments for Myeloma

5.5.3.1 Skeletal Survey

Skeletal survey, by conventional radiography, for metastatic disease will be performed at screening (within 28 days prior of randomization), and on study if clinically indicated (development of compression fracture does not exclude response). Use of conventional or low dose CT scan (ie, of the spine) or MRI bone survey is acceptable. If imaging is performed on treatment for assessment of progression, the site must use the same modality of imaging as used in screening. The number and location of skeletal lesions and whether they are lytic should be

recorded on the eCRF. On treatment survey should record whether there is an increase in the number or size of lytic lesions.

5.5.3.2 Assessment of Extramedullary Plasmacytoma

CT or MRI should be performed in all subjects if clinically indicated at baseline to assess for the presence of extramedullary plasmacytoma. To minimize unnecessary radiation in myeloma subjects where progression is primarily based on serum and urine M-protein, on study assessments should only be performed if clinically indicated (ie, pain, concern for disease progression), whether or not present at baseline, and at the time of CR/sCR assessment.

A sum of the products of the longest diameters and longest perpendicular diameter for all measurable lesions will be calculated at baseline. This sum will be used as the reference for on study assessments by which to characterize the objective tumor response.

All tumor measurements must be made in millimeters. All documented measurable lesions are to be followed throughout the trial. All assessments to be used for tumor response evaluation, including the baseline assessment, must be performed using the same method for repeat assessment. CT and MRI scanning are the preferable methods of assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less or with cuts of 5 (or 10) mm if spiral CT scanning is used. Imaging-based evaluation is preferred to evaluation by clinical examination. Evaluation by chest x-ray is less preferable than CT or MRI, and should only be used for well-defined lesions surrounded by aerated lung. Clinical examination is only acceptable when lesions are superficial, such as a skin nodule or palpable lymph node. Skin lesions must be documented by a photograph with a ruler. Ultrasound is not acceptable for documentation of measurable disease.

Duplicate copies of all imaging studies used for tumor response evaluation will be made available for review by the Sponsor upon request.

Measurable disease are lesions that can be accurately measured in 2 dimensions and both diameters must be ≥ 20 mm when evaluated by standard CT scanning or ≥ 10 mm when evaluated by spiral CT scanning. The minimum diameter size should be at least twice the slice thickness.

Non-measurable disease are all other lesions (or sites of disease), including those that are too small (ie, do not meet above criteria), occur within a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion (exception for effusions documented by cytology as not malignant or present at baseline without progression), lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques, and cystic lesions.

5.5.4 Definitions of Response Based on IMWG

See Table 5.5.4-1 and Table 5.5.4-2 for definitions of response and progression. All criteria are derived from IMWG.[21] All response categories require 2 consecutive assessments. The second of the 2 consecutive assessments should occur at the next planned tumor assessment (every 4 weeks after the first dose).

Table 5.5.4-1: IMWG Criteria for Response

Category	Criteria[a]
Stringent Complete response (sCR)	CR as defined below plus Normal serum free light chain (FLC) ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence.[c]
Complete response (CR)	The first two bullet points must be met. The remaining bullet points must be met only as indicated. Negative immunofixation on both serum and urine and, Bone marrow aspirate[b] containing < 5% plasma cells, No increase in size or number of lytic lesions should occur (development of a compression fracture does not exclude response) with disappearance of soft tissue plasmacytomas, Skeletal survey must be performed ONLY if clinically indicated.
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 < 100 mg per 24h. If the serum and urine M-protein are unmeasurable, a ≥ 90% decrease in the difference between involved and uninvolved FLC levels is required in place of M-protein criteria.
Partial response (PR)	All of the following conditions must be met for PR: Greater than or equal to 50% reduction in serum M-protein and Reduction of ≥ 90% in urinary M-protein or a decrease to < 200 mg/24 hours, If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of M-protein criteria. Greater than or equal to 50% reduction in the size of soft tissue plasmacytomas present at baseline, No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response). Skeletal survey must be performed ONLY if clinically indicated to confirm that lytic lesions have not increased and that no new lesions are seen; if done, this should occur at the 4-week confirmatory time point following initial determination of PR.

Table 5.5.4-1: IMWG Criteria for Response

Category	Criteria[a]
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR or progressive disease.

[a] All response categories require two consecutive assessments made at anytime; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

[b] Confirmation with repeat bone marrow biopsy not needed.

[c] Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.

Table 5.5.4-2: IMWG Criteria for Progression

Category	Criteria[a]
Progression of Disease (PD)	Progression describes a definite increase in disease activity relative to the nadir in subjects. One or more of the following constitutes PD: Increase of ≥ 25% in serum monoclonal paraprotein (must also be an absolute increase of at least 5 g/L)[b] and confirmed by at least one investigation, Increase of ≥ 25% urinary light chain excretion (which must also be an absolute increase of at least 200 mg/24-hours) and confirmed by at least one investigation, Only in subjects without measureabel serum and urine M-protein levels: the difference between involved and uninvolved FLC levels must increase by ≥ 25% and confirmed by at least one investigation. The absolute increase must be > 10 mg/dL. Increase of ≥ 25% plasma cell percentage in the marrow (which must also be an absolute increase of at least 10%) Definite increase in the size of lytic bone lesions or soft tissue plasmacytomas, Development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of a compression fracture does not exclude continued response and may not indicate progression), Development of hypercalcemia (corrected serum calcium greater than 11.5 mg/dL; 2.65 mmol/L) not attributable to any other cause.

[a] All categories require two consecutive assessments made at any time before classification as disease progression and/or the institution of any new therapy.

[b] For progressive disease, serum M-component increase of ≥ 1 g/dl is sufficient to define progression if starting M-component is ≥ 5 g/dL.

5.6 Pharmacokinetic Assessments

Blood samples for PK assessment will be drawn according to the PK sampling schedule given in Table 5.6-1. PK samples will be collected according to the schedule listed in Table 5.6-1 in all subjects received elotuzumab. Blood samples for the analysis of serum concentrations of elotuzumab should be drawn from the arm not used for infusion of study drug.

In addition, Development of anti-drug antibodies (ADA) to elotuzumab will be evaluated in all subjects received elotuzumab at specified time points as noted in Table 5.6-1.

Table 5.6-1: PK and ADA Sampling Schedule

Cycle Number	Study Day	Time (Event)[a]	PK	ADA
1	1	0 H (pre-dose)	X	X
		2 hours post-end of infusion	X	
	8	0 H (pre-dose)	X	
		2 hours post-end of infusion	X	
	15	0 H (pre-dose)	X	
		2 hours post-end of infusion	X	
	22	0 H (pre-dose)	X	
		2 hours post-end of infusion	X	
2	1	0 H (pre-dose)	X	X
		2 hours post-end of infusion	X	
	22	0 H (pre-dose)	X	
		2 hours post-end of infusion	X	
3	1	0 H (pre-dose)	X	X
		2 hours post-end of infusion	X	
	8	168 hours	X	
	15	0 H (pre-dose)	X	
4	1	0 H (pre-dose)	X	
6	1	0 H (pre-dose)	X	X
9	1	0 H (pre-dose)	X	X
12	1	0 H (pre-dose)	X	X
15	1	0 H (pre-dose)	X	X
18	1	0 H (pre-dose)	X	X
Every 3 cycles thereafter (eg, Cycle 21, 24, 27, etc.)	1	0 H (pre-dose)	X	X

Table 5.6-1: PK and ADA Sampling Schedule

Cycle Number	Study Day	Time (Event)[a]	PK	ADA
	End of Study / Discontinuation[b]		X	X
	30-Day Follow-up[b]		X	X
	60-Day Follow-up[b]		X	X

[a] For subjects who miss a dose(s) of elotuzumab, collect PK and ADA samples on the planned day, or if the sampling is unavailable, collect samples on the day (predose) that elotuzumab is restarted (noting the actual time of collection and dosing), and then continue following the schedule in Table 5.6-1.

[b] For subjects who discontinue elotuzumab only, but otherwise continue on study treatment, collect PK and ADA samples at the day of elotuzumab discontinuation, 30 and 60 days after the last elotuzumab dose.

[redacted]

5.8 Outcomes Research Assessments

Not Applicable

5.9 Other Assessments

Not Applicable

5.10 Results of Central Assessments

Not Applicable

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

> Related: There is a reasonable causal relationship between study drug administration and the AE.
>
> Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.)

Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 60 days of discontinuation of dosing.

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours, and the head of the study site to comply with procedures of the study site. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: worldwide.safety@bms.com.

SAE Facsimile Number: +1 (609) 818-3804.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject or a female partner of a male study participant is pregnant or may have been pregnant at the time of study exposure, including during the time to washout (90 days) plus one ovulatory cycle (30 days) for a total of 120 days; or plus one spermatogenesis cycle (90 days) for a total of 180 days after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
   AND
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

Second primary malignancies (SPMs) will be collected throughout the study. All SPMs that occur during the screening period and within 60 days of discontinuation of dosing will be reported as an SAE regardless of relationship to study drug. Additionally, any SPM that occurs after this timeframe and considered related to study drug will be reported as an SAE. All other SPMs will be collected and reported as adverse events.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

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 ≤ 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 set to evaluate add-on efficacy clinically for Elotuzumab with 40 subjects. The randomized ratio of ELd to Ld is 1:1.

8.2 Populations for Analyses

The following subject populations will be used in this study:

- 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.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary and secondary endpoints of Objective Response Rate (ORR) is defined as the proportion of treated 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 treated subjects.

8.3.2 Secondary Endpoint(s)

8.3.2.1 Objective Response Rate

See Section 8.3.1

8.3.2.2 Progression-Free Survival

The primary definition of Progression-free survival (PFS) 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 death does not occur more than 10 weeks (2 or more assessment visits) after the last tumor assessment. Clinical deterioration will not be considered progression.

The following censoring rules will be applied for PFS:

- Subjects who receive systemic secondary anti-myeloma therapy prior to documented progression will be censored on the date of the last tumor assessment prior to the initiation of the new therapy.
- Subjects who have an event (documented progression or death) > 10 weeks (2 assessment visits) after the last prior tumor assessment will be censored at the last prior assessment.

- Subjects who do not progress and who do not receive subsequent therapy will be censored at their last tumor assessment.
- PFS also will be analyzed applying an intent-to-treat (ITT) definition that utilizes all data on each randomly assigned subject until either a progression event or the end of the study. PFS under the ITT definition will be defined as the time from randomization to the date of the first documented tumor progression or to death due to any cause. Clinical deterioration will not be considered progression. Subjects who neither progress nor die will be censored on the date of their last tumor assessment. There will be no censoring for subsequent therapy prior to progression or for progression events following missing assessments.

PFS is elevated from an exploratory endpoint to a secondary endpoint in the protocol amendment 03. The study duration is expanded, and PFS is expected to be sufficiently mature at the updated targeted follow-up, which is the time of final PFS analysis for the randomized global phase 3 study for the subjects with previously untreated multiple myeloma.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Subject characteristics including demographics, baseline performance status, disease characteristics, and baseline laboratory parameters will be summarized by randomized treatment arm as well as pooled across randomized arms using descriptive statistics.

8.4.2 Efficacy Analyses

8.4.2.1 Primary Efficacy Analysis

The response rate and its corresponding exact one-sided 85% confidence interval will be calculated in the ELd arm. In addition, the two-sided 95% confidence interval will be computed for the ELd arm.

8.4.2.2 Secondary Efficacy Analysis

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 the Ld arm.

The PFS analyses will be conducted using both the primary and the ITT definitions of PFS. The PFS functions for each randomized arm will be estimated using the Kaplan-Meier product limit method. Two-sided, 95% confidence intervals for median PFS and the first and third quartiles will be computed by treatment arm. PFS rates at 1, and 2 years will be estimated from the KM curve. Each analysis will be performed after all subjects have been followed for the appropriate time.

[redacted]

8.4.3 Safety Analyses

Safety analyses will be conducted on all treated population. Adverse events and laboratory parameters will be summarized using CTCAE version 3.0. Summary tables will be presented on safety parameters for each treatment arm. Toxicity rates (worst CTC grade per subject) of adverse events and laboratory tests, both of any occurrence and severe (Grade ≥ 3) will be tabulated.

8.4.4 Pharmacokinetic Analyses

Summary statistics will be calculated for elotuzumab concentrations and summarized by scheduled collection time. 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.

[redacted]

8.4.6 Outcomes Research Analyses

Not Applicable

8.4.7 Other Analyses

Anti-Drug Antibodies (ADAs) will be summarized by cycle (samples are taken on Day 1 of each cycle, prior to elotuzumab administration) for subjects in the elotuzumab arm only. The number and percentage of subjects with a positive and negative result to the test for antibodies will be presented. For subjects with a positive result, their titer value will be summarized.

8.5 Interim Analyses

The primary analysis will be done 6 months after last subject's first treatment. 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.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any deviations must be documented.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB approval, as soon as possible the deviation or change will be submitted to:

- Head of the study site
- IRB for review and approval via the head of the study site
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s) via the head of the study site for review and approval; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, BMS must inform the IRB(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Source documents are defined as follows: subject identification code sheet, medical records, written informed consent, study drug management sheets. Certain CRF pages and/or electronic files may serve as the source documents: such as outcomes research assessments.

In addition, the study may be evaluated by BMS internal auditors, the IRB, and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records.

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

BMS will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The head of the study site must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The head of the study site must contact BMS prior to destroying any records associated with the study.

BMS will notify the head of the study site when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to the personnel designated by the head of the study site. Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the study drug storage manager designated by the head of the study site to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product and the non-investigational product(s). Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

BMS and the investigator will maintain an original and a copy of the signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception's must be discussed in the event that the subject chooses to forego complete abstinence.

11 LIST OF ABBREVIATIONS

Term	Definition
ADA	anti-durg antibodies
ADCC	antibody dependent cell-mediated cytotoxicity
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
BMS	Bristol-Myers Squibb
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CLT	total body clearance
Cmax	maximum observed concentration
Cmin	trough observed concentration
CR	complete response
CrCl	creatinine clearance
CRF	Case Report Form, paper or electronic
CS1	CD-2 subset 1
CT	computerized tomography
CYP	cytochrome p-450
DILI	drug induced liver injury
DLT	dose-limiting toxicity
DVT	deep venous thrombosis
EBMT	European Group for Blood and Bone Marrow Transplant
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Term	Definition
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ELd	elotuzumab, lenalidomide, (low-dose) dexamethasone
EPO	Erythropoietin
FLC	free light chain
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte macrophage colony stimulating factor
HIV	Human Immunodeficiency Virus
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
IMiDs	Immune Modulary Drugs
IMP	investigational medicinal products
IMWG	International Myeloma Working Group
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
ISS	International Staging System
IV	intravenous
Ld	lenalidomide, (low-dose) dexamethasone
LD	lenalidomide, (high-dose) dexamethasone
MGUS	Monoclonal Gammopathy of Undetermined Significance
MHLW	Ministry of Health, Labour and Welfare
MM	Multiple Myeloma
MPT	melphalan, prednisolone, thalidomide
MR	minor (minimal) response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network

Term	Definition
NK	natural killer
NKT	natural killer T-cell
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PE	pulmonary embolism
PFS	progression-free survival
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QD	quaque die, once daily
SAE	serious adverse event
SCID	severe combined immunodeficient
SCT	stem-cell transplantation
SPEP	serum protein electrophoresis
sCR	stringent complete response
[redacted]	[redacted]
SOP	Standard Operating Procedures
SPM	second primary malignancy
TTP	time to progression
ULN	upper limit of normal
UPEP	urine protein electrophoresis
USPI	United States Package Insert
VGPR	very good partial response
WBC	white blood cell
WOCBP	women of childbearing potential

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APPENDIX 1 INTERNATIONAL STAGING SYSTEM

Stage	Criteria	Median Survival (months)
I	Serum β2-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL	62
II	Not stage I or III[a]	44
III	Serum β2-microglobulin ≥ 5.5 mg/L	29

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[a] There are two categories for stage II: serum β2-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum β2-microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level.