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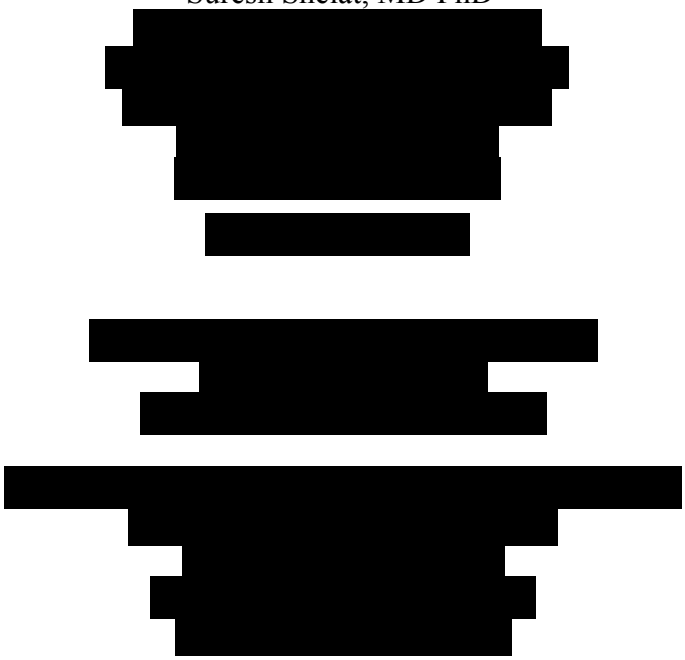
Clinical Protocol CA204006

A Phase 3, Randomized, Open Label Trial of Lenalidomide/dexamethasone With or Without Elotuzumab in Subjects with Previously Untreated Multiple Myeloma

Revised Protocol Number: 05
Incorporates Amendment 07

Study Director/Central Medical Monitor
Suresh Shelat, MD PhD



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.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 05	24-Aug-2016	Incorporates Amendment 07
Amendment 07	24-Aug-2016	• [redacted] • [redacted] • Remove the following sentence from Section 4.3.1. "On the days of elotuzumab administration, the dose of lenalidomide is to be administered at least 2 hours after completion of elotuzumab dosing. • Change referencing of Experimental treatment arm of lenalidomide/dexamethasone + elotuzumab from LdE to E-Ld. • [redacted] • Add Section 9.1.2.1 Source Documentation • Update Section 9.2.2 Study Drug Records
Revised Protocol 04	17-Aug-2015	Incorporates Amendment 6 and Administrative Letters 07 and 08
Amendment 06	17-Aug-2015	• Update statistical assumptions and protocol treatment rationale based on currently available published data • Clarify requirements for subjects with no measureable urine M protein at baseline • Inclusion of new PK/HAHA collection after Cycle 18 • Inclusion of updated safety information regarding use of adequate contraception based on recent elotuzumab PK data. • Change recommended diluent volume of elotuzumab from fixed volumes to range of 100-500 mL.
Administrative Letter 08	08-Dec-2014	Supersedes Administrative Letter 07, corrects typographical errors in Appendix 6 and Sec.4.3.2.2 of protocol
Administrative Letter 07	04-Nov-2014	Correct typographical errors and align text in Appendix 6 with corresponding text in Sec. 4.3.2.2 of protocol.
Revised Protocol 03	21-Aug-2014	Incorporates Amendment 5 and Administrative Letter 6
Administrative Letter 06	08-Jul-2014	Revision of typographical errors in the protocol and appendix.
Amendment 05	21-Aug-2014	• Planned Interim Analysis will now take place at 70% of events (338 events) compared to the previous timepoint of 241 (50%) progression events • BPI-SF pain severity and pain interference will be evaluated as a secondary endpoint, and formal comparison between treatment arms will be conducted, though it will not be included hierarchical testing. • [redacted]

Document	Date of Issue	Summary of Change
		[redacted] • Correction of typographical errors in the protocol and appendix documents.
Revised Protocol 02	21-May-2014	Incorporates Amendment 4 and Administrative Letters 1-5
Amendment 04	21-May-2014	• Elotuzumab infusion rate escalation plan added to decrease the infusion of elotuzumab to approximately 1 hour • Change to the UPEP efficacy testing to reduce the requirement of 24 hour urine collection in a subset of patients • Broadening of the medications that can be used for thromboprophylaxis. • Additional Clarifications in the protocol serve to reduce any ambiguity regarding study procedures, and provide additional guidance of the EBMT efficacy requirements.
Admin Letter 05	21-Aug-2013	Document change in BMS Medical Monitor
Admin Letter 04	25-Jan-2013	Document change in BMS Medical Monitor
Admin Letter 03	19-Jul-2012	Document change in BMS Medical Monitor
Admin Letter 02	24-May-2012	Correct error in Dexamethasone Dose Level Table 4.3.4.2B
Admin Letter 01	04-Apr-2012	Correct date of original protocol modified in error.
Revised Protocol 01	15-Mar-2012	Incorporates Amendment 02.
Amendment 02	15-Mar-2012	• Clarification of subject eligibility or study procedures. • Modification of screening requirements to conform to the standard of care and to enhance overall study conduct. • A revision was made to timing of when pregnancy testing must be completed. This change is in compliance with a recently approved, company-wide SOP for women of childbearing potential participating in clinical trials conducted by the Sponsor. • The inclusion criteria have been revised to clarify that refusal to undergo high dose therapy with SCT is NOT sufficient for entry onto 006 for a subject < 65 years old. There must be a comorbidity that prevents SCT for a subject < 65 years old. • Instructions for what should be done with missed doses of lenalidomide or dexamethasone. • Revisions are made to exclusion criteria for clarity and consistency throughout the development program. • The requirement to discontinue elotuzumab and lenalidomide if a subject becomes pregnant. • Timing and details surrounding when certain study assessments are performed. • An update to the shelf-life of reconstituted elotuzumab. • Correction of typographical errors.
Original Protocol	15-Mar-2011	Not applicable.

SYNOPSIS

Clinical Protocol CA204006

Title of Study: A Phase 3, Randomized, Open Label Trial of Lenalidomide/dexamethasone With or without Elotuzumab in Subjects with previously untreated Multiple Myeloma

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

Control Arm:

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

Investigational Arm:

- Elotuzumab
- Cycles 1 - 2: 10 mg/kg IV Days 1, 8, 15, and 22
- Cycles 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
- 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

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: 3

Research Hypothesis: The addition of elotuzumab to lenalidomide/dexamethasone will increase the Progression Free Survival (PFS).

Primary Objective: To compare the PFS of lenalidomide/dexamethasone + elotuzumab (E-Ld) versus lenalidomide/dexamethasone (Ld) in subjects with newly diagnosed, previously untreated multiple myeloma (MM).

Secondary Objectives:

- To compare objective response rate between treatment arms
- To compare overall survival between treatment arms
- To compare the change from baseline of the mean score of pain severity and the change from baseline of the mean score of pain interference using the Brief Pain Inventory - Short Form (BPI-SF) between treatment arms
- To assess PFS rates at 1, 2, 3, 4, and 5 years

[redacted]

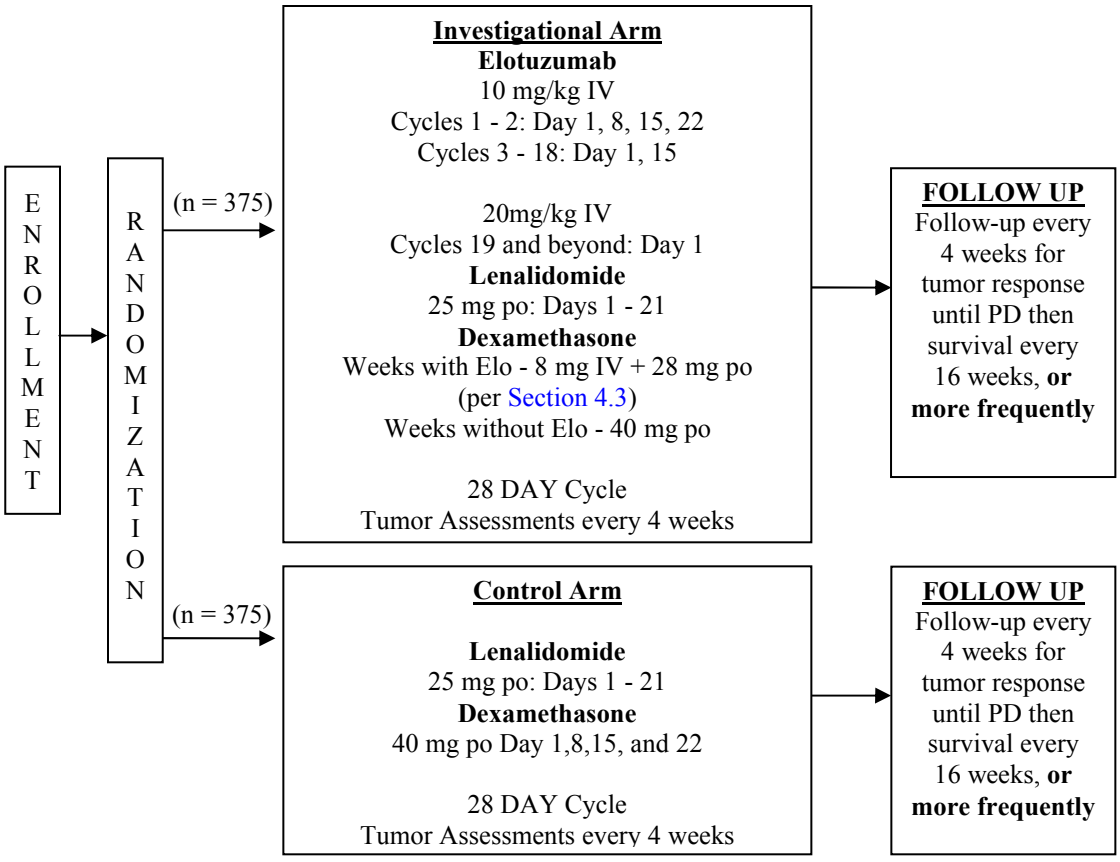
[redacted]

Figure 1: **Study Design**:

This is a Phase 3, open-label, multi-center trial investigating lenalidomide/dexamethasone with and without elotuzumab in subjects with newly diagnosed, untreated, symptomatic, measurable 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 lenalidomide/dexamethasone (Ld) or lenalidomide/dexamethasone/elotuzumab (E-Ld). The randomization will be stratified by:

- ISS stage (1 - 2 versus 3)
- Age (< 75 years old versus ≥ 75 years old)
- ECOG status (0 versus 1 - 2)



Tumor assessments, based on the EBMT criteria, must be conducted every 4 weeks (-1/+3 days) relative to the first dose of study medication until disease progression, death or withdrawal of consent. The date of progression, best response and date of response used in the efficacy analysis will be based on the independent review committee (IRC). Subjects will be followed at least every 16 weeks, or more frequently, after disease progression for survival and subsequent myeloma therapy. Cross-over between the arms is not permitted.

An independent Data Monitoring Committee (DMC) will review the safety of the trial on a routine basis. In addition there will be an interim analysis for safety and efficacy once the following two conditions have been met: at least 338 progression events (70%) have been observed and all subjects have been randomized.

Blood samples for pharmacokinetic and immunogenicity analysis will be collected in all subjects who received elotuzumab.

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 Assessments and Primary Endpoint:

Tumor response assessment by EBMT criteria will be evaluated during the trial for all randomized subjects. An IRC (Independent Review Committee) will conduct a blinded, independent review of these tumor assessments. The primary endpoint of PFS will be based on the IRC assessment.

Statistical Methods:

Power

The primary objective in this study is to compare PFS between treatment groups at the two-sided, 5% type I error rate. There will be 1 interim analysis of PFS, which will allow for early stopping for superiority. An O'Brien and Fleming α function will be employed to determine the stopping boundaries for superiority. The comparisons of PFS will be carried out using log-rank tests stratified by stage of disease (International Staging System 1 - 2 versus 3), ECOG performance status (0 versus 1 - 2), and age (< 75 years old versus ≥ 75 years old).

Approximately 750 subjects will be randomized to the 2 treatment groups in a one-to-one ratio to obtain at least 482 progression events (as per IRC), ie, documented progressions or deaths. Four hundred eighty two (482) events ensure that a two-sided test procedure with a family-wise type I error rate of 5% and 1 interim analysis after 70% of the total events (338) will have 90.5% power if the median PFS times in the control and experimental arms are 25 and 33.75 months, respectively, ie, if the hazard ratio of the experimental to control arm is 0.74. Assuming an accrual rate of 24 subjects per month, it will take approximate 60 months to obtain the required number of events, 31 months for accrual and 29 months for PFS follow-up.

Survival, a key secondary endpoint, will be compared at an interim analysis between the two arms at the time of the interim analysis of PFS provided that PFS and ORR analyses are positive. The final survival analysis will take place after 354 deaths, which is projected to occur 7 years (84 months) after the initiation of the study. An O'Brien and Fleming α-spending function will be used to obtain the nominal significance levels for the interim and final analyses of survival. Three hundred and fifty-four (354) deaths ensure that a two-sided 5% level sequential test procedure with one interim analysis will have 80% power for a 8.7 percentage point improvement in 4-year survival rate from 59.0% to 67.7%, ie, for a HR = 0.74.

Power calculations were done using East v5.1 software. (See Section 8.1, Sample Size Determination, for more detail.)

Endpoint Definitions and Analyses

The primary endpoint in this study is progression-free survival (PFS), which is defined as the time from randomization to the date of the first documented tumor progression, as determined by the IRC using EBMT criteria,

or to death. Subjects who neither progress nor die will be censored on the date of their last disease assessment, provided death does not occur more than 10 weeks after the last tumor assessment.

The following censoring rules will be applied to PFS:

- Subjects who receive systemic secondary anti-myeloma therapy prior to documented progression will be censored on the date of their last tumor assessment prior to initiation of new therapy
- Subjects who have an event > 10 weeks 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

See Section 8.3, Endpoint Definitions, for more detail on the definition of PFS.

A stratified log-rank test will be used to compare PFS between treatment arms. The factors will be the same as those used in the randomization. The hazard ratio of the experimental to the control arm and corresponding two-sided 95% confidence interval will be calculated using a stratified Cox proportional hazards model with treatment as the sole covariate. The Kaplan-Meier product limit method will be used to display PFS curves and PFS rates at 1-5 years will be obtained from those curves. Each rate will be estimated after all subjects have been followed for the appropriate time.

The key secondary endpoints are:

- Objective response rate
- Overall survival

Objective response rate (ORR) is defined as the proportion of randomized subjects who have a best overall response of partial response or better. Overall survival is the time from randomization until death. Subjects who do not die will be censored at the date of last contact.

A hierarchical procedure will be used to ensure a two sided family-wise type I error rate of 5% for testing the one primary and two key secondary endpoints. If there is a statistically significant improvement in PFS, then ORR will be compared between arms at the two-sided 5% level. If the comparison of ORR is also statistically significant, then survival will be compared between arms using a two-sided 5% level sequential test procedure.

Objective response rate will be compared between randomized arms using a two-sided 5% level Cochran-Mantel Haenszel (CMH) test stratified by the same factors used in the analysis of PFS. An associated odds ratio and 95% confidence interval will be calculated. The response rate and its corresponding 95% confidence interval will also be calculated for each treatment arm. There will be no interim comparison of this endpoint.

Survival will be compared between treatment arms using two-sided, stratified log-rank tests at the interim and final looks. The family-wise type I error rate for the sequential testing procedure will be 5% and the stratification factors will be the same as those used for the randomization. The significance level at the interim and final analyses of survival will be determined using an O'Brien and Fleming α spending function.

Other Secondary endpoints include change from baseline in mean score of pain severity and mean score of pain interference using the BPI-SF. The two endpoints will be tested at the 2-sided 2.5% level each and will not be part of the hierarchical testing procedure. For these two endpoints, comparison will be conducted using a longitudinal mixed model with treatment arm and time point (categorical) and baseline score as fixed effects and a banded covariance matrix (covariances are constant on each diagonal of the matrix).

TABLE OF CONTENTS

1 INTRODUCTION AND STUDY RATIONALE

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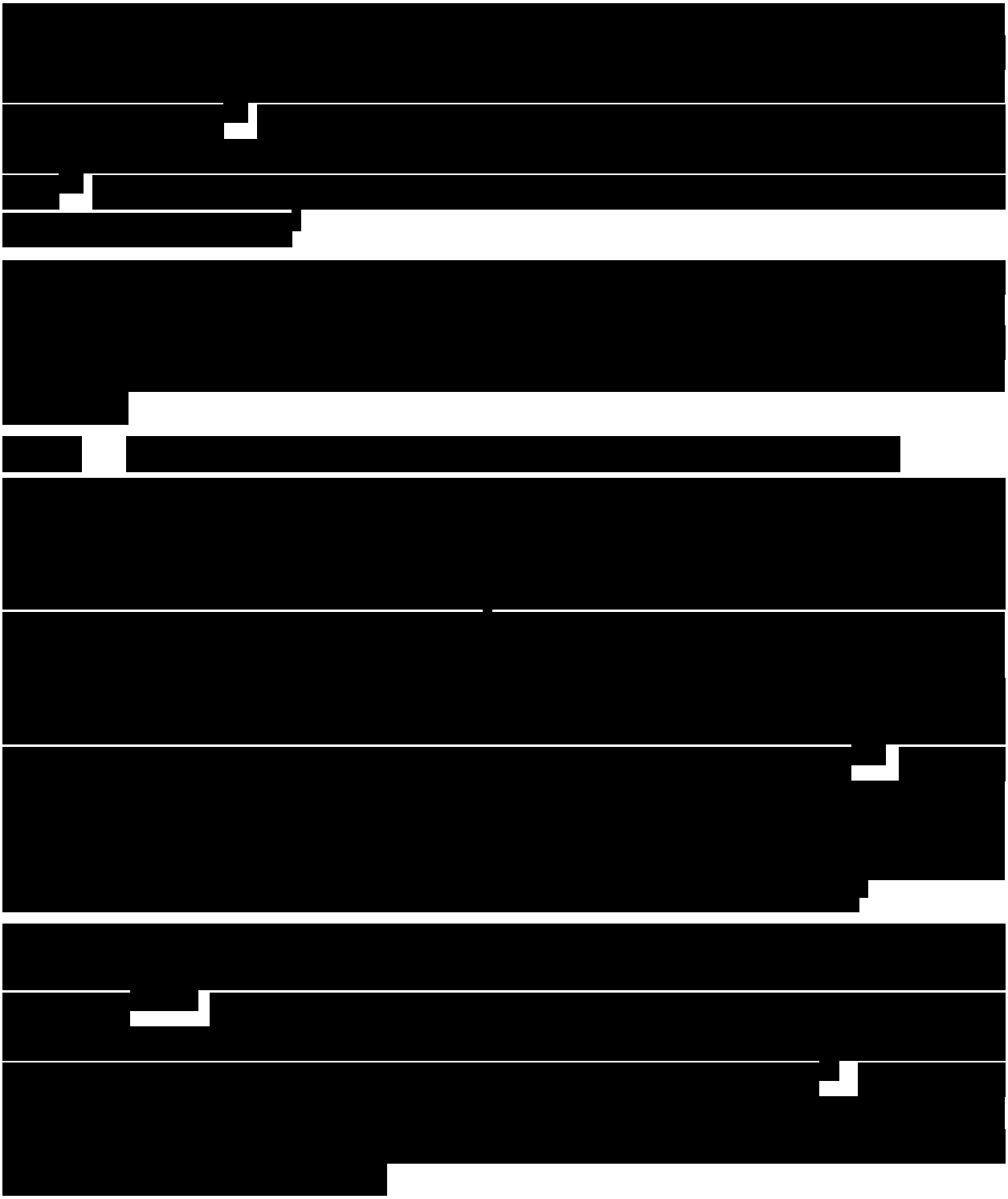

1.2 Research Hypothesis

The addition of elotuzumab to lenalidomide/dexamethasone will increase the progression free survival (PFS).

1.3 Objectives

1.3.1 Primary Objective

To compare PFS of lenalidomide/dexamethasone + elotuzumab (E-Ld) versus lenalidomide/dexamethasone (Ld) in subjects with newly diagnosed, untreated multiple myeloma (MM).

1.3.2 Secondary Objectives

- To compare objective response rate between treatment arms
- To compare overall survival between treatment arms
- To compare the change from baseline of the mean score of pain severity and the change from baseline of the mean score of pain interference using the Brief Pain Inventory- Short Form (BPI-SF) between treatment arms
- To assess PFS rates at 1, 2, 3, 4, and 5 years.

[redacted]

[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

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/Independent Ethics Committee (IRB/IEC) approval/favorable opinion 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.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

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/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator or sponsor should provide the IRB/IEC 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, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) 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/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, 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 their informed consent during the study, then 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 investigator, 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 consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

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 3, open-label, multi-center trial investigating lenalidomide/ dexamethasone with and without elotuzumab in subjects with newly diagnosed, untreated, symptomatic, measurable 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 lenalidomide/ dexamethasone (Ld) [Control Arm] or lenalidomide/dexamethasone/elotuzumab (E-Ld) [Investigational Arm]. The randomization will be stratified by:

- Stage of disease (International Staging System 1 - 2 versus 3), see Appendix 1
- Age (< 75 years old versus ≥ 75 years old)
- ECOG Performance status (0 versus 1 - 2)

Control Arm:

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

Investigational Arm:

- Elotuzumab
  - Cycles 1 - 2: 10 mg/kg IV Days 1, 8, 15, and 22
  - Cycles 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
- 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 no elotuzumab is administered:
    - 40 mg po

Figure 3.1-1: Study Schema

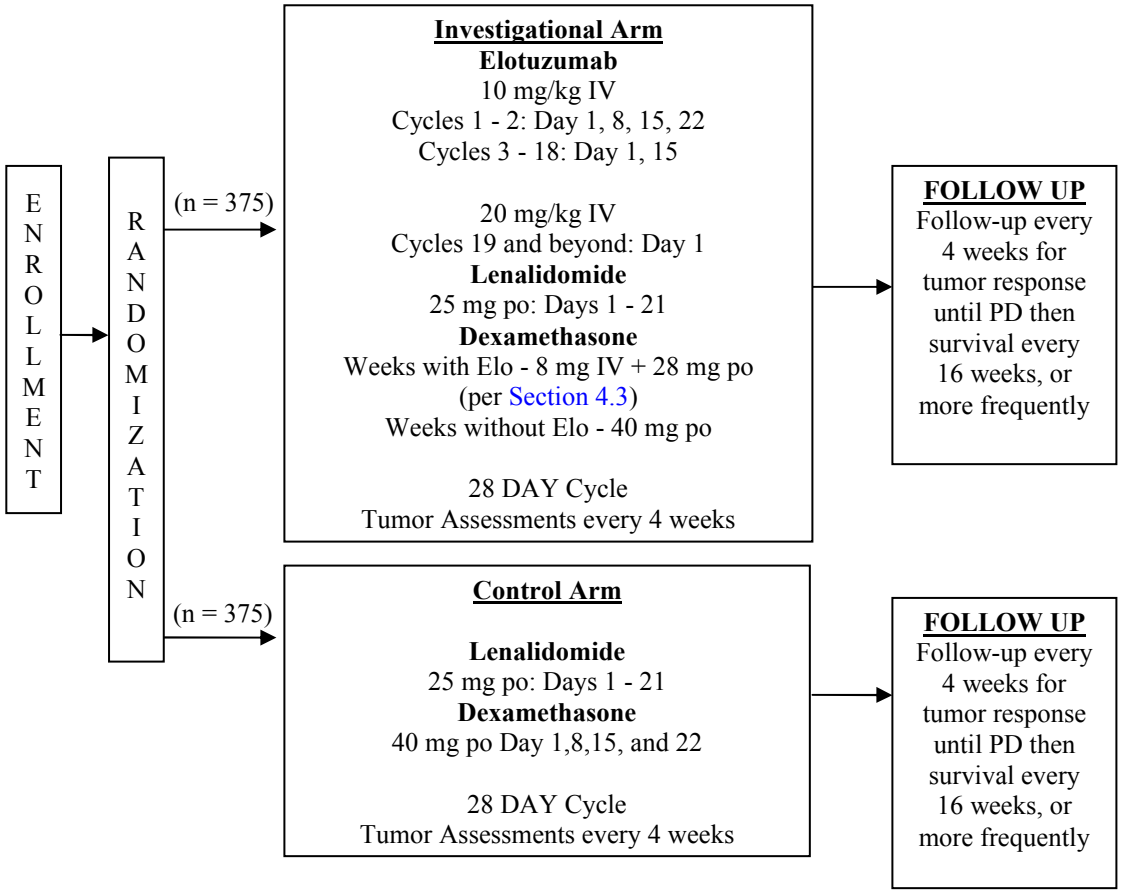

Figure 3.1-2: Dosing Schedule

Control Arm												
Cycle #	**1 - 2**				**3 - 18**				**19+**			
Day # (-1/+3 days)	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Lenalidomide - po	←25 mg Days 1 - 21→				←25 mg Days 1 - 21→				←25 mg Days 1 - 21→			
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
Investigational Arm												
Cycle #	**1 - 2**				**3 - 18**				**19+**			
Day # (-1/+3 days)	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Lenalidomide - po	←25 mg Days 1 - 21→				←25 mg Days 1 - 21→				←25 mg Days 1 - 21→			
Dexamethasone - po	28 mg	28 mg	28 mg	28 mg	28 mg	40 mg	28 mg	40 mg	28 mg	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	-	-	-

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

Tumor assessments, based on the EBMT criteria, will be conducted every 4 weeks (-1/+3 days) relative to the first dose of study medication until disease progression, death or withdrawal of consent. The date of progression, best response and date of response used in the primary efficacy analyses will be based on the independent review committee (IRC) assessments as well as the investigators. All subjects must continue to have protocol-specified tumor assessments until disease progression (even if the subject is off study therapy or has started on a new anti-myeloma therapy, as specified in the ITT definition of PFS in Section 8.3.1), death, or withdrawal of consent from the study. Once subjects reach disease progression, they shall be followed at least every 16 weeks after disease progression for overall survival and subsequent myeloma therapy. Cross-over between the arms is not permitted.

An independent DMC will conduct regular safety reviews throughout this trial. In addition, there will be a pre-planned interim analysis for safety and PFS once the following two conditions have been met: at least 338 (70%) progression events have been observed per IRC and all subjects have been randomized.

Subjects who receive any non-protocol specified systemic anti-myeloma therapy prior to documented progression will be discontinued from study treatment (see Section 3.5). However, tumor assessments should continue at 4 week intervals until documented progression to comply with the intent to treat analysis (Section 8.3.1).

Subjects will continue to be followed until the last subject has the last follow-up visit which is projected to occur approximately 7 years from the first randomized subject.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive study drug. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of the sponsor. The sponsor reserves the right to terminate access to study drug if any of the following occur: a) the marketing application is rejected by 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.

3.2.1 Withdrawal of Consent

Subjects should be encouraged to continue participation in the trial until the laboratory definition of disease progression is met (Section 5.4.5.5). 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 (as per the PFS ITT definition in Section 8.3.1). 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. Withdrawal of consent should be minimized because:

1. The subject in this trial who discontinues study therapy before progression will most likely subsequently be followed in any case by a healthcare provider locally or at the site via routine standard of care assessments (ie, monthly M-protein data, calcium, etc) and
2. In most cases, this protocol would not require any additional samples beyond those considered standard of care

If there is uncertainty about the progression criteria, investigators are encouraged to contact the BMS medical monitor/study director prior to:

1. starting a subject on another myeloma regimen or
2. performing the end of treatment visit for progression

Subjects who request to discontinue study drug will remain in the study and must continue 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 (and entered onto the appropriate CRF page), as to whether the withdrawal is from further:

1. study medication but subject is willing to continue to perform visits for PFS follow-up. study medication and study visits for PFS but agrees to provide the results of future myeloma assessments from another site/local site
2. study treatments, results from another site/local sites, but agrees to be contacted for overall survival follow-up

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.

3.2.2 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, obituary listings, 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.

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) Age ≥ 18 years or legal age of consent per local regulations.

b) ECOG performance status ≤ 2.

c) Life-expectancy > 3 months.

d) 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 CA204006 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) serum IgD M-protein ≥ 0.05 g/dL OR

(e) Urine M-protein ≥ 200 mg/24-hour

3. Age and Reproductive Status

a) 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 and women for up to 120 days, men for up to 180 days after the last dose of investigational product 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.

b) 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 the investigational product. 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.

c) Women must not be breastfeeding.

d) Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile; see Section 3.3.3 for the definition of WOCBP) and men.

e) Sexually active fertile men must use effective birth control if their partners are WOCBP. Men must agree to use a latex condom and a second form of birth control during sexual contact with WOCBP, even if they have had a successful vasectomy, and must agree to not donate semen during study drug therapy and for 180 days after therapy.

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

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Subjects with non-secretory or oligo-secretory or serum free light-chain only 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 2×10^9/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) Uncontrolled diabetes (defined as Hgb A1C ≥ 8.0%).

h) 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:

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg}}{72 \times \text{serum creatinine in mg/dl}} \times 0.85$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg}}{72 \times \text{serum creatinine in mg/dl}} \times 1.00$$

4) Prior Therapy or Surgery

a) Administration of systemic chemotherapy, biological, 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) Sex and Reproductive Status

a) Sexually active fertile men not using 2 forms of effective birth control if their partners are WOCBP.

7) 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 to ensure 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

Women of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Post menopause is defined as:

- Amenorrhea ≥ 24 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL or
- Women with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL or

NOTE: FSH level testing is not required for women ≥ 62 years old with amenorrhea of ≥ 1 year

- Women on hormone replacement therapy (HRT)

Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.

[redacted]

[redacted]

3.5 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (elotuzumab, lenalidomide, and dexamethasone) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- 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 5.4.5.5 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 4.3.2.2.
- 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.

All subjects who discontinue 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 or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Study Follow up

PFS and OS are key endpoints of the study. Post treatment study follow-up is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment prior to progression must continue to be followed for collection of protocol-defined PFS. Subjects who discontinue study therapy must also continue to be followed for overall survival data until death or the conclusion of the study.

BMS may request that survival data be collected on all randomized subjects outside of the protocol defined window, Table 5.1-3.

At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

4 TREATMENTS

All protocol-specified investigational and noninvestigational products are considered study drug.

4.1 Study Treatments

Table 4.1-1: Product Description: Treatment Period

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty)/Label Type	Appearance	Storage Conditions (per label)
Elotuzumab Powder for Solution for Infusion	400 mg/vial	20 mL Vial/ Open Label	TBD	Sterile, white to off-white, preservative-free, lyophilized cake	Store at 2 °C - 8 °C Protect from light. Do not freeze or shake.
Lenalidomide (Revlimid®)capsule	5 mg, 10 mg, 15 mg and 25 mg	21 capsules per bottle OR blisters containing 7 capsules each/ Commercial or Open Label	NA/wallet or carton containing 21 capsules/ Commercial or Open Label	5 mg hard white capsule with "5 mg REV" written on them 10 mg hard yellow/blue-green capsule with "10 mg REV" written on them 15 mg hard white/blue capsule with "15 mg REV" written on them 25 mg: hard white capsule with "25 mg REV" written on them	Store at 25 °C (77 ° F). Excursions permitted to 15 - 30 °C (59 - 86 °F)
Dexamethasone Tablets	2 mg and 4 mg & various strengths	Various packing configurations	NA	Various	Refer to label on container or package insert/summary of product characteristics
Dexamethasone Solution	4 mg/ml, 8 mg/ml & various strengths	Various packing configurations	NA	Various	Refer to label on container or package insert/summary of product characteristics

Lenalidomide (Revlimid®) capsules, dexamethasone tablets and solution for IV infusion will be obtained by the investigating site's standard prescribing procedures. Lenalidomide (Revlimid®) may be supplied by BMS according to country availability and specific regulatory requirements.

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

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) in a way different from 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, dexamethasone tablets and concentrate for solution for IV infusion.

4.1.2 Noninvestigational 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 noninvestigational products.

In this protocol, non-investigational product(s) are: diphenhydramine (or equivalent H1 blocker), ranitidine (or equivalent H2 blocker), acetaminophen, warfarin, low-molecular weight heparin and aspirin.

4.1.3 Handling 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 the Sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the Sponsor immediately.

The investigator (or assigned designee, ie, study pharmacist) will dispense the proper number of each strength tablet to the subject to satisfy dosing requirements until the subject's next visit. The subject must be instructed to return all unused study medications in the provided packaging at each subsequent visit.

Procedures for proper handling and disposal of anticancer drugs should be considered.

4.1.3.1 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, USP, and then further diluted in 0.9% sodium chloride normal saline, USP, as per the instructions in Appendix 6. 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 6.

4.1.3.2 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 90 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.[42] This program is called the Revlimid Risk Management Plan. 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.

Please see the US package insert/SMPC[48] for additional information for prescribing to, female subjects and male subjects about this restricted distribution program.

4.2 Method of Assigning Subject Identification

After the subject's eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. The following information is required for subject enrollment:

- Date of Birth
- Site number
- Date that informed consent was obtained

Instructions on the use of interactive voice response system will be provided at site initiation.

When it has been determined that a subject is eligible for randomization, a call will be placed to IVRS to obtain treatment assignment. Subjects will be randomized to lenalidomide/dexamethasone + elotuzumab (Arm A) or lenalidomide/dexamethasone alone (Arm B) in a 1:1 ratio. The randomization will be stratified by the following factors:

- Stage of Disease (International Staging System 1 - 2 versus 3)
- Age (< 75 years old versus ≥ 75 years old)
- ECOG Performance Status (0 versus 1 - 2)

and will be carried out via permuted blocks within each stratum.

4.3 Selection and Timing of Dose for Each Subject

4.3.1 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 (650 - 1000 mg po)

See Appendix 6 for elotuzumab dosing instructions.

Lenalidomide

Lenalidomide will be taken orally once daily for the first 3 weeks of a 4-week cycle. Subjects should not break, chew or open the capsules.

Table 4.3.1-1: Treatment Schedule

Control Arm												
Cycle #	**1 - 2**				**3 - 18**				**19+**			
Day # (-1/+3 days)	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Lenalidomide - PO	←25 mg Days 1 - 21→				←25 mg Days 1 - 21→				←25 mg Days 1 - 21→			
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
Investigational Arm												
Cycle #	**1 - 2**				**3 - 18**				**19+**			
Day # (-1/+3 days)	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**
Lenalidomide - PO	←25 mg Days 1 - 21→				←25 mg Days 1 - 21→				←25 mg Days 1 - 21→			
Dexamethasone - PO	28 mg	28 mg	28 mg	28 mg	28 mg	40 mg	28 mg	40 mg	28 mg	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	-	-	-

4.3.1.1 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 4.3.1) which will also serve as premedication for elotuzumab.

Intravenous and po dexamethasone doses are calculated to prevent an imbalance in dexamethasone exposure between the control and investigational arms (Refer to Section 4.3.1.2 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 (650 - 1000 mg po)

4.3.1.2 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 4.3.1.2-1. 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 4.3.1 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 4.3.1.2-1: 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 4.3.1.2.

[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 hrs prior to elotuzumab) **AND** 16 mg dexamethasone po (at least 3 hrs 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.

4.3.2 Guidelines for Elotuzumab Infusion in Subjects with Infusion Reactions

4.3.2.1 Grade 1 Infusion Reaction

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

4.3.2.2 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 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 4.3.1.2-1

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 2 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 mL/minute. If tolerated, all subsequent infusions may start at a rate per investigator's discretion, up to a maximum rate of 5 ml/minute.**

4.3.3 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.

4.3.3.1 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.

4.3.3.2 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 4.3.1.

4.3.3.3 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.

4.3.4 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.

4.3.4.1 Elotuzumab

No dose reduction is allowed for elotuzumab.

4.3.4.2 Dexamethasone Reductions

Dexamethasone dose reductions for toxicity must be performed as clinically indicated. Recommended management is described in Table 4.3.4.2-1and Table 4.3.4.2-2. Deviations to the recommended dose reductions are allowed based on the clinical judgment of the investigator.

Table 4.3.4.2-1: Dexamethasone Dose Reductions		
CTCAE 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 4.3.4.2-1 and Table 4.3.4.2-2.

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 4.3.1. 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 4.3.4.2-2: 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

4.3.4.3 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 4.3.4.3-1 and Table 4.3.4.3-2 is based on current standard of clinical practice.

Table 4.3.4.3-1: Treating Thrombocytopenia Related to Lenalidomide	
When Platelet Counts:	**Recommended Course**
• Fall to < 30,000/mm^3 • Return to ≥ 30,000/ mm^3	Interrupt lenalidomide treatment; follow complete blood counts weekly. Resume lenalidomide at 15 mg, Days 1 - 21, once daily.
For each subsequent drop < 30,000/ mm^3 Return to ≥ 30,000/ mm^3	Interrupt lenalidomide treatment. Resume lenalidomide at 5 mg less than previous dose, Days 1 - 21, once daily. Do not dose below 5 mg.

Table 4.3.4.3-2: Treating Neutropenia Related to Lenalidomide	
When Neutrophil Counts:	**Recommended Course**
Fall to < 1000/ mm^3 Return to ≥ 1000/ mm^3 and neutropenia is the only toxicity	Interrupt lenalidomide treatment, add G-CSF;[a] follow complete blood counts weekly. 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 Return to ≥ 1000/ mm^3	Interrupt lenalidomide treatment. 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 4.3.4.3-3: Lenalidomide Dose Adjustments in Subjects with Renal Impairment[a]

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

[a] 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.

4.4 Blinding/Unblinding

Not applicable.

4.5 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.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have

been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor.

4.6.2 Return of Study Drug

Study drug will not be returned to BMS after on site reconciliation. All unused and/or partially used study drug may be destroyed on site providing the site has an applicable standard operating procedure on file.

4.7 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Short-term Procedural Outline - Screening

Procedure	Screening Visit	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	Includes height and weight (Section 5.3.1) Within 14 days of randomization
Vital Signs	X	Temperature, BP, HR, RR (Section 5.3.1) 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 14 days of randomization
2-D Echocardiogram or MUGA	X	Section 5.3.3 (Within 28 days of randomization)
ECG	X	Section 5.3.3 (Within 28 days of randomization)
Laboratory Assessments for Safety		
CBC, differential, platelets	X	Section 5.3.4 (Within 14 days of randomization)
Serum Chemistry	X	Section 5.3.4 (Within 14 days of randomization)
Coagulation Tests	X	Section 5.3.4 (Within 14 days of randomization)
Serum β2-microglobulin	X	Within 28 days of randomization. Central lab analysis for stratification
Serum Albumin	X	Within 28 days of randomization. Central lab analysis for stratification.

Table 5.1-1: Short-term Procedural Outline - Screening		
Procedure	**Screening Visit**	**Notes**
Urinalysis	X	Section 5.3.4 (Within 14 days of randomization)
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	Section 5.4.2. Within 28 days of randomization. Central laboratory analysis.
Bone Marrow Aspiration/Biopsy	X	Section 5.4.2. Within 28 days of randomization. Bone marrow aspirate is mandatory. Bone marrow biopsy is optional.
Cytogenetic analysis and FISH	X	Sections 5.4.2 and 5.7. Central lab analysis.
Skeletal Survey	X	Within 28 days or randomization
CT/MRI assessment for extramedullary soft tissue plasmacytoma	X	Within 28 days of randomization, if clinically indicated.
Serum soluble major histocompatibility complex class I-related chain A (sMICA)	X	Section 5.7. Central laboratory analysis.
Clinical Drug Supplies		
Randomize	X	First dose of study drug must occur within 3 days of randomization
QOL assessments		
EORTC QLQ-C30	X	
EORTC QLQ-MY20	X	
Brief Pain Inventory - Short Form (BPI-SF)	X	
Healthcare Resource Utilization	X	

Table 5.1-2: Short-term Procedural Outline (CA204006) Cycles 1 & 2

Procedure	Day 1	Day 8	Day15	Day 22	Rest Days 23 - 28	Notes
Safety Assessments						
Targeted Physical Examination	X					Perform up to 3 days prior to dosing, include weight (Section 5.3.1)
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	X	X	X		Section 6.7
Concomitant Medications	X	X	X	X		Evaluate prior to dosing
Laboratory Tests for Safety						
CBC, differential, platelets	X	X	X	X		Section 5.3.4. Can be drawn up to 3 days prior to study visit.
Serum Chemistry	X	X	X	X		Section 5.3.4. Can be drawn up to 3 days prior to study visit.
Coagulation Tests	X	X	X	X		For subjects treated with warfarin thromboembolic prophylaxis
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 (CA204006) Cycles 1 & 2						
Procedure	**Day 1**	**Day 8**	**Day15**	**Day 22**	**Rest Days 23 - 28**	**Notes**
Efficacy Assessments						
Myeloma Urine and Serum Lab tests	Every 4 weeks from date of first dose of study drug **until disease progression.**					Section 5.4.2. Day 1 of each cycle (except Cycle 1 - refer to Screening visit for defined window) until disease progression, even if subject is on subsequent therapy; 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. In order to fulfill CR/sCR criteria, both serum and urine immunofixation must be performed and be negative for a minimum of 6 weeks, in addition to CR criteria in section 5.4.5.1 Subjects without measurable urine M protein at baseline and at the next two consecutive cycles do not have to submit q4 week urine samples with each cycle (but must submit q12 week urine samples). However, when SPEP M protein becomes undetectable, 24-hr UPEP collection must promptly resume and continue q4 weeks until SPEP becomes detectable.
Corrected Calcium	Every 4 weeks from date of first dose of study therapy, regardless of whether subject is on study therapy or subsequent therapy until disease progression.					Serum calcium and albumin from peripheral blood at D1 of each cycle until disease progression, even if subject is on subsequent therapy; if used as criteria for disease progression, must be confirmed by second value
Bone Marrow Aspiration/Biopsy	For confirmation of CR/sCR if applicable or, if clinically indicated at time of suspected disease progression					Section 5.4.2. Bone marrow aspirate is mandatory. Bone marrow biopsy is optional. However, if a patient has a CR and flow cytometry is unavailable then a bone marrow biopsy is required for immunohistochemistry. Plasma cell percentage and light chain restriction assessments must be performed.
Flow Cytometry	To assess for sCR, if applicable. Performed locally per institution standard practice.					Section 5.4.2. Performed locally per institution standard practice; Plasma cell percentage and light chain restriction assessments are required. If not available, IHC can be performed on bone marrow core biopsy.

Table 5.1-2: Short-term Procedural Outline (CA204006) Cycles 1 & 2

Procedure	Day 1	Day 8	Day15	Day 22	Rest Days 23 - 28	Notes
Serum Free Light Chain	To assess for sCR at the time of CR assessments					Section 5.4.2. Normal values require confirmatory values at least 6 weeks apart to fulfill criteria of sCR.
Skeletal Survey	If clinically indicated					Section 5.4.3.1
CT/MRI assessment for extramedullary soft tissue plasmacytoma	As clinically indicated and at the time of CR/sCR assessments					Section 5.4.3.2
Response per EBMT based criteria	Every 4 weeks from date of first dose of study drug until disease progression, regardless of whether patient is still on study therapy					Section 5.4.5 Response assessments require repeat values over 6 weeks minimum. Progression assessments require repeat values over any time interval.
Serum PK Elotuzumab arm only	<----------					Refer to Table 5.5.1-1 for specific time points
Human Anti-Human Antibody (HAHA) Elotuzumab arm only	<----------					Refer to Table 5.5.1-1for specific time points
Serum soluble major histocompatibility complex class I-related chain A (sMICA)	X*					*Cycle 2 Day 1 only. Section 5.7. Central lab analysis.
Dosing						
Premedication for Elotuzumab (Investigational Arm only)	X	X	X	X		
Elotuzumab Infusion (Investigational Arm only)	X	X	X	X		In Cycle 1 and 2, an elotuzumab dose that falls outside of the pre-specified window (-1 to +3 days) must be skipped. See Section 4.3.3.1.
Lenalidomide Administration	← Days 1 - 21 of each cycle →					
Dexamethasone Administration	X	X	X	X		Section 4.1
Dispense Lenalidomide	X					Dispense lenalidomide on Day 1 of cycle per the Revlimid Risk Management Plan

Table 5.1-2: Short-term Procedural Outline (CA204006) Cycles 1 & 2						
Procedure	**Day 1**	**Day 8**	**Day15**	**Day 22**	**Rest Days 23 - 28**	**Notes**
QOL assessments						
[redacted]	[redacted]					[redacted]
[redacted]	[redacted]					[redacted]
Brief Pain Inventory - Short Form (BPI-SF)	X					Complete up to 2 days prior to any study-related procedures, treatment or clinician assessment
[redacted]	[redacted]					[redacted]

Table 5.1-3: Long-term Procedural Outline (CA204006) Cycles 3 and Beyond									
Procedure	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Rest Days 23 - 28**	**End of Treatment**	**Days 30 & 60 Post End of Treatment**	**Every 16 weeks after progression**	**Notes**
Safety Assessments									
Targeted Physical Examination	X					X			Perform up to 3 days prior to dosing, includes weight, Section 5.3.1
Vital Signs	X		X*			X			Measure vital signs prior to administration of pre-medication, 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 Event Assessment	X		X*			X	X		Evaluate prior to dosing *Not required in Cycles 19 and beyond
Adverse Events Assessment	X		X*			X	X		Evaluate prior to dosing *Not required in Cycles 19 and beyond
Second Primary Malignancy	X		X			X	X	X	Section 6.7: Performed at 30 and 60 day ± 1 week EOT follow up visits. After 30 and 60 day EOT visits, second primary malignancy should be assessed every 16 weeks (± 2 weeks), or more frequently. Subjects should be followed monthly (if no Progression) or every 16 weeks (if Progression occurred), or more frequently.
Concomitant Medications	X		X*			X	X		Evaluate prior to dosing

Table 5.1-3: Long-term Procedural Outline (CA204006) Cycles 3 and Beyond

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 - 28	End of Treatment	Days 30 & 60 Post End of Treatment	Every 16 weeks after progression	Notes
Subsequent Myeloma Therapy						X	X	X	30 and 60 day visits may be performed ±1 week. After 30 and 60 day EOT visits and EBMT based progression subsequent myeloma should be assessed every 16 weeks (±2 weeks), or more frequently. Subjects should be followed monthly (if no Progression) or every 16 weeks (if Progression occurred), or more frequently. Start date and end date for second and third line therapy and date of progression after second line therapy will be collected.
Laboratory Tests for Safety									
CBC, differential, platelets	X		X*			X			Section 5.3.4 Can be drawn up to 3 days prior to visit. *Not required in Cycles 19 and beyond
Serum Chemistry	X		X*			X			Section 5.3.4 Can be drawn up to 3 days prior to visit *Not required in Cycles 19 and beyond
Coagulation Tests	X		X*			X			For subjects treated with warfarin thromboembolic prophylaxis *Not required in Cycles 19 and beyond

Table 5.1-3: Long-term Procedural Outline (CA204006) Cycles 3 and Beyond									
Procedure	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Rest Days 23 - 28**	**End of Treatment**	**Days 30 & 60 Post End of Treatment**	**Every 16 weeks after progression**	**Notes**
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. * Not required in Cycles 19 and beyond. However, patients with irregular menstrual cycles must have a pregnancy test every two weeks. ** WOCBP must have a pregnancy test 30, 60, and 90 days Post End of Treatment.

Table 5.1-3: Long-term Procedural Outline (CA204006) Cycles 3 and Beyond

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 - 28	End of Treatment	Days 30 & 60 Post End of Treatment	Every 16 weeks after progression	Notes
Efficacy Assessments									
Myeloma Urine and Serum Lab tests	Every 4 weeks from date of the first dose of study drug therapy until disease progression, regardless of whether subject is on study therapy or subsequent therapy.								Section 5.4.2. Day 1 of each cycle until disease progression , even if subject is on subsequent therapy; 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. In order to fulfill CR/sCR criteria, both serum and urine immunofixation must be performed and be negative for a minimum of 6 weeks, in addition to CR criteria in section 5.4.5.1. Subjects without measurable urine M protein at baseline and at the next two consecutive cycles do not have to submit q4 week urine samples with each cycle (but must submit q12 week urine samples). However, when SPEP M protein becomes undetectable, 24-hr UPEP collection must promptly resume and continue q4 weeks until SPEP becomes detectable.

Table 5.1-3: Long-term Procedural Outline (CA204006) Cycles 3 and Beyond									
Procedure	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Rest Days 23 - 28**	**End of Treatment**	**Days 30 & 60 Post End of Treatment**	**Every 16 weeks after progression**	**Notes**
Corrected Calcium	Every 4 weeks from date of first dose of study therapy until disease progression, regardless of whether subject is on study therapy or subsequent therapy.								Serum calcium and albumin from peripheral blood at D1 of each cycle until disease progression, even if subject is on subsequent therapy; if used as criteria for disease progression, must be confirmed by second value.
Bone Marrow Aspiration/Biopsy	For confirmation of CR/sCR if applicable or, if clinically indicated at time of suspected disease progression								Section 5.4.2. Bone marrow aspirate is mandatory. Bone marrow biopsy is optional if a patient has a CR and flow cytometry is unavailable then a bone marrow biopsy is required for immunohistochemistry. Plasma cell percentage and light chain restriction assessments are required.
Flow cytometry	To assess for sCR, if applicable. Performed locally per institution standard practice.								Section 5.4.2. Performed locally per institution standard practice; Plasma cell percentage and light chain restriction assessments are required. If not available, IHC can be performed on bone marrow core biopsy.
Serum Free Light Chain	To assess for sCR at the time of CR assessments								Section 5.4.2. Normal values require confirmatory values at least 6 weeks apart to fulfill criteria of sCR
Skeletal Survey	If clinically indicated								Section 5.4.3.1
CT/MRI assessment for extramedullary soft tissue plasmacytoma	As clinically indicated and at the time of CR/sCR assessments								Section 5.4.3.2
Response per EBMT-based criteria	**Every 4 weeks <u>from date of the first dose of study drug</u> until disease progression regardless of whether on study therapy or subsequent**								Section 5.4.5 Response assessments require repeat values over 6 weeks minimum. Progression assessments require repeat values over any time interval.
Serum PK Elotuzumab arm only	<----------								Refer to Table 5.5.1-1for specific time points

Table 5.1-3: Long-term Procedural Outline (CA204006) Cycles 3 and Beyond									
Procedure	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Rest Days 23 - 28**	**End of Treatment**	**Days 30 & 60 Post End of Treatment**	**Every 16 weeks after progression**	**Notes**
Human Anti-Human Antibody (HAHA) Elotuzumab arm only	<----------							---------->	Refer to Table 5.5.1-1for specific time points
Serum soluble major histocompatibility complex class I-related chain A (sMICA)						X			Section 5.7. Central lab analysis.
Survival Status							X	X	30 and 60 day visits may be performed ± 1 week. After 30 and 60 day EOT visits survival status should be assessed every 16 weeks ± 2 weeks, or more frequently.
Dosing									
Premedication for Elotuzumab (Investigational Arm only)	X		X*						*Not required in Cycles 19 and beyond
Elotuzumab Infusion (Investigational A only)	X		X*						*Not required in Cycles 19 and beyond 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. See Section 4.3.3.1
Lenalidomide Administration	Days 1 - 21								
Dexamethasone Administration	X	X	X	X					
Dispense Lenalidomide	X								Dispense lenalidomide on Day 1 of cycle per the Revlimid Risk Management Plan
QOL assessments									
[redacted]	[redacted]					[redacted]			[redacted]

Table 5.1-3: Long-term Procedural Outline (CA204006) Cycles 3 and Beyond

Procedure	Day 1	Day 8	Day 15	Day 22	Rest Days 23 - 28	End of Treatment	Days 30 & 60 Post End of Treatment	Every 16 weeks after progression	Notes
[redacted]	[redacted]					[redacted]			[redacted]
Brief Pain Inventory - Short Form (BPI-SF)	X					X			Complete up to 2 days prior to any study-related procedures, treatment or clinician assessment
[redacted]	[redacted]					[redacted]			[redacted]

5.2 Study Materials

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

- NCI CTCAE booklets version 3.0
- Elotuzumab Investigator Brochure
- Lenalidomide (Revlimid®) Package Insert
- Site Manual for operation of interactive voice response system
- Subject Dosing Diary
- Subject Quality of Life questionnaires
- Serious Adverse Event (SAE) case report form (CRF) pages
- Pregnancy Surveillance Forms.

5.3 Safety Assessments

Only data for the procedures and assessments specified in this protocol should be submitted to BMS. Additional procedures and assessments may be performed as part of standard of care; however, the data for these assessments should remain in the subject's medical record and should not be provided to BMS, unless specifically requested from the Sponsor. The local safety labs (CBC, electrolytes, coagulation test) may be collected up to 3 days prior to the visit. The local urine pregnancy test (collected within 24 hours of dosing) for females of reproductive potential **must be negative** for these subjects to proceed to dosing. The serum β2 microglobulin and albumin will be sent to the central lab for analysis for ISS stratification.

5.3.1 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 dosing. Subjects in the control arm will have vital signs measured once at each visit. Subjects randomized to the elotuzumab 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.

5.3.2 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.

5.3.3 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 to study medication.

5.3.4 Laboratory Assessments for Safety

Table 5.3.4-1: 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	X	X
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	X	X

Table 5.3.4-1: 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**
Lactate Dehydrogenase	X	X
BUN (or Urea)	X	X
Creatinine	X	X
Glucose	X	X
Calcium	X	X
Total Protein	X	X
Coagulation Test		
PT	X	X[b]
PTT	X	
INR	X	X[b]
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
Urinalysis	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 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

5.4 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 centrally at screening for stratification. If SPEP and UPEP M protein are performed at a local laboratory, results must be recorded in the CRF/eCRF as requested by Sponsor to properly assess efficacy per protocol criteria.

5.4.1 Efficacy Assessment

Response criteria according to Section 5.4.5 will be used for the efficacy analyses. 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 EBMT criteria, irrespective of dose delays or treatment cycle. **If subject does not have documented EBMT-based disease progression as defined in Section 5.4.5.5 (eg, disease progression was determined by sFLC or other non-protocol-defined criteria) at time of study drug discontinuation, then tumor assessments must continue to 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.** Subjects will be followed every 16 weeks (or more frequently) after disease progression for survival, subsequent myeloma therapy, and development of second primary malignancy.

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 IHC 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 absolute quantification (eg, g/dL or g/L for SPEP and mg/24 hrs for UPEP) must be performed. Any laboratory samples analyzed locally, including for efficacy, must be entered on the appropriate CRF as requested by Sponsor to properly assess efficacy per protocol criteria.

5.4.2 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.

Subjects without measureable urine M protein (< 200 mg/24 hours) at baseline and at the next two consecutive assessments 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. Therefore, at the time SPEP becomes undetectable, 24-hr UPEP collection should promptly resume and continue q4 weeks until SPEP becomes detectable.

Assessment of UPEP M protein and urine immunofixation at the time of possible CR/sCR is mandatory for all subjects, that is negative urine immunofixation for a minimum of 6 weeks is required to fulfill CR/sCR criteria, even in subjects with nonmeasurable values at baseline. Any local serum and urine myeloma lab tests that may also have been performed must also be reported in the CRF as requested by Sponsor to properly assess efficacy by protocol criteria.

1) **Serum**: serum protein electrophoresis (SPEP) for M protein quantification, total serum protein~~,~~ immunofixation, and quantitative immunoglobulin assay.
   a) Immunofixation of serum is required at baseline and to confirm CR regardless of whether measurable M-protein was present at baseline.
   b) All other serum tests will be followed at each tumor assessment. Confirmation of ≥ PR is required at least 6 weeks later.

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 consecutive assessments.
   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. Confirmation of ≥ PR is required at least 6 weeks later.

3) **Bone marrow aspiration/biopsy**:

Bone marrow sample	Local Laboratory	Central Laboratory
Aspirate[a]	**1)** *Samples required at* the following times to evaluate percentage plasma cells: **g) Screening (within 28 days of randomization)** **h) When subject is immunofixation negative in both serum and urine** (second bone marrow sample not required for confirmation) for a minimum of 6 weeks In addition, evaluate flow cytometry to assess plasma cell clonality (ie, lambda and kappa IHC or flow cytometry to assess light chain restriction). **a) At time of suspected disease progression, if needed** (see Section 5.4.5.5) to assess progression in subjects who's myeloma become nonsecretory	**1) Screening (within 28 days of randomization)** a) 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 by the central laboratory 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 prior to randomization, the local results must be entered into the eCRF.

4) **Serum free light chain**: Serum should be collected at baseline and time of serum and urine IFE negativity for a minimum of 6 weeks to confirm CR and be sent to the central lab for serum free light chain analysis. Two values at least 6 weeks apart should be provided. The measurement of sFLC is required to document sCR using Section 5.4.5, but is not a criteria for determining disease progression (see Sections 5.4.1 and 5.4.5.5).

5) Serum Corrected Calcium: Serum corrected calcium should be collected with each cycle for all subjects until disease progression.

5.4.3 Imaging Assessments for Myeloma

5.4.3.1 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.

5.4.3.2 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.

5.4.4 Independent Review Committee

The following information will be submitted to an Independent Review Committee (IRC) for final assessment of objective response based on:

1. The subject's laboratory results (electronically and via CRF)
2. All imaging results via CRF
3. Local pathology results via CRF
4. Local pathology results of bone marrow samples for confirmation of stringent CR.

The criteria for IRC review are defined in a separate IRC charter.

5.4.5 Definitions of Response

5.4.5.1 Complete Response (CR)/stringent CR (sCR)

A CR requires that all of the following criteria be achieved:

1. Negative immunofixation ("IF") on both serum and urine, maintained for a minimum of 6 weeks and
2. A bone marrow aspirate or biopsy containing < 5% plasma cells. It is not essential to perform a trephine biopsy, but if a biopsy is performed this must also contain < 5% plasma cells (although not required for documentation of CR using the EBMT criteria, light chain restriction (flow or IHC for kappa and lambda light chain in the bone marrow should also be assessed to assist in classification of stringent CR using the IMWG criteria)[17] and
3. If skeletal survey showed osteolytic bone lesions, there should be no increase in the size or number (development of a compression fracture does not exclude response) and
4. If screening scans showed extramedullary plasmacytomas, complete disappearance of any must be noted.
5. For assessment of stringent CR, per IMWG criteria, all criteria for CR must be upheld. In addition, bone marrow sample must be assessed for light chain restriction (as mentioned in bullet 2 above) and serum free light chains must be normalized at two time points at least 6 weeks apart, at the time of CR assessment.

5.4.5.2 Partial Response (PR)

Subjects in whom some, but not all, the criteria for CR are fulfilled are classified as PR, providing the remaining criteria satisfy the requirements for PR. This includes subjects in whom routine electrophoresis is negative but in whom IF has not been performed.

1. Greater than or equal to 50% reduction in serum M-protein, maintained for a minimum of 6 weeks.
2. Reduction of ≥ 90% in urinary light chain excretion or a decrease to < 200 mg/ 24 hours, maintained for a minimum of 6 weeks.
3. Greater than or equal to 50% reduction in the size of extramedullary plasmacytomas present at baseline (by radiography or clinical examination using bidimensional measurements).
4. If a skeletal survey is performed, no increase in the size or number of lytic lesions (development of a compression fracture does not exclude response).

5.4.5.3 Very Good Partial Response (VGPR)

VGPR, a subset of PR, is not formally included in the EBMT criteria but is derived from the IMWG criteria.[17] Because VGPR is commonly used to measure depth of response in MM, this response must be reported by investigator and IRC and is defined by:

1. Serum and Urine M-protein detectable by immunofixation but not on electrophoresis and that is confirmed in a subsequent assessment OR
2. 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h and that is confirmed in a subsequent assessment.

5.4.5.4 Minor (Minimal) Response (MR)

Subjects who have reduction in M-protein or plasmacytoma but do not meet the criteria for PR are classified as MR if they meet all the following definition:

1. Between 25 - 49% reduction in serum M-protein, maintained for a minimum of 6 weeks.
2. Between 50 - 89% reduction in urinary light chain excretion which still exceeds 200 mg/24 hours, maintained for a minimum of 6 weeks.
3. Between 25 - 49% reduction in the size of extramedullary plasmacytomas.
4. If a skeletal survey is performed, no increase in the size or number of lytic lesions (development of a compression fracture does not exclude response).

5.4.5.5 Progression of Disease (PD)

Progression

Progression describes a definite increase in disease activity relative to the nadir in 2 consecutive assessments in subjects not in CR, whereas the term "relapse from CR" applies to a recurrence of evident disease in subjects previously in CR. The date of EBMT based disease progression is the first date of two consecutive values fulfilling the criteria for disease progression.

Any of the following list is sufficient for PD:

1. Increase of > 25% in serum M-protein (also an absolute increase of at least 5 g/L) and confirmed by at least 1 investigation.
2. 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 1 investigation.
3. Increase of > 25% plasma cell percentage in the marrow (which must also be an absolute increase of at least 10%).
4. Definite increase in the size or number of lytic bone lesions or extramedullary plasmacytomas (development of a compression fracture does not exclude continued response and may not indicate progression).
5. Development of hypercalcemia (corrected serum calcium greater than 11.5 mg/dL; 2.8 mmol/L) not attributable to any other cause.

Relapse from CR (for subjects in CR)

Subjects who have documented CR and then achieve at least one of the following criteria are classified as relapse from CR. According to the EBMT criteria, relapse from CR is considered to be progression of disease. The date of EBMT based relapse from CR is the first date of two consecutive values fulfilling the criteria for relapse.

1. Reappearance of serum or urinary M-protein on immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal reconstitution.
2. Greater than or equal to 5% plasma cells in a bone marrow aspirate or on trephine bone biopsy.
3. Any of the definitions met for Progression.

5.4.5.6 Stable Disease/No Change

Does not meet criteria for any of the categories above.

[redacted]

[redacted]

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5.8 Outcomes Research Assessments

5.8.1 HRQoL Assessments

To assess the impact of treatment, subject's quality of life will be measured using 3 validated QoL instruments: [redacted]
and the Brief Pain Inventory- Short Form (BPI-SF).

All three questionnaires will be administered per the schedule in Table 5.1-1, Table 5.1-2, and Table 5.1-3. Subjects should fill out the questionnaire prior to any study-related procedures, treatment or clinician assessment in order to prevent these variables from influencing QoL results. Non-English speaking subjects will complete the questionnaire using validated language transitions developed and recommended for each instrument.

[redacted]

The BPI-SF is a 15-item (Appendix 5) instrument designed to assess pain in patients with cancer and other diseases.[50,51] It measures the pain intensity (5-item sensory dimension), and it also includes questions to measure the interference of pain in the patient's daily life, including general activity, mood, ability to walk, normal work both outside the home and housework, relations to other people, sleep, as well as enjoyment of life (7-item reactive dimension).[52] In multiple myeloma patients, significant associations were found between pain intensity measured by the BPI-SF and mood disturbance scores. As pain interference increased, so did levels of mood disturbance. A joint predictive model explained 74.6% of the variability in total QOL scores.[53] The BPI-SF has demonstrated both reliability and validity across cultures and languages, and has been used to study the effectiveness of pain treatment.[50] A score of 6 on a scale of 0 to 10 on any single item is generally considered to be clinically significant.[54]

Pre-testing was carried out in the UK, Norway, Sweden, Denmark, and Germany. Field testing of the module has been conducted in a range of Phase 3 trials.[55] The module has been validated in a large number of languages (see www.eortc.be/home/qol).

[redacted]

5.9 Other Assessments

Not applicable.

6 ADVERSE EVENTS

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

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 ***serious AE (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, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

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

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 "important medical event" or event life threatening)

- 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 for purpose other than remedying ill health state and was 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, care-giver respite, family circumstances, administrative).
- 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 or within 30 days of the last visit for screen failures.

The investigator must 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 must 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 must 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 of awareness of the event. 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: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission,

paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must 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, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must 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, or those that are 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 Abnormalities

The following laboratory 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 abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

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

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure,

including during at least 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 investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). 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 Medical Monitor (or designee)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 the sponsor. 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 an SAE (see Section 6.1.1 for reporting details.).

6.6 Potential Drug Induced Liver Injury

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 DILI 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, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these

procedures are required by the 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 which includes assessments during survival follow-up. 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

A data monitoring committee (DMC) will be established before the first subject is treated and will monitor safety throughout the study. (The DMC will receive SAE tables every 4 months and more comprehensive safety data every 8 months.) In addition, the DMC will review safety and efficacy data, including a formal comparison of PFS for early stopping, once the following two conditions have been met: at least 338 progression events have been observed and all subjects have been randomized. A separate charter will describe the activities of this committee. (Also see Section 8.5, Interim Analyses, for details on the interim analyses of safety and efficacy).

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The number of events and power for PFS were calculated assuming an exponential distribution in each arm. One interim analysis of PFS is planned. The comparisons of PFS will be carried out using log-rank tests stratified by stage of disease (International Staging System 1 - 2 versus 3), ECOG performance status (0 versus 1 - 2), and age (< 75 years old versus ≥ 75 years old). The interim analysis will allow for early stopping for superiority. An O'Brien and Fleming α spending function will be employed to determine the stopping boundaries.

Approximately 750 subjects will be randomized to the 2 treatment groups in a 1 to 1 ratio in order to obtain at least 482 progression events, ie, documented progressions or deaths as determined by the IRC. Four hundred and eighty-two (482) events ensure that a two-sided, 5% level, sequential test procedure with 1 interim analysis after 70% of the total events (338) will have 90.5% power if the median PFS times in the control and experimental arms are 25 and 33.75 months, respectively, ie, if the hazard ratio of the experimental to control arm is 0.74. Assuming an accrual rate of 24 subjects per month, it will take approximately 60 months to obtain the required number of events, 31 months for accrual and 29 months for PFS follow-up. It is projected that at the time of final PFS analysis (at least 482 events), an observed hazard ratio of 0.84 or less, which corresponds to a 4.8 month or greater improvement in median PFS (25 vs 29.8 months), would result in a statistically significant improvement in PFS for the elotuzumab-containing arm. In view of evolving results with frontline lenalidomide therapy, a reassessment of the sample size could be made. The decision to reevaluate sample size would be based on external data only and would not involve a change in the required number of PFS events.

Survival, a key secondary endpoint, will be compared between the two arms at the time of the interim analysis of PFS (if and only if both PFS and ORR are positive), and again after 354 deaths, which is projected to occur 7 years (84 months) after the initiation of the study. An O'Brien and Fleming α-spending function will be used to obtain the nominal significance levels for the interim and final analyses of survival. Three hundred and fifty-four (354) deaths ensure that a two-sided 5% level sequential test procedure with one interim analysis will have 80% power for a 8.7 percentage point improvement in 4-year survival rate from 59.0%[36] to 67.7%, ie, for a HR = 0.74.

Power calculations were done using East v5.1.

8.2 Populations for Analyses

The following subject populations will be used in this study:

- 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, patient-reported outcomes, and efficacy will be carried out on all randomized subjects. Analyses of safety will be based on all treated subjects.

8.3 Endpoint Definitions

8.3.1 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, using the criteria in Section 5.4.5.5, 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.

The main analysis of PFS will be by IRC assessments.

IRC 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.

Finally, PFS based on investigator assessments will also be analyzed applying both the primary and the ITT definitions.

8.3.2 Objective Response Rate

Best overall response is determined as the best assessment based on all study efficacy data for the subject. Subjects with objective response are subjects with a best overall response on study of partial response (PR) or better based on criteria in Section 5.4.5.

Objective Response Rate (ORR) is defined as the proportion of subjects with objective response among all randomized subjects. The main ORR analysis will be based on IRC assessments.

[redacted]

8.3.6 Survival

Survival is defined as the time from randomization to the date of death. A subject who has not died will have his or her survival duration censored at the date of last contact (‘last known date alive”).

[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 primary endpoint for the study is progression-free survival based on IRC assessment. The primary analysis of PFS will be to compare the 2 randomized arms at the interim and final looks via two-sided, log-rank tests stratified by stage of disease (International Staging System 1 - 2 versus 3), ECOG performance status (0 versus 1 - 2), and age (< 75 years old versus ≥ 75 years old). An O'Brien-Fleming α spending function will be employed to determine the significance levels and stopping boundaries at the interim and final looks. (See Section 8.5, Interim Analysis, for more detail).

Further analysis of PFS will include the computation of hazard ratios and estimation of PFS functions. The PFS hazard ratio of lenalidomide/dexamethasone + elotuzumab to lenalidomide/dexamethasone alone and an associated two-sided confidence interval will be computed using a stratified Cox proportional hazards model with treatment arm as the sole covariate. The alpha level (α) for the confidence interval will be the same as the nominal significance level for the hypothesis testing. The stratification factors will be the same as those used in the randomization. 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 randomized arm.

8.4.2.3 Secondary Efficacy Analyses

The key secondary endpoints are:

- Objective response rate (ORR)
- Overall survival

A hierarchical procedure will be used to ensure a two-sided, family-wise type I error rate of 5% for testing the one primary and two key secondary endpoints. If there is a statistically significant improvement in PFS, ORR will be compared between arms at the 5% level. If the comparison of ORR is also statistically significant at the 5% level, then survival will be compared between arms using a 5% level sequential test procedure.

Objective response will be compared between randomized arms using a two-sided 5% level Cochran-Mantel Haenszel (CMH) test stratified by the same factors used in the analysis of PFS. An associated odds ratio and 95% confidence interval will be calculated. The response rate and its corresponding 95% confidence interval will also be calculated for each treatment arm. There will be no interim comparison of this endpoint.

Survival will be compared between treatment arms using two-sided, stratified log-rank tests at the interim and final looks. The family-wise type I error rate for the sequential testing procedure will be 5% and the stratification factors will be the same as those used for the randomization. The significance level at the interim and final analyses of survival will be determined using an O'Brien and Fleming α spending function.

Other Secondary objectives are:

- Change from baseline of mean score of pain severity and change from baseline of mean score of pain interference (BPI-SF)

Each of the two comparisons will be made at the two-sided type I error of 2.5% and will be tested independent of the significance of the comparison of the progression-free survival, objective response rate and overall survival. See Section 8.4.7.1 for details about analyses.

8.4.3 Safety Analyses

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. Shift tables for selected laboratory parameters will be produced.

[redacted]

[redacted]

8.4.7 Outcomes Research Analyses

8.4.7.1 Analysis of HRQoL Data

All analyses will be conducted on randomized subjects. Questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number (ie, the number of subjects still on treatment), will be calculated and summarized at each assessment point. Subjects without any post-baseline assessment will be excluded from the analysis.

The comparison between the 2 treatment arms of the change from baseline in the mean score of pain severity will be conducted using a longitudinal mixed model with treatment arm, time point (categorical), and baseline score as fixed effects and a banded covariance matrix (constant covariances on each diagonal of the matrix). Similar model will be used to analyze change from baseline in mean score of pain interference.

Adjusted mean change from baseline at each assessment point will be graphically presented by randomized arm for the three questionnaires [redacted] and BPI-SF).

[redacted]

8.4.8 Other Analyses

[redacted]

PFS rates at 1, 2, 3, 4, and 5 years will be estimated from the KM curve. Each analysis will be performed after all subjects have been followed for the appropriate time. [redacted]

[redacted]

8.5 Interim Analyses

A data monitoring committee (DMC) will be established before the first subject is treated and will monitor safety throughout the study. (The DMC will receive SAE tables every 4 months and more comprehensive safety data every 8 months.) In addition, the DMC will review safety and efficacy data once the following two conditions have been met: at least 338 progression events have been observed and all subjects have been randomized.

A key feature of the interim analysis after at least 338 (70%) progression events will be a formal comparison of PFS between treatment arms. This formal comparison of PFS will allow for early stopping for superiority. The stopping boundaries will be derived based on the O'Brien and Fleming α spending function in East v5.1. (Under current accrual assumptions, the 338 progression event milestone will occur approximately 41 months after study start.)

The stopping boundaries for superiority will depend on the actual number of events observed at the time of the interim analysis, and will be determined using the interim monitoring tool in East v5.1. However, if there were exactly 338 events the DMC could stop the study for superiority if the p-value were ≤ 0.0148. (It should be noted that survival follow-up would continue even if the study were stopped at the interim analysis of PFS for superiority.)

A formal interim analysis of OS will be conducted provided that both the analyses of PFS and ORR are positive (refer to Section 8.4.2.3 for further detail). The final analysis of survival, provided that the survival portion of the study is not stopped early, will take place after at least 354 deaths have been observed, which is projected to occur approximately 7 years after the first subject is randomized. The nominal significance levels for the interim and final survival comparisons will be determined by an O'Brien and Fleming alpha spending function.

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/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

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

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(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)/IEC(s) for review and approval/favorable opinion; (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 an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS (or designee) 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. 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 (or designee) internal auditors 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 (or designee) 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

Bristol-Myers Squibb (or designee) 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 investigator 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 the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

Records for IMP and non-investigational products (whether supplied by BMS, its vendors, or the site) must substantiate IMP integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If...	Then...
Supplied by BMS (or its vendors):	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.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and

If...	Then...
stock or commercial supply, or a specialty pharmacy)	the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each subject, including unique subject identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

The sponsor 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 reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

For sites using the BMS (or designee) 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 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 the sponsor.

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).

The investigator will maintain a 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 SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or subinvestigator. For electronic CRFs, review and approval/signature is completed electronically through the BMS (or designee) 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 (or designee) electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

9.3 Publications

The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor'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 the sponsor 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. Sponsor 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
Adverse Reaction	An adverse event that is considered by either the investigator or the sponsor as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)

11 LIST OF ABBREVIATIONS

Term	Definition
ADCC	Antibody dependent cell-mediated cytotoxicity
AE	Adverse event
BMS	Bristol-Myers Squibb
CS1	CD-2 subset 1
CR	Complete response
CT	Computerized tomography
DILI	Drug induced liver injury
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
EBMT	European Group for Blood and Bone Marrow Transplant
ECG	Electrocardiogram
E-Ld	Lenalidomide, (low-dose) dexamethasone, elotuzumab
EORTC	European Organization for Research and Treatment of Cancer
EPO	Erythropoietin
FSH	Follicle-stimulating hormone
G-CSF	Granulocyte colony-stimulating factor
HAHA	Human-Anti-Human elotuzumab Antibodies
HRQoL	Health Related Quality of Life
HRT	Hormone replacement therapy
ICH	International Council on Harmonization
IF	Immunofixation
IHC	Immunohistochemistry
IMiDs	Immune Modulary Drugs
IMWG	International Myeloma Working Group
IRC	Independent Review Committee
ISS	International Staging System
IV	Intravenous
Ld	Lenalidomide (low-dose) dexamethasone
LD	Lenalidomide (high-dose) dexamethasone

Term	Definition
MM	Multiple Myeloma
MR	Minor (Minimal) Response
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NK	Natural Killer
NKT	Natural Killer T-cell
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral blood mononuclear cells
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial Response
SAE	Serious adverse event
SCID	Severe combined immunodeficient
sCR	Stringent complete response
sMICA	Soluble major histocompatibility complex class I-related chain A
SPM	Second primary malignancy
TEAE(s)	Treatment-emergent adverse event(s)
TTP	Time to progression
VGPR	Very Good Partial Response

APPENDIX 1 INTERNATIONAL STAGING SYSTEM

Stage	Criteria	Median Survival (months)
I	Serum β_2-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL	62
II	Not stage I or III[a]	44
III	Serum β_2-microglobulin ≥ 5.5 mg/L	29

[redacted]

[a] There are two categories for stage II: serum β_2-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum β_2-microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level.

APPENDIX 2 PERFORMANCE STATUS SCALES

STATUS	SCALES		STATUS
	KARNOFSKY	ZUBROD-ECOG-WHO	
Normal, no complaints	100	0	Normal activity
Able to carry on normal activities Minor signs or symptoms of disease	90	1	Symptoms, but fully ambulatory
Normal activity with effort	80		
Cares for self. Unable to carry on normal activity or to do active work	70	2	Symptomatic, but in bed < 50% of the day.
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Needs to be in bed > 50% of the day, but not bedridden
Disabled. Requires special care and assistance	40		
Severely disabled. Hospitalization indicated though death non imminent	30	4	Unable to get out of bed
Very sick. Hospitalization necessary. Active supportive treatment necessary	20		
Moribund	10		
Dead	0	5	Dead

[redacted]

APPENDIX 5 BRIEF PAIN INVENTORY (SHORT FORM)

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: _____/_____/_____ Time: _____

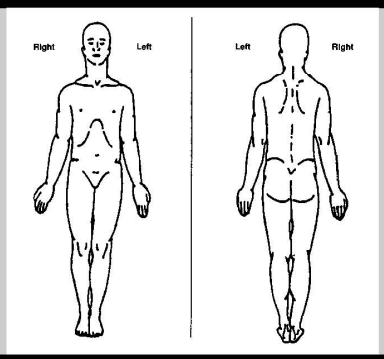
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

APPENDIX 6 PREPARATION AND ADMINISTRATION OF ELOTUZUMAB

Note: Subjects must be premedicated as described in Section 4.3.1 prior to elotuzumab infusion.

Dose Preparation Instructions

After dilution in normal saline, elotuzumab infusion must be completed within 8 hours if kept at room temperature (25 °C). In the United States and Puerto Rico, where a shortage of normal saline has been reported, dextrose 5% water (D5W) may be used. Normal saline is the preferred diluent and D5W should only be used if normal saline is not available. If a delay is anticipated after the dose has been diluted in normal saline, the prepared dose (properly identified) may be refrigerated at 2 °C to 8 °C for up to 24 hours. If stored under refrigerated conditions, the study drug solution should be equilibrated to room temperature (takes about 2 to 2.5 hours), and the container must be gently inverted to thoroughly mix the contents before administration. If the storage time limit is exceeded, the prepared dose solution must be discarded and the reason documented by the pharmacist in the study drug accountability records.

Elotuzumab will be administered to each subject as an IV infusion, using an automated infusion pump set at the appropriate rate according to the dose administration section (see Administration Instruction section below). The dose of elotuzumab will be calculated using the subject's predose weight on Day 1 of each cycle, and then added to 0.9% saline for infusion.

Reconstitute elotuzumab lyophilized study drug, as described in steps 1 to 5.

Step 1: For a 440 mg vial of lyophilized elotuzumab, draw 17 mL of Sterile Water for Injection (SWFI), USP into a syringe equipped with an 18-gauge or smaller needle.

Step 2: Remove the flip-top from the elotuzumab vial.

Step 3: Place the vial upright on a flat surface and, using standard aseptic techniques, insert the syringe needle into the vial through the center of the rubber stopper and deliver 17 mL (into the 20-mL vial containing 440 mg elotuzumab) SWFI, USP, into the vial. Slowly remove the syringe needle out of the vial. The final volume of the reconstituted solution is approximately 17.6 mL, which includes the volume displaced by the solid cake. The concentration of elotuzumab in the reconstituted solution is approximately 25 mg/mL.

Step 4: DO NOT SHAKE. Hold the vial upright and gently swirl the solution by rotating the vial to dissolve the lyophilized cake. Then gently invert the vial a few times in order to dissolve any powder that may be present on top of the vial or the stopper. Finally, hold the vial upright again and gently swirl the solution a few more times to dissolve any remaining particles. Avoid prolonged or vigorous agitation. DO NOT SHAKE.

Step 5: After the remaining solids are completely dissolved, allow the reconstituted solution to stand for 5 to 10 minutes.

It is acceptable to have small bubbles and/or foam around the edge of the vial. The reconstituted preparation results in a colorless to slightly yellow, clear to slightly opalescent solution containing approximately 25 mg/mL of elotuzumab.

Step 6: Once the reconstitution is completed, withdraw the calculated drug volume and further dilute with 100-500 ml of normal saline into an infusion bag (see Pharmacy Manual for details). The volume of saline or D5W can be adjusted so as not to exceed 5 ml/kg of patient weight at any given dose of elotuzumab. The resulting elotuzumab concentration must be from 1.0 mg/ml to 6.0 mg/ml. Elotuzumab solutions are compatible with polyvinyl chloride and polyolefin bags. Examples of such bags include Viaflo, MacoPharma Easyflex N, Macoflex N, B Braun Excel, and Braun Ecobag.

Drug volume will be calculated based on subject weight: For example, a subject receiving 10 mg/kg elotuzumab who weighs 80 kg on Day 1 [predose] will require 800 mg of study drug for infusion. Withdraw 32 mL of elotuzumab (25 mg/mL) from 2 vials and add to an infusion bag already containing 230 mL saline, for a total of 262 mL to be infused.

Similarly, an 80 kg subject receiving 20 mg/kg elotuzumab [predose] will require 1600 mg of study drug for infusion. Withdraw 64 mL of elotuzumab (25 mg/mL) from 4 vials and add to an infusion bag already containing 340 mL saline, for a total of 404 mL to be infused.

Use a new sterile needle for withdrawing solution from each vial.

The same vial must not be used to prepare elotuzumab for more than one subject. Used elotuzumab vials will be stored until study drug accountability has been completed by the BMS designee, and destruction or return is authorized. Used vials do not need to be refrigerated.

Note: Subjects must be premedicated as described in Section 4.3.1 prior to elotuzumab infusion.

Administration Instructions

1. Administer through a low-protein-binding 0.22 - micrometer or smaller in-line filter (placed as proximal to the subject as is practical). Prime the infusion line with study drug before starting the infusion.
2. Set the IV pump to deliver the infusion at the rate of 0.5 mL per minute (including the drug in the line). The total time of infusion will vary depending upon the maximum tolerated mL/min infusion rate as discussed above.
3. Record every time the infusion is started and stopped and the reason why the start and stop occurred.
4. Monitor the IV setup and the subject's IV site frequently during infusion, checking for the correct infusion rate and IV site infiltration.
5. Ensure that the full volume of elotuzumab is infused.
6. After elotuzumab has been infused from the line, discontinue the infusion, disconnect the IV tubing, and dispose of materials appropriately according to the facility's standard procedure.

The **first dose** of elotuzumab will be administered following premedications (described in Section 4.3.1) to each subject as an IV infusion, using an automated infusion pump set at an

initial rate of 0.5 mL per minute (30 mL/hour). Please refer to Section 4.3.2 for detailed information on the management of infusion reaction and re-initiation of infusion.

If a patient is in cycle 1, infusion rate escalation may begin at the second infusion of elotuzumab, if no infusion reaction was noted with the first IV administration. If subjects are beyond cycle 1, subjects may begin infusion rate escalation at any subsequent cycle, as long as no infusion reaction was noted for greater than 4 doses.

For those in cycle 1:

The **second dose** of elotuzumab must be initiated at an infusion rate of **3 mL** per minute if no infusion reactions were observed with the first elotuzumab infusion. If the subject does not experience an infusion reaction during the first 30 minutes of the second dose of elotuzumab, escalate the infusion rate to 4 **mL** per minute.

The **third dose** of elotuzumab must be initiated at an infusion rate of **5 mL** per minute if no infusion reactions were reported with the second elotuzumab infusion.

The **fourth and subsequent doses** of elotuzumab must be initiated at an infusion rate of **5 mL** per minute if no infusion reactions were reported.

Elotuzumab Infusion Rate (10 mg/kg)

The elotuzumab infusion rate will be increased gradually to a maximum of 5 mL/min as presented in Table 1. Table 1 represents an example starting from cycle 1; however, this can be applied to any cycle.

Table 1: Elotuzumab Infusion Rate Plan (10 mg/kg)

Infusion Rate	Duration of infusion	Volume delivered	Volume remaining
Cycle 1 Dose 1	**Total Duration: 2hrs 50min**		**262 mL***
0.5 mL/min	30 min	15 mL	247 mL
1 mL/min	30 min	30 mL	217 mL
2 mL/min	110 min	217 mL	0 mL
Cycle 1 Dose 2	**Total Duration: 1hrs 13min**		**262 mL**
3 mL/min	30 min	90 mL	172 mL
4 mL/min	43 min	172 mL	0 mL
Cycle 1 Dose 3 and 4	**Total Duration: 53min**		262 mL
5 mL/min	53 min	262 mL	0 mL
Cycle 2 +	**Total Duration: 53min**		**262 mL**
5 mL/min	53 min	262 mL	0 mL

* Volume for 80 kg subject. Total volume varies according to the subject weight.

Please note that infusion rate increase to the next higher level only if no infusion reactions encountered.

If no infusion reactions were observed during the infusion rate escalation over these four doses of elotuzumab, all following doses must commence at the maximum rate of 5 mL per minute so long as there are no infusion reactions. Escalation above 5 mL per minute is not permitted.

For subjects beyond cycle 1 who have not escalated the infusion rate:

Subjects who have not escalated elotuzumab infusion rates beyond 2 mL per minute, despite administration of more than 4 doses of elotuzumab, and who have not experienced any infusion reactions, **must** begin the rate escalation paradigm as described above. That is, a subject in cycle X day 1 of study therapy must begin the elotuzumab infusion rate escalation, aiming first for an infusion rate of 3 mL per minute as described for the **second** dose of elotuzumab above. If the subject does not experience an infusion reaction during the first 30 minutes of the second dose of elotuzumab, escalate the infusion rate to 4 mL per minute. On the next dose of elotuzumab, ie, cycle X day 15, the elotuzumab infusion rate must start at 5 mL per minute as described above for the **third dose** of elotuzumab, if no infusion reactions were noted. With the next dose of elotuzumab (ie, cycle X+1 day 1), if no infusion reactions were noted, the subject must maintain the infusion rate at 5 mL per minute as described above for the **third and subsequent doses** of elotuzumab.

For subjects beyond cycle 18 receiving elotuzumab 20 mg/kg once a month who have not escalated the infusion rate to 5 ml/min:

Elotuzumab Infusion Rate (20 mg/kg) in Cycle 19 and subsequent cycles

The elotuzumab infusion rate will be increased gradually to a maximum of 5 mL/min as presented in Table 2.

Subjects who have escalated to 5 mL/min at 10 mg/kg dose **must decrease the rate to 3 mL/min at the first infusion at 20 mg/kg.** Subjects will escalate as described below.

Table 2: Elotuzumab Infusion Rate Plan (20 mg/kg)

Infusion Rate	Duration of infusion	Volume delivered	Volume remaining
Dose 1 at 20 mg/kg	**Total Duration: 1 hrs 48.5 min**		**404 mL**
3 mL/min	30 min	90 mL	314 mL
4 mL/min	78.5 min	314 mL	0 mL
Dose 2 and 3 at 20 mg/kg	**Total Duration: 1 hr 21 min**		**404 mL**
5 mL/min	81 min	404 mL	0 mL

* Volume for 80 kg subject. Total volume varies according to the subject weight.

Please note that infusion rate increase to the next higher level only if no infusion reactions encountered.

See section 4.3.2 for management of infusion reactions.