Protocol for

Official Title of Study

A PHASE 3, MULTICENTER, RANDOMIZED, OPENLABEL STUDY TO COMPARE THE EFFICACY AND SAFETY OF POMALIDOMIDE, BORTEZOMIB AND LOW-DOSE DEXAMETHASONE VERSUS BORTEZOMIB AND LOW-DOSE DEXAMETHASONE IN SUBJECTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA

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A PHASE 3, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY TO COMPARE THE EFFICACY AND SAFETY OF POMALIDOMIDE, BORTEZOMIB AND LOW-DOSE DEXAMETHASONE VERSUS BORTEZOMIB AND LOW-DOSE DEXAMETHASONE IN SUBJECTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA

INVESTIGATIONAL PRODUCT (IP):	**Pomalidomide (CC-4047) for US; Pomalidomide (CC-4047) and Dexamethasone for Japan; Pomalidomide (CC-4047), Bortezomib, and Dexamethasone for ex-US**
PROTOCOL NUMBER:	**CC-4047-MM-007**
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SPONSOR NAME / ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{Please see appended electronic signature page.}	
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[redacted]	
Printed Name of Celgene Therapeutic Area Head and Title	
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.	

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:**_____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

PROTOCOL SUMMARY

Study Title

A Phase 3, Multicenter, Randomized, Open-label Study to Compare the Efficacy and Safety of Pomalidomide (POM), Bortezomib (BTZ) and Low-Dose Dexamethasone (LD-DEX) versus Bortezomib and Low-Dose Dexamethasone in Subjects with Relapsed or Refractory Multiple Myeloma (MM)

Indication

Relapsed or Refractory MM

Study Objectives

To compare the efficacy of POM + BTZ + LD-DEX with BTZ + LD-DEX in subjects with relapsed or refractory MM

Secondary Objectives:

To evaluate the safety and additional efficacy of POM + BTZ + LD-DEX versus BTZ + LD-DEX in subjects with relapsed or refractory MM.

Exploratory Objectives:

- To evaluate the differences in clinical benefits of POM + BTZ + LD-DEX versus BTZ + LD-DEX in subjects with relapsed or refractory MM
- To evaluate the differences in key efficacy variables of POM + BTZ + LD-DEX versus BTZ + LD-DEX within defined subgroups
- To evaluate the differences in health-related quality of life of POM + BTZ + LD-DEX versus BTZ + LD-DEX in subjects with relapsed or refractory MM
- To evaluate Minimal Residual Disease (MRD), genomic, molecular/mechanistic and immune biomarkers and their correlation to clinical outcome measures for only those subjects who give their consent (Optional)

Study Design Overview

This study is a multicenter, randomized, open-label, phase 3 study comparing the efficacy and safety of POM + BTZ + LD-DEX (Treatment Arm A) versus BTZ + LD-DEX (Treatment Arm B) in subjects with relapsed or refractory MM.

For Treatment Arm A (POM + BTZ + DEX), the dose was based on the results from the CC-4047-MM-005 (MM-005) Phase 1 dose escalation MTD study in which bortezomib was administered via IV infusion. In the MM-005 study, the maximum planned dose (MPD), POM (4 mg) + IV BTZ (1.3 mg /m^2) and DEX (20 mg subjects ≤ 75 years old/10 mg subjects > 75 years old) was reached without any DLTs. Considering an early POM single agent MTD study

(Richardson, 2013) as well as the findings in MM-005, the MPD was determined to be the optimal dose for the triple combination therapy. With the optimal dose determined, MM-007 was initiated using the MPD dose for the combination of POM + BTZ + LD-DEX (with IV BTZ).

During the conduct of the MM-005 study, subcutaneous (SQ) BTZ was approved as an alternative administration method for BTZ (23 Jan 2013). The SQ BTZ was reported to have a decreased incidence of neurotoxicity versus the IV BTZ (Velcade® Prescribing Information, 2014). To explore the SQ route of BTZ administration in combination with POM and DEX, the MM-005 protocol was amended to add a cohort of 6 subjects at the MPD/optimal dose for the combination of POM + BTZ + LD-DEX with BTZ administered via SQ injection. Based on the safety, efficacy and PK data for this SQ BTZ cohort (see Section 1.4) and general adoption in medical practice of SQ BTZ as standard of care due to decreased neurotoxicity, BTZ administration is now to be SQ for both arms in the MM-007 study (Treatment Arm A and B).

Subjects who consented to the original MM-007 protocol can continue with IV BTZ or switch to SQ BTZ at the discretion of the treating physician. Subjects randomized into MM-007 under IV BTZ treatment will not be replaced.

Approximately 544 subjects will be randomized equally (1:1 ratio) into the two treatment arms (272 subjects in each arm).

Based on the primary endpoint progression-free survival (PFS), at 2-sided significance level of 5%, with one interim analysis for futility only, an estimated total of 381 progression/death events are required to detect a 33% increase in median PFS in the POM treatment arm (Arm A; median = 12 months) compared to that in the comparator arm (Arm B; median = 9 months) with 80% power. In order to obtain PFS events from approximately 70% of the study ITT population for the final PFS analysis, a total of 544 randomized subjects are required to test the hypothesis. The interim analysis on PFS will take place when approximately 50% PFS information (191 events) has occurred. The interim results will be examined for futility only with the pre-specified type II error spending functions described in Section 10.9.

Celgene amended the protocol in Amendment 5 to perform the final PFS analysis earlier than originally planned (381 PFS events). Recently published data from a number of Phase 3 studies revealed that the PFS of the bortezomib with low-dose dexamethasone (BTZ+LD-DEX) arm on this study CC-4047-MM-007 (OPTIMISMM), that requires prior treatment with lenalidomide as per Protocol Inclusion Criteria #7 (Section 7.2), is expected to be shorter than the original OPTIMISMM protocol statistical assumption of 9 months (relevant median PFS data from Phase 3 ENDEAVOR, PANORAMA-1, and CASTOR studies ranging from 7 to 8 months) (Moreau, 2017; Palumbo, 2016; San-Miguel, 2014).

Subsequently, if the assumption for the pomalidomide, bortezomib and low-dose dexamethasone (POM+BTZ+LD-DEX) arm and other study assumptions remain unchanged, the number of PFS events required for the final analysis would be less than originally planned. The data cutoff date for the revised final PFS analysis will be October 2017, by which time approximately 320 PFS events are projected to be reached, representing an approximate 57% event rate (out of 559 randomized subjects). This would allow for 80% power to test a median PFS of 12 months in Arm A versus 8.8 months in Arm B, corresponding to an estimated hazard ratio of 0.73.

Overall survival (OS) will be tested if PFS and overall response rate (ORR) results are significant (see Section 10.10). With one planned interim analysis OS at the time of the final PFS analysis (estimated to be at approximately 50% OS information [190 deaths]), at a 2-sided significance level of 5%, a total of 379 deaths are required to detect a 33% increase in median OS in Treatment Arm A (40 months) compared with Treatment Arm B (30 months) with 75% power.

The OS assumption for the control arm (Treatment Arm B) are based on the published results of SUMMIT and APEX trials in relapsed MM treated with bortezomib (Richardson, 2003; Richardson, 2007c). Considering that LD-DEX will be given in combination with BTZ in this study (as opposed to the SUMMIT trial where LD-DEX was added later on to subjects under BTZ single agent therapy with suboptimal response) as well as published observational data of OS in patients receiving combination therapy of BTZ plus DEX (Ionita, 2009), the estimated median OS in the control arm (Treatment Arm B) using BTZ plus LD-DEX is 30 months. This is also supported by more recent data in the ENDEAVOR and PANORAMA-1 studies, where the OS ranged from 24.3 to 35.8 months (Moreau, 2017; San-Miguel, 2014).

Except for pregnancy test and urinalysis, all laboratory assessments will be performed centrally; however, tests that may result in dose interruption and/or modification should also be performed locally to allow for treatment related decisions during subject visits. All abnormal results from local laboratories used in treatment decisions or adverse event reporting must be entered into an unscheduled visit on the eCRF. An Independent Response Adjudication Committee (IRAC) will be set up for this trial to review efficacy data in a blinded manner. The IRAC will determine the tumor response to therapy and to confirm the time of disease progression (PD) (if disease progressed) at scheduled or unscheduled visits for each subject.

The safety and efficacy of the study will be monitored by an independent data monitoring committee (IDMC) who are not involved in the trial conduct. The IDMC will meet up and review unblinded trial data at pre-specified intervals throughout the trial. At time of the interim analysis, the IDMC will review the study data for futility assessment. In addition to the IDMC review, safety data will be monitored by the Celgene Medical Monitor and Safety Physician on an ongoing basis throughout the study. In the event when a significant safety issue is identified, the IDMC will be convened to make a recommendation as to the future conduct of the study.

The study will be conducted globally.

Screening

Potential study subjects will sign an informed consent prior to undergoing any study-related procedure. Subjects need to complete screening for protocol eligibility within 28 days of randomization, as outlined in Table 1, Table of Events. Subjects may have the choice to participate in an optional biomarker study conducted at selected clinical sites (where operationally and logistically feasible). If a subject chooses to participate in the biomarker study, he/she must give consent for the optional biomarker study.

Subjects must have discontinued anti-myeloma therapies at least 14 days prior to randomization (wash-out period). Subjects with myeloma-associated bone lesion may receive bisphosphonate therapy prior to study entry, unless such therapy is contraindicated.

Subjects who fail screening as a result of severe neutropenia or anemia will not be permitted to use growth factors or platelet/blood transfusion to become eligible.

Randomization

Subjects who meet all eligibility criteria will be randomized to either **Treatment Arm A** (POM + BTZ + LD-DEX) or **Treatment Arm B** (BTZ + LD-DEX) with equal probability (1:1 randomization ratio).

[redacted] The randomization procedure will be accomplished by a validated IVRS/IWRS, stratified by the following factors: 1) age (≤ 75 years old vs. > 75 years old); 2) number of prior anti-MM regimens (1 vs. >1); 3) Beta-2 microglobulin (β2M) at screening (< 3.5 mg/L vs. ≥ 3.5 mg/L - ≤ 5.5 mg/L vs. > 5.5 mg/L). A randomization authorization number is needed to initiate the IVRS/IWRS prior to subject enrollment.

Study Treatment Phase

Study treatment for each subject begins on the same day as, or within 4 days following randomization. Study visits with serial measurements of safety and efficacy will be performed as outlined in Table 1, Table of Events.

[redacted]

Tumor response, including progressive disease (PD), will be assessed according to the International Myeloma Working Group (IMWG) uniform response criteria (Durie, 2006); an exploratory assessment of response using the European Group for Blood and Marrow Transplantation (EBMT) (Bladé, 1998) response criteria will also be performed. All treatment decisions will be made by treating physicians based on response as assessed using the IMWG criteria.

The severity of AEs will be graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.0 or higher.

Thromboembolism prophylaxis during the study treatment is required for subjects in Treatment Arm A. Low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anti-coagulant will be given to all subjects assigned to Treatment Arm A as well as Treatment Arm B subjects who have a prior history of deep vein thrombosis (DVT) or pulmonary embolism (PE). At the discretion of the treating physician, other Treatment Arm B subjects may also receive antithrombotic therapy. Subjects who develop symptomatic DVT under study treatment will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method. Diagnostic algorithms will be provided in Appendix A.

Herpes Zoster Prophylaxis should be considered for all study subjects receiving bortezomib. Oral acyclovir or equivalent antiviral therapy per institutional guidelines is acceptable for herpes zoster prophylaxis.

During the study, subjects with myeloma-associated bone lesion may receive bisphosphonate therapy.

Radiation therapy to a pathological fracture site or to treat bone pain is permitted throughout the study.

The use of hematopoietic growth factors is permitted (the use of myeloid growth factors is encouraged when the absolute neutrophil count is less than 1,000/μL) at the discretion of the treating physician. Platelet and red blood cell transfusions are also permitted during the study. However, subjects who fail absolute neutrophil count (ANC), hemoglobin or platelet eligibility criteria at screening CANNOT be re-tested for the study after being treated with growth factors or platelet/blood transfusion. However, subjects who meet the ANC, hemoglobin and platelet eligibility criteria due to growth factor treatment or platelet/blood transfusion received prior to screening are acceptable and are not considered as screening failures.

Drugs known to prolong QT corrected (QTc) interval should be avoided unless deemed medically necessary. See Appendix G for link to a comprehensive list of drugs which are known to prolong QTc. A thorough QT study (CC-4047-CP-010) was conducted in healthy subjects according to the E14 Guidance to assess the potential of pomalidomide (POM) to delay cardiac re-polarization, especially as prolongation of the QT interval. The result of the QT prolongation assessment was observed to be negative, indicating a low risk of POM-associated QT prolongation.

Study Treatment Discontinuation

Subjects will continue study treatment until PD or unacceptable toxicity. An active treatment discontinuation visit should occur for all subjects at the time of permanent discontinuation from study treatment. The reason for discontinuation from study treatment will be documented in the electronic case report forms (eCRFs) for all subjects.

Progression-free Survival follow-up Phase

To ensure accuracy and completeness for the primary efficacy endpoint assessment of progression-free survival, subjects who permanently discontinued study treatment prior to PD will continue to be followed up in the PFS follow-up phase until PD. During this PFS follow-up period, efficacy assessments for response and PD per the IMWG uniform response criteria will be performed every 21 days (see Table 1, Table of Events). Subjects are not expected to start any other anti-myeloma therapy during the PFS follow-up phase prior to PD. Subjects are expected to have a visit at the time of discontinuation from the PFS follow-up period.

Long-term Follow-up Phase

All subjects will be followed in the long-term follow-up phase until death or for at least 5 years after the last subject is randomized into the study, or longer if clinically indicated (unless the follow-up is shorter due to withdrawal of consent, loss to follow-up, or death). Long-term follow-up will occur 4 times per year (every 3 months) after the 28 days post treatment discontinuation visit or PFS follow-up phase discontinuation visit, as applicable. During long-term follow-up the following information will be collected: survival, subsequent anti-myeloma regimens, date of progression and reason for progression based on the IMWG uniform response criteria, if available, for subjects who did not have PD during the study treatment or PFS follow-up period, and second primary malignancies (SPM).

Study Population

The study population comprises of relapsed or refractory MM subjects who had at least one but no more than three prior anti-myeloma regimens, and who have had received at least 2 consecutive cycles of lenalidomide treatment. Subjects who have received prior bortezomib therapy (either IV or subcutaneous) can enter the study. However, those who have received prior bortezomib therapy must not have had PD during therapy or within 60 days of their last dose of the bortezomib-containing regimen under the 1.3 mg/ m^2/dose twice weekly dosing schedule. See Section 7 of the protocol for a detailed description of the study population.

Length of Study

The study will consist of the following consecutive phases: Screening, Treatment, PFS follow-up (if applicable), and Long-term follow-up. The screening period may not exceed a 28-day window prior to start of study treatment (Cycle 1 Day 1). Subjects may continue on study treatment until PD or unacceptable toxicity. Subjects who discontinue treatment prior to PD should remain in the PFS follow-up phase of the study and be assessed for efficacy until PD. Once discontinued from the study treatment or the PFS follow-up period, subjects will enter the long-term follow-up phase and will be contacted every 3 months for at least 5 years after the last subject is randomized into the study, or longer if clinically indicated (unless the follow-up is shorter due to withdrawal of consent, loss to follow-up, or death).

Study Treatments

Pomalidomide will be provided to all sites by Celgene Corporation as an investigational product.

Investigative sites in the United States and Japan will use commercially available bortezomib (Velcade®) for this study and will dispense this drug to subjects via prescription. For investigative sites outside of the United States and Japan, bortezomib supplies will be provided by Celgene Corporation as commercial material labeled appropriately as Investigational Product (IP).

Investigative sites in the United States will use commercially available dexamethasone for this study and will dispense this drug to subjects via prescription. For investigative sites outside of the United States, dexamethasone supplies will be provided by Celgene Corporation as commercial material labeled appropriately as Investigational Product (IP).

Subjects will be randomized to Treatment Arm A or Treatment Arm B at a 1:1 ratio.

Treatment Arm A: Subjects randomized to Treatment Arm A (POM + BTZ + LD-DEX) will receive the following medications by 21-day treatment cycle:

- Oral POM 4 mg/day on Days 1 to 14 of each 21-day treatment cycle
- BTZ
  - For Cycles 1 – 8: 1.3 mg/m^2/dose on Days 1, 4, 8, and 11 of a 21-day cycle
  - For Cycles 9 onwards: 1.3 mg/m^2/dose on Days 1 and 8 of a 21-day cycle
- Oral DEX
  - For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle.

  - For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

Treatment Arm B: Subjects randomized to Treatment Arm B (BTZ + LD-DEX) will receive the following medications by 21 -day treatment cycle:

- BTZ
  - For Cycles 1 – 8: 1.3 mg/m^2/dose on Days 1, 4, 8, and 11 of a 21-day cycle
  - For Cycles 9 onwards: 1.3 mg/m^2/dose on Days 1 and 8 of a 21-day cycle
- Oral DEX
  - For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle.
  - For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

Overview of Efficacy Assessments

- Myeloma paraprotein (M-protein)
- Serum immunoglobulins
- Serum Free Light Chain
- Corrected serum calcium
- Bone marrow aspiration/biopsy
- Radiographic assessments of lytic bone lesions (skeletal survey)
- Extramedullary plasmacytoma (EMP) assessments

Overview of Safety Assessments

- Complete physical examination including vital signs
- Clinical laboratory evaluations (hematology, serum chemistry, urinalysis)
- Venous thromboembolism (VTE) monitoring
- Pregnancy testing / counseling
- Electrocardiogram (ECG)
- Concomitant medications and procedures
- AEs
- Second primary malignancies will be monitored as events of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report any second primary malignancies as serious adverse events regardless of causal relationship to study treatment (pomalidomide, bortezomib or dexamethasone), occurring at any time from the time of signing the informed consent up to and including the long-term follow-up period.

Overview of Other Assessments

- Eastern Cooperative Oncology Group (ECOG) performance status
- Cytogenetics
- Beta-2 microglobulin (β2M)
- [redacted]
- Hospital / Emergency department utilization
- Quality of Life (QoL) questionnaires (if permitted by local regulations)
  - The European Organization for Research and Treatment of Cancer QoL Questionnaire for Patients with Multiple Myeloma (EORTC QLQ-MY20) Module
  - The European Organization for Research and Treatment of Cancer QoL Questionnaire for Patients with Cancer (EORTC QLQ-C30) Module
  - The descriptive system of the EQ-5D
- Bone marrow and blood samples for Minimal Residual Disease (MRD), genomic, molecular/mechanistic and immune biomarkers at sites permitted by local regulations, where operationally and logistically feasible, and only for subjects who consent to participate in the optional biomarker study (Optional)

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1. INTRODUCTION

Multiple myeloma (MM) is a rare and incurable progressive neoplastic disease that accounts for 10% of all hematological malignancies. It was estimated in 2010 that 20,180 new cases and 10,650 deaths from the disease occurred in the United States (US) (Jemal, 2010).

Significant progress has been made in the treatment of newly diagnosed MM with different combinations of melphalan, prednisone, dexamethasone, doxorubicin, thalidomide, lenalidomide and proteasome inhibitors (bortezomib) or autologous stem cell transplant following high-dose chemotherapy in appropriate patients (National Comprehensive Cancer Network [NCCN] Clinical Practice Guidelines in Oncology for MM, 2012; Child, 2003; Fermand, 2005). In recent years, innovative therapies such as proteasome inhibitors and immunomodulators have improved the prognosis for previously treated MM subjects (Kumar, 2008). However, the disease follows a relapsing course in the majority of patients, regardless of treatment regimen or initial response to treatment. MM remains incurable using conventional treatments, with median survival duration of approximately 5 years (Richardson, 2007a). Therefore, there is a need for more effective therapeutic options for the treatment of relapsed or refractory multiple myeloma.

1.1. Treatment Options for Relapsed or Refractory Multiple Myeloma

The treatment options approved for use in relapsed and/or refractory MM currently include:

Panobinostat: Panobinostat in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent.

Lenalidomide plus dexamethasone: Lenalidomide in combination with dexamethasone for the treatment of patients with MM who have received at least one prior therapy (Revlimid Prescribing Information 2013).

Bortezomib: Bortezomib monotherapy for the treatment of patients with relapsed MM (Velcade® Prescribing Information, 2014).

Pegylated doxorubicin-liposomal plus bortezomib: Pegylated liposomal doxorubicin (PLD) in combination with bortezomib for the treatment of patients with MM who have not previously received bortezomib and have received at least one prior therapy (Velcade® Prescribing Information, 2014).

Carfilzomib: Carfilzomib for the treatment of multiple myeloma in patients who have received at least 2 prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy (Kyprolis® Prescribing Information, 2012).

Pomalidomide plus dexamethasone: Pomalidomide is a thalidomide analogue indicated, in combination with dexamethasone, for patients with multiple myeloma who have at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy (Pomalyst® / Imnovid® Prescribing Information, 2015).

Other options that may be considered for salvage therapy in MM patients include thalidomide alone or in combination with dexamethasone or other agents, lenalidomide monotherapy,

lenalidomide in combination with bortezomib and dexamethasone, or lenalidomide or bortezomib in combination with cyclophosphamide and dexamethasone (NCCN Clinical Practice Guidelines in Oncology for Multiple Myeloma, 2012).

The main considerations for choosing an appropriate treatment for relapsed MM are: risk level, prior therapy, duration of response to prior therapy, residual toxicity, age, physical condition, and whether or not the patient is a candidate for allogeneic stem cell transplantation (NCCN Clinical Practice Guidelines in Oncology for Multiple Myeloma, 2012; Kastritis, 2009).

1.2. Bortezomib in Relapsed or Refractory Multiple Myeloma

Bortezomib (Velcade®) was approved for the treatment of relapsed or refractory MM based on the results of a Phase 3 trial (APEX Trial) comparing bortezomib to high dose dexamethasone as salvage therapy. In an updated efficacy analysis of the APEX trial, the response rate was 43% with bortezomib vs. 18% for dexamethasone and the overall survival (OS) was 30 months with bortezomib vs. 23.7 months with dexamethasone (Richardson, 2007c).

The benefits of the adding dexamethasone to bortezomib therapy were shown in the SUMMIT trial in which 202 relapsed or refractory MM subjects were enrolled (Richardson, 2003). In this phase 2 study, patients received 1.3 mg/m^2 of bortezomib for up to eight cycles. In patients with a suboptimal response, oral dexamethasone (20 mg daily, on the day of and the day after bortezomib administration) was added to the regimen. Seventy-eight patients who had either stable or progressive disease (PD) while receiving bortezomib alone subsequently received dexamethasone in combination with bortezomib. Of these 78, a total of 74 patients could be evaluated for a response to this combination, and 13 of these patients (18 percent) had a minimal or partial response. In 6 of these 13 patients, the disease had previously been refractory to corticosteroid therapy. Bortezomib in combination with dexamethasone is therefore included in the NCCN clinical practice guidelines as a category 2A recommendation for salvage therapy in MM patients (NCCN Clinical Practice Guidelines in Oncology for MM, 2012).

The approval of Doxil® (doxorubicin HCl) in combination with bortezomib has led to more treatment options for relapsed or refractory MM. The approval of this regimen was based on a Phase 3 study in 646 patients showing a significant increase in median time to disease progression in Doxil plus bortezomib arm compared to bortezomib monotherapy arm (9.3 vs. 6.5 months, respectively). Starting from the 2010 NCCN clinical practice guidelines for Multiple Myeloma, this combination was recommended as superior over bortezomib monotherapy for relapsed / refractory MM. However, no data were submitted in support of the effectiveness of this combination treatment in patients who had received bortezomib previously (Orlowski, 2007).

Recently published data from a number of Phase 3 studies has revealed that the progression free survival (PFS) of the bortezomib with dexamethasone (BTZ+LD-DEX) arm on this study CC-4047-MM-007 (OPTIMISMM), that requires prior treatment with lenalidomide as per protocol Inclusion Criteria #7 (Section 7.2), is expected to be shorter than the original OPTIMISMM Protocol statistical assumption of 9 months (relevant median PFS data from Phase 3 ENDEAVOR, PANORAMA-1 and CASTOR studies ranging from 7 to 8 months) (Moreau, 2017; Palumbo, 2016; San Miguel 2014).

Subcutaneous (SQ) versus Intravenous (IV) bortezomib

The total system exposure after repeat dose administration (AUC_{last}) was shown to be similar following IV or SQ administration of BTZ. In addition, findings from an open-label, randomized, phase 3 non-inferiority study comparing the efficacy and safety of SQ versus IV administration of bortezomib supported the substitution of SQ administration for IV with a similar efficacy and safety profile and a decreased incidence of peripheral neuropathy (Velcade® Prescribing Information, 2014).

1.3. Pomalidomide (CC-4047)

Pomalidomide (CC-4047, 4-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione) is a novel immunomodulatory drug under development for the treatment of MM. Pomalidomide was first approved in the United States (US) on 08 Feb 2013 under the trade name Pomalyst®, and most recently has received full approval for the combination of pomalidomide with dexamethasone on 23 Apr 2015. Pomalidomide was approved in the European Union (EU) (Imnovid®, originally Pomalidomide Celgene®) on 05 Aug 2013 through the centralized authorization procedure. Pomalidomide shares a number of the beneficial pharmacologic properties of thalidomide and lenalidomide. An in vitro model of anti-tumor necrosis factor (TNF) activity has shown that pomalidomide has an IC_{50} of approximately 0.013 µM (13 nM) against TNF produced by lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells (PBMC). Thalidomide and lenalidomide, by comparison, have an IC_{50} of ~194 µM and 0.10 µM (100 nM), respectively (Corral, 1999; Muller, 1999). In LPS-stimulated human whole blood, IC_{50} for pomalidomide is 0.025 µM (25 nM) (Muller, 1999). In addition, pomalidomide has demonstrated a 10-fold higher potency for T cell co-stimulation than lenalidomide (Corral 1999, Teo 2005). Pomalidomide also augmented the activity of natural killer (NK) cells and enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) of targeted tumor cells in combination with therapeutic antibodies to tumor-specific surface antigens (Hayashi, 2005; Hernandez-Ilizaturri, 2005). Moreover, pomalidomide is also a potent inhibitor of the proliferation of MM cell lines in vitro. Concentrations of 2.73 to 27.3 ng/mL (0.01 to 0.1 µM) achieved a 50% inhibition of MM.1S and Hs Sultan cell proliferation. In contrast, at concentrations of 25.8 µg/mL (100 µM), thalidomide inhibited the proliferation of MM.1S and Hs Sultan cells by only 15% and 20%, respectively. Pomalidomide is also more potent than thalidomide or lenalidomide in inducing G1 growth arrest and apoptosis in MM cell lines and in patient MM cells that are resistant to melphalan, doxorubicin, and dexamethasone as well as in enhancing the anti-MM activity of dexamethasone (Hideshima, 2000). However, pomalidomide does not inhibit the proliferation of normal B cells but rather protects them from apoptosis, suggesting an additive property of this compound in helping the repopulation of the normal blood cells (Verhelle, 2007).

Of potential relevance to the refractory MM setting, pomalidomide appears to retain anti-proliferative activity against H929 and KMS-12-BM MM cells that have increased resistance to acute lenalidomide treatment following chronic exposure to lenalidomide (Adams, 2009; Rychak, 2011). Pomalidomide and dexamethasone were also synergistic at inhibition of cell proliferation in lenalidomide-resistant cell lines. Preliminary results from an in vitro experiment performed by the Celgene Research group (Adams, 2009; Rychak, 2011) demonstrate that MM cells treated long-term with lenalidomide plus dexamethasone and with pomalidomide plus

dexamethasone became resistant to lenalidomide/dexamethasone but retained their sensitivity to pomalidomide/dexamethasone. This suggests that the combination of pomalidomide plus dexamethasone may be useful in the treatment of MM that is refractory to lenalidomide plus dexamethasone. Experience with Pomalidomide in Relapsed and/or Refractory MM

The clinical experience with pomalidomide in relapsed and/or refractory MM is limited to 2 Celgene-sponsored trials and 2 investigator-initiated trials.

Celgene Phase 1b Study (CDC-407-00-001 / CC-4047-MM-001; Completed): This was a phase 1b single-center, ascending dose (1, 2, 5, and 10 mg), open-label study to identify the maximum tolerated dose (MTD) and evaluate the safety and efficacy of pomalidomide given continuously (cohort 1; Schey, 2004) or on alternate days (cohort 2; Streetly, 2008) in 45 subjects with MM who were considered refractory to treatment after at least two cycles of treatment or who relapsed after previous treatment. The MTD was 2 mg continuously and 5 mg on alternate days; the most common dose limiting toxicity (DLT) was grade 4 neutropenia. The most common AEs were neutropenia, thrombocytopenia, pharyngitis, cough, dyspnea, and hypoesthesia. Overall, 23 (51%) of 45 subjects had PR or better, including 6 CR and 12 VGPR. In cohort 1, the progression free survival (PFS) was 9.75 months and OS was 22.5 months; in cohort 2, the PFS was 10.5 months and OS was 35.9 months.

Celgene Phase 1b/2 Study (CC-4047-MM-002; Enrollment completed): This was a phase 1b/2 multicenter, randomized, open-label, dose escalation (2, 3, 4, and 5 mg) study to evaluate the MTD of pomalidomide alone (Phase 1) and the safety and efficacy of pomalidomide alone using a cyclic regimen (21 of 28 days) and in combination with low-dose dexamethasone (Phase 2) using a cyclic regimen (21 of 28 days) in subjects with relapsed and refractory MM who had received ≥ 2 prior anti-MM regimens. All subjects must have received prior treatment that included lenalidomide and bortezomib. In the phase 1b segment of the study, 38 subjects were enrolled. The MTD was 4 mg which was the dose selected for the phase 2 part of the study. The safety profile was similar across cohorts except for grade 4 neutropenia, which was the DLT and was experienced at the highest rate in the 5 mg cohort. A total of 221 subjects were enrolled in phase 2 (POM+LD-DEX n = 113; POM n = 108); 219 received ≥ 1 cycle of study treatment and 191 subjects were evaluable for response. Baseline characteristics were comparable between the two arms with a median of 5 (range 2–13) prior therapies in both arms; 74% of subjects in POM+LD-DEX and 76% of subjects in POM alone had prior autologous stem-cell transplantation (ASCT). The remaining subjects were elderly (aged > 75 yrs) or ineligible for ASCT; all subjects were exposed to corticosteroids and 84% in the POM+LD-DEX and 95% in POM alone arms were exposed to alkylators. Subjects were refractory to LEN (POM+LD-DEX 77% and POM alone 79%), BTZ (73% and 69%), or both drugs (61% and 59%). Among subjects who were randomized to receive POM alone, 61 (56%) subsequently went on to receive POM+LD-DEX due to progressive disease (PD) per protocol. A median of 5 (range 1–17) treatment cycles were received by subjects in both arms. Median treatment duration was 5.0 mos. Response of ≥ PR was seen in 34% of subjects in the POM+LD-DEX arm and 13% in the POM alone arm, including 1% complete response (CR) in each arm; ≥ MR was 45% vs. 29%, respectively. Median DOR was 7.7 months with POM+LD-DEX and 8.3 months with POM alone, and median PFS was 4.6 and 2.6 months, respectively. Median OS was comparable for both arms (14.4 and 13.6 months). Results from independent adjudication were similar, with ≥ PR in 30% of subjects in the POM+LD-DEX arm and 9% in the POM alone arm, including 1% and 0% CR, respectively, in each arm. ≥ MR was achieved with POM+LD-DEX in 45% and

with POM alone in 25%; PFS was 3.8 and 2.5 months, respectively. In the subgroup of subjects refractory to both lenalidomide and bortezomib, 30% and 16% of subjects treated with POM+LD-DEX or POM alone, respectively, achieved ≥ PR; ≥ MR was 45% and 30%, respectively. Median PFS was 3.8 months for POM+LD-DEX and 2.0 months for POM alone; median OS showed a similar trend (13.5 and 10.8 months, respectively). The main reason for treatment discontinuation was PD in both arms (POM+LD-DEX 51%; POM alone 44%); discontinuations due to adverse events (AEs) were 7% and 12%, respectively. Grade 3/4 AEs in POM+LD-DEX vs. POM alone, respectively, were: neutropenia 38% and 47%; febrile neutropenia 2% and 2%; thrombocytopenia 19% and 21%; anemia 21% and 17%; pneumonia 19% and 8%; and fatigue 10% and 8%. All grades of peripheral neuropathy, deep vein thrombosis, and renal failure occurred in 7% and 10%, 2% and 1%, and 2% and 1% of subjects for POM+LD-DEX vs. POM alone, respectively (Richardson, 2011a).

Investigator Initiated Phase 2 Study at the Mayo Clinic (PO-MM-PI-0010; Enrollment completed): This is a phase 2 open-label study of pomalidomide (2 mg continuous) plus low-dose dexamethasone (40 mg/day on days 1, 8, 15, and 22) in subjects with relapsed or refractory MM who had received 1-3 prior regimens (Lacy, 2009a). A total of 60 subjects were initially enrolled into this study. Thirty-eight (63%) of the 60 subjects had confirmed response including 3 CR and 17 VGPR. Responses were seen in 8 of 12 (66.7%) lenalidomide-refractory subjects, 6 of 16 (37%) thalidomide-refractory subjects, and 6 of 10 (60%) bortezomib refractory subjects. The most common Grade 3/4 hematological toxicity was neutropenia, and the most common non-hematological Grade 3/4 toxicities were fatigue and pneumonia.

Since responses were observed in some patients who were refractory to lenalidomide in the initial cohort of 60 subjects, an additional cohort of 34 subjects, who were refractory to prior lenalidomide therapy, was enrolled from November 2008 to April 2009. The overall response rate (≥ PR) was 32% for this cohort of 34 subjects. The most common Grade 3/4 hematologic toxicity was neutropenia (29%) and the most common Grade 3/4 non-hematologic toxicity was fatigue (9%), which was consistent with that observed in the initial cohort of 60 subjects (Lacy, 2010b).

Based on experience of Richardson, et al (Richardson, 2009a) where the MTD of pomalidomide was determined to be 4 mg, a phase 2 study was initiated by Lacy, et al to compare the two different dosing regimens in MM subjects who were refractory to both lenalidomide and bortezomib. Pomalidomide was given orally 2 mg/day or 4 mg/day, on Days 1 to 28 of a 28-day cycle, with dexamethasone 40 mg daily on Days 1, 8, 15 and 22. A total of 70 subjects were enrolled (35 in the 2 mg cohort and 35 in the 4 mg cohort). The most common Grade 3/4 hematologic toxicity was neutropenia, and the most common non-hematologic toxicity was fatigue. The overall response rate (≥ PR) was 25% and 29% for the 2 mg and 4 mg cohorts, respectively (Lacy, 2010c).

Investigator Initiated Phase 2 Study (PO-MM-PI-0024; Enrollment completed): This is a phase 2, multicenter, randomized, open-label study of pomalidomide plus dexamethasone in subjects with relapsed and refractory MM who have received bortezomib and lenalidomide, conducted by Intergroupe Français du Myelome (IFM). Subjects received a 4 mg dose of pomalidomide, given either in a continuous (28-day) or a cyclic (21-day out of 28-day cycles) regimen in combination with low-dose dexamethasone. The primary endpoint is the response rate, and the secondary endpoints are safety, time to response, time to disease progression, and

OS. Eighty-four subjects were enrolled into this study, 43 in the 4 mg 21/28 days arm (Cohort A) and 41 in the 4 mg 28/28 days arm (Cohort B). At the cut-off of 01 Mar 2011, overall response rate (ORR) was 34.9% in Cohort A and 34.1% in Cohort B, including 4.7% and 7.3% ≥VGPR, respectively. Overall, 40 (47.6%) subjects had stable disease (including minor response) and 3 subjects reached CR. The median PFS was 6.3 (4.1-9.1) months in either arm, and the median duration of response was 11.4 (3.7-13.6) months and 7.9 (4.0- not reached) months in Cohort A and in Cohort B, respectively. The median PFS was 4.2 (3.3-6.9) months for subjects with stable disease (SD) as compared to 12.6 (9.9-14.8) months in subjects that had a response. The primary toxicity was myelosuppression and was similar in both treatment arms (Leleu, 2011a).

The results of studies conducted thus far indicate that pomalidomide has activity in patients with relapsed and/or refractory MM, including patients who are refractory to lenalidomide and bortezomib. Confirmed response rates range between 30% and 60% at pomalidomide doses of between 2 and 4 mg/day in combination with dexamethasone. Notably, pomalidomide produces responses in subjects who are refractory to lenalidomide, another IMiDs® compound, aligning with the non-clinical results observed in lenalidomide-resistant cells (Adams, 2009; Rychak, 2011). The most common hematological toxicity experienced by these subjects is neutropenia (non-febrile), which can be managed by dose reductions or interruptions. The most common non-hematological toxicities are fatigue and pneumonia.

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of pomalidomide.

1.4. Experience with IMiDs® in Combination with Bortezomib in Relapsed and/or Refractory Multiple Myeloma

1.4.1. Pre-clinical

Preclinical studies have shown that both thalidomide and lenalidomide potentiate the activity of bortezomib in combination of dexamethasone (Mitsiades, 2002; Hideshima, 2000). Lenalidomide and dexamethasone have been shown to trigger myeloma cell apoptosis via caspase-8 and caspase-9, respectively. Bortezomib can activate both of these pathways and also can counteract the inhibitory effect of nuclear factor–kappa B (NF- κB) on the antimyeloma activity of dexamethasone. These molecular events potentiate the induction of a dual caspase-8 and caspase-9–mediated apoptotic cascade with poly(ADP-ribose) polymerase (PARP) cleavage, leading to enhanced antimyeloma activity.

1.4.2. Clinical

1.4.2.1. Lenalidomide and Bortezomib

The combination of an immune modulator (lenalidomide) with bortezomib, has shown promising efficacy as frontline and salvage treatment in MM patients. As frontline therapy, the combination of lenalidomide (25 mg), bortezomib (1.3 mg/m^2), and low-dose dexamethasone generated high response in a phase 1/2 study (Richardson, 2010c). This combination has also been shown to be well-tolerated and active in heavily pretreated relapsed / refractory MM

patients, including patients with prior treatment with lenalidomide, bortezomib, and/or thalidomide, and with prior stem cell transplantation (Richardson 2009a). In the phase I, dose-escalation study in relapsed/refractory MM, patients received lenalidomide on Days 1 through 14 and bortezomib on Days 1, 4, 8, and 11 of 21-day cycles. Dexamethasone was added for PD after two cycles. Thirty-eight patients were enrolled across 6 dose cohorts. The MTD was lenalidomide 15 mg/day plus bortezomib 1 mg/m^2/dose. Dose-limiting toxicities (n = 1 for each) were Grade 3 hyponatremia and herpes zoster reactivation, and Grade 4 neutropenia. The most common treatment-related, Grades 3 to 4 toxicities included reversible neutropenia, thrombocytopenia, anemia, and leukopenia. Of the 36 efficacy evaluable patients, 61% achieved ≥ MR. Of the 18 patients who had dexamethasone added, 83% achieved ≥ SD. Based on the promising results in the Phase 1 study, a Phase 2 study of lenalidomide, bortezomib, and dexamethasone in relapsed / refractory subjects was initiated. The updated efficacy and safety data for after more than 2 years of follow-up for the Phase 2 study were reported at the ASH 2010 annual meeting (Richardson, 2010). Sixty-four subjects were treated in the study, 78% achieved ≥ MR, 64% achieved ≥ PR, and 25% achieved CR / near CR. The most common toxicities were peripheral neuropathy (64%), fatigue (48%), neutropenia (30%) and thrombocytopenia (22%).

1.4.2.2. Pomalidomide With Bortezomib

In the Celgene-sponsored CC4047-MM-005 (MM-005) study, the dose escalation to determine the dose for the combination of POM+BTZ+DEX was performed using intravenous (IV) BTZ, as only the IV BTZ formulation was approved at the time the trial was initiated. In the first 4 cohorts of MM-005, the POM dose was escalated from 1 mg to 4 mg with the IV BTZ at 1 mg/m^2, and in the last dose-escalation cohort the POM dose was 4 mg with IV BTZ at 1.3 mg/m^2. An additional 7 subjects were enrolled into an expansion cohort to further confirm the safety and preliminary efficacy of the 4 mg POM + 1.3 mg/m^2 IV BTZ + LD-DEX dose. The combination of POM+ IV BTZ+DEX was generally well tolerated in this RRMM population which had progressed on or within 60 days after their last lenalidomide therapy and had prior proteasome inhibitor exposure. There were no DLTs in the first cycle and no discontinuations due to treatment-related AEs. The most common grade 3/4 toxicities were neutropenia (36%) and thrombocytopenia (27%). Promising activity in this population was also shown with an ORR of 71% and 38% ≥ VGPR (Richardson, 2013a).

Due to the approval of SQ BTZ with safety data showing a decreased incidence of peripheral neuropathy compared to IV BTZ (Velcade® Prescribing Information, 2014), the MM-005 protocol was amended in April 2013 to include an additional cohort of 6 subjects to explore the combination of 4 mg POM + 1.3 mg/m^2 BTZ + LD-DEX with BTZ administered subcutaneously (SQ). As of January 2014, all 6 subjects have been enrolled in the SQ BTZ cohort and have completed at least 3 cycles on study treatment. There were no DLTs during the first cycle and no discontinuations due to treatment-related toxicities. Only one subject discontinued after Cycle 3 due to non-treatment related cardiac arrest. The following Grade 3 toxicities were reported to in 1 subject each: insomnia, memory impairment, asthenia, fatigue, blood phosphorus decreased, nephrolithiasis, blood creatine phosphokinase increased. No Grade 4 toxicities have been reported. Currently, the ORR is 67% (1 CR, 2 VGPR, 1 PR, 2 SD) (data on file at Celgene).

2. STUDY OBJECTIVES

2.1. Primary Objectives

To compare the efficacy of POM + BTZ + LD-DEX with BTZ + LD-DEX in subjects with relapsed or refractory MM

2.2. Secondary Objectives

To evaluate the safety and additional efficacy of POM + BTZ + LD-DEX versus BTZ + LD-DEX in subjects with relapsed or refractory MM.

2.3. Exploratory Objectives

- To evaluate the differences in clinical benefits of POM + BTZ + LD-DEX versus BTZ + LD-DEX in subjects with relapsed or refractory MM
- To evaluate the differences in key efficacy variables of POM + BTZ + LD-DEX versus BTZ + LD-DEX within defined subgroups
- To evaluate the differences in health-related quality of life of POM + BTZ + LD-DEX versus BTZ + LD-DEX in subjects with relapsed or refractory MM
- To evaluate Minimal Residual Disease (MRD), genomic, molecular/mechanistic and immune biomarkers and their correlation to clinical outcome measures for only those subjects who give their consent (Optional)

Data from exploratory objectives may not be included in the Clinical Study Report, but will be reported in a separate biomarker analysis report at the completion of the study.

3. STUDY ENDPOINTS

3.1. Primary Endpoint

- Progression-Free Survival (PFS)

3.2. Secondary Endpoints

- Overall Survival (OS)
- Safety (type, frequency, seriousness and severity of AEs, and relationship of AEs to study drug or comparator)
- Overall response rate (ORR) (using the International Myeloma Working Group Uniform [IMWG] response criteria)
- Duration of response

3.3. Exploratory Endpoints

- ORR (using the European Group for Blood and Marrow Transplantation [EBMT] criteria)
- Time to response
- Time to progression (TTP)
- Efficacy analysis in subgroups
- Progression-free survival after next-line therapy (PFS2)
- [redacted]
- Clinical benefits (improvement in hemoglobin value, improvement in renal function, improvement of ECOG performance status, improvement in hypercalcaemia, improvement in non-myeloma immunoglobulins)
- The European Organization for Research and Treatment of Cancer QoL Questionnaire for Patients with Multiple Myeloma (EORTC QLQ-MY20) Module, the Cancer QoL Questionnaire for Patients with Cancer (EORTC QLQ-C30) Module, and the descriptive system of the EQ-5D
- Minimal Residual Disease (MRD), genomic, molecular/mechanistic and immune biomarkers for only those subjects who give their consent (Optional)

4. OVERALL STUDY DESIGN

4.1. Study Design

This study is a multicenter, randomized, open-label, phase 3 study comparing the efficacy and safety of POM + BTZ + LD-DEX (Treatment Arm A) versus BTZ + LD-DEX (Treatment Arm B) in subjects with relapsed or refractory MM.

For Treatment Arm A (POM + BTZ + DEX), the dose was based on the results from the CC-4047-MM-005 (MM-005) Phase 1 dose escalation MTD study in which bortezomib was administered via IV infusion. In the MM-005 study, the maximum planned dose (MPD), POM (4 mg) + IV BTZ (1.3 mg /m^2) and DEX (20 mg subjects ≤ 75 years old/10 mg subjects > 75 years old) was reached without any DLTs. Considering an early POM single agent MTD study (Richardson, 2013) as well as the findings in MM-005, the MPD was determined to be the optimal dose for the triple combination therapy. With the optimal dose determined, MM-007 was initiated using the MPD dose for the combination of POM + BTZ + LD-DEX (with IV BTZ).

During the conduct of the MM-005 study, subcutaneous (SQ) BTZ was approved as an alternative administration method for BTZ (23 Jan 2013). The SQ BTZ was reported to have a decreased incidence of neurotoxicity versus the IV BTZ (Velcade® Prescribing Information, 2014). To explore the SQ route of BTZ administration in combination with POM and DEX, the MM-005 protocol was amended to add a cohort of 6 subjects at the MPD/optimal dose for the combination of POM + BTZ + LD-DEX with BTZ administered via SQ injection. Based on the safety, efficacy and PK data for this SQ BTZ cohort (see Section 1.4) and general adoption in medical practice of SQ BTZ as standard of care due to decreased neurotoxicity, BTZ administration is now to be SQ for both arms in the MM-007 study (Treatment Arm A and B).

Subjects consented to the original MM-007 protocol can continue with IV BTZ or switch to SQ BTZ at the discretion of the treating physician. Subjects randomized into MM-007 under IV BTZ treatment will not be replaced.

Approximately 544 subjects will be randomized equally (1:1 ratio) into the two treatment arms (272 subjects in each arm).

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

The safety and efficacy of the study will be monitored by an independent data monitoring committee (IDMC) who are not involved in the trial conduct. The IDMC will meet up and review unblinded trial data at pre-specified intervals throughout the trial. At the time of the interim analysis, the IDMC will review the study data for futility assessment. In addition to the IDMC review, safety data will be monitored by the Celgene Medical Monitor and Safety Physician on an ongoing basis throughout the study. In the event when a significant safety issue is identified, the IDMC will be convened to make a recommendation as to the future conduct of the study.

The study will be conducted in sites globally.

4.2. Study Design Rationale

Randomization

Randomization is recognized as an appropriate means to minimize bias in subject selection for efficacy and safety assessments in clinical trials of 2 or more treatment groups. The study will utilize a centralized randomization procedure that will be accomplished by a validated interactive voice and web response system (IVRS/IWRS).

Stratification

To minimize potential imbalances between treatment groups in subject characteristics that may impact on study outcomes, randomization will be stratified by the following baseline factors: 1) age (≤ 75 years old vs. > 75 years old); 2) number of prior regimens of anti-MM therapies (1 vs. >1); 3) β2M at screening (< 3.5 mg/L vs. ≥ 3.5 mg/L - ≤ 5.5 mg/L vs. > 5.5 mg/L).

Multicenter

This study will be conducted in sites globally. The multicenter nature of the study provides reassurance to the generalizability of the study results.

Blinding

This is an open-label study. The study center staff and the enrolled subjects will not be blinded for treatment assignment. To objectively assess efficacy outcomes, an IRAC will be set up to review all efficacy data in a blinded manner. Any review of aggregate study data by Celgene personnel will also be performed in a blinded manner.

Study population

The study population includes relapsed or refractory MM subjects with at least one but no more than three prior anti-myeloma treatment regimens. APEX Trial, a Phase 3 trial that led to the approval of BTZ (Velcade®) for the treatment of relapsed or refractory MM, also included a similar subject population with 1 to 3 prior anti-MM therapies. All subjects must have been exposed to at least 2 consecutive cycles of a lenalidomide-containing prior anti-myeloma therapy. Subject who have received bortezomib-containing prior anti-myeloma therapy may be included. However, as subjects may be receiving BTZ+LD-DEX treatment (Treatment Arm B), they must not have had PD during therapy or within 60 days of the last dose of bortezomib-containing therapy under the 1.3 mg/m^2/dose twice weekly dosing schedule.

Comparator arm (bortezomib + low-dose dexamethasone)

Bortezomib (Velcade®) was approved for the treatment of relapsed or refractory MM based on the results of a phase 3 trial (APEX Trial) comparing bortezomib to high dose dexamethasone as salvage therapy (Richardson, 2005; Richardson, 2007). The addition of dexamethasone to bortezomib therapy was shown to add treatment benefit in the phase 2 SUMMIT Trial (Richardson, 2003; Richardson, 2006a). In a recent retrospective analysis, salvage therapy using dexamethasone in combination with bortezomib have demonstrated respectable PFS and OS outcomes in the MM patients received at least one prior therapy (Ionita, 2009).

In the recent update of NCCN Clinical Practice Guidelines in Oncology for MM, single agent bortezomib and bortezomib plus dexamethasone are Category 1 and Category 2A recommendations for MM salvage therapy, respectively (NCCN Clinical Practice Guidelines in

Oncology for MM, 2012 v1). Considering the clinical evidence of bortezomib, and recent data of bortezomib plus dexamethasone, a treatment regimen of bortezomib in combination with low-dose dexamethasone is consistent with the current standard of care in this previously treated MM patient population.

Therefore, the choice of therapy for the comparator arm in this study will be using bortezomib plus low-dose dexamethasone for this relapsed or refractory multiple myeloma (RRMM) population.

Treatment arm (pomalidomide + bortezomib + low-dose dexamethasone)

Pre-clinical data have shown synergistic anti-myeloma activity between thalidomide/ lenalidomide and bortezomib (Mitsiades, 2002; Hideshima, 2000).

The tolerability and promising activity of the combination of lenalidomide (an immunomodulator) and bortezomib (a proteasome-inhibitor) and dexamethasone have also been shown promising results in both the front-line and relapsed/refractory MM setting from Phase 1 and Phase 2 clinical studies (Richardson 2009a; Richardson 2010; Richardson 2010c).

Pomalidomide is a potent immunomodulatory drug in the same class as lenalidomide / thalidomide and has shown anti-myeloma activity in relapsed/refractory MM patients as a single agent and in combination with low-dose dexamethasone (see Section 1.3).

The results of clinical studies conducted thus far indicated that pomalidomide has activity in patients with relapsed/refractory MM, including patients whose disease has progressed after treatment with lenalidomide, bortezomib, or both. Confirmed overall response rate reached 47% in pomalidomide treated patients even at a dose of 2 mg/day (Lacy, 2010c). Notably, pomalidomide produces respectable response rates in subjects who are refractory to lenalidomide, or both lenalidomide and bortezomib, aligning with the non-clinical results observed in lenalidomide-resistant cells (Adams, 2009).

Based on the pre-clinical and clinical data, the addition of pomalidomide to bortezomib plus low-dose dexamethasone could be a promising combination regimen in relapsed/refractory MM, and therefore, is chosen to be further investigated in this Phase 3 confirmatory trial.

Treatment duration

In clinical studies where novo agents were investigated in subjects with relapsed or refractory malignant diseases, it is a common practice to continue investigational therapy until PD or development of unacceptable toxicity. Subjects in this trial will receive study treatment until PD or unacceptable toxicity. Subjects who discontinued study treatment prior to PD will be followed until PD. All subjects will be followed up for survival, subsequent anti-myeloma therapies, and second primary malignancies for at least 5 years after the last subject is randomized into the study or longer if clinically indicated (unless the follow-up is shorter due to withdrawal of consent, loss to follow-up, or death).

Dose

For Treatment Arm A (POM + BTZ + DEX), the dose was based on the results from the CC-4047-MM-005 (MM-005) Phase 1 dose escalation MTD study in which bortezomib was administered via IV infusion. In the MM-005 study, the MPD, POM (4 mg) + IV BTZ (1.3 mg /m^2) and DEX (20 mg subjects ≤ 75 years old/10 mg subjects > 75 years old) was reached

without any DLTs. Considering an early POM single agent MTD study (Richardson 2013) as well as the findings in MM-005, the MPD was determined to be the optimal dose for the triple combination therapy. With the optimal dose determined, MM-007 was initiated using the MPD dose for the combination of POM + BTZ + LD-DEX (with IV BTZ).

During the conduct of the MM-005 study, subcutaneous (SQ) BTZ was approved as an alternative administration method for BTZ (23 Jan 2013). The SQ BTZ was reported to have a decreased incidence of neurotoxicity versus the IV BTZ (Velcade® Prescribing Information, 2014). To explore the SQ route of BTZ administration in combination with POM and DEX, the MM-005 protocol was amended to add an additional cohort of 6 subjects at the MPD/optimal dose for the combination of POM + BTZ + LD-DEX with BTZ administered via SQ injection. Based on the safety, efficacy and PK data for this SQ BTZ cohort (see Section 1.4) and general adoption in medical practice of SQ BTZ as standard of care due to decreased neurotoxicity, BTZ administration is now changed to SQ for both arms in the MM-007 study (Treatment Arm A and B).

For Treatment Arm B, the dose of BTZ will be the approved dose and schedule for relapsed or refractory MM (Velcade® Prescribing Information, 2014).

Subjects consented to the original MM-007 protocol can continue with IV BTZ or switch to SQ BTZ at the discretion of the treating physician. Subjects randomized into MM-007 under IV BTZ treatment will not be replaced.

The DEX dose will be the same in both treatment arms.

Efficacy

Tumor response, including progressive disease (PD), will be assessed according to the IMWG uniform response criteria (Durie, 2006); an exploratory assessment of response using the EBMT (Bladé, 1998) response criteria will also be performed. All treatment decisions will be made by the treating physicians based on response as assessed using the IMWG criteria.

An IRAC will conduct blinded assessment for tumor response (including assessment of SD and of PD) incrementally during the study. The IRAC adjudicated response data will be used for the efficacy analysis of the study in all interim and final study reports.

To ensure consistency across centers, tumor response assessments will be based on lab reports from central laboratories in this study.

Exploratory Biomarkers

The following assessments will be explored in subjects at selected clinical sites (where operationally and logistically feasible) who consent to participate in the optional exploratory biomarker study.

MRD and Clonal Heterogeneity

The assessment of tumor response to therapy in MM has long been based on serum and/or urine electrophoresis and serum/urine immunofixations. With recent therapies, the CR rates have increased dramatically. Currently, the most recent results using combination therapies in relapsed MM patients are showing CR rates from 30 to 50%. Many patients are expected to reach deeper response than CR. Assessment of Minimal Residual Disease would allow us to understand how the combination therapy affects the clinical outcome in the patients enrolled in

this study. The second aspect of interest for us is to explore how disease clones evolve within the patients. By using Next-generation Sequencing-based tests, we will investigate the prevalence and progression of clonal heterogeneity in the patients. Finally, we will compare two separate MRD measurement tests and determine their sensitivity and specificity.

Mechanistic Biomarkers

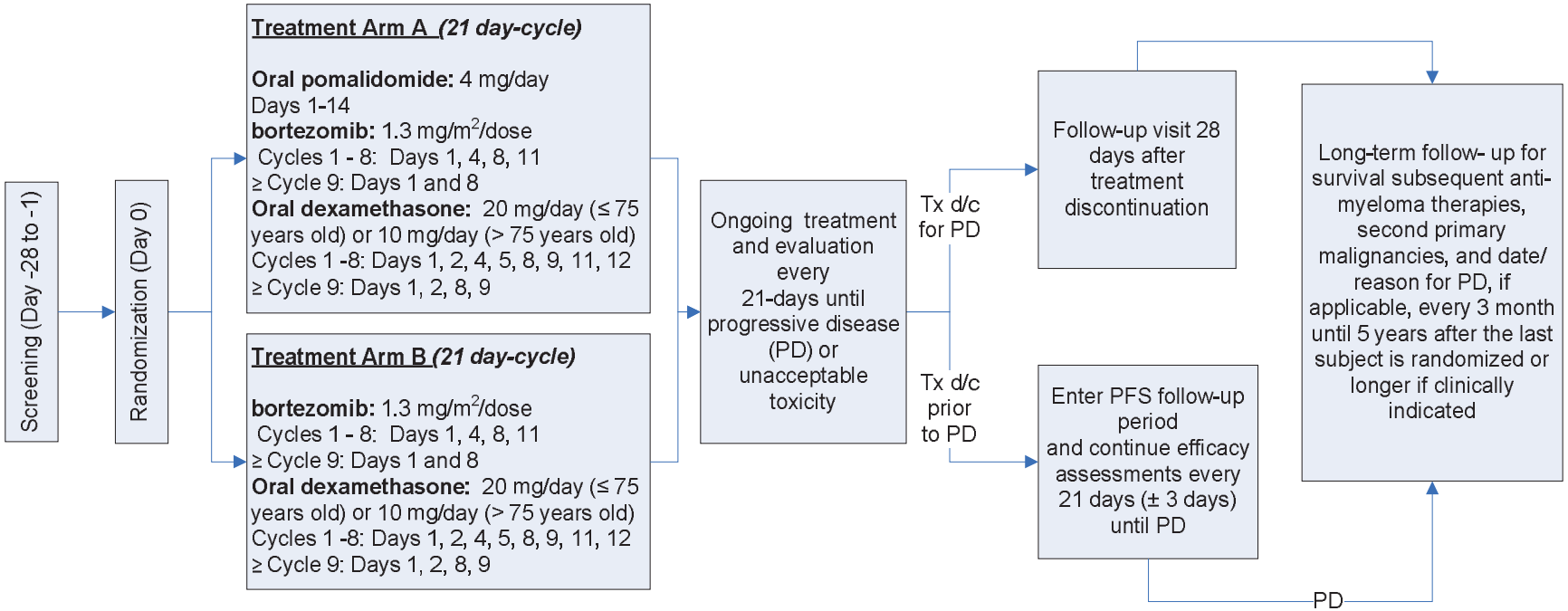
Recent research on the mechanism of action of lenalidomide, pomalidomide and thalidomide suggest that in tumor cells and T cells, cereblon, a component of E3 ubiquitin ligase complexes, is a target for binding by these compounds. These studies showed that the loss of cereblon (CRBN) or a binding partner, such as DDB1, decreases or eliminates the anti-tumor and immunomodulatory activity of lenalidomide and pomalidomide respectively (Ito, 2010; Zhu, 2011; Lopez-Girona, 2012). A number of recent studies have reported correlation between baseline (pre-treatment level of cereblon measured by gene expression or by immunohistochemical methods) to clinical outcomes in subjects treated with regimens containing lenalidomide, pomalidomide or thalidomide. These studies have not used validated assays for the measurement of cereblon by either method. In addition, the measurement of cereblon (and other potential biomarkers) in the maintenance setting is an open scientific question. Thus, we would like to use validated assays for both gene expression and immunohistochemical methods and measure baseline and on treatment cereblon levels to investigate whether there is any potential correlation of cereblon level to clinical outcomes. Recently, Aiolos and Ikaros have been identified as two substrates of CRBN. Together with CRBN, assessment of these proteins can also help us understand mechanistic as well as diagnostic aspect of the IMiD-based therapies.

In some subjects, we will also quantify subsets of immune cells and may assay their functions from whole blood samples (at baseline and during treatment) to explore whether and how during therapy, immune functions are modulated by the two arms of therapy.

Genomic Biomarkers

Genomic translocations, mutations and chromosomal copy number alterations define myeloma at diagnosis and its natural history of progression. Therefore, understanding the molecular events through genomic analysis would provide us with a deeper understanding of disease biology and its interaction with therapeutic interventions. In this study we will employ multiple techniques to understand how the myeloma genomic and epigenomic alternations contribute to clinical outcomes following the therapies.

Figure 1: Study Schema



4.3. Study Duration

Screening

Potential study subjects will sign an informed consent prior to undergoing any study-related procedure. Subjects need to complete screening for protocol eligibility within 28 days of randomization, as outlined in Table 1, Table of Events.

Subjects must have discontinued anti-myeloma therapies at least 14 days prior to randomization (wash-out period).

Subjects with myeloma-associated bone lesion may receive bisphosphonate therapy prior to study entry, unless such therapy is contraindicated.

Subjects who failed screening as a result of neutropenia or anemia will not be permitted to use growth factors to become eligible.

Subjects who failed screening will be permitted to be rescreened for eligibility.

Randomization

Subjects who meet all eligibility criteria will be randomized to either **Treatment Arm A** (POM + BTZ + LD-DEX) or **Treatment Arm B** (BTZ + LD-DEX) with equal probability (1:1 randomization ratio).

[redacted] The central randomization procedure will be accomplished by a validated IVRS/IWRS, stratified by the following baseline factors: 1) age (≤ 75 years old vs. > 75 years old); 2) number of prior anti-myeloma regimens (1 vs. >1); 3) β2M at screening (< 3.5 mg/L vs. ≥ 3.5 mg/L - ≤ 5.5 mg/L vs. > 5.5 mg/L).

Study Treatment Phase

Study treatment for each subject begins on the same day as or within 4 days following randomization. Study visits with serial measurements of safety and efficacy will be performed as outlined in Table 1, Table of Events.

[redacted]

Tumor response, including progressive disease (PD), will be assessed according to the IMWG uniform response criteria (Durie, 2006); an exploratory assessment of response using the EBMT (Bladé, 1998) response criteria will also be performed. All treatment decisions will be made by treating physicians based on response as assessed using the IMWG criteria.

The severity of AEs will be graded according to the NCI CTCAE version 4.0 or higher.

Thromboembolism prophylaxis during the study treatment is required for subjects in Treatment Arm A. Low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anti-coagulant will be given to all subjects assigned to Treatment Arm A as well as Treatment Arm B subjects who have a prior history of DVT or PE. At the discretion of the treating

physician, other Treatment Arm B subjects may also receive antithrombotic therapy. Subjects who develop symptomatic DVT under study treatment will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method. Diagnostic algorithms will be provided in Appendix A.

Herpes Zoster Prophylaxis should be considered for all study subjects receiving bortezomib. Oral acyclovir or equivalent antiviral therapy per institutional guidelines is acceptable for herpes zoster prophylaxis.

During the study, subjects with myeloma-associated bone lesion may receive bisphosphonate therapy.

Radiation therapy to a pathological fracture site or to treat bone pain is permitted throughout the study.

The use of hematopoietic growth factors is permitted (the use of myeloid growth factors is encouraged when the absolute neutrophil count is less than 1,000/μL) at the discretion of the treating physician. Platelet and red blood cell transfusions are also permitted during the study.

However, subjects who fail absolute neutrophil count (ANC), hemoglobin or platelet eligibility criteria at screening CANNOT be re-tested for the study after being treated with growth factors or platelet/blood transfusion. However, subjects who meet the ANC, hemoglobin and platelet eligibility criteria due to growth factor treatment or platelet/blood transfusion received prior to screening are acceptable and are not considered as screening failures.

Drugs known to prolong QT corrected (QTc) interval should be avoided unless deemed medically necessary. See Appendix G for link to a comprehensive list of drugs which are known to prolong QTc. A thorough QT study (CC-4047-CP-010) was conducted in healthy subjects according to the E14 Guidance to assess the potential of Pomalidomide (POM) to delay cardiac re-polarization, especially as prolongation of the QT interval. The result of the QT prolongation assessment was observed to be negative, indicating a low risk of POM-associated QT prolongation.

Study Treatment Discontinuation

Subjects will continue study treatment until PD or unacceptable toxicity. An active treatment discontinuation visit should occur for all subjects at the time of permanent discontinuation from study treatment. The reason for discontinuation from study treatment will be documented in the eCRFs for all subjects.

Progression-free Survival (PFS) follow-up Phase

To ensure accuracy and completeness for the primary efficacy endpoint assessment of PFS, subjects who permanently discontinued study treatment prior to PD will continue to be followed up in the PFS follow-up phase until PD. During this PFS follow-up period, efficacy assessments for response and PD using the IMWG criteria should be performed every 21 days (see Table 1, Table of Events). Subjects are not expected to start any other anti-MM therapy during the PFS follow-up phase prior to PD. Subjects are expected to have a visit at the time of discontinuation from the PFS follow-up period.

Long-term Follow-up Phase

All subjects will be followed in the long-term follow-up phase for at least 5 years after the last subject is randomized into the study, or longer if clinically indicated (unless the follow-up is shorter due to withdrawal of consent, loss to follow-up, or death). Long-term follow-up will occur 4 times per year (every 3 months) after the 28 days post treatment discontinuation visit or PFS follow-up phase discontinuation visit, as applicable. During long-term follow-up the following information will be collected: survival, SPM, subsequent anti-myeloma regimens, date of progression and reason for progression based on the IMWG uniform response criteria, if available, for subjects who did not have PD during the study treatment or PFS follow-up period.

4.4. End of Trial

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

5. TABLE OF EVENTS

Table 1: Table of Events

	Screening Day -28 to Day -1	Active Treatment (each 21-day cycle)				Active Treatment Discontinuation (± 3 Days)	Follow-up visit (28 days post active treatment discontinuation)[a] (± 3 Days)	PFS Follow-up Phase (every 21 days)[b] (± 3 Days)	PFS Follow-up Phase Discontinuation (± 3 Days)	Long-term follow-up every 3 months (± 2 weeks)
		Day 1[c]	Day 4[d] (Cycles 1-8 only)	Day 8[d]	Day 11[d] (Cycles 1-8 only)					
Informed Consent	X	--	--	--	--	--	--	--	--	--
Inclusion/Exclusion Criteria	X	--	--	--	--	--	--	--	--	--
Demographics	X	--	--	--	--	--	--	--	--	--
Medical History	X	--	--	--	--	--	--	--	--	--
Prior anti-myeloma therapies, radiotherapy, surgeries	X	--	--	--	--	--	--	--	--	--
Disease Diagnosis[e]	X									
Randomization[f]	--	X (Cycle 1 only)	--	--	--	--	--	--	--	--
Safety Assessments										
Physical Exam	X	X	--	--	--	X	--	--	--	--
Vital Signs[g]	X	X	X	X	X	X	--	--	--	--
Height	X	--	--	--	--	--	--	--	--	--
Weight	X	X	X	X	X	X	--	--	--	--
Body Surface Area (BSA) calculation[h]	--	X	X	X	X	--	--	--	--	--
VTE Monitoring	--	X	X	X	X	X	--	--	--	--

Table 1: Table of Events (Continued)

	Screening Day -28 to Day -1	Active Treatment (each 21-day cycle)				Active Treatment Discontinuation (± 3 Days)	Follow-up visit (28 days post active treatment discontinuation)[a] (± 3 Days)	PFS Follow-up Phase (every 21 days)[b] (± 3 Days)	PFS Follow-up Phase Discontinuation (± 3 Days)	Long-term follow-up every 3 months (± 2 weeks)
		Day 1[c]	Day 4[d] (Cycles 1-8 only)	Day 8[d]	Day 11[d] (Cycles 1-8 only)					
12-Lead Electrocardiograph (ECG)[i]	X	X[i]	--	--	--	X	--	--	--	--
Hematology[j,k]	X	X[l]	X	X	X	X	--	X[m]	X[m]	--
Serum Chemistry[n,k]	X	X[l]	X	X	X	X	--	X[o]	X[o]	--
C-Reactive Protein (CRP) and Creatine Kinase	X	X[l]	--	--	--	X	--	--	--	--
Urinalysis[p]	X	X[l]	--	--	--	X	--	--	--	--
Estimation of Renal Function[q,k]	X	X[l]	--	--	--	X	--	--	--	--
Pregnancy Counseling	X	X	--	--	--	X	--	--	--	--
Pregnancy Test for FCBP[s]	X[s]	X[s]	--	X[s,] (Cycle 1 and 2 only)	--	X[s]	X[s]	X[s]	--	--
Adverse Events	X[u]									--
Monitoring of Second Primary Malignancies	X[v]									
Prior/Concomitant Medications and Procedures	*After signing the ICD and until 28 days after discontinuation from treatment.*									--

Table 1: Table of Events (Continued)

	Screening Day -28 to Day -1	Active Treatment (each 21-day cycle)				Active Treatment Discontinuation (± 3 Days)	Follow-up visit (28 days post active treatment discontinuation)[a] (± 3 Days)	PFS Follow-up Phase (every 21 days)[b] (± 3 Days)	PFS Follow-up Phase Discontinuation (± 3 Days)	Long-term follow-up every 3 months (± 2 weeks)
		Day 1[c]	Day 4[d] (Cycles 1-8 only)	Day 8[d]	Day 11[d] (Cycles 1-8 only)					
Efficacy Assessments										
Bone Marrow Aspiration and/or Biopsy[w] and cytogenetics	X	--	--	--	--	--	--	--	--	--
Quantitative Serum Immunoglobulin Levels[x]	X	X[l]	--	--	--	X	--	X	X	--
Serum protein electrophoresis (sPEP) and 24-hour Urine electrophoresis (uPEP)[y]	X	X[l]	--	--	--	X	--	X	X	--
Serum and urine immunofixation[z]	X[z]	X[z, l]	--	--	--	X[z]	--	X[z]	X[z]	--
Serum free light-chain (FLC) assay[aa]	X	X[l]	--	--	--	X	--	X	X	--
Skeletal Survey (by x-ray)[bb]	X	--	--	--	--	--	--	--	--	--
Extramedullary Plasmacytoma (EMP) Assessments[cc]	X	X	--	--	--	X	--	X	X	--
Assessment of Response[dd]	--	X (starting at Cycle 2)	--	--	--	X	--	X	X	--
Survival	--	--	--	--	--	--	--	--	--	X
Subsequent Myeloma Regimens	--	--	--	--	--	--	--	--	--	X
Progression data (date and reason)[ee]	--	--	--	--	--	--	--	--	--	X

Table 1: Table of Events (Continued)

	Screening Day -28 to Day -1	Active Treatment (each 21-day cycle)				Active Treatment Discontinuation (± 3 Days)	Follow-up visit (28 days post active treatment discontinuation)[a] (± 3 Days)	PFS Follow-up Phase (every 21 days)[b] (± 3 Days)	PFS Follow-up Phase Discontinuation (± 3 Days)	Long-term follow-up every 3 months (± 2 weeks)
		Day 1[c]	Day 4[d] (Cycles 1-8 only)	Day 8[d]	Day 11[d] (Cycles 1-8 only)					
Study Treatment Dispensation										
Oral Pomalidomide accountability / dispensation[ff]	--	X	--	--	--	--	--	--	--	--
Oral Dexamethasone dispensation[gg]	--	X	--	--	--	--	--	--	--	--
SQ Bortezomib administration[hh]	--	X	X	X	X	--	--	--	--	--
Other Assessments										
ECOG Performance Status[ii]	X	X	--	--	--	X	--	X	X	--
Serum Beta-2 Microglobulin[jj]	X	--	--	--	--	--	--	--	--	--
Quality of Life[kk]	--	X	--	--	--	X	--	--	--	--
Healthcare resource utilization[ll]	--	X					--	--	--	--
[redacted]										

Table 1: Table of Events (Continued)

	Screening Day -28 to Day -1	Active Treatment (each 21-day cycle)				Active Treatment Discontinuation (± 3 Days)	Follow-up visit (28 days post active treatment discontinuation)[a] (± 3 Days)	PFS Follow-up Phase (every 21 days)[b] (± 3 Days)	PFS Follow-up Phase Discontinuation (± 3 Days)	Long-term follow-up every 3 months (± 2 weeks)
		Day 1[c]	Day 4[d] (Cycles 1-8 only)	Day 8[d]	Day 11[d] (Cycles 1-8 only)					
Bone marrow aspirate and blood sample for MRD, genomic and molecular/mechanistic biomarkers studies[mm oo]	X	--	--	--	--	X	--	--	--	--
Blood samples for immune biomarker studies[pp]	X	--	--	X (Cycle 1 and 3 only)	--	--	--	--	--	--

[a] The follow-up visit 28 days post-active treatment discontinuation is only required for subjects who do not enter the PFS follow-up phase.

[b] To ensure appropriate follow-up for the primary endpoint of progression-free survival, subjects who discontinue from active treatment prior to PD will continue to be followed in the PFS follow-up period until PD.

[c] At Cycle 1 all assessments must be performed within ± 1 day of Day 1. For Cycle 2 onwards, all assessments must be performed within ±3 days of Day 1. If the start of a new cycle is delayed > 7 days from the protocol-defined 21-day dosing cycle, an unscheduled visit must be performed for efficacy assessments prior to initiation of the next cycle or if the delay is greater than 21 days, these efficacy assessments must be performed every 21 days (±3 days) until a new cycle can begin. For subsequent cycles following a delayed cycle, efficacy assessments should be performed at the start of each new cycle. These efficacy assessments include: ECOG performance status, myeloma paraprotein protein electrophoresis and immunofixation, serum immunoglobulins, serum free light chain assay, serum hematology (for hemoglobin), serum chemistry (for corrected serum calcium and creatinine), and if applicable, clinical and/or radiological extramedullary plasmacytoma assessment, skeletal survey, and bone marrow aspirate/biopsy.

[d] For Treatment Arm A (POM+BTZ+LD-DEX), if a subject permanently discontinues BTZ, the Day 4, 8 and 11 visits/assessments are no longer required for that subject, with the exception of any required pregnancy testing.

[e] Date of confirmed initial diagnosis and, if available, the myeloma stage at time of initial diagnosis per the Salmon-Durie Criteria and/or the International Staging System (ISS) (Appendix H) will be collected as part of the disease diagnosis assessment.

[f] Once a subject is randomized, study treatment must be initiated within 4 days.

[g] Vital signs include blood pressure, temperature, respiratory rate and heart rate.

[h] The body surface area (BSA) used to determine the bortezomib dose will be collected. If local pharmacy SOP requires subject weight to be used from Day 1 of the current treatment cycle, this will be acceptable unless the physician feels there is a clinically significant change in the subject's weight that would require modification to the bortezomib total dose.

[i] All ECGs will be performed and reviewed locally. During the study treatment phase ECGs will be performed at Cycle 3 Day 1, then every third cycle thereafter (Cycle 6 Day 1, Cycle 9 Day 1, etc.). Subjects with QT or borderline QT prolongation but otherwise non-clinically significant will require more frequent ECG monitoring at the discretion of the investigator.

[j] Assessment of hematology includes: white blood cell count with differential, ANC, ALC, hemoglobin, hematocrit, platelet count, and mean corpuscular volume.

[k] These assessments will be performed by the central laboratory; however, tests that may result in dose interruption and/or modification should also be performed locally to allow for treatment related decisions during subject visits. At Study Day 1 subject must meet eligibility criteria based on local or central lab results prior to initiating study therapy. All abnormal results from local laboratories used in treatment decisions or adverse event reporting must be entered into an unscheduled visit on the eCRF.

[l] If screening visit laboratory tests were done ≤ 7 days prior to randomization, these laboratory assessments are not required to be repeated at Cycle 1 Day 1, except for those test related to protocol exclusion (ANC, platelets, hemoglobin, corrected calcium, SGOT/AST or SGPT/ALT, total bilirubin, creatinine clearance) and the screening results were within 10% range of the exclusion criteria. A 24-hour urine sample obtained as a standard of care assessment prior to informed consent can be utilized for this study if it was performed ≤ 7 days prior to the Screening Visit and meets the protocol requirements for collection and analysis.

[m] Only hemoglobin will be assessed during the PFS follow-up phase visits and at the PFS follow-up phase discontinuation visit.

[n] Assessment of serum chemistry includes: total protein, albumin, corrected serum calcium, phosphorous, glucose, uric acid, total bilirubin, direct bilirubin (only when total bilirubin is increased), alkaline phosphatase, AST/SGOT, ALT/SGPT, GGT, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, lactate dehydrogenase, magnesium. If a PD is noted based on corrected serum calcium level, a repeat serum chemistry test should be performed as soon as possible to confirm PD.

[o] Only corrected serum calcium and serum creatinine will be assessed during the PFS follow-up phase visits and at PFS follow-up phase discontinuation visit.

[p] Assessment of urinalysis includes: specific gravity, pH, glucose, bilirubin, protein, ketones, blood and, if feasible, microscopic analysis [casts, bacteria, RBCs, and WBCs]. This assessment will be performed by the local laboratory only and as per local practice.

[q] Estimation of renal function will be assessed using the creatinine clearance (CrCl) calculated based on the Cockcroft-Gault formula (Appendix F) or the CrCl directly calculated from the 24-hour urine collection method. Cockcroft-Gault formula: CrCl (mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dL]); for females, the formula is multiplied by 0.85.

[redacted]

[s] FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study treatment. The first pregnancy test must be performed within 10-14 days prior to the start of study treatment and the second pregnancy test must be performed within 24 hours prior to the start of study treatment. The subject may not receive study treatment until the study doctor has verified that the results of these pregnancy tests are negative. FCBP with regular or no menstrual cycles must agree to have pregnancy tests every 7 days (weekly) for the first 4 weeks of study participation (Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 8) and then every 3 weeks (starting at Cycle 3 Day 1) while on study, at treatment discontinuation, and 4 weeks following treatment discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 4 weeks and then every 2 weeks starting with Cycle 3 Day 1 while on study, at treatment discontinuation, and at 2 weeks and 4 weeks following treatment discontinuation. For FCBP entering the PFS follow-up phase following treatment discontinuation, the post treatment discontinuation pregnancy testing must still be performed at 4 weeks following treatment discontinuation for FCBP with regular or no menstrual cycles or at 2 weeks and 4 weeks following treatment discontinuation for FCBP irregular menstrual cycles.

[redacted]

[u] All AEs will be recorded by the Investigator from the time the subject signs informed consent (IC) to at least 28 days after the last dose of study treatment (pomalidomide, bortezomib or dexamethasone) for subjects not continuing in the PFS follow-up Phase. Only study/protocol related AEs will be recorded by the Investigator for subjects who continue in the PFS follow-up phase of the study. AEs that lead to study treatment discontinuation should be followed until resolution or stabilization. SAEs, regardless of relationship to the study treatment (pomalidomide, bortezomib, and/or dexamethasone), that occur from the time the subject signs informed consent to at least 28 days after the last dose of study drug (Pomalidomide, bortezomib, or dexamethasone), and those made known to the Investigator at any time thereafter that are suspected of being related to study treatment (Pomalidomide, bortezomib and/or dexamethasone) must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

[v] Screening for synchronous malignancies will be performed during the screening visit. Second Primary Malignancies (SPMs) will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the subject is in. This includes any SPM, regardless of causal relationship to study treatment (pomalidomide, bortezomib or dexamethasone), occurring at any time from the time of signing the informed consent up to and including the long-term follow-up period. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the eCRF and subject's source documents. Documentation on the diagnosis of the SPM must be provided at the time of reporting as a serious adverse event (eg, any confirmatory pathology, histology or cytology results, cytogenetics, flow cytometry, X-rays, CT scans, etc.). For all subjects who develop SPMs, all corresponding diagnostic reports (eg, pathology, cytogenetics, flow cytometry) from the MM diagnosis confirmation performed at screening, and if applicable, from any subsequent bone marrow assessments performed during the treatment or PFS follow-up phase of the study (for confirmation of CR or other clinical reason) and from the diagnostic tumor samples obtained at SPM determination, will be required for secondary malignancy confirmation.

[w] At screening, a bone marrow aspirate (and biopsy if necessary) is required and must be obtained within 28 days prior to randomization/enrollment to obtain a current estimate of the % plasma cells in the marrow. Analysis for % plasma cells in the marrow will be performed locally. A portion of the bone marrow aspirate will be submitted to a central laboratory for cytogenetic studies via fluorescent in situ hybridization [FISH] analyses. After screening, a bone marrow aspirate (or biopsy if necessary) must be performed to confirm a CR, and may otherwise be repeated as clinically indicated at the discretion of the treating physician. Celgene may request a redacted copy of the pathology reports for post-baseline bone marrow biopsies and/or aspirates.

[x] Quantitative immunoglobulin assessment includes IgG, IgA, IgM for all subjects, IgE or IgD only for subjects with the respective myeloma sub-type (IgE or IgD). Quantitative immunoglobin assessment should be repeated at time of CR confirmation. This assessment will be performed by the central laboratory.

[y] Serum and 24-hour urine protein electrophoresis (sPEP/uPEP) assessments will be performed by a central laboratory. Investigator evaluation of disease response should be based solely on the central laboratory results, not local results. If a response or PD is noted based on sPEP and/or uPEP results, a repeat test should be conducted as soon as possible to confirm the response or PD.

[z] Serum and urine immunofixation tests (IFE) are performed at screening to identify the immunoglobulin subtype of MM. Thereafter, the IFE assays are triggered to be performed whenever M-protein is undetectable by sPEP and uPEP to confirm CR. This assessment will be performed by the central laboratory. Investigator evaluation of disease response should be based solely on the central laboratory results.

[aa] Serum FLC assay should be repeated at the time of CR confirmation. This assessment will be performed by the central laboratory.

[bb] A skeletal survey by x-ray will be performed at screening and thereafter when clinically indicated. All skeletal survey films and analyzed locally by the site investigator/radiologist. If a skeletal survey was performed within 60 days prior to the start of Cycle 1, it may be used for the screening assessment.

[cc] If EMPs are clinically assessable, clinical assessment will be performed at screening, at every Cycle Day 1, at treatment discontinuation, every 21 days during the PFS follow-up phase, at PFS follow-up phase discontinuation, and when clinically indicated to confirm a response (≥ PR). If EMPs are only assessable radiographically (x-ray and/or conventional [spiral] CT/MRI scan), scans are required at screening, at Cycle 3 Day 1, every 3 cycles thereafter (Cycle 6 Day 1, Cycle 9 Day 1, etc.) during treatment, at treatment discontinuation, every 63 days during the PFS follow-up phase, at PFS follow-up phase discontinuation, and when clinically indicated to confirm a response (≥ PR). The radiographic modality used at screening (eg, x-ray) must be repeated at each assessment time point throughout the study. All scans will be reviewed locally only. The individual EMPs (both clinically and radiographically assessable) must be consistently labeled using the same numerical and descriptive values (eg, EMP#1 left rib, EMP #2 liver) throughout the study at the specified time points requested by the protocol.

[dd] Response will be assessed using the IMWG criteria (Appendix B). All treatment decisions will be made by the treating physicians based on response as assessed using the IMWG criteria.

[ee] The date of progression and reason for progression based on the IMWG uniform response criteria, if available, will be collected during long-term follow-up for subjects who did not have PD during the active treatment or the PFS follow-up phase if applicable.

[ff] Subject will take oral dose of POM on Days 1 to 14 of each 21-day cycle. For additional details, see Section 6.4.5.

[gg] Subject will take oral dexamethasone on Days 1, 2, 4, 5, 8, 9, 11, and 12 of Cycles 1 to 8, and on Days 1, 2, 8 and 9 for of each 21-day cycle from Cycle 9 and onward.

[hh] Bortezomib doses must be at least 72 hours apart. Missed doses cannot be made up.

[ii] See Appendix E for the ECOG Performance Status Scale.

[jj] The serum β2M test will be performed centrally at the screening visit only. The test result should be available prior to randomization to allow for appropriate stratification.

[kk] Quality of Life (QoL) instruments (EORTC QLQ-MY20 and EORTC QLQ-C30) and the descriptive system of the EQ-5D will be provided to each subject to complete on the first day of every cycle (including Cycle 1) at the beginning of the Cycle Day 1 visit prior to any study treatment (POM, BTZ, DEX) administration and at treatment discontinuation. If the collection of such information is prohibited per local regulations or is not operationally or logistically feasible, such assessments will not be considered as mandatory. See Appendix I for QoLs.

[ll] Information for hospitalizations or emergency department visits that occur during the active treatment period will be collected.

[redacted]

[redacted]

[nn] The biomarker sampling will only be performed at sites where such sampling is permitted per local regulations, operationally and logistically feasible, and only for subjects who give their consent. For investigative sites where biomarker sampling will be performed, if an assessment is not done due to insufficient sample or subject non-compliance with the sampling requirement it will not be considered a deviation from the protocol. All biomarker samples will be destroyed 5 years after completion of the study or earlier if required by law.

[oo] Bone marrow aspirate and a whole blood sample for MRD, genomic and molecular/mechanistic biomarkers studies will be submitted to a central laboratory at the following timepoints: at screening (if sufficient bone marrow aspirate material is available after samples are prepared for the local pathology analysis and central cytogenetic analysis); at time of CR confirmation and at treatment discontinuation (if sufficient bone marrow aspirate material is available after samples are prepared for the local pathology analysis); at time of PD or treatment discontinuation (only if a bone marrow aspirate is performed for a subject as part of standard of care and sufficient material is available after samples are prepared for the local pathology analysis). Sampling will only be performed at sites where such sampling is permitted per local regulations, operationally and logistically feasible, and only for subjects who give their consent.

[pp] Blood samples for immune biomarkers studies will be collected and submitted to a central laboratory at the following timepoints: screening, Cycle 1 Day 8, and Cycle 3 Day 8. Sampling will only be performed at sites where such sampling is permitted per local regulations, operationally and logistically feasible, and only for subjects who give their consent.

6. PROCEDURES

6.1. Study Entry

6.1.1. Screening

Prior to screening, subject must sign an informed consent. All screening assessments must be completed within 28 days prior to start of Cycle 1, with the exception of the skeletal survey, for which previous results (if the survey was done within 60 days prior to randomization) can be used as baseline assessments.

Confirmation of diagnosis, medical and surgical history, and review of concomitant medications should be documented during the screening period as well. All prior radiotherapy, surgeries, and anti-myeloma therapies must be recorded in the eCRF, including approximate dates for each therapy and the date of progression for each regimen. Date of confirmed initial diagnosis and, if available, the myeloma stage at time of initial diagnosis per the Salmon-Durie Criteria and/or the International Staging System (ISS) (Appendix H) will be collected as part of the disease diagnosis assessment. See Table 1 for all the required assessments during screening.

If screening visit laboratory tests were done ≤ 7 days prior to enrollment/randomization, these laboratory assessments are not required to be repeated at Cycle 1 Day 1, except for those test related to protocol exclusion (ANC, platelets, hemoglobin, corrected calcium, SGOT/AST or SGPT/ALT, total bilirubin, creatinine clearance) for which screening results were within 10% range of the exclusion criteria.

The start of study treatment dosing is designated as Cycle 1 Day 1. All assessments should be performed on Day 1 (± 1 Day) in Cycle 1 and within a ± 3 days window for other required visits during the active treatment and PFS follow-up phase. Long-term follow-up will be performed every 3 months (± 2 weeks).

6.1.2. Wash-out

Subjects' most recent systemic anti-myeloma drug therapy must be discontinued at least 14 days prior to randomization. For those who used investigational anti-myeloma agents, a minimum wash-out of 28 days or 5 half-lives (whichever is longer) of treatment is required.

6.1.3. Randomization

This study will utilize centralized randomization by IVRS/IWRS. A set of randomization authorization number will be pre-loaded in the IVRS/IWRS system prior to the study initiation.

Celgene trial staff will review and verify specific eligibility criteria for all subjects prior to allowing randomization of subjects via the IVRS/IWRS. Celgene trial staff will be required to activate a subjects in the IVRS/IWRS before site staff may randomize and obtain the treatment assignment via IVRS/IWRS. Once a subject is randomized, study treatment must be initiated within 4 days.

Designated research personnel at each investigational sites will be assigned password protected, coded identification numbers which gives them the access to call into IVRS/IWRS to enroll subjects.

6.2. Safety Assessments

For Treatment Arm A (POM+BTZ+LD-DEX), if a subject permanently discontinues BTZ, the Day 4, 8 and 11 visits/assessments are no longer required for that subject, with the exception of any required pregnancy testing.

6.2.1. Adverse Events

All Adverse Events (AEs) will be recorded by the Investigator from the time the subject signs informed consent to at least 28 days after the last dose of study drug (pomalidomide, bortezomib, or dexamethasone) for subjects not continuing in the PFS follow-up Phase. Only study/protocol related AEs will be recorded by the Investigator for subjects who continue in the PFS follow-up phase of the study. AEs that lead to study discontinuation should be followed until resolution or stabilization.

6.2.1.1. Serious Adverse Events

Serious Adverse Events (SAEs), regardless of relationship to study treatment (ie, pomalidomide, bortezomib, and/or dexamethasone), that occur from the time the subject signs informed consent to at least 28 days after the last dose of study drug (pomalidomide, bortezomib, or dexamethasone), and those made known to the Investigator at any time thereafter that are suspected of being related to study treatment (pomalidomide, bortezomib and/or dexamethasone) must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

6.2.1.2. Second Primary Malignancies

Screening for synchronous malignancies will be performed during the screening visit.

Second Primary Malignancies (SPMs) will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the subject is in. This includes any SPM, regardless of causal relationship to study treatment (pomalidomide, bortezomib or dexamethasone), occurring at any time from the time of signing the informed consent up to and including the long-term follow-up period. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the eCRF and subject's source documents. Documentation on the diagnosis of the SPM must be provided at the time of reporting as a serious adverse event (eg, any confirmatory pathology, histology or cytology results, cytogenetics, flow cytometry, X-rays, CT scans, etc.). For all subjects who develop SPMs, all corresponding diagnostic reports (eg, pathology, cytogenetics, flow cytometry) from the MM diagnosis confirmation performed at screening, and if applicable, from any subsequent bone marrow assessments performed during the treatment or PFS follow-up phase of the study (for confirmation of CR or other clinical reason) and from the diagnostic tumor samples obtained at SPM determination, will be required for secondary malignancy confirmation.

6.2.2. Prior and Concomitant Medications and Procedures

All prior and concomitant therapies (prescription and non-prescription) taken and any procedures performed after the subject signs the informed consent, during the course of the treatment, and 28 days after treatment discontinuation will be collected and recorded on the subject's eCRF. Drugs known to prolong QT corrected (QTc) interval should be avoided unless deemed medically necessary. See Appendix G for link to a comprehensive list of drugs which are known to prolong QTc.

6.2.3. VTE Monitoring

All prior venous thrombotic events (VTE) and pulmonary embolisms that occurred will be collected with complete medical history during the screening period. Clinical review of sign/symptoms for possible VTEs will be performed at every scheduled visit during study treatment, and at treatment discontinuation. Subjects who develop symptomatic DVT will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method per institutions standard of care. See Appendix A for DVT and PE diagnostic algorithms.

6.2.4. Complete Physical Exam and Measurement of Vital Signs, Height, and Weight

A complete physical exam (skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems) will be performed at screening, on Day 1 of every cycle starting at Cycle 1, and at treatment discontinuation.

Measurement of vital signs (blood pressure, temperature, heart rate, and respiration rate) will be performed at screening, at every scheduled visit during study treatment, and at treatment discontinuation.

Measurement of height will be performed at screening only. Measurement of weight will be performed at screening, at every scheduled visit during study treatment, and at treatment discontinuation.

Body Surface Area used to calculate each BTZ dose will be collected in the eCRFs.

Investigators are to report any clinically significant abnormal findings as adverse events.

6.2.5. Electrocardiogram

12-lead electrocardiogram (ECG) monitoring will be performed at screening, on Cycle 3 Day 1 and on Day 1 of every third cycle thereafter (Cycle 6 Day 1, Cycle 9 Day 1, etc.) during treatment, and at treatment discontinuation. Subjects with QT or borderline QT prolongation but otherwise non-clinically significant will require more frequent ECG monitoring at the discretion of the investigator. All ECGs will be performed and reviewed locally.

6.2.6. Laboratory Assessments for Safety Parameters

Except for pregnancy tests and urinalysis, all safety-related laboratory assessments will be performed centrally; however, tests that may result in dose interruption and/or modification should also be performed locally to allow for treatment related decisions during subject visits. All results from local laboratories used in treatment decisions or adverse event reporting must be entered into an unscheduled visit on the eCRF. At Study Day 1 subject must meet eligibility criteria based on local or central lab results prior to initiating study therapy.

If screening visit laboratory tests were done ≤ 7 days prior to enrollment/randomization, these laboratory assessments are not required to be repeated at Cycle 1 Day 1, except for those test related to protocol exclusion (ANC, platelets, hemoglobin, corrected calcium, SGOT/AST or SGPT/ALT, total bilirubin, creatinine clearance) for which screening results were within 10% range of the exclusion criteria.

- **Hematology laboratory tests:** Hematology includes: white blood cell count with differential, ANC, absolute lymphocyte count (ALC), hemoglobin, hematocrit, platelet count, and mean corpuscular volume. Hematology will be performed at screening, at every scheduled visit during study treatment, at treatment discontinuation, every 21 days during the PFS follow-up phase and at PFS follow-up phase discontinuation. During the PFS follow-up phase and at PFS follow-up phase discontinuation only hemoglobin will be assessed. This assessment must be performed by the central laboratory; however, laboratory tests that may result in dose interruption and/or modification should also be performed locally to allow for timely treatment related decisions during subject visits.
- **Serum chemistry laboratory tests:** Serum chemistry includes: total protein, albumin, corrected serum calcium, phosphorous, glucose, uric acid, total bilirubin, direct bilirubin (only when total bilirubin is increased), alkaline phosphatase, AST/SGOT, ALT/SGPT, GGT, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, lactate dehydrogenase, magnesium. Serum chemistry labs will be performed at screening, at every scheduled visit during study treatment, at treatment discontinuation, every 21 days during the PFS follow-up phase and at PFS follow-up phase discontinuation. During the PFS follow-up phase and at PFS follow-up phase discontinuation only corrected serum calcium and creatinine will be assessed. If a PD is noted based on corrected serum calcium level, a repeat serum chemistry test should be performed as soon as possible to confirm the PD.
- **C-reactive protein and creatine kinase** assessments will be performed at screening, on Day 1 of every cycle starting at Cycle 1 and at treatment discontinuation.
- **Urinalysis:** Urinalysis includes: specific gravity, pH, glucose, bilirubin, protein, ketones, blood and, if feasible, microscopic analysis [casts, bacteria, RBCs, and WBCs]. Urinalysis will be performed at screening, at every cycle Day 1 starting at Cycle 1, and at treatment discontinuation. Urinalysis will be performed by local laboratory only and as per local practice.
- **Renal Function:** The creatinine clearance (CrCl) will be calculated based on the Cockcroft-Gault formula or the CrCl directly calculated from the 24-hour urine collection method at screening, at every cycle Day 1 starting at Cycle 1, and at treatment discontinuation. Cockcroft-Gault formula: CrCl (mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dL]); for females, the formula is multiplied by 0.85.

6.2.7. Pregnancy Counseling (males and females)

Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted for all subjects at screening, and thereafter for subjects randomized to Treatment Arm

A (POM+BTZ+LD-DEX) at Cycle 1 Day 1 prior to dosing, every 21 days during treatment, and at treatment discontinuation. [redacted]

6.2.8. Contraception and Pregnancy Testing Requirements

Acceptable contraception methods need to be aligned to Regulatory guidelines/regulations for respective countries and as outlined in the local label (as applicable). There must be one highly effective contraceptive method and one additional effective contraceptive method used for this study as specified in the Pregnancy Prevention Plan. Contraception and pregnancy testing timelines for using contraception and pregnancy testing frequencies must be within the Regulatory guidelines/regulations for the respective country and Celgene requires additional pregnancy precautions as outlined in the Pregnancy Prevention Plan.

All Females of Child Bearing Potential (FCBP) must have two medically supervised negative serum or urine pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting the study. The first pregnancy test must be performed within 10-14 days prior to the start of study treatment and the second pregnancy test must be performed within 24 hours prior to the start of study treatment. FCBP with regular or no menstrual cycles must agree to have pregnancy tests every 7 days (weekly) for the first 4 weeks of study treatment (Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 8) and then every 3 weeks (starting at Cycle 3 Day 1) while on study, at treatment discontinuation, and 4 weeks following treatment discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 4 weeks and then every 2 weeks (starting at Cycle 3 Day 1) while on study, at treatment discontinuation, and at 2 weeks and 4 weeks following treatment discontinuation. Study treatment may not be dispensed for FCBP until the investigator has verified that the result of the pregnancy test is negative.

6.3. Efficacy Assessments

Response (efficacy) assessments must be conducted at the same time points for all subjects during their participation in this study in order to accurately compare PFS between the treatment arms. Therefore, every effort must be made to perform these assessments on schedule. These efficacy assessments include: myeloma paraprotein protein electrophoresis and immunofixation, serum immunoglobulins, serum free light chain assay, serum hematology (for hemoglobin), serum chemistry (for corrected serum calcium and creatinine), and if applicable, clinical and/or radiological extramedullary plasmacytoma assessments, skeletal survey, and bone marrow aspirate/biopsy.

Efficacy assessments are to be performed at the start of each new cycle. If the start of a new cycle is delayed for more than 7 days from the protocol-defined 21-day dosing cycle, an unscheduled visit must be performed for efficacy assessments prior to initiation of the next cycle. If the treatment delay is greater than 21 days, efficacy assessments must be performed every 21 days until a new cycle can begin. For subsequent cycles following a delayed cycle, efficacy assessments should be performed at the start of each new cycle. Treatment response must be assessed using results from the central laboratory.

6.3.1. Laboratory Assessments for Efficacy Parameters

All efficacy laboratory assessments will be performed centrally. Data generated by central laboratories will prevail over locally generated information in the evaluation of the subject's efficacy results.

If screening visit results are ≤ 7 days prior to enrollment/randomization, these laboratory assessments are not required to be repeated at Cycle 1 Day 1.

- **Myeloma paraprotein (M-Proteins) protein electrophoresis:** Serum protein electrophoresis (quantified from the serum protein electrophoresis [sPEP] test) and urine protein electrophoresis (quantified from the urine protein electrophoresis [uPEP] test performed on 24-hour urine collection), will be performed at screening and at every cycle on Day 1, at treatment discontinuation, every 21 days during the PFS follow-up phase, at PFS follow-up phase discontinuation. If a response or PD is noted based on sPEP and/or uPEP results, sPEP and uPEP tests should be repeated as soon as possible to confirm the response or PD. Investigator evaluation of disease response should be based solely on the central laboratory results, not on results from local laboratories. In the event that results from the M-protein samples submitted to the central laboratory were not obtained or not analyzable (tube broken, sample hemolyzed, etc.), an additional sample should be provided to the central laboratory immediately.
- **Myeloma paraprotein (M-Proteins) immunofixation:** Serum and urine immunofixation (IFE) tests are performed at screening to identify the immunoglobulin subtype of MM and thereafter are triggered to be performed whenever M-protein is undetectable / too few to quantify in both sPEP and uPEP assays.
- **Serum immunoglobulins** assessment will be performed at screening and at every cycle on Day 1, at treatment discontinuation, every 21 days during the PFS follow-up phase, at PFS follow-up phase discontinuation, and at the time of CR confirmation. Quantitative immunoglobulin assessment includes IgG, IgA, IgM for all subjects and IgE or IgD only for subjects with the respective myeloma sub-type (IgE or IgD).
- **Serum Free Light Chain** assay will be performed at screening and at every cycle on Day 1, at treatment discontinuation, every 21 days during the PFS follow-up phase, at PFS follow-up phase discontinuation, and at the time or CR confirmation.

6.3.2. Bone Marrow Aspiration and/or Biopsy and Cytogenetics

At screening, a bone marrow aspirate (and biopsy if necessary) is required and must be obtained within 28 days prior to randomization/enrollment to obtain a current estimate of the % plasma cells in the marrow. Analysis for % plasma cells in the marrow will be performed locally. A portion of the bone marrow aspirate will be submitted to a central laboratory for cytogenetic studies via fluorescent in situ hybridization [FISH] analyses.

After screening, a bone marrow aspirate (or biopsy if necessary) must be performed to confirm a CR, and may otherwise be repeated as clinically indicated at the discretion of the treating

physician. Celgene may request redacted copies of post-baseline pathology reports from subsequent bone marrow biopsies and/or aspirates.

See Section 6.4.6.1 for additional bone marrow aspirate/biopsy sampling details for biomarker studies.

6.3.3. Skeletal Survey

A skeletal survey by x-ray will be performed at screening and when clinically indicated thereafter. All skeletal survey films and analyzed locally by the site investigator/radiologist. If a skeletal survey was performed within 60 days prior to the start of Cycle 1, it may be used as screening assessment. Refer to Appendix D for detailed requirements.

6.3.4. Extramedullary Plasmacytoma Assessments

If extramedullary plasmacytomas (EMPs) are clinically assessable, clinical assessment will be performed at screening, at every Cycle Day 1, at treatment discontinuation, every 21 days during the PFS follow-up phase and at PFS follow-up phase discontinuation.

If EMPs are only assessable radiographically (x-ray and/or conventional [spiral] CT/MRI scan), scans are required at screening, at Cycle 3 Day 1, every 3 cycles thereafter (Cycle 6 Day 1, Cycle 9 Day 1, etc.) during treatment, at treatment discontinuation, every 63 days during the PFS follow-up phase, at PFS follow-up phase discontinuation, and when clinically indicated to confirm a response (≥ PR). The radiographic modality used at screening (eg, x-ray) must be repeated at each assessment time point throughout the study. All scans will be reviewed locally only.

The individual EMPs (both clinically and radiographically assessable) must be consistently labeled using the same numerical and descriptive values (eg, EMP#1 left rib, EMP #2 liver) throughout the study at the specified time points requested by the protocol.

6.3.5. Assessment of Response

6.3.5.1. Investigators' Assessment for Tumor Response

Starting from Cycle 2, response will be assessed using results from central laboratories by the investigators using the IMWG criteria (Appendix B) at every cycle on Day 1 and at the treatment discontinuation visit, every 21 days during the PFS follow-up phase and at PFS follow-up phase discontinuation. All treatment discontinuation decisions due to disease progression will be made by treating physicians based on response as assessed using results from central laboratories by the IMWG criteria, except for new or increase in bone lesions or soft tissue plasmacytomas.

6.3.5.2. IRAC Assessment for Tumor Response

An IRAC will be formed by a group of experts in the MM disease area to review efficacy data in a blinded manner. For each subject, the IRAC will determine tumor response at scheduled or unscheduled visits, and the time of PD (if disease progressed). In addition, the IRAC will determine the best overall response of each subject up to time of the data cut-off for interim and final analyses.

The IRAC will adjudicate blinded efficacy data incrementally according to IRAC Charter during the study. The IRAC adjudicated response data will be used for efficacy analysis in all interim and final analyses. Primary efficacy analyses will be conducted in tumor response data, including progressive disease (PD) that are assessed by the IRAC according to the IMWG uniform response criteria (Durie, 2006) (Appendix B); an exploratory analysis using response data assessed by the EBMT (Bladé, 1998) (Appendix C) response criteria will also be performed.

6.3.6. Overall Survival and Subsequent Anti-MM Therapies

All long-term follow-up phase subjects will be contacted four (4) times a year (every 3 months) to obtain survival status for at least 5 years after the last subject is randomized into the study, or longer if clinically indicated. Cause of death is to be recorded on the eCRF and the subject's hospital medical record. All subsequent anti-myeloma therapies must be collected on the eCRF. The date of PD and reason for progression based on the IMWG uniform response criteria, if available, will also be collected during long-term follow-up for subjects who did not have PD during the study treatment or PFS follow-up period, if applicable.

6.4. Other Assessments

6.4.1. ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status will be performed at screening, at every cycle Day 1 starting at Cycle 1, at treatment discontinuation, every 21 days during the PFS follow-up phase and at PFS follow-up phase discontinuation. See Appendix E for the ECOG Performance Status Scale.

6.4.2. Serum Beta-2 Microglobulin (β2M)

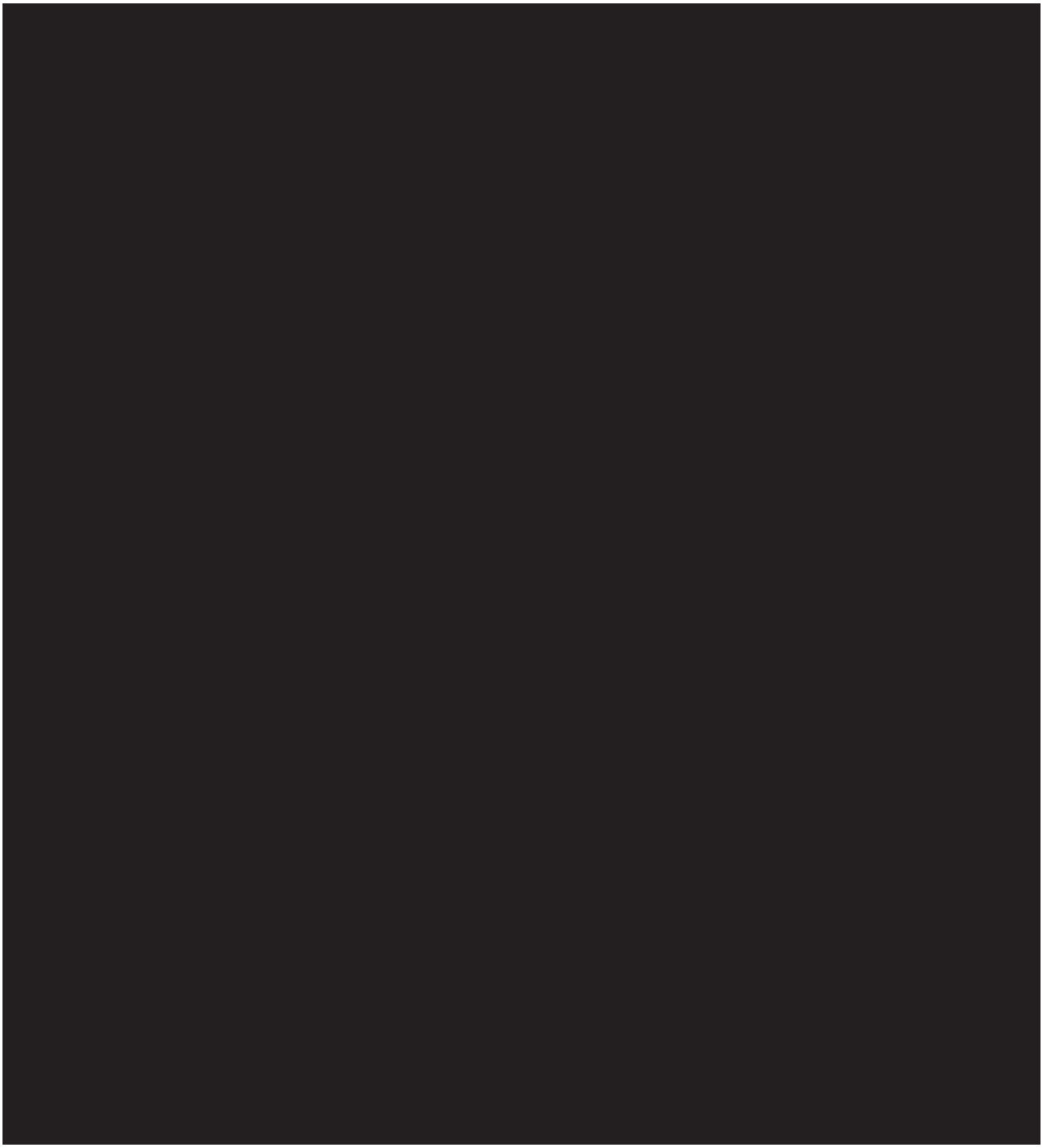
The serum β2M test will be performed centrally at the screening visit only. The test result should be available prior to randomization to allow for appropriate stratification.

6.4.3. Healthcare Resource Utilization

Information for hospitalizations or emergency department visits that occur during the active treatment period will be collected.

6.4.4. Quality of Life (QoL)

Quality of Life (QoL) instruments ([EORTC QLQ-MY20] and [EORTC QLQ-C30]) and the descriptive system of the EQ-5D will be provided to each subject to complete on the first day of every cycle (including Cycle 1) at the beginning of the Cycle Day 1 visit prior to any study treatment (POM, BTZ, DEX) administration and at treatment discontinuation. If the collection of such information is prohibited per local regulations or is not operationally or logistically feasible, such assessments will not be considered as mandatory. See Appendix I for QoLs.



6.4.6. Exploratory Biomarker Sampling

The biomarker sampling will only be performed at sites where such sampling is permitted per local regulations, operationally and logistically feasible, and only for subjects who give their consent. For investigative sites where biomarker sampling will be performed, if an assessment is not done due insufficient sample or subject non-compliance with the sampling requirement, it will not be considered a deviation from the protocol. All biomarker samples will be destroyed 5 years after completion of the study or earlier if required by law.

6.4.6.1. Minimal Residual Disease (MRD), Genomic, Molecular/Mechanistic Biomarkers

Bone marrow aspirate/biopsy and a whole blood sample for MRD, genomic and molecular/mechanistic biomarkers studies will be submitted to a central laboratory at the following timepoints:

- At screening (if sufficient bone marrow aspirate material is available after samples are prepared for the local pathology and central cytogenetic analysis)
- At time of CR confirmation (if sufficient bone marrow aspirate material is available after samples are prepared for the local pathology analysis)
- At time of PD or treatment discontinuation (only if a bone marrow aspirate is performed for a subject as part of standard of care and sufficient material is available after samples are prepared for the local pathology analysis)

6.4.6.2. Immune Biomarkers

Blood samples for immune biomarkers studies will be collected and submitted to a central laboratory at the following timepoints: screening, Cycle 1 Day 8, and Cycle 3 Day 8.

7. STUDY POPULATION

7.1. Number of Subjects and Sites

This study will enroll approximately 544 subjects (272 in each arm) at sites globally.

7.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Must be ≥ 18 years at the time of signing the informed consent form.
2. The subject must understand and voluntarily sign an informed consent document prior to any study-related assessments/procedures.
3. Must be able to adhere to the study visit schedule and other protocol requirements.
4. Subjects must have documented diagnosis of multiple myeloma and have measurable disease by serum or urine protein electrophoresis (sPEP or uPEP): sPEP ≥ 0.5 g/dL or uPEP ≥ 200 mg/24 hours.
5. All subjects must have had at least 1 but no greater than 3 prior anti-myeloma regimens. (note: induction with or without bone marrow transplant and with or without maintenance therapy is considered one regimen.)
6. All subjects must have documented disease progression during or after their **last** anti-myeloma therapy.
7. All subjects must have received prior treatment with a lenalidomide-containing regimen for at least 2 consecutive cycles.
8. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.
9. Females of childbearing potential (FCBP[†]) must agree to utilize two reliable forms of contraception simultaneously or practice complete abstinence from heterosexual contact for at least 4 weeks before starting study treatment, while participating in the study treatment phase (including dose interruptions), and for at least 4 weeks after the last dose of POM or 3 months after the last dose of BTZ, whichever is longer, and must agree to regular pregnancy testing during this timeframe.
10. Females must agree to abstain from breastfeeding during study treatment and for at least 4 weeks after study treatment discontinuation.
11. Males must agree to use a latex or synthetic condom during any sexual contact with FCBP while participating in the study treatment phase and for at least 4 weeks after the last dose of POM or 3 months after the last dose of BTZ, whichever is longer, even if he has undergone a successful vasectomy.

[†]This protocol defines a female of childbearing potential as a sexually mature woman who: 1) is menstruating, amenorrheic from previous medical treatments, under 50 years, and/or perimenopausal. Adult females not of childbearing potential are defined as females who have had a natural menopause (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, have not had menses at any time in the preceding 24 consecutive months), a hysterectomy or bilateral oophorectomy.

12. Males must also agree to refrain from donating sperm while on pomalidomide and for 4 weeks after discontinuation from this study treatment.
13. All subjects must agree to refrain from donating blood while on study treatment and for 4 weeks after discontinuation from this study treatment.
14. All subjects must agree not to share medication.

7.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subjects who had documented progressive disease during therapy or within 60 days of the last dose of a bortezomib-containing therapy under the 1.3 mg/m^2 dose twice weekly dosing schedule
2. Peripheral neuropathy Grade 3, Grade 4 or Grade 2 with pain within 14 days prior to randomization
3. Non-secretory multiple myeloma
4. Any of the following laboratory abnormalities:
   - Absolute neutrophil count (ANC) < 1,000/μL
   - Hemoglobin < 8 g/dL (< 4.9 mmol/L)
   - Platelet count < 75,000/μL for subjects in whom < 50% of bone marrow nucleated cells are plasma cells; or a platelet count < 30,000/ μL for subjects in whom ≥ 50% of bone marrow nucleated cells are plasma cells
   - Corrected serum calcium > 13.5 mg/dL (> 3.4 mmol/L)
   - Serum SGOT/AST or SGPT/ALT > 3.0 x upper limit of normal (ULN)
   - Serum total bilirubin > 1.5 x ULN
5. Subjects with severe renal impairment (Creatinine Clearance [CrCl] <30 mL/min) requiring dialysis
6. Subjects with prior history of malignancies, other than MM, unless the subject has been free of the disease for ≥ 5 years with the exception of the following non-invasive malignancies:
   - Basal cell carcinoma of the skin
   - Squamous cell carcinoma of the skin
   - Carcinoma *in situ* of the cervix
   - Carcinoma *in situ* of the breast
   - Incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) or prostate cancer that is curative.
7. Previous therapy with pomalidomide

8. History of anaphylaxis or hypersensitivity to thalidomide, lenalidomide, bortezomib, boron, mannitol, or dexamethasone
9. ≥ Grade 3 rash during prior thalidomide or lenalidomide therapy
10. Incidence of gastrointestinal disease that may significantly alter the absorption of pomalidomide
11. Subjects with any one of the following:
    - Clinically significant abnormal ECG finding at screening
    - Congestive heart failure (New York Heart Association Class III or IV)
    - Myocardial infarction within 12 months prior to starting study treatment
    - Unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris
12. Subjects who received any of the following within the last 14 days of initiation of study treatment:
    - Plasmapheresis
    - Major surgery (kyphoplasty is not considered major surgery)
    - Radiation therapy other than local therapy for myeloma associated bone lesions
    - Use of any systemic anti-myeloma drug therapy
13. Use of any investigational agents within 28 days or 5 half-lives (whichever is longer) of treatment
14. Subjects with conditions requiring chronic steroid or immunosuppressive treatment, such as rheumatoid arthritis, multiple sclerosis, and lupus, which likely need additional steroid or immunosuppressive treatments in addition to the study treatment. Includes subjects receiving corticosteroids (> 10 mg/day of prednisone or equivalent) within 3 weeks prior to enrollment.
15. Subjects unable or unwilling to undergo protocol required thromboembolism prophylaxis or herpes zoster prophylaxis will not be eligible to participate in this study
16. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study
17. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subjects from signing the informed consent form
18. Pregnant or breastfeeding females
19. Known seropositive for or active viral infection with human immunodeficiency virus (HIV)
20. Known active viral infection with hepatitis A virus (HAV).
21. Known seropositive for or active viral infection with hepatitis B virus (HBV):
    - Subjects who are HBsAg negative and viral DNA negative are eligible.

- Subjects who had hepatitis B but have received an antiviral treatment and show non-detectable viral DNA for 6 months are eligible.
- Subjects who are seropositive because of hepatitis B virus vaccine are eligible.

22. Known seropositive for or active viral infection with hepatitis C virus (HCV):
    - Subjects who had hepatitis C but have received an antiviral treatment and show no detectable viral RNA for 6 months are eligible.

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product(s)

This section contains a summary of prescribing information on pomalidomide, bortezomib, and dexamethasone; full prescribing information and labeling should be reviewed and is contained in the respective current US Prescribing Information, EU Summary of Product Characteristics (SmPC), or equivalent document for the specific region/country.

CC-4047 Pomalidomide

Pomalidomide will be supplied as Investigational Product (IP) by Celgene Corporation for all countries as 1 mg, 2 mg, 3 mg, and 4 mg capsules for oral administration. IP will be packaged in bottles containing a 21-day supply. IP should be stored as instructed in the IP packaging label, in an area free of environmental extremes and must be accessible only to study personnel.

Bortezomib (Velcade®)

Investigative sites in the United States and Japan will use commercially available bortezomib (Velcade®) for this study and will dispense this drug to subjects via prescription. The package insert should be consulted for handling, reconstitution, administration, and storage details.

For investigative sites outside of the United States and Japan, bortezomib supplies will be provided as commercial material labeled appropriately as Investigational Product (IP) by Celgene Corporation. Bortezomib will be provided in a 3.5 mg vial as Powder for Solution for Injection. IP should be stored as instructed in the IP packaging label, in an area free of environmental extremes, and must be accessible only to study personnel. Bortezomib must be reconstituted by a healthcare professional. Each 3.5 mg single-use vial of bortezomib must be reconstituted with 1.4 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. Dissolution of the lyophilised powder is completed in less than 2 minutes. After reconstitution, each ml solution contains 2.5 mg bortezomib. The reconstituted solution is clear and colorless, with a final pH of 4 to 7. The reconstituted solution must be inspected visually for particulate matter and discoloration prior to administration. If any discoloration or particulate matter is observed, the reconstituted solution must be discarded. The reconstituted solution should be used immediately after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. However, the chemical and physical in-use stability of the reconstituted solution has been demonstrated for 8 hours at 25°C stored in the original vial and/or a syringe. The total storage time for the reconstituted medicinal product should not exceed 8 hours prior to administration.

As bortezomib 2.5 mg/ml reconstituted solution for injection is to be administered subcutaneously, local injection site reactions may occur. In these cases a less concentrated bortezomib solution (reconstituted to 1 mg/ml instead of 2.5 mg/ml) may be administered subcutaneously.

Dexamethasone

Investigative sites in the United States will use commercially available dexamethasone for this study and will dispense this drug to subjects via prescription.

For investigative sites outside of the United States, dexamethasone supplies will be provided as commercial material labeled appropriately as Investigational Product (IP) by Celgene Corporation. Dexamethasone will be provided as 2 mg and 4 mg strength tablets. The 2 mg tablets will be packaged in 50-count bottles and 4 mg tablets will be packaged in 20-count blister cards. IP should be stored as instructed in the IP packaging label, in an area free of environmental extremes, and must be accessible only to study personnel.

Other recommended/required concomitant medications per the protocol such as aspirin (or other antithrombotic or anti-coagulants), viral prophylaxis, and growth factors will be provided by the investigative site. Celgene will not provide these medications.

8.2. Treatment Administration and Schedule

Subjects will be randomized in a 1:1 ratio to Treatment Arm A or B, respectively.

Subjects taking oral pomalidomide will be instructed to return the study drug bottles (and any remaining study drug) at the next visit for drug accountability purposes. For FCBP, study drug will not be dispensed until the investigator has verified that the results of the pregnancy test are negative. Any FCBP other than the subject should not handle study drug unless wearing gloves.

8.2.1. Treatment Arm A: (POM + BTZ + LD-DEX)

Treatment Arm A: Subjects randomized to Treatment Arm A (POM + BTZ + LD-DEX) will receive the following:

- Oral POM 4 mg/day on Days 1 to 14 of each 21-day treatment cycle

[redacted]

- BTZ
  - For Cycles 1 – 8: 1.3 mg/m^2/dose on Days 1, 4, 8, and 11 of a 21-day cycle
  - For Cycles 9 onwards: 1.3 mg/m^2/dose on Days 1 and 8 of a 21-day cycle

Bortezomib doses must be at least 72 hours apart.

Bortezomib will be administered SQ for all subjects consented after Protocol Amendment 1 activation. Subjects consented prior to Protocol Amendment 1 activation may continue to receive IV bortezomib or may be switched to SQ bortezomib at the treating physician's discretion.

- Oral DEX
  - For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle.
  - For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

8.2.2. Treatment Arm B: (BTZ + LD-DEX)

Treatment Arm B: Subjects randomized to Treatment Arm B (BTZ + LD-DEX) will receive the following:

- BTZ
  - For Cycles 1 – 8: 1.3 mg/m^2/dose on Days 1, 4, 8, and 11 of a 21-day cycle
  - For Cycles 9 onwards: 1.3 mg/m^2/dose on Days 1 and 8 of a 21-day cycle

Bortezomib doses must be at least 72 hours apart.

Bortezomib will be administered SQ for all subjects consented after Protocol Amendment 1 activation. Subjects consented prior to Protocol Amendment 1 activation may continue to receive IV bortezomib or may be switched to SQ bortezomib at the treating physician's discretion.

- Oral DEX
  - For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle.
  - For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

8.3. Overdose

Overdose, as defined for this protocol, refers to pomalidomide, bortezomib and dexamethasone dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of pomalidomide, bortezomib, or dexamethasone assigned to a given patient, regardless of any associated adverse events or sequelae.

- PO any amount over the protocol-specified dose
- IV 10% over the protocol-specified dose
- SC 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form. See Section 11.1 for the reporting of adverse events associated with overdose.

8.4. Dose Modification and Interruption

Dosing interruptions and reductions are permitted throughout the study. Subjects will be evaluated for adverse events at each visit with the NCI CTCAE (version 4.0 or higher) used as a

guide for the grading of severity. Dosing is to be modified in subjects who experience a dose-limiting toxicity (DLT) as described in the following appropriate sections.

In the event of any pomalidomide dose reduction for a subject randomized to Treatment Arm A in the United States, site staff must contact IVRS/IWRS to record the new dose level and obtain the new study treatment assignment. For sites in Japan, in the event of a dose reduction for POM and/or DEX for subjects randomized to Treatment Arm A or B, site staff must contact IVRS/IWRS to record the new dose level and obtain the new study treatment assignment. In the event of any dose reductions for subjects randomized to either Treatment Arm A or B outside of the United States and Japan, site staff must contact IVRS/IWRS to record the new dose level and obtain the new study treatment assignment.

If the treatment has been interrupted and the next cycle is delayed beyond 21 days after Day 1 of the prior cycle, then Day 1 of the next cycle will be defined as the first day that treatment is resumed.

For Treatment Arm A (POM+BTZ+LD-DEX):

- If POM dosing is withheld, then BTZ and LD-DEX dosing may be continued at the discretion of the treating physician.
- If POM is permanently discontinued, then the subject must be permanently discontinued from all study treatments.
- If BTZ dosing is withheld or permanently discontinued, then POM and LD-DEX may be continued at the discretion of the treating physician.
- If BTZ and LD-DEX dosing is withheld or permanently discontinued, then POM may be continued at the discretion of the treating physician.
- If both POM and BTZ dosing is withheld, then LD-DEX must also be withheld.
- If LD-DEX dosing is withheld or permanently discontinued, then POM and BTZ may be continued.

For Treatment Arm B (BTZ+LD-DEX):

- If BTZ dosing is withheld, then LD-DEX dosing must also be withheld.
- If BTZ is permanently discontinued, then the subject must be permanently discontinued from all study treatments.
- If LD-DEX is withheld or permanently discontinued, then BTZ may be continued.

8.4.1. Dose Modification Instructions for Pomalidomide

Detailed instructions for pomalidomide dose interruptions and reductions are provided in Table 2 and Table 3 outlines the dose reduction steps for pomalidomide.

Table 2: Dose Modification Instructions for Pomalidomide (Treatment Arm A only)

Toxicity	Dose Modification
Neutropenia Grade 4 neutropenia (ANC < 500/μL) or Febrile neutropenia (fever ≥ 38.5°C and ANC < 1,000/μL)	Withhold the dose for remainder of cycle. If the subject was not receiving Granulocyte colony-stimulating factor (G-CSF) therapy, G-CSF therapy may be started at the discretion of the treating physician. On Day 1 of the next cycle, the dose of pomalidomide may be maintained if neutropenia was the only pomalidomide-related toxicity requiring a dose modification and G-CSF treatments are continued. Otherwise, decrease by one dose level at start of next cycle. Note, ANC must be ≥ 1000/ μL to resume dosing.
Thrombocytopenia Grade 4 Thrombocytopenia (Platelets <25,000/μL)	Withhold the dose for remainder of cycle. Dosing may resume at one dose level lower once the platelet count has recovered to ≥ 50,000/μL.
Rash = Grade 3	Withhold dose for remainder of cycle. Decrease by one dose level when dosing is resumed at next cycle (rash must be resolved or improved to ≤ Grade 1 before dose resumption).
Rash = Grade 4 or Blistering	Permanently discontinue study treatment.
Constipation ≥ Grade 3	Withhold dose for remainder of cycle. Initiate bowel regimen. Decrease by one dose level when dosing is resumed at next cycle (constipation must be resolved or improved to ≤ Grade 2 before dose resumption).
Venous Thromboembolic Event (VTE) ≥ Grade 3	Withhold dose for remainder of cycle. Initiate anticoagulation treatment. Maintain dose level when dosing resumed at next cycle at discretion of treating physician.
Other ≥ Grade 3 pomalidomide-related adverse events[a]	Withhold dose for remainder of cycle. Decrease by one dose level when dosing resumed at next cycle (adverse event must be resolved or improved to ≤ Grade 2 before restarting dosing).

[a] For Grade 3 or 4 AEs that are not considered to be related to pomalidomide, the treating physician should consult with the Celgene Medical Monitor for dose interruptions and reductions.

To initiate a new cycle of pomalidomide following a dose interruption, the neutrophil count must be ≥ 1000/μL with or without G-CSF, the platelet count must be ≥ 50,000/μL, and non-hematologic AEs must be resolved or improved as outlined in Table 2.

If recovery from toxicities is prolonged and POM dose withholding is beyond 14 days, then the dose of pomalidomide should be decreased by one dose level when dosing is resumed in the new cycle.

Table 3 outlines the dose reduction steps for pomalidomide.

Table 3: Pomalidomide Dose Reduction Steps

Dose Level	Oral Pomalidomide Dose (Days 1-14 of 21-day cycle)
Starting Dose	4 mg
Dose Level -1	3 mg
Dose Level -2	2 mg
Dose Level -3	1 mg

The minimum permitted dose level for pomalidomide is 1 mg. No dose re-escalation is permitted for pomalidomide.

8.4.2. Dose Modification Instructions for Bortezomib

Table 4 details instructions for bortezomib dose interruptions and reductions and Table 5 outlines the dose reduction levels for bortezomib; however, dose modification decisions for bortezomib will be at the treating physician's discretion per the full prescribing information and labeling in the respective current US Prescribing Information, EU Summary of Product Characteristics (SmPC), or equivalent document for the specific region/country.

Table 4: Bortezomib Dose Modification

Toxicity	Bortezomib Dose Modification
≥ Grade 3 non-hematological toxicity (excluding neuropathy)	Withhold bortezomib until the symptoms of the toxicity have resolved, bortezomib therapy may be reinitiated at reduced bortezomib dosing by 1 dose level
Grade 4 hematological toxicity	Withhold bortezomib until the symptoms of the toxicity have resolved, bortezomib therapy may be reinitiated at reduced bortezomib dosing by 1 dose level
Grade 1 neuropathy without pain or loss of function	No action
Grade 1 neuropathy with pain or Grade 2 neuropathy	Reduce bortezomib dosing by one level
Grade 2 neuropathy with pain or Grade 3 neuropathy	Withhold bortezomib until toxicity resolves, bortezomib therapy may be reinitiated at a reduced dose level of 0.7 mg/m^2 and change treatment schedule to once per week (Days 1 and 8 of a 21-day cycle)
Grade 4 neuropathy	Permanently discontinue study treatment

Table 5: Bortezomib Dose Reduction Levels

Dose Level	Bortezomib Dose Level (Cycle 1-8: Days 1, 4, 8, 11 of a 21-day cycle Cycle ≥ 9: Days 1, 8 of a 21-day cycle)
Starting Dose	1.3 mg/m^2
Dose Level -1 (25% reduction from starting dose)	1 mg/m^2
Dose Level -2 (25% reduction from dose level -1)	0.7 mg/m^2

The minimum permitted dose level for bortezomib is 0.7 mg/m^2. No dose re-escalation is permitted for bortezomib.

8.4.3. Dose Modification Instructions for Low-Dose Dexamethasone

Table 6 details instructions for low-dose dexamethasone dose interruptions and reductions and Table 7 outlines the dose reduction steps for low-dose dexamethasone, however; dose withholding / resumption decision is at the treating physician's discretion per the full prescribing information and labeling in the respective current US Prescribing Information, EU Summary of Product Characteristics (SmPC), or equivalent document for the specific region/country.

Table 6: Dose Reductions for Low-Dose Dexamethasone Related Toxicities

Toxicity	Low-Dose Dexamethasone Dose Modification
Dyspepsia = Grade 1-2	Maintain dose and treat with histamine (H2) blockers or equivalent. Decrease by one dose level if symptoms persist.
Dyspepsia ≥ Grade 3	Withhold dose until symptoms are controlled. Add H2 blocker or equivalent and decrease one dose level when dosing is resumed.
Edema ≥ Grade 3	Use diuretics as needed and decrease dose by one dose level.
Confusion or mood alteration ≥ Grade 2	Withhold dose until symptoms resolve. When dosing is resumed decrease dose by one dose level.
Muscle weakness (steroid myopathy) ≥ Grade 2	Withhold dose until muscle weakness ≤ Grade 1. When dosing is resumed decrease dose by one dose level.
Hyperglycemia ≥ Grade 3	Decrease dose by one dose level. Treat with insulin or oral hypoglycemic agents as needed.
Acute pancreatitis	Discontinue dexamethasone from treatment regimen.
Other ≥ Grade 3 dexamethasone-related adverse events	Stop dexamethasone dosing until the adverse event resolves to ≤ Grade 2. Decrease by one dose level when dosing is resumed.

If recovery from toxicities is prolonged and LD-DEX dose withholding is beyond 14 days, then the dose of dexamethasone will be decreased by one dose level when dosing is resumed in the new cycle.

Table 7: Low-Dose Dexamethasone Dose Reduction Steps

Dose Level	≤ 75 years old Dose (Cycle 1-8: Days 1, 2, 4, 5, 8, 9, 11, 12 of a 21-day cycle Cycle ≥ 9: Days 1, 2, 8, 9 of a 21-day cycle)	> 75 years old Dose (Cycle 1-8: Days 1, 2, 4, 5, 8, 9, 11, 12 of a 21-day cycle Cycle ≥ 9: Days 1, 2, 8, 9 of a 21-day cycle)
Starting Dose	20 mg	10 mg
Dose Level -1	12 mg	6 mg
Dose Level -2	8 mg	4 mg

Dexamethasone should be discontinued if subject is unable to tolerate 8 mg if ≤ 75 years old or 4 mg if > 75 years old.

8.5. Method of Treatment Assignment

This study will utilize the IVRS/IWRS for randomization. Designated research personnel at each investigational sites will be assigned password protected, coded identification numbers which gives them the authorization to call into IVRS/IWRS to randomize eligible subjects.

Celgene trial staff will review specific eligibility criteria for all screened subjects prior to randomization of subjects via the IVRS/IWRS. Celgene trial staff will be required to activate a subjects in the IVRS/IWRS before site staff may randomize and obtain the treatment assignment via IVRS/IWRS.

For sites in the US, in the event of any dose reduction for POM, site staff must contact IVRS/IWRS to record the new dose level and obtain the new study treatment assignment. For sites in Japan, in the event of a dose reduction for POM and/or DEX, site staff must contact IVRS/IWRS to record the new dose level and obtain the new study treatment assignment. For sites outside the US and Japan, in the event of any dose reductions for POM, BTZ and DEX, site staff must contact IVRS/IWRS to record the new dose level and new study treatment assignment.

8.6. Packaging and Labeling

The label(s) for IP will include sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

8.7. Investigational Product Accountability and Disposal

US Sites:

Pomalidomide will be provided to all US sites by Celgene and labeled as Investigational Product (IP), as such, the investigator(s) or designee(s) is responsible for taking an inventory of each shipment of IP received, and comparing it with the accompanying study drug shipping order form. The investigator(s) or designee(s) will verify the accuracy of the information on the form

and call the IVRS to register the study medication received at the site. At the study site, IP will be stored according to the storage conditions described on the IP packaging label in a locked, safe area to prevent unauthorized access. The IP must be stored as directed on IP packaging label at controlled temperature and a temperature log must be maintained in the source documents.

Pomalidomide IP accountability prior to dispensation will be assessed by the investigator or designee. Applicable information such as lot number, capsule count and expiration date should be collected, as well as information provided by the subject or the caregiver (eg, subject dosing diary). Investigational Product accountability should be assessed before drug dispensing for each subsequent treatment cycle in the treatment phase, starting on Day 1 of Cycle 2, and at the Treatment Discontinuation visit. The investigator(s) or designee(s) is responsible for accounting for all IP that is issued to and returned by the subject during the course of the study according to applicable regulatory requirements. Any unused IP must be returned by a study subject and retained by the investigative site for accountability to be conducted by a Celgene representative (or designee). If any IP is lost or damaged, its disposition should be documented. At the periodic monitoring visits, a Celgene representative (or designee) will conduct IP accountability and address any discrepancies. Upon satisfactory reconciliation of all IP, returned IP may be destroyed. At the conclusion of the study, all remaining study drug will be counted, reconciled with dispensing records, documented, and destroyed at the clinic site or allocated drug destruction location after completion of drug accountability by a Celgene representative (or designee). The Celgene representative (or designee) will ensure that a final report of drug accountability to the unit dose level (ie, tablet) is prepared and placed in both the investigator study file and the central clinical study file.

Celgene Corporation will instruct the investigator(s) on the return, disposal and destruction of Pomalidomide. A copy of the site's Standard Operating Procedure (SOP) for drug destruction may be collected by the sponsor (or designee). Any revisions to a site's destruction process must be provided and approved by the sponsor (or designee) prior to implementation on this protocol. Any site without a sponsor (or designee) approved destruction SOP and process will be required to return IP to Celgene.

Ex-US Sites:

At sites outside of the United States and Japan, Celgene will provide Pomalidomide, Dexamethasone and Bortezomib (Velcade) labeled as Investigational Product (IP). At Japanese sites, Celgene will provide pomalidomide and dexamethasone labeled as Investigational Product (IP). Each investigative site participating in this study will be responsible for accountability of all Celgene-provided drug products. The investigator(s) or designee(s) is responsible for taking an inventory of each shipment of each product received, and comparing it with the accompanying study drug shipping order form. The investigator(s) or designee(s) will verify the accuracy of the information on the form and call the IVRS to register the study medication received at the site. At the study site, all IP will be stored according to the storage conditions described on the IP packaging label in a locked, safe area to prevent unauthorized access. The IP must be stored as directed on IP packaging label at controlled temperature and a temperature log must be maintained in the source documents.

Pomalidomide, Dexamethasone and Bortezomib accountability prior to dispensation/ administration will be assessed by the investigator or designee. Applicable information such as lot number, capsule/tablet count, vial administered and expiration date should be collected, as well as information provided by the subject or the caregiver (eg, subject dosing diary). Investigational Product accountability should be assessed before drug dispensing for each subsequent treatment cycle in the treatment phase, starting on Day 1 of Cycle 2, and at the Treatment Discontinuation visit. The investigator(s) or designee(s) is responsible for accounting for all IP that is issued to and returned by the subject during the course of the study according to applicable regulatory requirements. Any unused IP must be returned by a study subject and retained by the investigative site for accountability to be conducted by a Celgene representative (or designee). If any IP is lost or damaged, its disposition should be documented. At the periodic monitoring visits, a Celgene representative (or designee) will conduct IP accountability and address any discrepancies. Upon satisfactory reconciliation of all IP, returned IP may be destroyed. At the conclusion of the study, all remaining study drug will be counted, reconciled with dispensing records, documented, and destroyed at the clinic site or allocated drug destruction location after completion of drug accountability by a Celgene representative (or designee). The Celgene representative (or designee) will ensure that a final report of drug accountability to the unit dose level (ie, tablet) is prepared and placed in both the investigator study file and the central clinical study file.

Celgene Corporation will instruct the investigator(s) on the return, disposal and destruction of each IP. A copy of the site's Standard Operating Procedure (SOP) for drug destruction may be collected by the sponsor (or designee). Any revisions to a site's destruction process must be provided and approved by the sponsor (or designee) prior to implementation on this protocol. Any site without a sponsor (or designee) approved destruction SOP and process will be required to return IP to Celgene.

8.8. Investigational Product Compliance

US & Ex-US sites

The Investigator and/or designee will document the number of capsules of pomalidomide issued to and returned by each subject at each study visit. The Investigator and/or designee will also be responsible for documenting subject compliance for bortezomib and dexamethasone for the study. Study site personnel will review the dosing information with the subject (or legally authorized representative) on scheduled clinic visit days. Study site personnel will perform an IP administration compliance check and record this information in the subject's source documentation and on the appropriate CRF. Administration of all IP will be recorded including dispensing, dosing, and any changes in dosage administration such as interruption or reduction in dosing due to an AE.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Permitted Concomitant Medications and Procedures

Other therapies considered necessary for the subject's well being may be administered at the discretion of the investigator. These therapies may include antibiotics, analgesics, antihistamines, or other medications and transfusions of red blood cells, platelets, or fresh frozen plasma given to assist in the management of complications associated with MM or its therapy.

Subjects with myeloma-associated bone lesion may receive bisphosphonate therapy throughout the study, unless such therapy is contraindicated. The use of hematopoietic growth factors is permitted (the use of myeloid growth factors is encouraged when the absolute neutrophil count is less than 1,000/μL) at the discretion of the treating physician.

Subjects who fail absolute neutrophil count (ANC), hemoglobin or platelet eligibility criteria at screening CANNOT be re-tested for the study after being treated with growth factors or platelet/blood transfusion. However, subjects who meet the ANC, hemoglobin and platelet eligibility criteria due to growth factor treatment or platelet/blood transfusion received prior to screening are acceptable and are not considered as screening failures.

Radiation therapy to a pathological fracture site or to treat bone pain is permitted. Such subjects are allowed to remain on the treatment phase of the study.

The use of steroids is limited to the dexamethasone dose described in the study. Please see Section 9.2 for further details.

All therapies administered during the study will be recorded on the Concomitant Medication eCRF page.

In the event of any treatment emergent adverse events, the treating physician may order any medically necessary unscheduled local laboratory procedures or exams to be performed.

9.2. Prohibited Concomitant Medications and Procedures

Concomitant use of other approved or investigational anti-myeloma therapy while the subject is taking study treatment is prohibited. Subsequent anti-myeloma treatment should not be initiated prior to PD.

Chronic use of steroids or any other immunosuppressive therapies is prohibited in this study. Use of inhaled, topical, intranasal corticosteroids or local steroid injections (eg, intra-articular injection) is permitted.

Drugs known to prolong QT corrected (QTc) interval should be avoided unless deemed medically necessary. See Appendix G for link to a comprehensive list of drugs known to prolong QTc. A thorough QT study (CC-4047-CP-010) was conducted in healthy subjects according to the E14 Guidance to assess the potential of Pomalidomide (POM) to delay cardiac re-polarization, especially as prolongation of the QT interval. The result of the QT prolongation assessment was observed to be negative, indicating a low risk of POM-associated QT prolongation.

9.3. Required Concomitant Medications and Procedures

Recent or active cancer is a recognized prothrombotic risk factor for increasing the risk of VTE. Increased plasma viscosity related to monoclonal paraproteinemia has been implicated as a risk factor for VTE in MM subjects. Clinical studies have shown that thalidomide and lenalidomide in combination with dexamethasone or other chemotherapeutic agents increase the risk of VTE (Baz, 2005; Weber, 2007). Aspirin has been reported to be effective in reducing the incidence of deep vein thrombosis (DVT) in MM subjects treated with thalidomide or lenalidomide (Baz, 2005). For the current study, low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anti-coagulant will be given during the study to all subjects assigned to Treatment Arm A, as well as to Treatment Arm B subjects who have a prior history of deep vein thrombosis (DVT) or pulmonary embolism (PE). Antithrombotic prophylaxis will be recorded on the eCRF at each visit. At the discretion of the treating physician, other Treatment Arm B subjects may receive the same antithrombotic prophylaxis as those in Treatment Arm A. Subjects who develop symptomatic DVT will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method. The IDMC will review safety data on a regular basis to ensure subjects are adequately protected from any potential risk. Diagnostic algorithms are provided in Appendix A.

As per the Velcade® Prescribing Information (October 2014), antiviral prophylaxis should be considered in subjects being treated with bortezomib. In the randomized studies in previously untreated and relapsed MM, herpes zoster reactivation was more common in subjects treated with bortezomib (13%) than in the control groups (4-5%). Herpes simplex was seen in 2-8% in subjects treated with bortezomib and 1-5% in the control groups. In the previously untreated MM study, herpes zoster virus reactivation in the bortezomib, melphalan, and prednisone arm was less common in subjects receiving prophylactic antiviral therapy (3%) than in subjects who did not receive prophylactic antiviral therapy (17%). In the post-marketing experience, rare cases of herpes meningoencephalitis and ophthalmic herpes have been reported.

10. STATISTICAL ANALYSES

10.1. Overview

This is a multicenter, randomized, open-label study to compare the efficacy and safety of POM + BTZ + LD-DEX versus BTZ + LD-DEX. For the POM + BTZ + LD-DEX treatment arm, the dose is based on the MTD study CC-4047-MM-005 using the same treatment combination POM + BTZ + LD-DEX.

10.2. Study Population Definitions

Three study populations will be used for analysis:

- The intent-to-treat (ITT) population: All randomized subjects. The primary efficacy analysis will be based on this population
- Safety population: All randomized subjects who take at least one dose of study medication. All safety analyses will be based on this population
- Efficacy Evaluable (EE) population: All ITT subjects who take at least one dose of study medication and who have a baseline and at least one post-baseline efficacy assessment

10.3. Sample Size and Power Considerations

Based on the primary endpoint PFS, at 2-sided significance level of 5%, with one interim analysis for futility only, an estimated total of 381 disease progression/death events are required to detect a 33% increase in median PFS in the POM treatment arm (Treatment Arm A; median = 12 months) compared to that in the comparator arm (Treatment Arm B; median = 9 months) with 80% power. In order to obtain PFS events from approximately 70% of the study ITT population for the final PFS analysis, a total of 544 randomized subjects are required to test the hypothesis. The interim analysis on PFS will take place when approximately 50% PFS information (191 events) has occurred. The interim analysis results will be examined for futility only with the pre-specified type II error spending functions described in Section 10.9.

Celgene amended the protocol in Amendment 5 to perform the final PFS analysis earlier than originally planned (381 PFS events). Recently published data from a number of Phase 3 studies revealed that the progression-free survival (PFS) of the bortezomib with low-dose dexamethasone (BTZ+LD-DEX) arm on this study CC-4047-MM-007 (OPTIMISMM), that requires prior treatment with lenalidomide as per Protocol Inclusion Criteria #7 (Section 7.2), is expected to be shorter than the original OPTIMISMM protocol statistical assumption of 9 months (relevant median PFS data from Phase 3 ENDEAVOR, PANORAMA-1 and CASTOR studies ranging from 7 to 8 months) (Moreau, 2017; Palumbo, 2016; San-Miguel, 2014).

Subsequently, if the assumption for the pomalidomide, bortezomib and low-dose dexamethasone (POM+BTZ+LD-DEX) arm and other study assumptions remain unchanged, the number of PFS events required for the final analysis would be less than originally planned. The data cutoff date for the revised final PFS analysis will be October 2017, by which time approximately 320 PFS events are projected to be reached, representing an approximate 57% event rate (out of 559 randomized patients). This would allow for 80% power to test a median PFS of 12 months in Arm A versus 8.8 months in Arm B, corresponding to an estimated hazard ratio of 0.73.

Overall survival (OS) will be tested if PFS and ORR results are significant (see Section 10.10). With one planned interim analysis OS at the time of the final PFS analysis (estimated to be at approximately 50% OS information), at a 2-sided overall significance level of 5%, a total of 379 deaths are required to detect a 33% increase in median OS in the POM treatment arm (Treatment Arm A; median = 40 months) compared with that of the comparator arm (Treatment Arm B; median= 30 months) with 75% power.

Sample size calculation is conducted using EAST® Version 6.

10.4. Background and Demographic Characteristics

All baseline demographic and disease characteristics will be presented by treatment. Continuous variables such as subjects' age, height, weight, and some baseline disease characteristics will be summarized using descriptive statistics, while categorical and ordinal variables such as gender, race and some baseline disease characteristics will be summarized using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

10.5. Subject Disposition

Subject disposition (analysis population allocation, randomized, dosed, discontinued, along with primary reason for discontinuation) will be summarized by treatment using frequency and percent for both study treatment and follow-up phases. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

10.6. Efficacy Analysis

10.6.1. Primary Endpoint: Progression Free Survival (PFS)

Progression free survival (PFS) will be calculated as the time between the randomization and PD, as determined by the IRAC based on the International Myeloma Working Group Uniform Response criteria (IMWG), or death in the study treatment or PFS follow-up phase, whichever occurs earlier. PFS using the EBMT response criteria will also be performed as an exploratory analysis.

Subjects who withdrew study treatment for any reason or received other anti-myeloma therapy without documented PD (as determined by the IRAC) will be censored on the date of their last response assessment in the study treatment phase prior to the study treatment discontinuation or initiation of other anti-myeloma therapy, respectively. Subjects who are in the study treatment phase at the time of the data cut-off date without PD will be censored on the date of their last adequate response assessment. These rules are based on the FDA guidance for cancer trial endpoints (FDA Guidance, 2007), and the following table (Table 8) specifies the application of the guidance for various common situations for the calculation of PFS.

Table 8: Censoring Rules for PFS

Situation	Date of Progression or Censoring	Situation Outcome
No baseline assessments and alive after 2 scheduled assessments	Randomization	Censored
Death within the first two scheduled assessments without any adequate response assessment	Date of death	Event
Progression documented between scheduled assessments	Earliest of: **1.** Date of M-protein assessment showing increase in serum monoclonal paraprotein and/or urine paraprotein **2.** Date of bone marrow assessment showing increase in bone marrow plasmacytosis and plasma cells **3.** Date of plasmacytoma assessment showing appearance of new soft tissue plasmacytomas or increase in size of existing plasmacytoma(s) **4.** Date of skeletal survey showing appearance of new lytic bone lesions or increase in the size of the existing bone lesions **5.** Date of lab test showing development of hypercalcemia serum calcium >11.5 mg/dl	Event
Death between adequate assessments	Date of death	Event
No progression	Date of last adequate assessment with evidence of no progression	Censored
Study discontinuation for reasons other than disease progression or death	Date of last adequate assessment with evidence of no progression	Censored
New anti-myeloma /non-protocol treatment started prior to progression	Date of last adequate assessment with evidence of no progression prior to the start of new anti-myeloma treatment	Censored
Death or progression after an extended lost-to-follow-up time (two or more missed scheduled assessments)	Date of last adequate assessment with evidence of no progression	Censored

PFS will be compared between treatment arms using a log-rank test stratified by the three baseline factors used in the randomization. In terms of the survival functions for treatment arm comparison, the null and alternative hypotheses are as follows:

$$H_0: Sa(t) = Sc(t) \text{ for all } t$$
versus
$$H_1: Sc(t) \neq Sa(t) \text{ for all } t$$

where Sc is the survivor function for the control arm and Sa is the survival function for the treatment arm.

The Kaplan-Meier method will be used to estimate the survival distribution functions for each treatment arm. The median PFS along with the two-sided 95% confidence interval for the median will be estimated. In addition, the probabilities of progression –free survival at specific time-points (eg, 26, 52, 78, and 104 weeks) will be computed, with corresponding standard errors (Greenwood's formula, Klein and Moeschberger 2003). The plots of survival curves using the Kaplan-Meier method will be presented. A Cox proportional hazards model will be used to estimate hazard rate (risk) ratio along with 95% CIs.

An unstratified log-rank test will be performed as a secondary analysis for PFS, in addition to the stratified analysis described above.

10.6.2. Secondary Endpoints

10.6.2.1. Overall Survival

Overall survival (OS) is calculated as the time from randomization to death from any cause. Subjects who died will be considered as having OS events on the date of death. All subjects who are lost to follow-up prior to the date of data cut-off or who withdrew consent from the trial will be censored at the last date known to be alive. Subjects who are still in the study treatment phase at the date of data cut-off will be censored at the last available date that the subject is known to be alive, or data cut-off date, whichever is earlier.

OS will be compared between treatment arms (ie, POM + BTZ + LD-DEX vs. BTZ + LD-DEX). The same statistical methods used for the PFS analysis will be used for the OS analysis. The analysis of OS will be based on all data available, including the survival data from the study treatment phase, PFS follow-up phase and the long-term follow-up phase.

10.6.2.2. Response Assessment by the IMWG Criteria

Tumor response, including PD, will be assessed by the investigators and the IRAC, using the IMWG criteria (Appendix B). The primary analysis for response will be based on the IRAC's assessments. The response assessments by investigators will be presented separately.

The overall response rate [ORR; as defined as at least a PR] will be calculated as the number of confirmed responders divided by the number of subjects by treatment in the ITT population. The ORR together with the relative proportions in each response category (ie, stringent CR [sCR], CR, very good PR [VGPR], PR, SD, and PD) by treatment using the IMWG criteria will be examined. Confirmed responses that are documented after the initiation of other anti-myeloma treatment will not be counted as responses. However, these subjects will be included in the denominator for ORR calculation.

Comparisons of ORR between treatment arms will be performed using a stratified Cochran-Mantel-Haenszel test by adjusting for the stratification factors. The distribution of subjects in the 6 response categories (excluding the 'Response not Evaluable (NE)' category) will be compared between treatment arms using the Wilcoxon rank sum test (1=sCR, 2 = CR, 3 = VGPR, 4 = PR, 5 = SD, 6 = PD).

10.6.2.3. Duration of Response

Duration of myeloma response is defined as the duration from the time when the IMWG response criteria are first met for sCR or CR or VGPR or PR until the first date the response criteria are met for PD or until the subject died from any cause, whichever occurs first. Duration of response for subjects last known to be alive with no progression after a sCR or CR or VGPR or PR will be censored at the date of last adequate response assessment. Subjects with confirmed responses that occurred after receiving any other anti-myeloma therapy will be censored at the last adequate assessment prior to the initiation of such treatment. Subjects who are non-responders will be excluded from this analysis. Duration of response will be analyzed using the same statistical method as that for PFS.

10.7. Safety Analysis

All safety analyses will be conducted in the safety population by treatment arms.

Adverse events (AEs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 14 or higher. The intensity of AEs will be graded according to the NCI CTCAE version 4.0 or higher.

Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first dose date of the study treatment and within 28 days after the last dose date. TEAEs, AEs leading to study medication discontinuation, AEs leading to dose reduction/interruption, AEs related to study medication, serious AEs and AE leading to death will be summarized by system organ class, and preferred term for each treatment arm. A summary of AEs with NCI CTCAE grade 3 or higher, as well as the most frequent AEs (preferred terms), AEs by relationship to study treatment, will be provided. A summary of AEs by dosing cycle based on onset date will also be provided.

If a subject experiences the same preferred term multiple times then the event will be counted only once and by greatest severity.

All deaths and reasons for death will be summarized. Death within 28 days of the first dose of study medication and within 28 days of the last dose of study medication will be summarized separately.

Clinical laboratory values will be graded according to NCI CTC version 4.0 or higher for applicable tests. Baseline grade and worst grade during treatment for selected laboratory results will be summarized. Shift from baseline to the worst grade observed during the treatment for selected laboratory results will also be provided.

For vital signs, shift from baseline to worst during the treatment in below, within, and above the normal ranges will be displayed in cross–tabulations. Summary statistics (N, Mean, Standard Deviation, Median, Minimum, and Maximum) of observed and change from baseline values will be presented.

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

Graphical displays will be provided where useful to assist in the interpretation of results.

10.8. Exploratory Endpoints

10.8.2. Exploratory Efficacy Analysis

10.8.2.1. Response using the EBMT Criteria

Tumor response, including PD, using the EBMT criteria (Appendix C) will be assessed by the IRAC only. The ORR together with the relative proportions in each response category will be examined. Responses after subjects receive other anti-myeloma treatments will be counted as the response for the new treatments received instead of the original study assigned treatments and will not be included in the response rate analysis.

Comparisons of ORR between treatment arms (2x2 table) will be performed using Fisher's exact test and odds ratio will be presented together with its 95% confidence intervals. The distribution of subjects in the 5 response categories (excluding the 'Response not Evaluable (NE)' category) will be compared between treatment arms using the Wilcoxon rank sum test (1= CR, 2 = PR, 3 = minimal response [MR], 4 = SD, 5 = PD).

10.8.2.2. Time to Progression and Time to Response

Time to progression (TTP) is defined as the time from randomization to the first documented disease progression based on the IMWG response criteria by the IRAC. Censoring for TTP is the same as for PFS except that death is not counted as an event. The same statistical methods used for PFS analysis will be used for the TTP analysis.

Time to response is calculated as the time from randomization to the initial documented response (PR or better) based on IMWG criteria. Time to response (responders only) will be compared between treatment arms using the Wilcoxon rank sum test, with subjects with the longest time to response having the highest rank.

10.8.2.3. Time to Treatment Failure

As a sensitivity analysis for PFS, time to treatment failure (TTF) will be calculated as the time from randomization to discontinuation of study treatment for any reason, including disease progression as determined by IRAC or investigator using either IMWG or EBMT response criteria, treatment discontinuation due to toxicity, initiation of other anti-myeloma treatment, and death. Subjects who have not discontinued the study treatment phase or the PFS follow-up phase at the time of analysis will be censored on the date of last assessment.

The same statistical methods used for the PFS analysis will be used for the TTF analysis.

10.8.2.4. Progression-free Survival 2 (PFS2)

PFS2 is defined as the time from randomization to second objective disease progression, or death from any cause, whichever occurs first, based on the ITT population. Patients who are alive and for whom a second objective disease progression has not been observed should be censored at the last time known to be alive and without second objective disease progression.

The Kaplan-Meier method will be used to estimate the survival distribution functions for each treatment arm. A Cox proportional hazards model will be used to estimate hazard rate (risk) ratio along with 95% CIs.

10.8.2.5. Sub-group Analysis

The effect of treatment on the key efficacy variables PFS, ORR and OS will be investigated within subgroups including following variables by their baseline values:

- Region (US vs. ex-US)
- Age group (≤ 75 years vs. > 75 years);
- Gender (Male vs. Female);
- ECOG Performance Status (0, 1 vs. 2)
- Baseline cytogenetic categories
- Number prior anti-myeloma regimen (1 vs. >1);
- β2M at screening (< 3.5 mg/L vs. ≥ 3.5 m/L – ≤ 5.5 mg/L vs. ≥ 3.5 mg/L)
- Prior bone marrow or peripheral stem transplantation (Yes vs. No)

The methods described in previous sections will be used for each subgroup separately.

Additional multivariate analyses on PFS and OS will be conducted to evaluate the treatment effect while adjusting for the above-mentioned factors.

10.8.3. Clinical Benefits

Clinical benefits include the following:

- Improvement in hemoglobin value (defined as at least one category improvement from baseline in CTCAE grade for hemoglobin level)

- Improvement in renal function (defined as at least one category improvement from baseline in CTCAE grade for serum creatinine),
- Improvement of ECOG performance status (defined as at least one category improvement from baseline in ECOG)
- Improvement in hypercalcaemia (defined as at least one category improvement from baseline in CTCAE grade for calcium level)
- Improvement in non-myeloma immunoglobulins (restoration to normal level)

Clinical benefits defined above will be compared between treatment arms using the Wilcoxon rank sum test, with subjects with the longest time to clinical benefit having the highest rank.

10.8.4. Quality of Life (QoL)

The European Organization for Research and Treatment of Cancer QoL Questionnaire for Patients with Multiple Myeloma (EORTC QLQ-MY20) Module and the European Organization for Research and Treatment of Cancer QoL Questionnaire for Patients with Cancer (EORTC QLQ-C30) Module will be used in this study.

The EORTC QLQ-C30 and EORTC-QLQ-MY20 will be analyzed using change from baseline and percentage of change from baseline according to the functional scores and the recommendations in the EORTC scoring manual.

EQ-5D scores will be derived for each subject using country-specific weights (primary analysis will be done using UK weights). Using EQ-5D scoring instructions, overall scores will be analyzed using change from the screening assessment at each post-screening time point. The worst change from screening among all available post-screening measurements for each subject will also be analyzed.

The expectation is that treatment with POM + BTZ + LD-DEX will not impact subjects QoL as compared with BTZ + LD-DEX.

Change scores from baselines will be analyzed using MIXED model using baseline covariates where appropriate.

Details will be given in the statistical analysis plan.

10.8.5. Healthcare Resource Utilization

Healthcare resource utilization measurements, including hospitalizations or emergency department visits that occur during the active treatment period, will be summarized by treatment arm using appropriate descriptive statistics.

10.8.6. Exploratory Biomarker Analysis

Exploratory analyses will be performed to investigate MRD, genomic, molecular/mechanistic and immune biomarkers which may predict the response or resistance to POM and overall survival, event free survival and response rates. Since the number of samples collected may be small, descriptive statistics will be performed for the quantitative analyses if warranted.

10.9. Interim Analysis

One interim PFS analysis is planned when approximately 50% of the PFS information is reached, ie, 191 out of the total of 381 PFS events required for the final PFS analysis. The results of the interim PFS analysis will be used for futility assessment only, for which a non-binding stopping boundary will be applied based on gamma function with gamma = -6.

Since the interim analysis has been planned and implemented prior to Protocol Amendment 5, it is not impacted by Amendment 5.

Overall Survival will be evaluated twice in this study: the first OS analysis will be conducted at the final PFS analysis, at approximately 320 events. The projected number of deaths will be approximately 50% of the total number of deaths (379) required for the final OS analysis. The second or final OS analysis will be conducted when the study reaches 379 deaths. The superiority stopping rule is for the interim analysis of OS only (at the time of final PFS), using a step-down approach. If the final PFS analysis shows significant difference between treatment arms ($p < 0.05$, 2-sided), and the ORR analysis also shows significant difference ($p < 0.05$, 2-sided), then the interim analysis for superiority and stopping will be carried out for OS. The superiority boundary for OS is based on Lan-Demets implementation of the Pocock boundaries, which spends more alpha at earlier look of the data.

10.10. Statistical Approaches for Control of Alpha and Other Considerations

The secondary endpoints for which claims may be made in the label include overall survival and overall response rate. There will be two PFS analyses (including one futility analysis), one ORR analysis and two OS analyses.

The family-wise type I error rate will be controlled by a step-down approach from PFS to ORR and then to OS comparison. Specifically, ORR will only be tested if null hypothesis for PFS is rejected at 2-sided 5% significance level; OS interim analysis will only be carried out if null hypothesis for ORR is rejected at 2-sided 5% significance level.

Specifically, when the number of PFS events is reached for the final PFS analysis, PFS will be tested first. If the value of the log-rank statistic for PFS is significant at the final analysis ($p < 0.05$, 2-sided), then overall response rate (ORR) will be tested next, at the same significance level of 5%, 2-sided. If the test of ORR is significant, then OS will be tested at the overall 5% significance level, 2-sided.

The significance level of the OS analysis will be based on the number of death events at the time of the analysis (eg, total number of 379 deaths in 2 arms required for the final analysis), using the Pocock superiority boundary for each of the two OS comparisons (interim OS at the time of the final PFS analysis, and the final OS analysis). The step-down approach is taken at the time of the final PFS analysis. ORR will be tested at the same significance level of 2-sided 0.05 level if PFS is tested significant, and the OS interim analysis will be performed only if the tests for PFS and ORR are both significant at the 2-sided 5% significance level – and then the OS comparison between treatment arms will be conducted in which a group sequential test with an overall Type I error probability of 5% (2-sided) is run for the hypothesis.

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to a study treatment (pomalidomide, bortezomib, or dexamethasone) should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms. All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent to at least 28 days after the last dose of study treatment (ie, pomalidomide, bortezomib, or dexamethasone) for subjects not continuing in the PFS follow-up Phase. Only study/protocol related AEs will be recorded by the Investigator for subjects who continue in the PFS follow-up phase of the study. AEs that lead to study discontinuation should be followed until resolution or stabilization.

Serious Adverse Events (SAEs), regardless of relationship to study treatment (pomalidomide, bortezomib, and/or dexamethasone), that occur from the time the subject signs informed consent to at least 28 days after the last dose of study drug (pomalidomide, bortezomib, or dexamethasone), and those made known to the Investigator at any time thereafter that are suspected of being related to study treatment (pomalidomide, bortezomib and/or dexamethasone) must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

Note that second primary malignancies will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm (Section 11.5).

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

11.2.1. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);

- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the subject is in (see Section 11.5). This includes any SPM, regardless of causal relationship to study treatment (pomalidomide, bortezomib, or dexamethasone), occurring at any time from the time of signing the informed consent up to and including the long-term follow-up period. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation on the diagnosis of the SPM must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results, X-rays, CT scans, etc.).

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.

- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to study treatment (POM, BTZ, DEX), action taken regarding study treatment (POM, BTZ, DEX), and outcome.

11.2.2. Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity/intensity of the event.

The severity of AEs will be graded based upon the subject's symptoms according to the current active minor version of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0 or higher.); http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

AEs that are not defined in the NCI CTCAE should be evaluated for severity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

11.2.3. Causality

The Investigator must determine the relationship between the administration of study treatment and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	Means a causal relationship of the adverse event to study treatment administration **is unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	Means there is a **reasonable possibility** that the administration of study treatment caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the study treatment and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional study treatment that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

11.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

11.2.5. Action Taken

The Investigator will report the action taken with study treatment (pomalidomide, bortezomib, dexamethasone) as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or reduction of study treatment, as appropriate) and report if concomitant and/or additional treatments were given for the event.

11.2.6. Outcome

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered or death (due to the SAE).

11.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of study treatment dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a

part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

11.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or partner of childbearing potential of a male subject are immediately reportable events.

11.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test in a female of childbearing potential regardless of disease state) occurring while the subject is on study treatment, or within 3 months after last dose of bortezomib or 28 days after last dose of pomalidomide whichever occurs later, are considered immediately reportable events. Study treatment is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling. The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

11.4.2. Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking investigational product should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

11.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile,

or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the subject is in. This includes any SPM, regardless of causal relationship to study treatment (pomalidomide, bortezomib and/or dexamethasone), occurring at any time from the time of signing the informed consent up to and including the long-term follow-up period. Events of SPM are to be reported using the SAE report form or approved equivalent and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation on the diagnosis of the SPM must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results, X-rays, CT scans, etc.).

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to study treatment [pomalidomide, bortezomib and/or dexamethasone]) that occur from the time the subject signs informed consent to at least 28 days after the last dose of study treatment (pomalidomide, bortezomib or dexamethasone) and those made known to the Investigator at any time thereafter that are suspected of being related to study treatment (pomalidomide, bortezomib and/or dexamethasone). SAEs occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

11.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

11.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to Pomalidomide based on the Investigator Brochure.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and

presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

For the purpose of regulatory reporting in the EEA, Celgene Drug Safety will determine the expectedness of events suspected of being related to the other IP [bortezomib and/or dexamethasone], based on the EU SmPCs.

Events of e.g. disease progression for the disease under study (including deaths due to disease progression for indications that are considered to be fatal) will be assessed as expected adverse events and will not be reported as expedited safety reports to regulatory authorities.

Celgene or its authorized representative shall notify the Investigator of the following information (in Japan, Celgene KK shall notify the Heads of the Institutes in addition to the Investigator(s)):

- Any AE suspected of being related to the use of study treatment (pomalidomide, bortezomib, dexamethasone) in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
- In Japan, measures taken in foreign countries to ensure patient safety, study reports that indicates potential risk of cancer, etc., or biannual SAE report according to the local regulations.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 15.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information contact information, please refer to the Serious Adverse Event Report Form / Completion Guidelines or to the Pregnancy Report Form / Completion Guidelines.

12. DISCONTINUATIONS

The following events are considered sufficient reasons for discontinuing a subject from the study treatment phase:

- Adverse Event(s)
- Pregnancy
- Progressive Disease (PD)
- Protocol violation
- Withdrawal of consent
- Death
- Lost to follow-up
- Study Terminated by Sponsor

The following events are considered sufficient reasons for discontinuing a subject from the PFS follow-up phase:

- Progressive Disease (PD)
- Protocol violation
- Withdrawal of consent
- Death
- Lost to follow-up
- Study Terminated by Sponsor

The following events are considered sufficient reasons for discontinuing a subject from the Long-term follow-up phase:

- Withdrawal of consent
- Death
- Lost to follow-up
- Completion of follow-up (5 years after the last subject is randomized)
- Study Terminated by Sponsor

The reason for discontinuation from each phase of the study will be captured in the eCRFs and source document as applicable.

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

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or Back-up Medical Monitor by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that both Clinical Research Physician/Medical Monitor and Back-up Medical Monitor cannot be reached, please contact the Celgene Global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page).This Celgene Global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on call Celgene Medical Monitor, who will then contact you promptly.

Note: The back-up 24 hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician/Medical Monitor or Back-up Medical Monitor for emergency calls.

13.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, IP will be identified on the IP package labeling.

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

14.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent document and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

14.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original informed consent document signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. The revised informed consent document signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

14.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed informed consent document, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

14.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

14.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

14.7. Ongoing Information for Institutional Review Board / Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

14.8. Closure of the Study

Celgene reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc.).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

15. DATA HANDLING AND RECORDKEEPING

15.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

15.2. Data Management

Data will be collected via electronic CRF (eCRFs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

15.3. Record Retention

Essential documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

16. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

16.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. Before the study is initiated at a site visit or at an investigator meeting, all aspects of the study are reviewed with the Investigator and the staff. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. At each monitoring visit, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative for accuracy, adherence to the protocol and Good Clinical Practice.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

16.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (eg, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

17. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will follow Celgene's publication policy (MA-SOP-105) which typically is based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

18. REFERENCES

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19. APPENDICES

Appendix A: VTE Algorithms

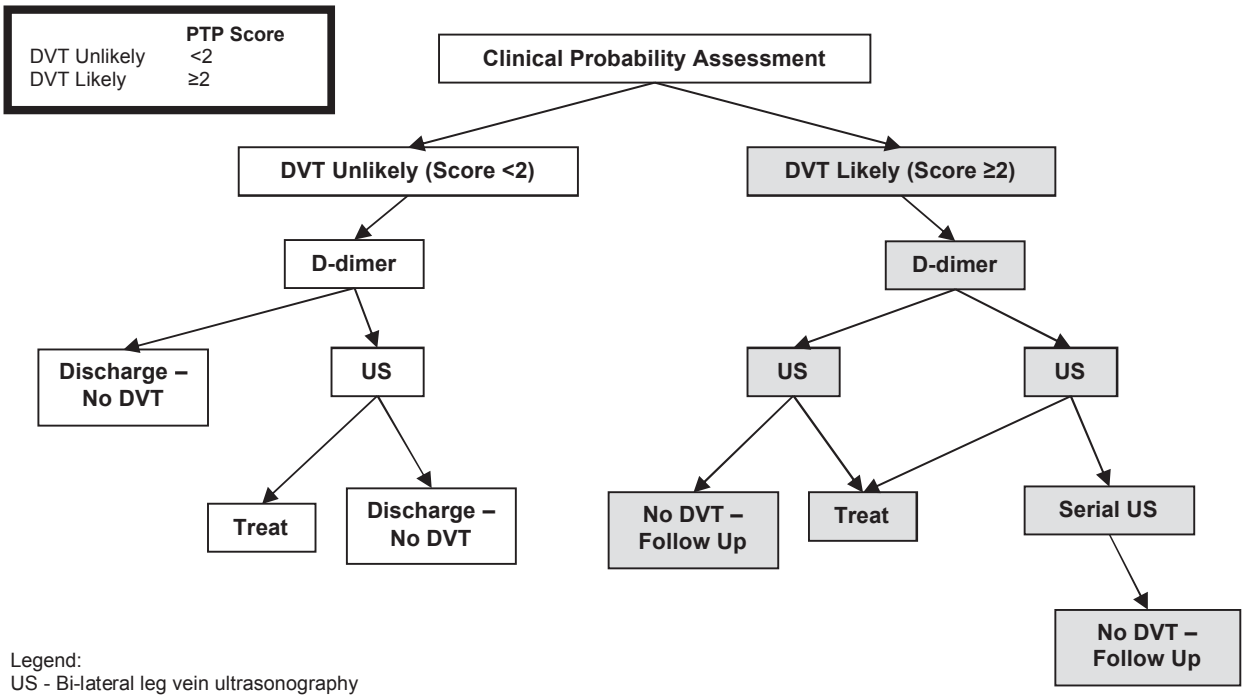
VTE Diagnostic Procedure

1. Refer to the DVT Pre-Test Probability Score Table. Add up the score and determine the patient's pre-test probability for DVT.
2. Refer to the DVT Diagnostic Algorithm. According to the pre-test probability follow the relevant diagnostic algorithm.

Wells[1] DVT Pre-Test Probability (PTP) Score

Clinical Characteristic	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3cm > asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented deep-vein thrombosis	1
Alternative diagnosis as likely or greater than that of DVT	-2

[1] Wells PS, Anderson D et al. Evaluation of D-dimer in the Diagnosis of Suspected Deep Vein Thrombosis. N Engl J Med Sept 25, 2003 349(13): 1227-35.



Legend:
US - Bi-lateral leg vein ultrasonography

Adapted from 6B6 D-Dimer™ The Essential Element Wall Chart

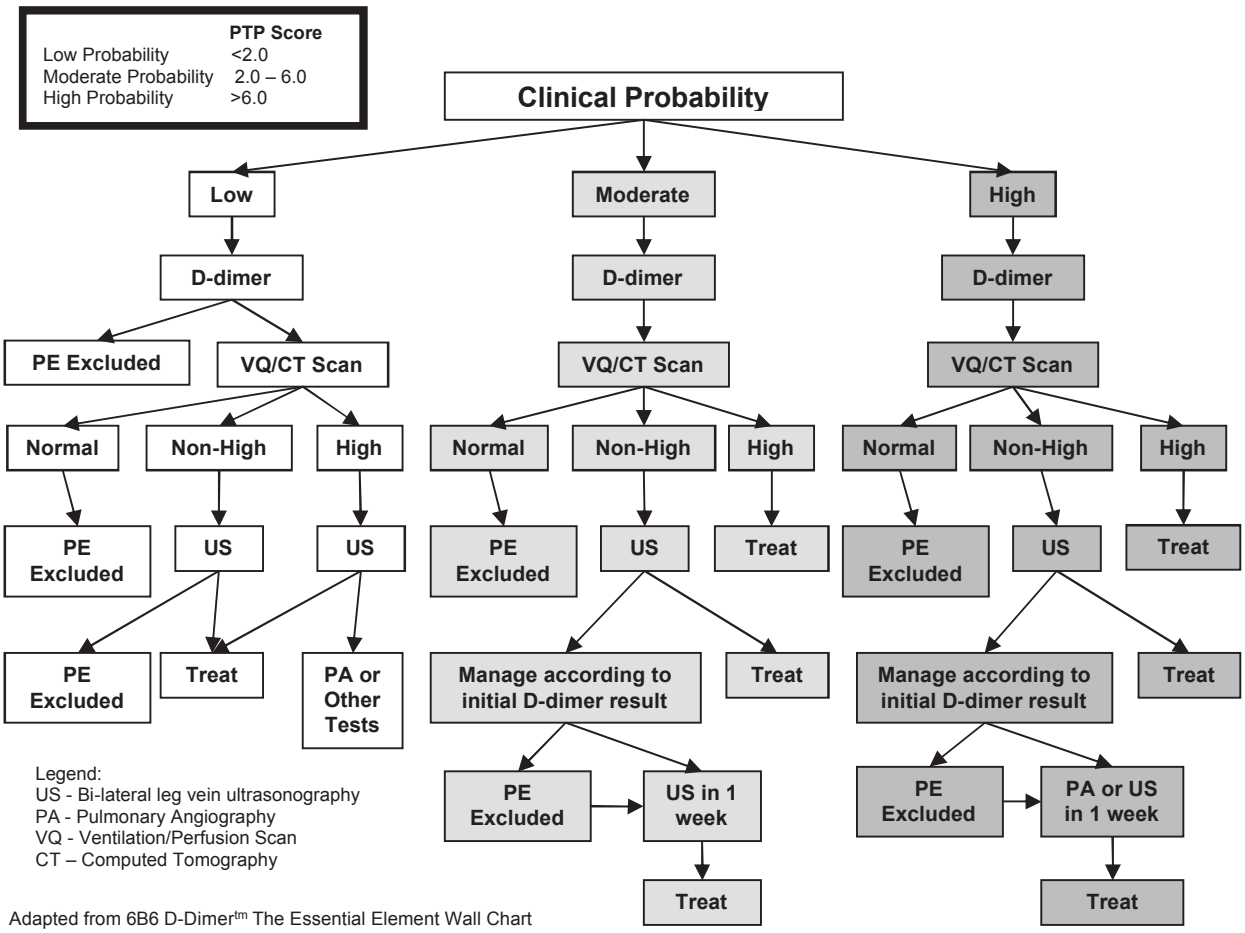
PE Diagnostic Procedure

1. Refer to the PE Pre-Test Probability Score Table. Add up the score and determine the patient's pre-test probability for PE.
2. Refer to the PE Diagnostic Algorithm. According to the pre-test probability follow the relevant diagnostic algorithm.

Wells[a] PE Pre-Test Probability (PTP) Score

Clinical Characteristic	Score
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3.0
An alternative diagnosis is less likely than PE	3.0
Heart rate greater than 100 beats/min	1.5
Immobilization or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy (at treatment, treated in the last 6 months or palliative)	1.0

[a] Wells PS, Anderson D, et al. Derivation of a simple Clinical Model to Categorize Patients Probability of Pulmonary Embolism: Increasing the Models Utility with SimpliRED D-dimer. Thromb Haemost 2000;83:416-20.



Adapted from 6B6 D-Dimer[tm] The Essential Element Wall Chart

Appendix B: International Myeloma Working Group Response Criteria

Response Category	Response Criteria[a]
SCR	CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow[p] by immunohistochemistry or immunofluorescence
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hours
PR	≥ 50% reduction of serum M-Protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours If the serum and urine M-protein are unmeasurable[d] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and the serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above, if present at baseline a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
SD[e]	Not meeting criteria for CR, VGPR, PR, or progressive disease
Relapse Category[f]	**Relapse Criteria**
Progressive disease	**Requires only one of the following:** Increase of ≥ 25% from nadir in: Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)[g] Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 hours) In patients without measurable serum and urine M-protein levels the difference between involved and uninvolved FLC levels, the absolute increase must be > 100 mg/dL. Bone marrow plasma cell percentage, the absolute % must be ≥ 10%[n] Definite development of new bone lesions or soft tissue plasmacytomas increase in the size of existing bone lesions or soft tissue plasmacytomas. Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder.

Appendix B: International Myeloma Working Group Response Criteria (Continued)

Relapse Category[f]	Relapse Criteria
Clinical relapse (Not used for TTP or PFS)	**Clinical relapse requires one or more of**: Development of new soft tissue plasmacytoma or bone lesions Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion Hypercalcemia (> 11.5 mg/dL [2.65 mmol/L]) Decrease in hemoglobin of ≥ 2 g/dl (1.25 mmol/L) Rise in serum creatinine by 2 mg/dL or more (177 μmol/L or more)
Relapse from CR[1]	**Any one or more of the following:** Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of ≥ 5% plasma cells in the bone marrow[h] Appearance of any other sign or progression

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

[b] Confirmation with repeat biopsy not necessary.

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

[d] Applicable only to patients who have 'measurable' disease defined by at least one of the following three measurements: Serum M-protein ≥ 1 g/dl, Urine M-protein ≥ 200 mg/24 hour, Serum FLC assay involved FLC level ≥ 10 mg/dl provided serum FLC ration is abnormal.

[e] Not recommended for use as an indicator of response; stability of disease is best described by providing the time too progression estimates).

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

[g] For progressive disease, serum M-component increases of ≥ 1 gm/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

[h] Relapse from CR has the 5% cutoff versus 10% for other categories or relapse.

[i] To only be used if the end point studied is disease-free survival. For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

Appendix C: European Group for Blood and Marrow Transplantation Criteria

Response	Criteria for Response
Complete response (CR)[a]	Complete response (CR) requires all of the following: 1. Absence of the original monoclonal paraprotein in serum and urine by immunofixation, maintained for a minimum of 42 days (6 weeks). The presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR 2. < 5% plasma cell in a bone marrow aspirate and also on bone marrow biopsy, if biopsy is performed. However, if absence of monoclonal protein is sustained for at least 42 days (6 weeks), it is not necessary to repeat the bone marrow, except in patients with non-secretory myeloma where the marrow examination must be repeated after an interval of at least 42 days (6 weeks) to confirm CR. 1. No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response). If absence of monoclonal protein is sustained for at least 42 days (6 weeks), it is not necessary to repeat the skeletal survey. 2. Disappearance of soft tissue plasmacytomas.
Partial Response (PR)	Partial response (PR) requires all of the following 1. ≥50% reduction in the level of serum monoclonal paraprotein, maintained for a minimum of 42 days (6 weeks). 2. Reduction in 24-hour urinary light chain extraction by ≥ 90% or to <200 mg, maintained for a minimum of 42 days (6 weeks). 3. For patients with non-secretory myeloma, ≥ 50% reduction in plasma cells in bone marrow aspirate and on bone marrow biopsy, if a biopsy is performed, maintained for a minimum of 42 days (6 weeks). 4. ≥ 50% reduction in the size of the soft tissue plasmacytomas (by radiography or clinical examination) 5. No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response). If the reduction of the monoclonal protein required for PR is sustained for at least 42 days (6 weeks), it is not necessary to repeat the skeletal survey.

Appendix C: European Group for Blood and Marrow Transplantation Criteria (Continued)

Response	Criteria for Response
Minimal Response (MR)	Minimal response (MR) requires all of the following: 1. 25-49% reduction in the level of serum monoclonal paraprotein, maintained for a minimum of 42 days (6 weeks). 2. Reduction in 24-hour urinary light chain extraction by 50-89%, which still exceeds 200 mg per 24 hours, maintained for a minimum of 42 days (6 weeks). 3. For patients with non-secretory myeloma, 25-49% reduction in plasma cells in bone marrow aspirate and on bone marrow biopsy, if a biopsy is performed, maintained for a minimum of 42 days (6 weeks). 4. 25-49% reduction in the size of the soft tissue plasmacytomas (by radiography or clinical examination). 5. No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response). **If the reduction of the monoclonal protein required for MR is sustained for at least 42 days (6 weeks), it is not necessary to repeat the skeletal survey.**
Stable Disease	Not meeting the criteria for either MR or PD
Progressive disease (for patients not in CR)	One or more of the following: > 25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 5 g/L and confirmed by at least one repeated investigation > 25% increase in the 24 h urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 h and confirmed by at least one repeated investigation > 25% increase in plasma cells in a bone marrow aspirate or biopsy, which must also be an absolute increase of at least 10% Definite increase in the size of existing bone lesions or soft tissue plasmacytomas. Development of new lytic bone lesions or soft tissue plasmacytomas (development of a compression fracture does not exclude continued response and may not indicate PD). Development of hypercalcaemia (corrected serum calcium >11.5 mg/dL [2.8 mmol/L]) not attributable to any other cause.

[a] If some, but not all, the criteria for CR are fulfilled; the response is classified as a partial response (PR) provided that all other requirements for PR are satisfied. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

Appendix D: Skeletal (Bone) Survey Films

The following are the minimum plain radiological films required for the skeletal (bone) survey:

- Lateral skull
- AP and lateral cervical spine
- AP and lateral thoracic spine
- AP and lateral lumbar spine
- PA chest
- AP pelvis
- AP upper extremities, shoulder to elbow
- AP lower extremities, hip to knee

Other radiological films may be necessary to view symptomatic areas or known pre-existing lesions in skeletal regions not included in the films above.

Appendix E: ECOG Performance Status Scale

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry our work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix F: Cockcroft-Gault Estimation Of Creatinine Clearance (CrCl)

Cockcroft-Gault estimation of creatinine clearance (CRcl): CRcl (mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dl]); for females, the formula is multiplied by 0.85 (Cockcroft, 1976; Luke, 1990).

Appendix G: QT Drugs by Risk Group

To access a current list of QT-prolonging drugs grouped by risk of torsades, possible risk of torsades, and conditional risk of torsades visit http://www.qtdrugs.org/.

Appendix H: Staging Systems for Multiple Myeloma

Table 9: Staging Systems for Multiple Myeloma

Stage	Durie-Salmon Criteria[a]	ISS Criteria[b]
I	*All of the following:* Hemoglobin value > 10 g/dL Serum calcium value normal or < 12 mg/dL Bone x-ray, normal bone structure (scale 0), or solitary bone plasmacytoma only Low M-component production rates IgG value < 5 g/dL; IgA value < 3 g/dL Urine light chain M-component on electrophoresis < 4 g/24h	Serum beta-2 microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL
II	Neither Stage I nor Stage II	Neither Stage I nor Stage II
III	*One or more of the following:* Hemoglobin value < 8.5 g/dL Serum calcium value normal or > 12 mg/dL Advanced lytic bone lesions (scale 3) High M-component production rates IgG value > 7 g/dL; IgA value > 5 g/dL Urine light chain M-component on electrophoresis > 12 g/24h	Serum beta-2 microglobulin ≥ 5.5 mg/L
Subclassification Criteria A Normal renal function (serum creatinine value < 2.0 mg/dL) B Abnormal renal function (serum creatinine value ≥ 2.0 mg/dL)		Not applicable

[a] Durie BGM, Salmon SE. A clinical staging system for multiple myeloma. Cancer 1975; 36:842-854.

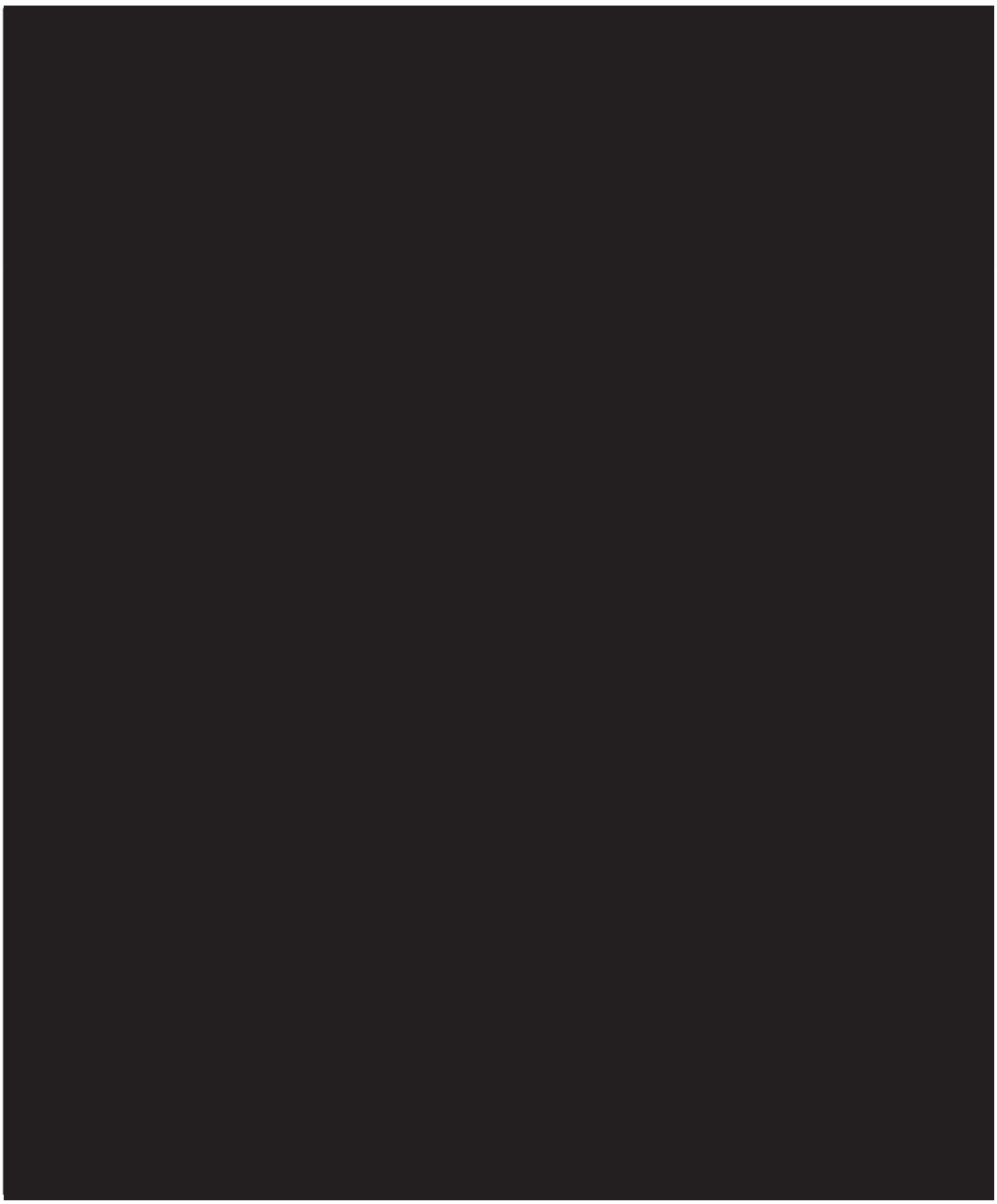
[b] Greipp P, San Miquel J, Durie B, et al. International staging system for multiple myeloma. Journal of Clinical Oncology 2005;23:3412-3420.

Appendix I:Quality of Life Questionnaires

The following Quality-of-Life Questionnaires will be used for this study:

- The European Organization for Research and Treatment of Cancer QoL Questionnaire for Patients with Multiple Myeloma (EORTC QLQ-MY20) Module, and
- The European Organization for Research and Treatment of Cancer QoL Questionnaire for Patients with Cancer (EORTC QLQ-C30) Module, and
- The descriptive system of the EQ-5D, which will be used for converting the information into utilities for economic analysis.

EOTRC Multiple Myeloma Module (QLQ-MY20)



EORTC QLQ-C30 (QLQ-C30)

EQ-5D

Appendix J: List of Abbreviations

Table 10: List of Abbreviations

Abbreviation	Definition
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALC	Absolute lymphocyte count
ALL	Acute Lymphocytic Leukemia
ALT	Alanine aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute neutrophil count
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AP	Anteroposterior
ASCT	Autologous Stem Cell Transplant
AST	Aspartate aminotransferase
B2M	Beta-2 microglobulin
βHCG	Beta-human chorionic gonadotropin
BSA	Body Surface Area
BTZ	Bortezomib
[redacted]	
CLL	Chronic Lymphocytic Leukemia
CR	Complete response
CrCl	Creatinine clearance
CRBN	Cereblon
CRF	Case Report Form
CRP	Clinical Research Physician
CT	computed tomography
DDB1	DNA damage-binding protein 1
DEX	Dexamethasone
DLT	Dose limiting toxicity
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Definition
eCRF	Electronic case report form
EE	Efficacy evaluable
EMBT	European Group for Blood and Marrow Transplant
EMP	Extramedullary plasmacytoma
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Live Questionnaire
EU	European Union
FCBP	Female of Childbearing Potential
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
GCP	Good clinical practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma glutamyl transpeptidase
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IC50	half maximal inhibitory concentration
ICH	International Committee on Harmonization
IDMC	Independent data monitoring committee
IFE	Immunofixation
IgA	Immunoglobulin A
IgD	Immunoglobulin D
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
iMiD	Immunomodulating drug
IMWG	International Myeloma Working Group
IP	Investigational product
IRAC	Independent Response Adjudication Committee
IRB/EC	Institutional Review Board / Ethics Committee
ITT	Intent to treat

Abbreviation	Definition
IUD	Intrauterine device
IV	Intravenous
IVRS/IWRS	Interactive voice/web response system
Kd	Carfilzomib with dexamethasone
LD-DEX	Low-dose dexamethasone
LPS	Lipopolysaccharide
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MR	Minimal Response
MRI	Magnetic Resonance Imaging
MPD	Maximum planned dose
MRD	Minimal Residual Disease
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable
NK	Natural killer
ORR	Overall Response Rate
OS	Overall survival
PA	posteroanterior
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PE	Pulmonary embolism
PFS	Progression-free survival
PK	Pharmacokinetics
PLD	Pegylated liposomal doxorubicin
POM	Pomalidomide
PR	Partial response
QoL	Quality of Life
RBC	Red blood cell
RRMM	Relapsed or Refractory Multiple Myeloma

Abbreviation	Definition
SAE	Serious adverse event
sCR	Stringent complete response
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
sPEP	Serum protein electrophoresis
SPM	Second Primary Malignancy
SQ	Subcutaneous
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNF	Tumor necrosis factor
TNM	tumor, nodes, metastasis
TTF	Time to treatment failure
TTP	Time-to-progression
Tx d/c	Treatment discontinuation
ULN	Upper limit of normal
uPEP	Urine protein electrophoresis
[redacted]	
Vd	Bortezomib with dexamethasone
VGPR	Very Good Partial Response
VTE	Venous thromboembolism
WBC	White blood cell

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: [redacted]
Title: [redacted]
Date: Friday, 16 June 2017, 08:53 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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1. JUSTIFICATION FOR AMENDMENT

Recently published data from a number of Phase 3 studies has revealed that the progression-free survival (PFS) of the bortezomib with low-dose dexamethasone (BTZ+LD-DEX) arm on study CC-4047-MM-007 (OPTIMISMM), that requires prior treatment with lenalidomide as per protocol Inclusion Criteria #7 (Section 7.2), is expected to be shorter than the current OPTIMISMM protocol statistical assumption of 9 months (relevant median PFS data from Phase 3 ENDEAVOR, PANORAMA-1 and CASTOR studies ranging from 7 to 8 months) (Moreau, 2017; Palumbo, 2016; San-Miguel, 2014).

Subsequently, if the assumption for the pomalidomide, bortezomib, and low-dose dexamethasone (POM+BTZ+LD-DEX) arm and other study assumptions remain unchanged, the number of PFS events required for the final analysis would be less than originally planned in the study protocol and has been reached.

Therefore, Celgene proposes to amend the protocol to perform the final PFS analysis before the originally planned PFS events (381) are reached. The estimated time for applicable approvals of this protocol amendment is approximately October 2017, which will be used as the cutoff date for the revised final PFS analysis. By that time, with a 5-month follow-up time for the last subject enrolled, approximately 320 PFS events are projected to be reached, representing an approximate 57% event rate (out of 559 randomized subjects). This would allow for 80% power to test a hazard ration of 0.73. Celgene considers the study data to be mature for the primary endpoint (PFS), and the expected treatment difference to be achievable as well as clinically meaningful. The median follow-up time is expected to be approximately 16 months, considered appropriate as supported by recently reported relapsed or refractory multiple myeloma (RRMM) registration trials in similar patient settings (Dimopoulos, 2016; Moreau, 2016; Moreau, 2017; Palumbo, 2016; San-Miguel, 2014). Therefore, the number of PFS events required for the final PFS analysis is amended to approximately 320.

Updated statistical considerations for the study will be specified in the protocol amendment and revised statistical analysis plan (SAP).

Main changes included in this amendment have been made to the Protocol Summary, Section 1.2, Section 10.3, Section 10.9, and Section 18 References.

Referenced publications:

Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;375(14):1319-31.

Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;374(17):1621-34. doi:10.1056/NEJMoa1516282.

Moreau P, Joshua D, Chng WJ, Palumbo A, Goldschmidt H, Hájek R, et al. Impact of prior treatment on patients with relapsed multiple myeloma treated with carfilzomib and dexamethasone vs bortezomib and dexamethasone in the phase 3 ENDEAVOR study. Leukemia. 2017;31(1):115-22.

Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med. 2016;375(8):754-66.

San-Miguel JF, Hungria VT, Yoon SS, Beksac M, Dimopoulos MA, Elghandour A, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol. 2014;15(11):1195-206. doi:10.1016/S1470-2045(14)70440-1.

1. JUSTIFICATION FOR AMENDMENT

The efficacy data reported by Lacy[1] were updated with longer follow-up and 12 additional events which resulted in accurate progression-free survival (PFS). Based on that, the assumption of median PFS has been adjusted in Study CC-4047-MM-007 which resulted in the revision of the study sample size.

Significant changes included in this amendment are summarized below:

- **Revision in overall sample size**
  - The assumption of the median PFS duration of the experimental arm (Arm A) has been adjusted from 12.6 months to 12 months and the study power has been reduced from 85% to 80%.
  - The revised sample size will assume a median PFS of 9 months in the control arm (Arm B) versus 12 months in the experimental arm (Arm A), with 80% power at 2-sided significance level of 5%. This will require 381 PFS events and a total of 544 subjects to be enrolled for an approximately 70% event rate.
  - The interim analysis on PFS will take place when approximately 50% PFS information (191 events) has occurred.
  - The OS interim analysis will take place when approximately 50% OS information (190 deaths) has occurred.

Updated Sections: Protocol Summary, Section 4.1, Section 7.1, Section 10.3, Section 10.9, Section 10.10

The amendment also includes minor updates to the following sections:

- Clarification on the timing between randomization and study treatment start (Cycle 1 Day 1)
- Addition for requests of redacted pathology reports from unscheduled bone marrow biopsies or aspirates performed to confirm a Complete Response (CR)

Updated Sections: Protocol Summary, Table 1 Table of Events, footnote f and w, Section 4.3, Section 6.1.3, Section 6.3.2, Section 10.8.2.4

1. Lacy, Martha Q., MD, et al. " 304 Pomalidomide, Bortezomib and Dexamethasone (PVD) for patients with relapsed Lenalidomide Refractory Multiple Myeloma (MM)." ASH 2014. Oral presentation-December 8, 2014

1. JUSTIFICATION FOR AMENDMENT

The Celgene sponsored study of pomalidomide in combination with dexamethasone in relapsed/refractory multiple myeloma showed a median progression-free survival (PFS) and overall survival (OS) of 4.0 and 12.7 months respectively[1]. More recent published data revealed that the triplet combination of cyclophosphamide, pomalidomide and dexamethasone (CPD) achieved an overall response rate (ORR) of 65%, a median PFS of 9.2 months and a median OS of 16.4 months[2] and the triplet combination of pomalidomide, bortezomib and dexamethasone (PVD) reported high clinical activity with an 81% ORR (complete response [CR]+very good partial response [VGPR]+partial response [PR]) and a median PFS of 17.7 months[3]. These efficacy results suggest that the addition of a third agent to pomalidomide with dexamethasone significantly increases the efficacy in relapsed/refractory multiple myeloma.

Due to the enrollment challenges experienced in the CC-4047-MM-007 study, with 117 subjects enrolled over the course of 32 months, Celgene convened a European Advisory Board meeting. The recommendation was for Celgene to evaluate the likely treatment effect based upon recent published data, to re-evaluate the protocol required statistical power, and to consider expanding the study to include sites globally.

Considering the Advisory Board recommendations and the encouraging efficacy results reported with triplet combinations, specifically PVD[3]; Celgene has revised the study's statistical assumptions by increasing the estimated PFS of the experimental arm (PVD) from 12 months to 12.6 months (treatment difference increased from 33% to 40% over the control arm), and by reducing the study power from 90% to 85%; resulting in a sample size reduction. Further, Celgene has expanded the study globally in order to ensure enrollment targets are met within appropriate timeframes.

Significant changes included in this amendment are summarized below:

- **Approval status of Pomalyst in the United States has been updated following full approval notification on 23 April 2015**
- **Reduction in overall sample size**
    - The primary purpose of this protocol amendment is to take into account recent published evidence and thereby re-evaluate the statistical assumptions for the study. The estimated PFS duration of the experimental arm (PVD) has been adjusted from 12 months to 12.6 months (increased from 33% to 40% over the control arm) and the study power has been reduced from 90% to 85%, resulting in a sample size reduction from approximately 782 subjects to 450 subjects.
        - Based on the primary endpoint PFS, at one-sided significance level of 0.025 with an interim analysis for futility, a total of 318 disease progression/death events are required to detect a 40% increase in median PFS in the pomalidomide (POM) treatment arm (Treatment Arm A; median = 12.6 months) compared to that in the comparator arm (Treatment Arm B; median = 9 months) with 85% power. Considering

subjects could be lost to follow-up, approximately 450 subjects will be enrolled in this study.

- At one-sided significance level of 0.025 and with one planned interim analysis on overall survival (OS) at the time of the final PFS analysis (estimated to be at 50% OS information [147 deaths]), a total of 293 deaths are required to detect a 40% increase in median OS in the POM treatment arm (Treatment Arm A; median = 42 months) compared with that of the comparator arm (Treatment Arm B; median = 30 months) with 80% power.

- **Updates to time points for contraceptive requirements and pregnancy testing**
  - The time points for contraceptive requirements and pregnancy testing for females of child-bearing potential (FCBP) following last dose of study treatment have been updated to be consistent with both pomalidomide and bortezomib prescribing information

The amendment also includes several other minor clarifications and corrections:

- Clarification on the timing of pomalidomide dosing in subjects enrolled into Treatment Arm A
- Clarification on the timing of bortezomib dosing in subjects enrolled into both Treatment Arm A and B
- Incorporation of study drug dispensation strategy for sites participating in Japan
- Clarification of how Celgene Drug Safety will determine the expectedness of events with suspected relationship to the Investigational Product, for the purposes of regulatory reporting in the EEA
- Addition of the QTc study conclusion has been updated
- Additional editorial changes and corrections

References:

1. San Miguel et al, Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013a;14(11):1055-66.
2. Baz R et al, Pomalidomide, cyclophosphamide, and dexamethasone is superior to pomalidomide and dexamethasone in relapsed and refractory myeloma: results of a multicenter randomized phase II study. Blood. 2014;124(21): Abstract 303.
3. Lacy MQ et al, Pomalidomide, bortezomib and dexamethasone (PVD) for patients with relapsed lenalidomide refractory multiple myeloma (MM). Blood. 2014;124 (21).Abstract 304.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

The main purpose of this protocol amendment is to allow for the expansion of trial enrollment to countries and sites outside of the US in order to aid in completing enrollment. The changes outlined throughout this document are required in order to expand globally; including updates to the Investigational Product sections and the collection of both Exploratory Biomarker samples and Quality of Life information.

Additional editorial changes are made to comply with Celgene Corporation required language and can be found in sections pertaining to Overdose, End of Trial and Pregnancy. Typographical errors have also been corrected.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Updated route of administration for the bortezomib in both treatment arms to subcutaneous from intravenous
  - For Treatment Arm A (POM + BTZ + DEX), the dose was based on the results from the CC-4047-MM-005 (MM-005) Phase 1 dose escalation MTD study in which bortezomib was administered via IV infusion. In the MM-005 study, the maximum planned dose (MPD), POM (4 mg) + IV BTZ (1.3 mg /m^2) and DEX (20 mg subjects ≤ 75 years old/10 mg (subjects > 75 years old) was reached without any DLTs. Considering an early POM single agent MTD study (Richardson, 2013) as well as the findings in MM-005, the MPD was determined to be the optimal dose for the triple combination therapy. With the optimal dose determined, MM-007 was initiated using the MPD dose for the combination of POM + BTZ + LD-DEX (with IV BTZ). During the conduct of the MM-005 study, subcutaneous (SQ) BTZ was approved as an alternative administration method for BTZ (23 Jan 2013). The SQ BTZ was reported to have a decreased incidence of neurotoxicity versus the IV BTZ (Velcade® Prescribing Information, 2012). To explore the SQ route of BTZ administration in combination with POM and DEX, the MM-005 protocol was amended to add an additional cohort of 6 subjects at the MPD/optimal dose for the combination of POM + BTZ + LD-DEX with BTZ administered via SQ injection. Based on the safety, efficacy and PK data for this SQ BTZ cohort and general adoption in medical practice of SQ BTZ as standard of care due to decreased neurotoxicity, BTZ administration is now changed to SQ for both arms in the MM-007 study (Treatment Arm A and B).
- Added quality of life assessment to allow for an exploratory evaluation of the differences in health-related quality of life of POM + BTZ + LD-DEX versus BTZ + LD-DEX in subjects with relapsed or refractory MM
- Added biomarker sampling to allow for an exploratory evaluation of Minimal Residue Disease (MRD), genomic, molecular/mechanistic and immune biomarkers and their correlation to clinical outcome measures
- Added an endpoint to allow for an exploratory evaluation of the Progression-free survival after next-line therapy (PFS2)
- Corrected to specify that all subjects will be followed in the long-term follow-up phase until death or for at least 5 years after the last subject is randomized into the study, or longer if clinically indicated (unless the follow-up is shorter due to withdrawal of consent, loss to follow-up, or death). Initially it was written that all subjects would be followed in the long-term follow-up phase until death or for at least 5 years after the subject's randomization date.

- Clarified references to investigational product (pomalidomide) versus study treatment (pomalidomide, bortezomib, dexamethasone) since pomalidomide is being provided as IP by Celgene Corporation, while investigative sites will use commercially available bortezomib and dexamethasone and will dispense these drugs to subjects via prescription.
- Clarified that samples for possible additional genetic studies for analysis of SPM risk factors will only be prepared and stored if acceptable per the local institutional policies for such sampling/storage of samples and only if sufficient sample is available after local pathology and central cytogenetic analysis is completed.
- Clarified that for subjects who are diagnosed with a SPM, bone marrow aspirate, bone marrow biopsy and peripheral blood smears will be sent for central pathology review only if acceptable per the local institutional policies.
- Corrected that the reporting period for AEs will be from time of consent to 28 days after last dose of study treatment (pomalidomide, bortezomib, dexamethasone) versus 28 days after the treatment discontinuation visit.
- Added antiviral prophylaxis to the list of other recommended/required concomitant medications per the protocol since per protocol (and bortezomib label) oral acyclovir or equivalent antiviral therapy per institutional guidelines is required for herpes zoster prophylaxis.
- Clarified how VTE monitoring is to be performed for the study.
- Updated Adverse Event section of the protocol per updates to the Celgene template language
- Updated for change in Medical Monitor.
- The amendment also includes several other minor clarification and corrections.