A MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY WITH POMALIDOMIDE IN COMBINATION WITH LOW DOSE DEXAMETHASONE IN SUBJECTS WITH REFRACTORY OR RELAPSED AND REFRACTORY MULTIPLE MYELOMA

INVESTIGATIONAL PRODUCT (IP):	Pomalidomide (CC-4047)
PROTOCOL NUMBER:	CC-4047-MM-010
ORIGINAL DATE FINAL:	23 May 2012
AMENDMENT 1 DATE FINAL:	30 May 2013
EudraCT NUMBER:	2012-001888-78
IND NUMBER:	066188
SPONSOR NAME / ADDRESS:	Celgene Corporation [redacted]

MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

Contact Information:	
Name:	Nicolas Leupin, MD
Title:	Responsible Clinical Research Physician
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

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 Multicenter, Single-arm, Open-label Study with Pomalidomide in Combination with Low Dose Dexamethasone in Subjects with Refractory or Relapsed and Refractory Multiple Myeloma.

Indication

Refractory multiple myeloma (MM) or relapsed and refractory MM.

Objectives

Primary Objective

Evaluate the safety of the combination of pomalidomide (POM) and low dose dexamethasone (LD-DEX) in a large cohort of subjects with refractory MM or relapsed and refractory MM.

Secondary Objectives

- Analyze the population pharmacokinetics of POM and assess POM exposure response relationships in subjects with refractory MM or relapsed and refractory MM administered POM and LD-DEX.
- Evaluate efficacy of the combination of POM and LD-DEX in subjects with refractory MM or relapsed and refractory MM.
- Evaluate the relationship between cytogenetic profiles and the combination of POM and LD-DEX in terms of response and outcome.

[redacted]

Study Endpoints

Primary Endpoint

Adverse events (AEs) assessment (type, frequency, seriousness, severity, relationship to POM and/or DEX and outcomes), including second primary malignancies (SPM)

Secondary Endpoints

- POM exposure
- POM population pharmacokinetics and exposure-response
- Overall response rate (ORR)
- Time to response
- Duration of response (DoR)
- Progression-free survival (PFS)

- Time to progression (TTP)
- Overall survival (OS)
- Analysis of cytogenetic profiles

[redacted]

Study Design

This is an international, multicenter, single-arm, open-label study of POM in combination with LD-DEX in subjects with refractory MM or relapsed and refractory MM.

This study consists of the following consecutive phases: Screening, Treatment and Follow-up. Study visits and evaluations will be performed as outlined in Table 1 ("Table of Events").

Screening Phase

Study subjects will sign an informed consent document (ICD) prior to undergoing any study-related procedure. Subjects may have the choice to participate in an optional biomarker study conducted at selected clinical sites. If a subject chooses to participate in the biomarker study, he/she must give consent for the optional biomarker study. Subjects will undergo screening for protocol eligibility within 28 days prior to Cycle 1 Day 1, as outlined in Table 1, Table of Events.

Subjects who meet all eligibility criteria will receive the study treatment and will be maintained on the pregnancy prevention program for the duration of the study.

The inclusion procedure will be accomplished by a validated interactive voice/web response system (IVRS/IWRS).

Treatment Phase

Study treatment administration should start within 72 hours after enrollment (which is defined as enrollment on the IVRS/IWRS) of the subject into the study, provided that the inclusion/ exclusion criteria are still met. Otherwise, the subject will need to be re-screened. Each subject will receive the following study treatment until progressive disease (PD), or as long as they benefit from therapy according to the opinion of the responsible study Investigator and discussed with the Sponsor:

- POM administered orally at the starting dose of 4 mg on Days 1-21 of a 28-day cycle,
- LD-DEX administered orally at the starting dose of 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle.

Pharmacokinetic (PK) blood samples for POM quantification will be collected at specified time-points during the course of the study from all subjects from selected sites with PK capability.

[redacted]

[redacted]

In addition, the bone marrow aspirate collected from all subjects during screening will be used for cytogenetic analysis (once eligibility has been confirmed), and an additional aspirate will be required for those subjects who discontinue the study treatment due to disease progression in order to identify any change in their cytogenetic profile.

Follow-up Phase

All study subjects will enter the follow-up phase after study treatment discontinuation. During follow-up the following information will be collected from all subjects every 3 months for up to 5 years after last subject enrollment or longer if clinically indicated: SPMs, survival, subsequent anti-myeloma treatments (type of treatment, start and stop dates, best response whenever possible) and date of progression.

Study Population

This is a multicenter, international, single-arm, open label, phase IIIb study of POM and LD-DEX in subjects with refractory MM or relapsed and refractory MM conducted in Europe and Israel. The study is anticipated to enroll approximately 720 subjects with refractory MM or relapsed and refractory MM and fulfilling the eligibility criteria outlined below.

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 ICD.
2. The subject must understand and voluntarily sign an ICD prior to any study related assessments/procedures being conducted.
3. Must be able to adhere to the study visit schedule and other protocol requirements.
4. Subjects must have documented diagnosis of MM and have measurable disease (serum M-protein ≥ 0.5 g/dL or urine M-protein ≥ 200 mg/24 hours).
5. Subjects must have undergone prior treatment with ≥ 2 treatment lines of anti-myeloma therapy. Induction therapy followed by autologous stem cell transplant (ASCT) and consolidation/ maintenance will be considered as one line. A new treatment line is always started after progressive disease.
6. Subjects must have either refractory or relapsed and refractory disease defined as documented disease progression during or within 60 days of completing their last myeloma therapy.

   Primary Refractory: Subjects who have never achieved any response better than PD to any previous line of anti-myeloma therapy.

   Relapsed and Refractory: Subjects who have relapsed after having achieved at least stable disease for at least two cycles of treatment to at least one prior regimen and then developed PD on or within 60 days of completing their last myeloma therapy.

7. All subjects must have received at least 2 consecutive cycles of prior treatment that included lenalidomide and bortezomib, either alone or in combination regimens.

   All subjects must have failed both lenalidomide and bortezomib and medical records must be available that provide documentation of the following criteria for refractoriness that make the subject eligible for the study.

   - All subjects must have failed treatment with the last lenalidomide-containing regimen in one of the following ways:
     - Documented PD during or within 60 days of completing last treatment with lenalidomide, regardless of the response achieved, or
     - In case of prior response (≥ partial response - PR) to lenalidomide and PD > 60 days, subjects must have relapsed within 6 months after the last dose of treatment with lenalidomide-containing regimens.
   - All subjects must have failed treatment with the last bortezomib-containing regimen in one of the following ways:
     - Documented PD during or within 60 days of completing treatment with bortezomib, regardless of the response achieved, or
     - In case of prior response (≥ PR) to bortezomib and PD > 60 days, subjects must have relapsed within 6 months after the last dose of treatment with bortezomib-containing regimens,

     Or for non-progressive subjects:

     - Subjects who have less than minor response (MR) and have developed intolerance/toxicity after a minimum of two cycles of a bortezomib-containing regimen. Toxicity such as > grade 2 peripheral neuropathy or ≥ grade 2 painful neuropathy. Peripheral neuropathy must resolve to grade 1 prior to study entry.

8. Subjects must have received adequate prior alkylator therapy in one of the following ways:
   a. As part of a stem cell transplant; or
   b. A minimum of 4 consecutive cycles of an alkylator based therapy; or
   c. Progression on treatment with an alkylator; provided that the subject received at least 2 cycles of an alkylator-containing therapy.
9. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.
10. Females of childbearing potential (FCBP[1]) must agree to utilize two reliable forms of contraception simultaneously or practice complete abstinence from heterosexual contact for at least 28 days before starting study drug, while participating in the study (including dose interruptions), and for at least 28 days after study treatment discontinuation and must agree to regular pregnancy testing during this timeframe. (NOTE: True abstinence:

[1] A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., who has had menses at any time in the preceding 24 consecutive months).

When this is in line with the preferred and usual lifestyle of the subject. *[Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]*)

11. Females must agree to abstain from breastfeeding during study participation and 28 days after study drug discontinuation.
12. Males must agree to use a latex condom during any sexual contact with FCBP while participating in the study and for 28 days following discontinuation from this study, even if he has undergone a successful vasectomy.
13. Males must also agree to refrain from donating semen or sperm while on POM and for 28 days after discontinuation from this study treatment.
14. All subjects must agree to refrain from donating blood while on study therapy and for 28 days after discontinuation from this study treatment.
15. All subjects must agree not to share medication.

Exclusion Criteria

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

1. Any of the following laboratory abnormalities:
   - Absolute neutrophil count < 800/μL.
   - 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. Platelet transfusion is not allowed within the previous 3 days before screening.
   - Creatinine Clearance (CrCl) < 45 mL/min according to Cockcroft-Gault formula. If CrCl calculated from the 24-hour urine sample is ≥ 45 mL/min, subject will qualify for the study.
   - Corrected serum calcium > 14 mg/dL (> 3.5 mmol/L).
   - Hemoglobin < 8 g/dL (< 4.9 mmol/L; prior red blood cells transfusion or recombinant human erythropoietin use is permitted).
   - Serum SGOT/AST or SGPT/ALT > 3.0 x upper limit of normal (ULN).
   - Serum total bilirubin > 2.0 mg/dL (34.2 μmol/L); or > 3.0 x ULN for subjects with hereditary benign hyperbilirubinemia.
2. Prior history of malignancies, other than MM, unless the subject has been free of the disease for ≥ 5 years. Exceptions include the following:
   - Basal or squamous cell carcinoma of the skin
   - Carcinoma *in situ* of the cervix or breast
   - Incidental histological finding of prostate cancer (TNM stage of T1a or T1b).
3. Previous therapy with POM.

4. Hypersensitivity to thalidomide, lenalidomide, or DEX (this includes ≥ Grade 3 rash during prior thalidomide or lenalidomide therapy).
5. Peripheral neuropathy ≥ Grade 2.
6. Subjects who received an allogeneic bone marrow or allogeneic peripheral blood stem cell transplant less than 12 months prior to initiation of study treatment and who have not discontinued immunosuppressive treatment for at least 4 weeks prior to initiation of study treatment and are currently dependent on such treatment.
7. Subjects who are planning for or who are eligible for stem cell transplant.
8. Subjects with any one of the following:
   - Congestive heart failure (NY 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.
9. Subjects who received any of the following within the last 14 days of initiation of study treatment:
   - Major surgery (kyphoplasty is not considered major surgery)
   - Use of any anti-myeloma drug therapy.
10. Use of any investigational agents within 28 days or five half-lives (whichever is longer) of treatment, unless approved by the Sponsor.
11. Incidence of gastrointestinal disease that may significantly alter the absorption of POM.
12. Subjects unable or unwilling to undergo antithrombotic prophylactic treatment.
13. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subjects from signing the ICD.
14. Pregnant or breastfeeding females.
15. Known human immunodeficiency virus (HIV) positivity, active infectious hepatitis A, B or C or chronic hepatitis B or C.

Length of Study

This study will remain open to enrollment for an estimated 18-24 months, or until subject enrollment numbers are complete, whichever occurs first. Subjects will be followed for up to 5 years after last subject enrollment or longer if clinically indicated.

The study will consist of the following consecutive phases: Screening, Treatment and Follow-up. The screening period may be up to 28 days prior to start of study treatment. Subjects may remain in the study until study treatment is discontinued for any reason or documented PD or as long as they benefit from therapy according to the opinion of the responsible study Investigator and discussed with the Sponsor. Once discontinued from the study treatment, subjects will be followed for OS and occurrence of SPM every 3 months for up to 5 years after last subject enrollment or longer if clinically indicated.

Study Treatment

All subjects will be treated with open label POM. POM will be supplied as Investigational Product by Celgene Corporation as 1 mg, 2 mg, 3 mg, and 4 mg capsules for oral administration. Study drug will be packaged in bottles containing a 21-day supply of POM. The dosing schedule is as follows:

- POM is administered orally at the starting dose of 4 mg on Days 1-21 of a 28-day cycle,
- LD-DEX is administered orally at the starting dose of 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle.

Allowed Medications

Low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anti-coagulant will be given to all subjects. Antithrombotic prophylaxis will be recorded in the electronic case report (eCRF) form at each visit. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method.

Prior to study entry and during the treatment phase, subjects with myeloma-associated bone disease may receive bisphosphonate therapy, as well as other agents that may be used for myeloma-associated bone disease, such as denosumab and teriparatide, unless such therapy is contraindicated.

Hematopoietic growth factors are allowed as per the recommendations of the European Society for Medical Oncology (ESMO) guidelines (Crawford, 2010). Platelet and/or red blood cell transfusions are permitted throughout the study, including the screening period, at the discretion of the investigator. If platelet transfusions are given during the screening period, the screening platelet assessment must be done a minimum of 3 days (72 hours) after the completion of the transfusion.

An independent Data Monitoring Committee (DMC) will review safety data on an ongoing basis throughout the study.

Prohibited Medications

Concomitant use of other anti-myeloma therapy while the subject is taking study drug is prohibited. Subsequent treatment for MM should not be initiated until the PD is documented. The need for radiation therapy is considered to be a treatment failure. However, an exception (i.e., subjects are allowed to remain on the treatment phase of the study) is made for radiation therapy to a pathological fracture site to enhance bone healing or to treat post-fracture pain that is refractory to narcotic analgesics because pathological bone fractures do not, by themselves, fulfill a criterion for disease progression. Chronic use of steroids other than the study drug (dexamethasone) or any other immunosuppressive therapies are prohibited in this study.

Drugs known to prolong QT corrected (QTc) interval should be avoided unless deemed medically necessary. See Appendix F for a comprehensive list of drugs which are known to elongate the QTc.

Guidelines for dose modifications for POM and DEX are further described in Section 8.2.

Treatment Discontinuation

Subjects will continue study treatment until the documentation of confirmed PD, intolerable toxicity, death, withdrawal of participation/consent in the study, or loss to follow-up, or as long as they benefit from therapy according to the opinion of the responsible study Investigator and discussed with the Sponsor. This study will not use Central Imaging or Central efficacy assessment review. Response will be based on Investigator's assessment using local laboratory results.

Subjects are not expected to start any other anti-myeloma therapy before progression. A discontinuation visit will be required for all subjects who discontinue treatment.

Overview of Safety Assessments

- Serum/urine beta-human chorionic gonadotropin (β-HCG) (FCBP only).
- Vital signs.
- Clinical laboratory evaluations (hematology, serum chemistry, urinalysis).

  Laboratory measure for safety and efficacy assessments will utilize local, accredited laboratories with agreement that the same laboratory will be used for each site for the period of the study.

  An abnormal laboratory value is considered to be an AE if the abnormality results in discontinuation from the study; requires treatment, modification/interruption of investigational product (IP) dose, or any other therapeutic intervention; or is judged to be of significant clinical importance by the Investigator.

  Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event (SAE).
- Venous thromboembolism (VTE) monitoring
- Electrocardiogram (ECG)
- Concomitant medications and procedures
- Adverse events of all grades will be recorded on the eCRF throughout the study from signing of the ICD until 28 days after discontinuation from the study treatment including AE type, frequency, seriousness, severity, relationship to study drug, and outcomes.

  Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 4.0, May 2009). Summaries will be provided by system organ class, and preferred term.
- Second primary malignancies will be monitored as events of interest and should be included as part of the assessment of AEs throughout the course of the study. Investigators must report any SPM as SAE regardless of causal relationship to investigational product (IP) (POM with or without LD-DEX), occurring at any time from the time of signing the ICD until the end of their follow-up.

For all subjects who develop SPM, sites will be required to submit all diagnostic reports (e.g., pathology, cytogenetics, flow cytometry results) from the MM diagnostic confirmation samples submitted at screening and all reports for the tumor samples from the SPM diagnosis. For SPMs diagnosed at another institution, (outside of the investigational site) sites will be required to make every effort to obtain these reports for second primary malignancy confirmation.

Overview of Pharmacokinetic Assessments

- Population PK model describing the sparse plasma PK data of POM and associated inter-individual variability, potential inter-occasional variability and residual variability.
- Influence of covariates of extrinsic factors (body weight, CrCl, etc) on the population PK parameters of POM.
- Bayesian prediction of individual exposure of POM in subjects following oral administration for exposure response analysis, and
- Potential models describing the potential exposure - response relationships between plasma exposures of POM (Bayesian individual exposure) and response variables (clinical efficacy endpoints and/or clinical safety endpoints), as appropriate.

Overview of Efficacy Assessments

- Myeloma paraprotein
- Serum immunoglobulins
- Serum Free Light Chain
- Beta-2 Microglobulin
- Bone marrow aspiration/biopsy
- Radiographic assessments of lytic bone lesions
- Extramedullary plasmacytoma (EMP) assessments
- ECOG performance status

Investigator's assessment for ORR, will be provided per International Myeloma Working Group (IMWG) criteria, and time to response, DoR, TTP and PFS will be calculated based on the Investigator's response assessment. Subject also will be followed-up for OS. All time-to-event endpoints will be estimated from the time of study enrollment, except DoR which will be estimated as the time from response.

Overview of Cytogenetic Assessments

- Bone marrow aspirate taken during screening and for those subjects who discontinue the study treatment due to disease progression will be used to assess:
  - cytogenetic profiles
  - disease course

- response to treatment

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to evaluate the safety of the combination of POM and LD-DEX in a large cohort of subjects with refractory MM or relapsed and refractory MM.

2.2. Secondary Objectives

The secondary objectives of the study are to

- Analyze the population pharmacokinetics of POM and assess POM exposure response relationships in subjects with refractory MM or relapsed and refractory MM administered POM and LD-DEX.
- Evaluate efficacy of the combination of POM and LD-DEX in subjects with refractory MM or relapsed and refractory MM.
- Evaluate the relationship between cytogenetic profiles and the combination of POM and LD-DEX in terms of response and outcome.

3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary study endpoint is the incidence of adverse events (type, frequency, seriousness, severity, relationship to POM and/or DEX and outcomes), including second primary malignancies (SPM).

3.2. Secondary Endpoints

The secondary endpoints include:

- POM exposure.
- POM population pharmacokinetics and exposure-response.
- Overall response rate (ORR).
- Time to response.
- Duration of response (DoR).
- Progression-free survival (PFS).
- Time to progression (TTP).
- Overall survival (OS).
- Analysis of cytogenetic profiles

4. OVERALL STUDY DESIGN

4.1. Study Design

This is an international, multicenter, single-arm, open-label study of POM in combination with LD-DEX in subjects with refractory MM or relapsed and refractory MM conducted in Europe and Israel.

The study is anticipated to enroll approximately 720 subjects with refractory MM or relapsed and refractory MM.

This study consists of the following consecutive phases: a Screening phase within 28 days prior to Cycle 1 Day 1, a Treatment phase and a Follow-up phase which starts following discontinuation from study treatment, every 3 months for up to 5 years after last subject enrollment or longer if clinically indicated.

Each subject will receive POM administered orally at the starting dose of 4 mg on Days 1-21 of a 28-day cycle and LD-DEX administered orally at the starting dose of 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle. Dose modifications and interruptions are permitted throughout the study.

Subjects will continue study treatment until the documentation of confirmed PD, intolerable toxicity, death, withdrawal of participation in the study, withdrawal of consent, or are lost to follow-up, or as long as they benefit from therapy according to the opinion of responsible study Investigator and discussed with the Sponsor.

Adverse events (primary endpoint) will be recorded and graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) (Version 4.0, May 2009). Second primary malignancies will be monitored every 3 months for up to 5 years after last subject enrollment as events of interest throughout the course of the study. An independent Data Monitoring Committee (DMC) will review safety data on an ongoing basis throughout the study.

Tumor response, based on the Investigator's assessment, will be evaluated according to the International Myeloma Working Group (IMWG) response criteria (Durie, 2006).

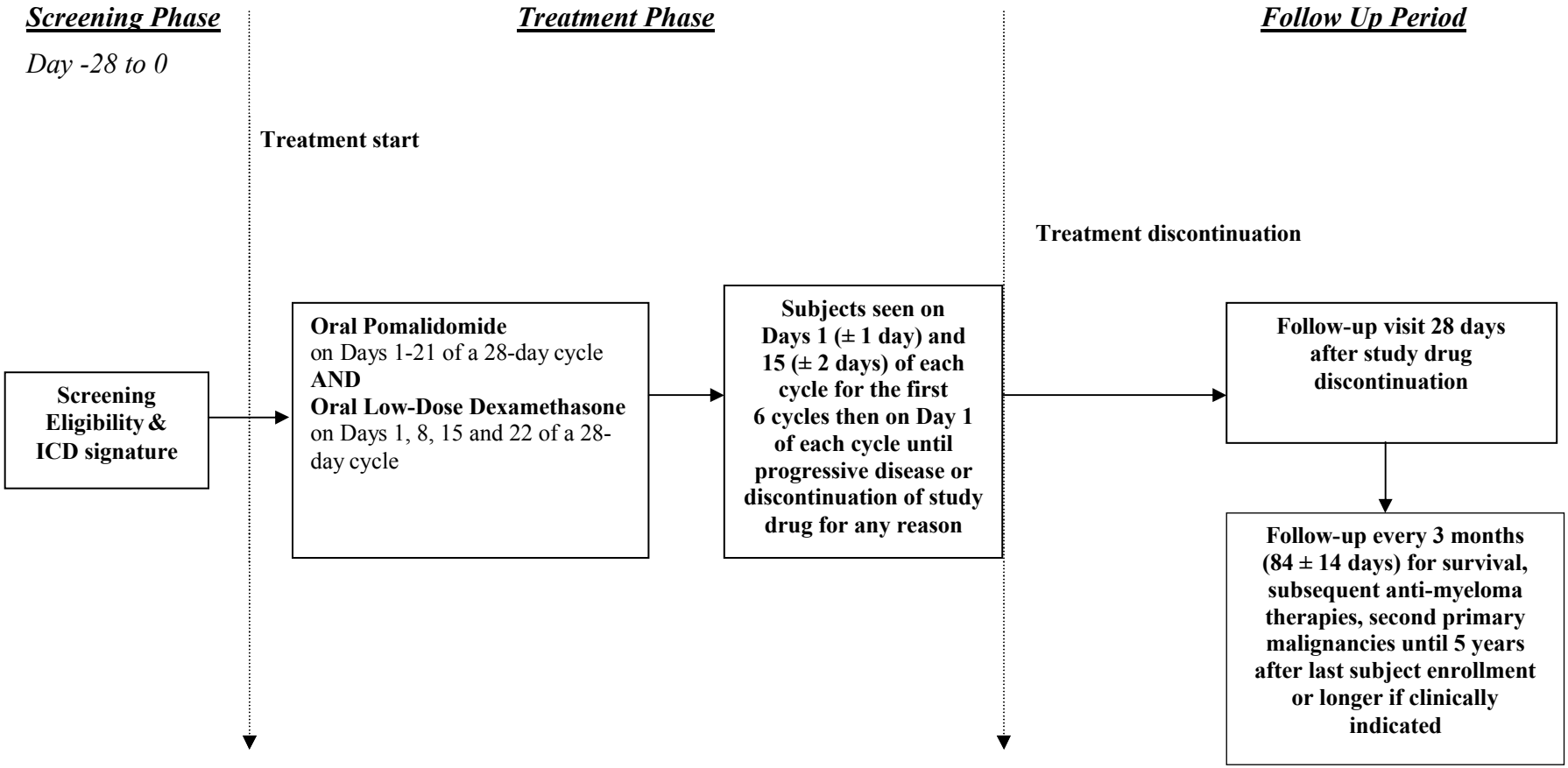
Population pharmacokinetics and exposure-response analyses will be performed at selected sites on the PK data obtained from the PK blood samples.

Analysis of biomarkers will also be explored in subjects at selected clinical sites, who consent to participate in the optional exploratory biomarker study.

All subjects will be maintained on the POM pregnancy prevention program (Appendix D) for the duration of the study.

For all subjects who enroll into this study, study visits and serial measurements of safety and efficacy will be performed as outlined in Table 1, Table of Events. The Overall Study Design is described in Figure 1.

Figure 1: Overall Study Design



4.3. Study Duration

This study will consist of the following consecutive phases: Screening, Treatment and Follow-up.

Screening Phase (Day -28 to Day 0)

Potential study subjects will sign the ICD prior to undergoing any study-related procedure. Subjects may have the choice to participate in the optional biomarker study conducted at selected sites. If a subject chooses to participate in the exploratory biomarker study, he/she must give consent for the optional biomarker analysis.

Subjects will undergo screening for protocol eligibility within 28 days prior to Cycle 1 Day 1, as outlined in Table 1, Table of Events.

Subjects must have discontinued anti-myeloma therapies at least 14 days prior to initiation of study treatment (wash-out period). Hematopoietic growth factors, platelet and/or red blood cell (RBC) transfusions are allowed throughout the study, including the screening period, at the discretion of the investigator. It is recommended that myeloid and erythroid growth factors be utilized as per ESMO guidelines (Crawford, 2010). Primary prophylaxis for the prevention of neutropenia is highly recommended in subjects who are at high risk based on age, medical history and disease characteristics. If platelet transfusions are given during the screening period, the screening platelet assessment must be done a minimum of 3 days (72 hours) after the completion of the transfusion. Subjects who meet all eligibility criteria will receive the study treatment and will be maintained on the pregnancy prevention program for the duration of the study.

The inclusion procedure will be accomplished by a validated interactive voice/web response system (IVRS/IWRS).

Treatment Phase

Study treatment administration should start within 72 hours after enrollment of the subject in the study (which is defined as enrollment on the IVRS/IWRS), provided that the inclusion/exclusion criteria are still met. Otherwise, the subject will need to be re-screened. Each subject will receive the following study treatment:

- POM administered orally at the starting dose of 4 mg on Days 1-21 of a 28-day cycle,
- LD-DEX administered orally at the starting dose of 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle.

Subjects will be seen at Day 1 (± 1 day) and Day 15 (± 2 days) of each cycle for the first 6 cycles then at Day 1 (± 1 day) of each following cycles and may remain on the study until documented PD (according to IMWG criteria) or discontinuation of study drug for any reason or as long as they benefit from therapy according to the opinion of responsible study Investigator and discussed with the Medical Monitor.

Sparse PK blood samples for POM quantification will be collected on Day 15 (± 2 days) of Cycle 1 through 6 at specified time-points during the course of the study from all subjects at selected sites with PK capability. These PK samples are necessary to characterize the steady-

state PK and exposure-response characteristics of POM when it is administered with LD-DEX in the refractory or relapsed and refractory population.

Bone marrow aspirate, bone marrow biopsy (if available) and blood samples will be collected for exploratory biomarker analysis from subjects at selected sites, who consent to participate in the optional biomarker study. The bone marrow aspirate and bone marrow biopsy (if available) will be collected during screening when the procedure is performed for study entry and at response assessment or at disease progression when clinically indicated.

Study visits and evaluations will be performed as outlined in Table 1 ("Table of Events").

Follow-up Phase

All study subjects will enter the follow-up phase after study treatment discontinuation. During the follow-up the following information will be collected from all subjects every 3 months for up to 5 years after last subject enrollment: SAEs including SPM, survival, subsequent anti-myeloma treatments (type of treatment, start and stop dates, best response whenever possible) and date of progression.

5. TABLE OF EVENTS

Table 1: Table of Events

Procedures[a]	Screening (Days -28 to 0)	Day 1 (± 1 day) of Every Cycle	Day 15 (± 2 days) Cycles 1-6 Only	Treatment Discontinuation	Follow-up visit (28 days post treatment discontinuation)	Long-term Follow-up Every 3 Months (84 ± 14 days) for Up to 5 Years After Last Subject Enrollment
Entry Assessments						
Informed Consent Document (ICD)	X					
ICD for exploratory biomarker studies (at selected sites)	X					
Inclusion/exclusion criteria	X					
Demographics (age, gender)	X					
Medical History	X					
Cytogenetic data from medical history[c]	X					
Prior anti-myeloma therapies, radiotherapy, surgeries	X					
Disease Diagnosis[d]	X					
Safety Assessments						
Adverse event query[e]	After signing ICD and until 28 days after discontinuation from treatment					
Second Primary Malignancy[f]	After signing ICD and up to 5 years after last subject enrollment or longer if clinically indicated					
Physical Exam	X	X		X		
Vital Signs[g]	X	X		X	X	
Hematology[h]	X	X	X	X		
Serum Chemistry[i]	X	X	X	X		
Urinalysis[j]	X	X		X		

Table 1: Table of Events (Continued)

Procedures[a]	Screening (Days -28 to 0)	Day 1 (± 1 day) of Every Cycle	Day 15 (± 2 days) Cycles 1-6 Only	Treatment Discontinuation	Follow-up visit (28 days post treatment discontinuation)	Long-term Follow-up Every 3 Months (84 ± 14 days) for Up to 5 Years After Last Subject Enrollment
Estimation of Renal Function[k]	X	X	X	X		
[redacted]		[redacted]		[redacted]		
ECG[l]	X			X		
[redacted]		[redacted]				
Pregnancy testing for FCBP[n]	X	X		X	X	
Pregnancy Counseling	X	X		X		
Efficacy Measurements						
ECOG Performance Status	X	X		X		
Bone Marrow Aspiration and/or Biopsy[o]	X					
Serum Beta-2 Microglobulin	X					
Quantitative Serum Immunoglobulin Levels[p]	X	X		X		
Serum protein electrophoresis (SPEP) and 24-hour Urine electrophoresis (UPEP)[q]	X	X		X		
Serum free light-chain (FLC) assay[r]	X	X		X		
Extramedullary Plasmacytoma (EMP) Assessments[s]	X	X		X		
Skeletal Survey (by x-ray/CT)[t]	X					
Assessment of Response [u]		X		X		
Survival Status						X
Subsequent Anti-myeloma Regimens[v]					X	X

Table 1: Table of Events (Continued)

Procedures[a]	Screening (Days -28 to 0)	Day 1 (± 1 day) of Every Cycle	Day 15 (± 2 days) Cycles 1-6 Only	Treatment Discontinuation	Follow-up visit (28 days post treatment discontinuation)	Long-term Follow-up Every 3 Months (84 ± 14 days) for Up to 5 Years After Last Subject Enrollment
Other Assessments						
PK sampling (cycles 1 to 6 only)[w]			X			
Cytogenetic analysis[bb]	X			X		
[redacted]	[redacted]			[redacted]		
[redacted]	[redacted]			[redacted]		
Investigational Product Dispensation						
Oral POM dispensation/ accountability[x]		X		X		
Oral DEX dispensation/ accountability[y]		X		X		

AE = adverse event; ANC = absolute neutrophil count; ALC = Absolute lymphocyte count; CR = complete response; Dex = dexamethasone; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FCBP = females of childbearing potential; LD = low-dose; PD = progressive disease; PK = pharmacokinetic; Pom = Pomalidomide; PR = partial response; RBC = red blood cell; SAE = serious adverse event; SPM = second primary malignancy; VTE = venous thrombotic events; WBC = white blood cell.

[a] Laboratory tests for hematology and biochemistries, vital signs and ECG are recommended and should be performed according to the current standard of care, unless specified in this protocol. If screening visit results are ≤ 7 days prior to enrollment, these laboratory assessments do not have to be repeated at Cycle 1 Day 1.

[b] Day 15 visit will be performed during Cycle 1 to Cycle 6 only. If medically justified, a 5-day window is allowed at Day 15

[c] Results for any local cytogenetic testing, if available as part of medical history, will be collected in the eCRFs.

[d] Date of initial diagnosis and myeloma stage per the International Staging System and/or the Durie-Salmon Staging System (Appendix G) at initial diagnosis (if available) will be collected as part of the disease diagnosis assessment.

[e] All AEs should be assessed starting after the subject signs the informed consent until 28 days after treatment discontinuation. AEs that lead to study discontinuation should be followed until resolution or stabilization. SAEs, regardless of relationship to the investigational product (POM or DEX), that occur from the time the subject signs informed consent to at least 28 days after treatment discontinuation and those made known to the investigator at anytime thereafter that are suspected of being related to investigational product must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event.

[f] Second primary malignancies (SPM) will be monitored as events of interest and must be reported as SAEs. This includes any SPM, regardless of causal relationship to IP (POM or LD-DEX), occurring at any time from the time of signing the ICD 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 SAE (e.g., 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 (e.g., pathology, cytogenetics, flow cytometry) from the MM diagnosis confirmation performed at screening and from the diagnostic tumor samples obtained at SPM determination, will be required for SPM

confirmation. Tissue from bone marrow aspirates performed on study and tissue from the diagnostic sample obtained at SPM determination will be collected. If the SPM determination is made at an institution besides the study institution, every effort will be made to collect these samples and reports.

[g] Vital signs include blood pressure, temperature, respiratory rate and heart rate. The measurement of height will be performed at screening only. The measurement of weight will be performed at screening, at Day 1 of each cycle, and at the treatment discontinuation.

[h] Assessment of hematology includes: white blood cell count with differential, ANC, ALC, hemoglobin, hematocrit, platelet count, mean corpuscular volume and reticulocyte count. This assessment will be performed by the local laboratory. Reticulocyte count will be not performed on Day 15 of every cycle.

[i] Assessment of serum chemistry includes: total protein, albumin, calcium, corrected serum calcium, glucose, total bilirubin, direct bilirubin (only when total bilirubin is increased), alkaline phosphatase, AST/SGOT, ALT/SGPT, GGT, sodium, potassium, creatinine, lactate dehydrogenase, creatinine kinase, and C-reactive protein. If PD is noted based on corrected serum calcium level, a repeat serum chemistry test should be performed as soon as possible to confirm PD. This assessment will be performed by the local laboratory. On Day 15 of every cycle serum biochemistry includes only: total bilirubin, alkaline phosphatase, AST/SGOT, ALT/SGPT, GGT, sodium, potassium, creatinine, lactate dehydrogenase.

[j] Assessment of urinalysis includes: specific gravity, pH, glucose, bilirubin, protein, ketones, and blood. Microscopic analysis [casts, bacteria, RBCs, and WBCs] should be performed if clinically indicated. This assessment will be performed by the local laboratory.

[k] The assessment will be performed using the Cockcroft-Gault formula for estimation of creatinine clearance (CrCl). CrCl also needs to be determined based on a 24 hour urine collection at screening visit. 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.

[l] ECGs will be performed at Screening visit and at study discontinuation, and the time as clinically indicated at the discretion of the treating physician during the study. All ECGs will be performed and reviewed locally.

[redacted]

[n] FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The subject may not receive study drug 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 28 days of study participation and then every 28 days while on study, at treatment discontinuation, and 28 days following treatment discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at treatment discontinuation, and at days 14 and 28 following treatment discontinuation.

[o] A bone marrow aspirate (and biopsy if necessary) is mandatory and must be obtained within 28 days prior to enrollment to obtain a current estimate of the % plasma cells in the marrow. Analysis for % plasma cells in the marrow will be performed locally. After screening, a bone marrow aspirate (or biopsy if necessary) must be performed to document a response ≥ CR, and may otherwise be repeated as clinically indicated at the discretion of the treating physician. In subjects, who consent to participate in the exploratory biomarker analysis, bone marrow aspirate, and bone marrow biopsy (if available) material will be collected while the subject is undergoing the procedure mandatory for study entry. Bone marrow aspirate and bone marrow biopsy (if available) material will also be collected when those subjects participating in the biomarker analysis undergo additional bone marrow procedures while on study when clinically indicated.

[p] This assessment will be performed by the local laboratory. Quantitative immunoglobin assessment (IgG, IgA, IgM, IgE and IgD) should also be performed at the time of response confirmation (≥ CR). All subjects will be evaluated for IgG, IgA and IgM. Testing for IgE and IgD is only required for subjects with the respective (IgE or IgD) subtype.

[q] 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. This assessment will be performed by the local laboratory. If a response (≥ PR) or PD is noted based on SPEP and/or UPEP results, a repeat test should also be conducted as soon as possible to confirm the response or PD. Also, serum and urine immunofixation (IFE) tests are performed at screening to identify the immunoglobulin subtype of MM and thereafter are required to be performed whenever M-protein is undetectable in both serum and urine by protein electrophoresis studies. Serum and urine IFE tests should also be performed at the time of response confirmation (≥ CR).

[r] This assessment will be performed by the local laboratory. Serum FLC assay should also be performed at the time of response confirmation (≥ CR).

[s] Assessment/measurement at specified time-points only required if EMPs are present. If EMPs are clinically assessable, clinical assessment will be performed at screening, at every Cycle Day 1, and at treatment 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, and when clinically indicated to confirm response (≥ PR). All scans will be reviewed locally only.

[t] A skeletal survey by x-ray or if clinically indicated, a CT-scan will be performed at screening and when clinically indicated per the investigator's discretion. If a skeletal survey was performed within 60 days prior to the start of Cycle 1, it may be used for the screening assessment if approved by Sponsor. All skeletal survey films or CT scans will be performed and analyzed locally by the site investigator/radiologist. Refer to Appendix C for detailed requirements.

[v] Subsequent anti-myeloma regimens: type of treatment, start and stop dates, date of progression and best response whenever possible.

[w] PK samples: Cycles 1, 2 and 3. Day 15: pre-dose and Cycles 4,5 and 6 Day 15: one sample per visit.
It is encouraged that the PK sample at each of these 3 visits at Cycles 4, 5 and 6 be at a different time post administration of POM.

[x] Subject will take oral dose of POM on Days 1 to 21 of each 28-day cycle.

[y] Subject will take oral LD-DEX on Days 1, 8, 15, and 22 of each 28-day cycle.

[bb] Cytogenetic analysis will be performed using FISH (at local laboratory) at study entry using the bone marrow aspirate that needs to be performed to estimate the % of the plasma cells. In addition, cytogenetic analysis will be performed for those subjects who discontinue treatment due to disease progression. If study treatment is discontinued due to toxicity, then cytogenetic analysis should be postponed until disease progression. If possible subsequent relapse should also be documented by FISH. The same technique and the same approach should be used for a subject thoughout the study.

6. PROCEDURES

Study Entry

Prior to screening, subjects must sign an ICD for the main study and have the choice of also signing the ICD for the exploratory biomarker study (at selected sites only). All screening assessments must be completed within 28 days prior to start of Cycle 1, with the exception of the skeletal survey, which may be performed within 60 days prior to initiation of study treatment.

Subjects may have the choice to participate in the optional biomarker study conducted at selected sites. If a subject chooses to participate in the exploratory biomarker study, he/she must give consent for the optional biomarker analysis. Confirmation of diagnosis (including date of confirmed initial diagnosis and, if available, myeloma stage at time of initial diagnosis per the Salmon-Durie Criteria and/or the International Staging System [Appendix G]) medical, prior cancer and surgical history, and review of concomitant medications should be documented during the screening period. All prior radiotherapy, surgeries, and anti-myeloma therapies must be recorded in the electronic case report form (eCRF), including approximate dates for each therapy and the date of progression for each regimen. Results for any local cytogenetic testing (preferably fluorescence *in situ hybridization* - FISH - results), as part of medical history, will be collected in the eCRF. For all eligible subjects, cytogenetic analysis is also required upon study entry based on the bone aspirate sample taken during screening. See Table 1 "Table of Events" for all the required assessments during screening.

If the subject's safety and efficacy laboratory assessments performed at screening are within 7 days of enrollment into the study, they do not need to be repeated at Cycle 1 Day 1 and can be used as baseline results. The start of study drug dosing is designated as Cycle 1 Day 1. A 14-day wash-out period is required for any prior anti-myeloma therapy before study treatment is initiated. Assessments should be performed on Day 1 (± 1 day) and on Day 15 (± 2 days) of every cycle for the first 6 cycles then on Day 1 (± 1 day) for the following cycles during the treatment and at treatment discontinuation. In exceptional cases and if medically justified, a 5-day window at Day 15 of every cycle will be acceptable (for Cycles 1 to 6). Long term follow-up will be performed every 84 days (± 14 days).

Safety Assessments

Adverse Events

All AEs should be assessed starting after the subject signs the ICD until 28 days after treatment discontinuation. Adverse events that lead to study discontinuation should be followed until resolution or stabilization.

Serious Adverse Events

Serious adverse events, regardless of relationship to the IP (POM or DEX), that occur from the time the subject signs the ICD to at least 28 days after treatment discontinuation and those made known to the investigator at anytime thereafter that are suspected of being related to the IP (POM or DEX) must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event.

Second Primary Malignancies

Second primary malignancies will be monitored every 3 months for up to 5 years after the last subject is enrolled as events of interest and must be reported as SAEs. This includes any SPM, regardless of causal relationship to the IP (POM with or without DEX), occurring at any time from the time of signing the ICD 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 SAE (e.g., 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 (e.g., pathology, cytogenetics, flow cytometry) from the MM diagnosis confirmation performed at screening and from the diagnostic tumor samples obtained at SPM determination, will be required for SPM confirmation.

For SPMs diagnosed at another institution, (outside of the investigational site) sites will be required to make every effort to obtain these reports for SPM confirmation.

[redacted]

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

A complete physical exam will be performed at screening, at Day 1 of every cycle starting at Cycle 1, and at treatment discontinuation. Any on study abnormal and clinically significant findings are to be reported as adverse events.

Measurement of vital signs (blood pressure, temperature, heart rate and respiration rate) will be performed at screening, at Day 1 of each Cycle, at treatment discontinuation, and at the 28 days post treatment discontinuation visit.

Measurement of height will be performed at screening only. Measurement of weight will be performed at screening, at Day 1 of each Cycle, and at treatment discontinuation.

Electrocardiogram

Electrocardiogram (ECG, 12-lead) monitoring will be performed at Screening visit, discontinuation visit and as clinically indicated at the discretion of the treating physician during the study. All ECGs will be performed and reviewed locally.

Laboratory Assessments for Safety Parameters

All laboratory assessments for safety parameters will be performed locally.

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

- **Hematology Laboratory Tests.** Hematology includes: white blood cell (WBC) count with differential, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), hemoglobin, hematocrit, platelet count, mean corpuscular volume and reticulocyte count. Hematology will be performed at screening, on Day 1 (± 1 day) and Day 15 (± 2 days) of every cycle for the first 6 cycles then on Day 1 (± 1 day) for the following cycles, and at treatment discontinuation. Reticulocyte count will be not performed on Day 15 of each cycle.
- **Serum Chemistry Laboratory Tests.** Serum chemistry includes: total protein, albumin, calcium, corrected serum calcium, glucose, total bilirubin, direct bilirubin (only when total bilirubin is increased), alkaline phosphatase, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), gamma-glutamyl tranpeptidase (GGT), sodium, potassium, creatinine, lactate dehydrogenase, creatinine kinase, and C-reactive protein. Serum chemistry labs will be performed at screening, on Day 1 (± 1 day) of every cycle, and at treatment discontinuation. If PD is noted based on corrected serum calcium level, a repeat serum chemistry test should be performed as soon as possible to confirm PD. Serum biochemistry will also be performed on Day 15 (± 2 days) of every cycle during the first 6 cycles and includes only: total bilirubin, alkaline phosphatase, AST/SGOT, ALT/SGPT, GGT, sodium, potassium, creatinine, lactate dehydrogenase.
- **Urinalysis.** Urinalysis includes: specific gravity, pH, glucose, bilirubin, protein, ketones, and blood. Microscopic analysis (casts, bacteria, RBCs, and WBCs) should be performed if clinically indicated. Urinalysis will be performed at screening, on Day 1 (± 2 days) of every cycle, and at treatment discontinuation.
- **Estimation of Renal Function.** The assessment will be performed using the Cockcroft-Gault estimation of CrCl.

  Cockcroft-Gault Formula (Cockcroft, 1976; Luke, 1990)

  CrCl (mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dL]); for females, the formula is multiplied by 0.85.

  CrCl also needs to be determined based on a 24-hour urine collection at screening visit. Estimation of renal function will be performed at screening, on Day 1 (± 1 day) and Day 15 (± 2 days) of every cycle for the first 6 cycles then on Day 1 (± 1 day) for the following cycles, and at treatment discontinuation. 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.

If a major discrepancy is observed between Cockcroft-Gault estimation and urine measurement, the further management of the subject will be discussed with the Sponsor.

Pregnancy Counseling (Males and Females)

Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted for all subjects at screening, Day 1 of every cycle during treatment and at treatment discontinuation visit for all subjects. Please refer to Pomalidomide Pregnancy Risk Minimization Plan in Section 11.4 and Appendix D.

Pregnancy Testing for Females of Child Bearing Potential (FCBP)

All 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. The subject may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative. Females of Child Bearing Potential with regular or no menstrual cycles must agree to have pregnancy tests every 7 days (weekly) for the first 28 days of study participation and then every 28 days while on study, at treatment discontinuation, and 28 days following treatment discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at treatment discontinuation, and at Days 14 and 28 following treatment discontinuation).

Efficacy Assessments

Disease progression status will be assessed by the investigator at each treatment cycle and at treatment discontinuation. Tumor response including progressive disease will be assessed according to the IMWG uniform response criteria (Durie, 2006). All treatment decisions will be made by the treating physician based on response as assessed using the IMWG criteria.

Survival status will be collected for all subjects during the treatment phase and the long-term follow-up phase.

All efficacy assessments will be performed and reviewed locally. These efficacy assessments include labs used as part of standard care: Eastern Cooperative Oncology Group (ECOG) performance status, serum beta-2 microglobulin, myeloma paraprotein protein electrophoresis and immunofixation, serum immunoglobulins, serum free light chain assay, and if applicable, clinical and/or radiological extramedullary plasmacytoma assessment, skeletal survey, and bone marrow aspirate/biopsy.

If a new cycle is delayed greater than seven days (> 7 days, but less than 28 days) from the protocol-defined 28-day dosing cycle, an unscheduled visit should be performed for efficacy assessments prior to initiation of the next cycle. If the delay is greater than 28 days, these efficacy assessments should be performed every 28 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.

The efficacy assessment will be documented in the source documents and recorded on the eCRF.

ECOG Performance Status

ECOG Performance Status will be performed at screening, at Day 1 of every Cycle, and at treatment discontinuation. See Appendix H for the ECOG Performance Status Scale.

Laboratory Assessments for Efficacy Parameters

All laboratory assessments for efficacy parameters will be performed locally.

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

- **Serum beta-2 microglobulin**: The serum beta-2 microglobulin sample will be collected at screening only.
- **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 or any other validated method, will be performed at screening, at every cycle on Day 1 and at treatment discontinuation. 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. 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 (≥ PR) or PD.
- **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 required to be performed whenever M-protein is undetectable in both serum and urine by protein electrophoresis studies. Serum and urine IFE tests should also be performed at the time of response confirmation for ≥ CR.
- **Serum Immunoglobulins** assessment will be performed at screening and at every cycle on Day 1, at treatment discontinuation, and at the time of response confirmation for ≥ CR. All subjects will be evaluated for IgG, IgA and IgM. Testing for IgE and IgD is only required for subjects with the respective (IgE or IgD) subtype.
- **Serum Free Light Chain** assay will be performed at screening, at every cycle on Day 1, at treatment discontinuation, and at the time of response confirmation for ≥ CR.

Bone Marrow Aspiration and/or Biopsy

A bone marrow aspirate (and biopsy if necessary) is mandatory and must be obtained within 28 days prior to enrollment to obtain a current estimate of the % plasma cells in the marrow. After screening, a bone marrow aspirate (or biopsy if necessary) must be performed to document a ≥ CR, and may otherwise be repeated as clinically indicated at the discretion of the treating physician. Analysis of bone marrow will be performed locally.

Subjects who signed the additional consent may undergo optional biomarker assessments at a selected number of sites. For those subjects who consent to participate in the optional biomarker analysis, bone marrow aspirate and bone marrow biopsy (if available) material will be collected

during the mandatory bone marrow assessment at screening and during other bone marrow assessments that are clinically indicated. No additional intervention will be required at screening, only additional volume of aspirate will be withdrawn, or excess material from the biopsy will be utilized for the biomarker study.

Extramedullary Plasmacytoma Assessments

Extramedullary plasmacytoma assessments/measurements at specified time-points are only required if EMPs are present.

If EMPs are clinically assessable, clinical assessment will be performed at screening, at every Cycle Day 1, and at treatment 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, and when clinically indicated to confirm a response ≥ PR. All scans will be reviewed locally only.

Skeletal Survey

A skeletal survey by x-ray or if clinically indicated, a CT scan will be performed at screening and when clinically indicated per the investigator's discretion. If a skeletal survey was performed within 60 days prior to the start of Cycle 1, it may be used for the screening assessment if approved by the Sponsor. All skeletal survey films or scans will be performed and analyzed locally by the site investigator/radiologist. Refer to Appendix C for detailed requirements.

Assessment of Response

Response, including PD, will be assessed using the IMWG criteria (Appendix I) at Day 1of each Cycle and at the treatment discontinuation visit.

Overall Survival and Subsequent Anti-MM Therapies

During the follow-up period, survival status and subsequent therapies for MM must be collected and entered into the eCRF. All subjects will be assessed 4 times a year (every 3 months) to determine survival status for up to 5 years after last subject enrollment. Primary cause of death (medical condition) is to be recorded in the eCRF and the subject's medical record. All subsequent therapies given for MM must be collected and entered into the eCRF.

Other Assessments

Cytogenetic analysis

Previous results from cytogenetic analyses performed on subjects at their time of diagnosis are required to be recorded in the eCRF. The bone marrow aspirate taken during screening for disease staging and characterization will also be used to undertake the cytogenetic analysis at study entry for all eligible subjects. In addition, a further bone marrow aspirate is required for cytogenetic analysis for those subjects who discontinue study treatment due to disease progression. The sites should apply standard, consistent FISH methodology for these analyses, with all samples analyzed at their local laboratory.

Pharmacokinetic Study

Pharmacokinetic samples for POM quantification will be collected from all subjects at selected sites with PK capability from Cycle 1 to Cycle 6 inclusive. Dosing information and sample collection information including dose (mg), dosing date, dosing time (24 hour clock), and actual PK sampling time (24 hour clock) should be accurately documented on the appropriate source documentation and eCRF pages.

Detailed instructions for sample collection, processing, storage, shipping and handling can be found in Appendix J.

Pharmacokinetic blood samples will be collected from subjects at the following time-points:

- Cycles 1, 2, and 3 Day 15: pre-dose
- Cycles 4, 5 and 6 Day 15: one sample per visit. It is encouraged that the PK sample at each of these 3 visits be at a different time post administration of POM.

Subjects should take POM at approximately the same time in the morning during Cycles 1, 2, and 3. On Day 15 (± 2 days) of Cycles 1, 2, and 3, POM will be administered to subjects in the morning at the study site after the collection of the pre-dose PK blood sample. Dexamethasone should be administered after completion of the PK sample collection. Starting with Cycle 4, subjects may take POM at any time during the day, but are encouraged to take POM at a similar time every day. On Day 15 (± 2 days) of Cycles 4, 5 and 6, subjects will be asked to report the actual dosing time of their last dose of POM (i.e. if visit is on Day 15, last dose could be either their Day 14 or Day 15 dose) to the study staff during their visit at the study site. A PK blood sample will be collected during their visit.

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

7. STUDY POPULATION

7.1. Number of Subjects and Sites

This is a multicenter, single-arm, open label, phase IIIb study of POM and LD-DEX in adult subjects with refractory MM or relapsed and refractory MM.

This study is anticipated to enroll approximately 720 subjects with refractory MM or relapsed and refractory MM in European countries and Israel.

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 document (ICD).
2. The subject must understand and voluntarily sign an ICD prior to any study related assessments/procedures being conducted.
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 (serum M-protein ≥ 0.5 g/dL or urine M-protein ≥ 200 mg/24 hours).
5. Subjects must have undergone prior treatment with ≥ 2 treatment lines of anti-myeloma therapy. Induction therapy followed by ASCT and consolidation/maintenance will be considered as one line. A new treatment line is always started after progressive disease.
6. Subjects must have either refractory or relapsed and refractory disease defined as documented disease progression during or within 60 days of completing their last myeloma therapy.

   Primary Refractory: Subjects who have never achieved any response better than PD to any previous line of anti-myeloma therapy.

   Relapsed and Refractory: Subjects who have relapsed after having achieved at least stable disease for at least two cycles of treatment to at least one prior regimen and then developed PD on or within 60 days of completing their last myeloma therapy.
7. All subjects must have received at least 2 consecutive cycles of prior treatment that included lenalidomide and bortezomib, either alone or in combination regimens.

   All subjects must have failed both lenalidomide and bortezomib and medical records must be available that provide documentation of the following criteria for refractoriness that make the subject eligible for the study.

   - All subjects must have failed treatment with the last lenalidomide-containing regimen in one of the following ways:
     - Documented PD during or within 60 days of completing last treatment with lenalidomide, regardless of the response achieved, or

  - In case of prior response (≥ partial response - PR) to lenalidomide and PD > 60 days, subjects must have relapsed within 6 months after the last dose of treatment with lenalidomide-containing regimens.

- All subjects must have failed treatment with the last bortezomib-containing regimen in one of the following ways:
  - Documented PD during or within 60 days of completing treatment with bortezomib, regardless of the response achieved, or
  - In case of prior response (≥ PR) to bortezomib and PD > 60 days, subjects must have relapsed within 6 months after the last dose of treatment with bortezomib-containing regimens,

  Or for non-progressive subjects:

  - Subjects who have less than MR response and have developed intolerance/toxicity after a minimum of two cycles of a bortezomib-containing regimen. Toxicity such as > grade 2 peripheral neuropathy or ≥ grade 2 painful neuropathy. Peripheral neuropathy must resolve to grade 1 prior to study entry.

8. Subjects must have received adequate prior alkylator therapy in one of the following ways:
   - As part of a stem cell transplant; or
   - A minimum of 4 consecutive cycles of an alkylator based therapy; or
   - Progression on treatment with an alkylator; provided that the subject received at least 2 cycles of an alkylator-containing therapy.
9. ECOG performance status score of 0, 1, or 2.
10. Females of childbearing potential (FCBP[2]) must agree to utilize two reliable forms of contraception simultaneously or practice complete abstinence from heterosexual contact for at least 28 days before starting study drug, while participating in the study (including dose interruptions), and for at least 28 days after study treatment discontinuation and must agree to regular pregnancy testing during this timeframe. (NOTE: True abstinence: When this is in line with the preferred and usual lifestyle of the subject. *[Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]*).
11. Females must agree to abstain from breastfeeding during study participation and 28 days after study drug discontinuation.
12. Males must agree to use a latex condom during any sexual contact with FCBP while participating in the study and for 28 days following discontinuation from this study, even if he has undergone a successful vasectomy.

[2] A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., who has had menses at any time in the preceding 24 consecutive months).

13. Males must also agree to refrain from donating semen or sperm while on POM and for 28 days after discontinuation from this study treatment.
14. All subjects must agree to refrain from donating blood while on study therapy and for 28 days after discontinuation from this study treatment.
15. All subjects must agree not to share medication.

7.3. Exclusion Criteria

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

1. Any of the following laboratory abnormalities:
   - Absolute neutrophil count < 800/μL.
   - 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. Platelet transfusion is not allowed within the previous 3 days before screening.
   - Creatinine Clearance < 45 mL/min according to Cockcroft-Gault formula. If creatinine clearance calculated from the 24-hour urine sample is ≥ 45 mL/min, subject will qualify for the study.
   - Corrected serum calcium > 14 mg/dL (> 3.5 mmol/L).
   - Hemoglobin < 8 g/dL (< 4.9 mmol/L; prior RBC transfusion or recombinant human erythropoietin use is permitted).
   - Serum SGOT/AST or SGPT/ALT > 3.0 x upper limit of normal (ULN).
   - Serum total bilirubin > 2.0 mg/dL (34.2 μmol/L); or > 3.0 x ULN for subjects with hereditary benign hyperbilirubinemia.
2. Prior history of malignancies, other than MM, unless the subject has been free of the disease for ≥ 5 years. Exceptions include the following:
   - Basal or squamous cell carcinoma of the skin
   - Carcinoma *in situ* of the cervix or breast
   - Incidental histological finding of prostate cancer (TNM stage of T1a or T1b).
3. Previous therapy with POM.
4. Hypersensitivity to thalidomide, lenalidomide, or DEX (this includes ≥ Grade 3 rash during prior thalidomide or lenalidomide therapy).
5. Peripheral neuropathy ≥ Grade 2.
6. Subjects who received an allogeneic bone marrow or allogeneic peripheral blood stem cell transplant less than 12 months prior to initiation of study treatment and who have not discontinued immunosuppressive treatment for at least 4 weeks prior to initiation of study treatment and are currently dependent on such treatment.
7. Subjects who are planning for or who are eligible for stem cell transplant.

8. Subjects with any one of the following:
   - Congestive heart failure (NY 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.
9. Subjects who received any of the following within the last 14 days of initiation of study treatment:
   - Major surgery (kyphoplasty is not considered major surgery)
   - Use of any anti-myeloma drug therapy.
10. Use of any investigational agents within 28 days or five half-lives (whichever is longer) of treatment, unless approved by the Sponsor.
11. Incidence of gastrointestinal disease that may significantly alter the absorption of POM.
12. Subjects unable or unwilling to undergo antithrombotic prophylactic treatment.
13. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subjects from signing the ICD or participating in the study.
14. Pregnant or breastfeeding females.
15. Known human immunodeficiency virus (HIV) positivity, active infectious hepatitis A, B or C or chronic hepatitis B or C.

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product(s)

Pomalidomide will be supplied as Investigational Product by Celgene Corporation as 1 mg, 2 mg, 3 mg, and 4 mg capsules for oral administration. Investigational product will be packaged in bottles containing a 21 day supply of POM.

Celgene will provide commercial supplies of DEX 2 mg and 4 mg tablets for oral administration, labeled appropriately for investigational use as per the regulations of the relevant country health authority.

Other recommended/required concomitant medications per the protocol such as aspirin (or other antithrombotic or anti-coagulants) and growth factors are commercially available, and will be provided at the site by investigator(s) prescription. Celgene will not provide these medications.

8.2. Treatment Administration and Schedule

All study drug doses will be administered orally and subjects will be instructed about the dosing schedules for the study. Subjects enrolled in this study will receive:

- Oral POM at the starting dose of 4 mg on Days 1-21 of a 28-day cycle,
- Oral LD-DEX at the starting dose of 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle.

Subjects will also 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 may not be dispensed until the investigator has verified that the results of the pregnancy test are negative. Females of childbearing potential other than the subject should not handle study drug unless wearing gloves.

All subjects enrolled into the study will continue study treatment until progressive disease or unacceptable toxicity.

Dose Modification and Interruption

In the event of any dose reduction for POM, site staff must contact IVRS 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 28 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.

Subjects will be evaluated for AEs at each visit with the NCI-CTCAE (version 4.0) as a guide for the grading of severity. Dosing interruptions and reductions are permitted throughout the study.

Dose Modification Instructions for Pomalidomide

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

If POM administration is withheld, LD-DEX should also be withheld. If POM is discontinued permanently, then the subject must be permanently discontinued from all study treatments.

Table 2: Dose Modification Instructions for Pomalidomide

Toxicity	Dose Modification
Neutropenia Grade 4 neutropenia (ANC < 500/μL) or Febrile neutropenia (ANC < 1,000/μL with a single temperature of > 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour)	Hold the dose for remainder of cycle. If the subject was not receiving GCSF therapy, GCSF therapy may be started at the discretion of the treating physician. On Day 1 of the next cycle, the dose of POM may be maintained if neutropenia was the only POM-related toxicity requiring a dose modification and GCSF treatments are continued. Otherwise, decrease by one dose level at start of next cycle. Note, ANC must be ≥ 800/ μL to re-start dosing
Thrombocytopenia Grade 4 Thrombocytopenia (Platelets <25,000/μL)	Hold the dose for remainder of cycle. Dosing may resume at one dose level lower once the platelet count has recovered to ≥ 30,000/μL.
Rash = Grade 3	Hold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (rash must resolve to ≤ Grade 1 before restarting dosing).
Rash = Grade 4 or Blistering	Discontinue subject from POM treatment regimen.
Constipation ≥ Grade 3	Hold dose for remainder of cycle. Initiate bowel regimen. Decrease by one dose level when dosing restarted at next cycle (constipation must resolve to ≤ Grade 2 before restarting dosing).
VTE ≥ Grade 3	Hold dose for remainder of cycle. Initiate anticoagulation treatment. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.
Hypo/hyperthyroidism ≥ Grade 2	Hold dose for remainder of cycle. Initiate appropriate medical therapy. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.
Other ≥ Grade 3 POM-related[a] adverse events	Hold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (adverse event must resolve to ≤ Grade 2 before restarting dosing).

GCSF = granulocyte-colony stimulating factor; POM = pomalidomide; VTE = venous thrombotic event.
[a] For Grade 3 or 4 AEs that are not considered to be related to study drug, the treating physician should consult with the Sponsor for dose interruptions and reductions.

To initiate a new cycle of POM following a dose interruption, the neutrophil count must be ≥ 800/μL with or without GCSF, the platelet count must be ≥ 30,000/μL, and non-hematologic AEs must have recovered as outlined in Table 2.

If recovery from toxicities is prolonged beyond 14 days, then the dose of POM will be decreased by one dose level when dosing is restarted.

Table 3: Pomalidomide Dose Reduction Steps

Dose Level	Oral POM Dose (Days 1-21 of 28-day Cycle)	Oral POM Dose (Days 1-21 of 28-day Cycle)	Oral POM Dose (Days 1-21 of 28-day Cycle)	Oral POM Dose (Days 1-21 of 28-day Cycle)
Starting Dose	4.0 mg[a]	3.0 mg	2.0 mg	1.0 mg
Dose Level -1	3.0 mg	2.0 mg	1.0 mg	Not applicable
Dose Level -2	2.0 mg	1.0 mg	Not applicable	Not applicable
Dose Level -3	1.0 mg	Not applicable	Not applicable	Not applicable

[a] Planned starting dose in the present study.

The minimum permitted dose level for POM is 1.0 mg. No dose re-escalation is permitted for POM.

Dose Modification Instructions for Low-Dose Dexamethasone

Table 4 details instructions for LD-DEX dose interruptions and reductions and Table 5 outlines the dose reduction steps for LD-DEX; however, the full product information and labeling contained in the current DEX Package Insert should also be reviewed.

If LD-DEX is held or permanently discontinued due to toxicity, POM may be continued.

Table 4: 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	Hold dose until symptoms are controlled. Add H2 blocker or equivalent and decrease one dose level when dose restarted.
Edema ≥ Grade 3	Use diuretics as needed and decrease dose by one dose level.
Confusion or mood alteration ≥ Grade 2	Hold dose until symptoms resolve. When dose restarted decrease dose by one dose level.
Muscle weakness (steroid myopathy) ≥ Grade 2	Hold dose until muscle weakness ≤ Grade 1. When dose restarted 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 subject from dexamethasone treatment regimen.
Other ≥ Grade 3 dexamethasone-related adverse events	Stop DEX dosing until the adverse event resolves to ≤ Grade 2. Decrease by one dose level when DEX dosing is resumed.

If recovery from toxicities is prolonged beyond 14 days, then the dose of DEX will be decreased by one dose level when dose is restarted.

Table 5: Low-Dose Dexamethasone Dose Reduction Steps

Dose Level	≤75 Years Old Dose (Days 1, 8, 15, 22 of a 28-day Cycle)	>75 Years Old Dose (Days 1, 8, 15, 22 of a 28-day Cycle)
Starting Dose	40 mg	20 mg
Dose Level -1	20 mg	12 mg
Dose Level -2	10 mg	8 mg

Dexamethasone should be discontinued if subject is unable to tolerate 10 mg if ≤75 years old or 8 mg if >75 years old.

8.3. Method of Treatment Assignment

This study will utilize the IVRS for enrollment. Designated research personnel at each investigational site will be assigned password protected, coded identification numbers which gives them the authorization to call into IVRS to enroll subjects. For drug assignment at each cycle start and in the event of any dose reduction, site staff must contact IVRS to record the new dose level and obtain the new study treatment assignment.

8.4. Packaging and Labeling

The label(s) for the IP POM 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.

Celgene will provide commercial supplies of DEX labeled appropriately for investigational use as per the regulations of the relevant country health authority.

Additional information may be included on the label as applicable per local regulations.

8.5. Investigational Product Accountability and Disposal

Celgene will instruct the Investigator on the return, disposal and/or destruction of IP and/or medical device materials if applicable.

8.6. Investigational Product Compliance

The investigator will document the number of capsules of POM and DEX issued to and returned by each subject at each study visit.

10. STATISTICAL ANALYSES

10.1. Overview

The final statistical analyses will be performed when all subjects have completed/discontinued the study including the follow-up phase.

10.2. Study Population Definitions

The safety population is the primary population for this study

Safety Population

The safety population is defined as all enrolled subjects who receive at least one dose of the study treatment. The safety population shall be used for all safety analyses.

Intention-to-Treat (ITT) Population

The ITT population is defined as all enrolled subjects (which is defined as enrollment on the IVRS/IWRS) regardless of whether they received any of the of the study treatment or not. The ITT population shall be used for all efficacy analyses.

Per-protocol (PP)

The PP population is defined as all enrolled subjects who receive at least one dose of the study treatment and do not have any known protocol deviations. The PP population shall be used for analysis of both safety and efficacy based endpoints.

Subject screening shall continue up to approximately 720 evaluable subjects for the primary endpoint have been enrolled. Subjects are defined as evaluable if they have received at least one dose of POM with or without LD-DEX. Subjects retrospectively found to be non-eligible for the study or not receiving any study medication will not be replaced.

10.3. Sample Size and Power Considerations

The profile of AEs considered related to POM is well defined based on studies of the IP in this indication [MM-002 (Richardson, 2013a), IFM 2009-02 (Leleu, 2013) and the recently published data from the MM-003 study (Dimopoulos 2012)].

The current study will support a more detailed evaluation of the safety profile of POM plus LD-DEX. The sample size in this study has been determined to enable the characterization of uncommon adverse events. The initial sample size of 500 subjects permitted the evaluation of previously undocumented adverse drug reactions with an incidence of 3/500 (0.6%) assuming a power of 95%. Increasing the initial sample size of the study will increase the chances of detecting uncommon adverse events (defined as events with a frequency of <1% and > 0.1%).

Two hundred and twenty additional subjects will be enrolled, bringing the total sample size to 720 subjects. This increase has been made to help detect adverse drug reactions with an incidence of 0.4%, assuming a power of 95%. This rate of incidence will therefore be confirmed if at least 1 such AE is observed in the treated 720 subjects.

A sample size of 720 subjects will, in addition to allowing identification of infrequent AEs, allow confirmation of the percentage of subjects observed as having a Grade 3 or 4 AE as indicated in the MM-002 study (N = 112) at the time of the interim analysis (88.40%). With a 99% confidence level, we expect the percentage of subjects observed with a Grade 3 or 4 AE to lie within the range 85.32% to 91.48% (i.e. 88.4 ± 3.08).

At least 320 subjects with complete PK samples should enable informative population PK and exposure-response analyses. This is based on an assumption of a 2-fold improvement in exposure-response analysis over dose-response analysis.

10.4. Background and Demographic Characteristics

Subject demographic and medical continuous data including age, height, weight, and baseline characteristics will be summarized using descriptive statistics (median, minimum and maximum value), while gender and other categorical demographic and medical history variables will be provided using frequency tabulations showing frequency of occurrence and corresponding percentage. 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, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent. A summary of subjects enrolled by site will be provided. Protocol violations will be summarized using frequency tabulations.

10.6. Efficacy Analysis

Overall Response Rate

The overall response rate (ORR; as defined as the rate of at least PR) will be calculated as the percentage of confirmed responders, as well as being summarized by each response category (i.e., stringent complete response (SCR), CR, VGPR, PR, SD, and PD) in the ORR using the IMWG criteria. A response that is documented after the initiation of another anti-myeloma treatment will not be counted as a response. However, these subjects will be included in the denominator for the ORR calculation. Subjects without an assessment shall be considered a non-responder.

Time to Response

Time to response is calculated as the time from study enrollment to the first documented response (PR or better) based on IMWG criteria. Subjects without a documented response will be censored at the time of their last tumor assessment (or at the time of trial enrollment if no assessment was conducted).

Duration of Response

Duration of response, calculated for responders only, is defined as time from the initial documented response (PR or better) to the first confirmed PD. Subjects without a documented progression will be censored at the time of their last tumor assessment.

Time to Progression

Time to progression will be calculated as the time from study enrollment until PD (as determined by the site investigator based on the IMWG criteria). Subjects not experiencing a documented progression will be censored at the time of their last tumor assessment (or at the time of trial enrollment if no assessment was conducted).

Progression-free Survival

Progression-free survival will be calculated as the time from study enrollment until the time of PD (as determined by the site investigator based on the IMWG criteria) or death from any cause on study treatment. Subjects not experiencing a documented progression will be censored at the time of their last tumor assessment (or at the time of trial enrollment if no assessment was conducted).

Overall Survival

Overall survival will be calculated as the time from study enrollment until the time of death from any cause. If no death is recorded the subject will be censored at the time the subject was last known to be alive.

All time-to-event type endpoints will be assessed using the Kaplan-Meier method to calculate the median time along with the corresponding 95% confidence interval.

10.7. Safety Analysis

Data from all subjects receiving any of the study treatment will be included in the safety analyses.

Adverse Events

Adverse events will be coded according to the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded according to the NCI-CTCAE (version 4.0, May 2009).

Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first treatment of the study medication and within 28 days after the last dose. All TEAEs, AEs leading to study medication discontinuation, AEs leading to dose reduction/ interruption, AEs related to the IP, SAEs and AE leading to death will be summarized by cycle and 28 day period after last cycle as well as by subject (worse recorded grade) per event type (organ class and preferred tern) and grade. A summary of AEs with NCI-CTCAE grade 3 or higher, as well as the most frequent preferred terms, will also be provided.

Additional analyses of the primary endpoint shall include subgroup analyses including AEs by selected demographic characteristics such as gender and age grouping in addition to amount of therapy administered such as time on treatment (1 complete cycle, 2 complete cycles etc.).

Deaths

Deaths during treatment (defined as deaths from the first dose and within 30 days after the last dose of study medication) and during the long-term follow-up phase shall be summarized by frequency of occurrence and corresponding percentage by cause of death per period (during treatment or follow-up) as well as overall.

Clinical Laboratories

Clinical laboratory values will be graded according to NCI-CTCAE (version 4.0, May 2009) 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.

Vital Signs

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.

Electrocardiogram

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.

10.8. Interim Analysis

No formal interim analysis is planned.

10.9. Pharmacokinetic Analysis

Pharmacokinetic samples will be collected from subjects to determine POM concentrations in plasma. Population PK analysis will be performed using plasma concentration data of POM. Population estimates of PK parameters of POM such as apparent oral plasma clearance (CL/F) and apparent volume of distribution (V/F) will be estimated, and intra- and inter-subject variability of these parameters will be characterized. The effect of demographics/covariates (e.g., age, body weight, gender, prior treatment and use of concomitant medications, etc.) on the PK of POM will be evaluated.

Other PK parameters will be determined and reported as deemed appropriate. If the data are insufficient for population PK analysis, only the concentrations of POM will be reported.

10.10. Exposure-Response Analysis

An exploratory exposure-response (ER) analysis will be performed to assess whether POM exposure improves the PD, safety and efficacy endpoints and estimate the minimal plasma POM level and/or duration to effect a desired change in the PD/safety/efficacy endpoints.

The key exposure data are serum drug concentration, Cmax, Cmin and AUC derived from the population PK analysis. The key efficacy and safety endpoints include AEs, ORR, time to response, DoR, PFS, TTP, and OS. Other efficacy and safety endpoints may also be explored, as appropriate.

The exploratory ER analysis will include graphical examination of potential relationship of POM exposure and efficacy/safety endpoints; PK/PD modeling as appropriate to define the change of PD, safety, and efficacy endpoint versus. POM exposure quantitatively. In addition, trial

simulation based on appropriate model supported by data may be performed to assess the robustness of the exposure-response trend.

[redacted]

10.12. Cytogenetic Analysis

Survival rates can vary considerably among MM subgroups [redacted]. In particular, subjects with cytogenetic profiles that show a deletion of 17p132,5 or t(4;14),1,3 as detected by FISH, retain their poor prognosis despite the use of single or tandem autologous stem cell transplantation [redacted] and maintenance with thalidomide [redacted]. As shown, cytogenetics in relapsed and/or refractory MM still has an impact on the outcome. So far only very limited data are available on the role of POM in subjects harboring 'high-risk' cytogenetic abnormalities [redacted]. To further investigate the role of POM in high-risk subjects and to understand the cytogenetic changes that occur throughout the disease course, cytogenetic profiles will be analyzed at initial diagnosis, at study entry, and at relapse.

Subjects will be classified according to their cytogenetic profiles and certain efficacy analyses will be performed based on those subgroups.

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 (i.e., 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 an investigational product 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 other appropriate tests and procedures.

All AEs will be recorded by the investigator from the time the subject signs ICD to at least 28 days after treatment discontinuation. AEs that lead to study discontinuation should be followed until resolution or stabilization. AEs and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety immediately (i.e., 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.

11.2. Evaluation of Adverse Events

A qualified investigator will evaluate all AEs as to:

11.2.1. Seriousness

A SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (i.e., 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.

SPMs will be monitored as events of interest and must be reported as SAEs (see Section 11.5). This includes any SPM, regardless of causal relationship to IP (POM with or without DEX), occurring at any time from the time of signing the ICD 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 SAE (e.g., 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 (e.g., 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 (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of 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 IP, action taken regarding IP, and outcome.

11.2.2. Severity / Intensity

For both AEs and SAEs, the investigator must assess the severity of the event.

The severity of AEs will be graded based upon the subject's symptoms according to the current active minor version of NCI-CTCAE (Version 4.0, May 2009):

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 IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	The temporal relationship of the adverse event to IP administration makes **a causal relationship unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	The temporal relationship of the adverse event to IP administration makes **a causal relationship possible**, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP 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 IP as a result of an AE or SAE, as applicable (e.g., discontinuation or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

11.2.6. Outcome

The investigator will report the outcome of the event for both AEs and SAEs.

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 (death due to another cause) 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 IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance by the Investigator.

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.

11.4. Pregnancy

11.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. Investigational product 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 Initial Pregnancy Report Form, or approved equivalent form. The female should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further

evaluation and counseling. The exposure of any pregnant female (e.g., caregiver or pharmacist) to POM is also an immediately reportable event.

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 Follow-up Pregnancy Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic 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 IP 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 screen of the eCRF. 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.

SPMs will be monitored as events of interest and must be reported as SAEs. This includes any SPM, regardless of causal relationship to IP (POM with or without DEX), occurring at any time from the time of signing the ICD 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 eCRF and subject's source documents. Documentation on the diagnosis of the SPM must be provided at the time of reporting as a SAE (e.g., 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 IP [POM with or without DEX]) that occur from the time the subject signs ICD to at least 28 days after treatment discontinuation and those made known to the investigator at anytime thereafter that are suspected of being related to IP (POM with or without DEX). SAEs occurring prior to treatment will be captured.

SAEs, regardless of relationship to the IP, that occur from the time the subject signs ICD to at least 28 days after treatment discontinuation and those made known to the investigator at

anytime thereafter that are suspected of being related to IP (POM with or without DEX) must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event.

The SAE report should provide a detailed description of the SAE and include summaries 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 must 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 Institutional Review Board/ Ethics Committee (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 (e.g., 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 POM based on the Investigator Brochure.

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, DEX, based on the US Prescribing Information (PI).

AEs such as PD, death related to PD (in the absence of serious IP-related events) and serious events due to the relapse of the studied indication will not be subject to expedited reporting by the sponsor to regulatory authorities.

Celgene or its authorized representative shall notify the investigator of the following information:

Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (i.e., SUSAR);

Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

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 Local Drug Safety Affiliate Office 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 treatment:

- AEs
- PD
- Withdrawal of consent from study treatment

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

- Withdrawal of consent from study
- Protocol violation
- Death
- Lost to follow-up
- Completion of 5 years from last subject enrolled post-enrollment follow-up.

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

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

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

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page).This 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/Contract Research Organization 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(s) or Medical Monitor or designee for emergency calls.

13.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, IP will be identified on the 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 GCP 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 ICD 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 (e.g., medical records, office charts, hospital charts and study-related charts) for source data verification. The investigator must ensure timely and accurate completion of eCRFs and queries.

14.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a 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 ICD 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 ICD 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 ICD. The revised ICD 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 ICD, 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. Amendments that are administrative in nature do not require IRB/EC approval but will be submitted to the IRB/EC for information purposes.

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

Before the start of the study, the study protocol, ICD, 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. 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 ICD 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 AEs 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 (e.g., 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 eCRFs or CD-ROM.

15.2. Data Management

Data will be collected *via* eCRF. 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 ICD 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;
- 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, eCRFs, 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, IP storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative for accuracy, adherence to the protocol and GCPs.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs 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 eCRFs 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 GCP Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene Standard Operating Procedures (SOPs) to evaluate compliance with GCP 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/ECs, regulatory authorities (e.g., 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 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. The primary publication is agreed to derive from the data set from the entire study. Publications related to individual country subsets will follow the primary publication unless there is specific importance related to the observation and agreement with Celgene is gained.

19. APPENDICES

Appendix A: Declaration of Helsinki

The Declaration of Helsinki can be found at: http://www.wma.net/e/policy/b3.htm.

Appendix C: Skeletal (Bone) Survey

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.

If clinically indicated CT scans are allowed but they should meet the same requirements as above.

Appendix D: Pomalidomide Pregnancy Risk Minimization Plan for Celgene Clinical Trials

This appendix applies to all subjects receiving pomalidomide therapy. The following Pregnancy Risk Minimization Plan documents are included in this Appendix:

a. Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods (Appendix D-1);

3. Pomalidomide Education and Counselling Guidance Document (Appendix D-2);
4. Pomalidomide Information Sheet (Appendix D-3).

1. The Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Appendix D-1) provides the following information:
   - Potential risks to the fetus associated with pomalidomide exposure
   - Definition of Female of Childbearing Potential (FCBP)
   - Pregnancy testing requirements for subjects receiving pomalidomide who are females of childbearing potential
   - Acceptable birth control methods for both female of childbearing potential and male subjects receiving pomalidomide in the study
   - Requirements for counselling of all study subjects receiving pomalidomide about pregnancy precautions and the potential risks of fetal exposure to pomalidomide
2. The Pomalidomide Education and Counselling Guidance Document (Appendix D-2) must be completed and signed by either a trained counselor or the Investigator at the participating clinical center prior to each dispensing of pomalidomide study treatment. A copy of this document must be maintained in the subject records.
3. The Pomalidomide Information Sheet (Appendix D-3) will be given to each subject receiving pomalidomide study therapy. The subject must read this document prior to starting pomalidomide study treatment and each time they receive a new supply of study drug.

Appendix D-1: Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

Pomalidomide was found to be teratogenic in a developmental study in rabbits. Pomalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If pomalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby.

Criteria for Females of Childbearing Potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Counseling

For a female of childbearing potential, pomalidomide is contraindicated unless all of the following are met (ie, all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol (Appendix D-1)
- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The investigator must ensure that females of childbearing potential:

- Comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, pomalidomide is contraindicated unless all of the following are met (ie, all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The effect of pomalidomide on spermatogenesis is not known and has not been studied. Therefore, male subjects taking pomalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) dose interruptions; and 4) for at least 28 days after study treatment discontinuation. (NOTE: True abstinence: When this is in line with the preferred and usual lifestyle of the subject. *[Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]*).

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. All FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in subjects with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not

recommended. If a subject is currently using combined oral contraception the subject should switch to another one of the effective methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before Starting Study Drug

Female Subjects

All FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The subject may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Subjects

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Subjects

- All FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study drug discontinuation, and at Day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study drug discontinuation, and at Days 14 and 28 following study drug discontinuation.
- At each visit, the investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a study subject, study drug must be immediately discontinued.

- Pregnancy testing and counselling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Subjects

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to pomalidomide must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study subject during study participation, the investigator must be notified immediately.

Additional Precautions

- Subjects should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Subjects should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Male subjects should not donate semen or sperm during therapy or for at least 28 days following discontinuation of study drug.
- Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.

Appendix D-2: Pomalidomide Education and Counselling Guidance Document

To be completed prior to each dispensing of study drug.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (mm/dd/yyyy)

(Check the appropriate box to indicate risk category)

Female: ☐

If female, check one:

- ☐ FCBP (Female of childbearing potential): sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)
- ☐ NOT FCBP

Male: ☐

Do Not Dispense study drug if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual contact) at least 28 days prior to therapy, during therapy and during dose interruption.**

FCBP:

I verified that the required pregnancy tests performed are negative.

I counseled FCBP regarding the following:

- Potential risk of fetal exposure to pomalidomide: If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking pomalidomide. The teratogenic potential of pomalidomide in humans cannot be ruled out. All FCBP must agree not to become pregnant while taking pomalidomide.
- Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact (at least 28 days prior to therapy, during therapy, during dose interruption and 28 days after discontinuation of study drug).
- That even if she has amenorrhea she must comply with advice on contraception.

- Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
  - Highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants)
    - Tubal ligation
    - Partner's vasectomy
  - Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical Cap
- Pregnancy tests before and during treatment, even if the subject agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10-14 days and the second within 24 hours of the start of study drug.
- Frequency of pregnancy tests to be done:
  - Every week during the first 28 days of this study and a pregnancy test every 28 days during the subject's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
  - If the subject missed a period or has unusual menstrual bleeding.
  - When the subject is discontinued from the study and at Day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after study drug discontinuation.
- Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug and for 28 days after stopping study drug.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
- Do not break, chew, or open study drug capsules.
- Return unused study drug to the study doctor.

4. Provide Pomalidomide Information Sheet to the subject.

FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):

- I counseled the female NOT of childbearing potential regarding the following:
  - Potential risk of fetal exposure to pomalidomide (Refer to item #2 in FCBP)
  - NEVER share study drug with anyone else.
  - Do not donate blood while taking study drug and for 28 days after stopping study drug.
  - Do not break, chew, or open study drug capsules
  - Return unused study drug capsules to the study doctor.

5. Provide Pomalidomide Information Sheet to the subject.

MALE:

- I counseled the male subject regarding the following:
  - Potential study drug fetal exposure to pomalidomide (Refer to item #2 in FCBP).
  - To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 28 days after stopping study drug.
  - Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant
  - NEVER share study drug with anyone else.
  - Do not donate blood while taking study drug and for 28 days after stopping study drug.
  - Do not donate semen or sperm while taking study drug and for 28 days after stopping study drug.
  - Do not break, chew, or open study drug capsules.
  - Return unused study drug capsules to the study doctor.

6. Provide Pomalidomide Information Sheet to the subject.

Investigator/Counselor Name (Print): _____
(circle applicable)

Investigator/Counselor Signature: _____ Date: _____/_____/_____
(circle applicable)

Maintain a copy of the Education and Counselling Guidance Document in the subject records.

Appendix D-3: Pomalidomide Information Sheet

FOR SUBJECTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Pomalidomide Information Sheet before you start taking study drug and each time you get a new supply. This Pomalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about pomalidomide?

1. **Pomalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Pomalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Pomalidomide has not been tested in pregnant women but may also cause birth defects. Pomalidomide was found to cause birth defects when tested in pregnant rabbits. **If you are a female who is able to become pregnant:**
    - Do not take study drug if you are pregnant or plan to become pregnant
    - You must either not have any sexual relations with a man or use two reliable, separate forms of effective birth control at the same time:
        - for 28 days before starting study drug
        - while taking study drug
        - during dose interruptions of study drug
        - for 28 days after stopping study drug
    - You must have pregnancy testing done at the following times:
        - within 10 – 14 days and again 24 hours prior to the first dose of study drug
        - weekly for the first 28 days
        - every 28 days after the first month or every 14 days if you have irregular menstrual periods
        - if you miss your period or have unusual menstrual bleeding
        - 28 days after the last dose of study drug (14 and 28 days after the last dose if menstrual periods are irregular)
    - Stop taking study drug if you become pregnant during treatment
        - If you suspect you are pregnant at any time during the study, you must stop study drug immediately and immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation.
    - **Do not breastfeed while taking study drug**
    - The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not of childbearing potential:

In order to ensure that an unborn baby is not exposed to pomalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to the fetus in females of child bearing potential whose male partner is receiving pomalidomide is unknown at this time.

1. Male subjects (including those who have had a vasectomy) must either **not have any sexual relations with a pregnant female or a female who can become pregnant,** or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
    - While you are taking study drug
    - During dose interruptions of study drug
    - For 28 days after you stop taking study drug

    b. **Male subjects should not donate sperm or semen** while taking study drug and for 28 days after stopping study drug.
    c. **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they get pregnant.**

7. **Restrictions in sharing study drug and donating blood:**

1. **Do not share study drug with other people. It must be kept out of the reach of children and should never be given to any other person.**
2. **Do not donate blood** while you take study drug and for 28 days after stopping study drug.
3. **Do not break, chew, or open study drug capsules.**
4. You will be supplied with no more than one cycle of study drug
5. Return unused study drug capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

Appendix E: National Cancer Institute-Common Terminology Criteria for Adverse Events

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0 (May 2009) can be viewed on-line at the following NCI web site:

http://ctep.cancer.gov/reporting/ctc.html.

Appendix G: 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 III
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

[redacted]

Appendix H: ECOG Performance Status Scale

Table 10: Eastern Cooperative Oncology Group Performance Status Grade

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

[redacted]

Appendix I: International Myeloma Working Group Response Criteria

Table 11: 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[b] by immunohistochemistry or immunofluorescence[c]
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 subjects without measurable serum and urine M-protein levels the difference between involved and uninvolved FLC levels, the absolute increase must be > 100 mg/l. Bone marrow plasma cell percentage, the absolute % must be ≥ 10%[h] 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.

Table 11: 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 [i]	**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 subjects 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/24hour, 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 g/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 subjects should also be evaluated using criteria listed above for progressive disease.

Appendix J: Pharmacokinetic Sample Handling Instructions

All required labels will be prepared by the Central Lab. Labels must contain the following information:

- Protocol No.: **CC-4047-MM-010**
- Subject ID number
- Visit: e.g., Cycle 1, Day 15
- Nominal Collection Time (if applicable): e.g, pre-dose
- Sample Type: **Plasma (primary) or Plasma (back-up)**

All blood and plasma collection tubes and storage vials should be labeled and chilled on wet ice **prior to** sample collection and processing.

Blood Sample Collection

- Fill an ice bucket with a sufficient amount of ice to pre-chill all collection tubes before blood draw.
- Collect approximately 3 mL of whole blood into a pre-chilled **K3 EDTA** tube.
- Accurately record the time of blood collection.
- Gently invert the tube 3 to 5 times and immerse it in the ice bath immediately to prevent possible compound degradation at room temperature.

Blood Sample Processing to Obtain Plasma

- Within 30 minutes of collection, the blood sample must be centrifuged at 1,500 g (about 3,000 rpm) for 10 min at 4°C to obtain plasma with refrigerated centrifuge
- Transfer approximately 1 mL of plasma into each of the two pre-labeled, pre-chilled, citric acid-containing polypropylene storage tubes (one primary and one back-up, to be provided by Celgene). Keep storage tubes on ice before they are ready to be transferred into a freezer.
- Within 60 minutes of blood collection, transfer plasma samples in storage vials into a –20°C freezer, where they will remain stored until shipping.
- Immediately record the time of sample entry into the freezer.

NOTE: All secondary (backup) samples will be maintained at the Central Lab until they are requested by the Celgene representative to be shipped to the bioanalytical laboratory (or another facility) or be destroyed at the investigator site.

PK Sample Shipment

- All PK sample label information on the storage tubes have to be checked against the requisition form and then the samples must be shipped frozen and on dry ice to the central lab.

Sample Collection Documents to Accompany Shipment(s)

A copy of the completed specimen inventory log(s) must accompany the shipment, and must list the following information at minimum:

- Sponsor name: Celgene Corp
- Celgene Study Number: CC-4047-MM-010
- Subject ID Numbers
- Visit: e.g., Cycle 1, Day 15
- Nominal collection times
- Sample types (eg, primary plasma or back-up plasma)

Appendix K: List of Abbreviations

Table 12: List of Abbreviations

Abbreviation	Definition
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
BMSC	Bone marrow stromal cell
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form
CT	Computerized tomography
DEX	Dexamethasone
DLT	Dose limiting toxicity
DMC	Data monitoring committee
DoR	Duration of response
DVT	Deep vein thrombosis
EAP	Expanded access program
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EEA	European Economic Area
EMP	Extramedullary plasmacytoma
ER	Exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
FCBP	Females of childbearing potential
FISH	Fluorescence *in situ hybridization*

Table 12: List of Abbreviations (Continued)

Abbreviation	Definition
FLC	Free light-chain
GCP	Good clinical practice
GCSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transpeptidase
HCG	Human chorionic gonadotropin
HD-DEX	High-dose dexamethasone
HIV	Human immunodeficiency virus
ICD	Informed consent document
ICH	International Conference on Harmonization
IFE	Immunofixation
Ig	Immunoglobulin
IL	Interleukin
IMWG	International Myeloma Working Group
IP	Investigational product
IRB/EC	Institutional review board/ Ethics Committee
ITT	Intention-to-treat
IVRS/IWRS	Interactive voice/web response system
LD-DEX	Low-dose dexamethasone
LLN	Lower limit of normal
LPS	Lipopolysaccharide
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MR	Minor response
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall response rate

Table 12: List of Abbreviations (Continued)

Abbreviation	Definition
OS	Overall survival
PD	Progressive disease
PD	Pharmacodynamics
PE	Pulmonary embolism
PFS	Progression-free survival
PK	Pharmacokinetics
POM	Pomalidomide
PP	Per protocol
QTc	QT corrected
PR	Partial response
RBC	Red blood cell
RR	Response rate
SAE	Serious adverse event
SCR	Stringent complete response
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SNP	Single-nucleotide polymorphism
SOP	Standard Operating Procedures
SPEP	Serum protein electrophoresis
SPM	Second primary malignancy
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
TNM	Tumor, node, metastasis
TTP	Time to disease progression
ULN	Upper limit of normal
UPEP	Urine protein plectrophoresis
US	United States
VGPR	Very Good Partial Response
vs.	Versus
VTE	Venous thrombotic event

Abbreviation	Definition
WBC	White blood cells