Protocol Title: A Controlled, Parallel-Group, Randomized, Open-Label Study to Evaluate Two Lenalidomide Dose Regimens When Used in Combination With Low Dose Dexamethasone for the Treatment of Subjects with Relapsed Multiple Myeloma

STUDY DRUG	**Lenalidomide (Revlimid®)**
PROTOCOL NUMBER:	**RV-PI-MM-0345**
DRAFT VERSION:	
DATE FINAL:	**9-17-2009**
AMENDMENT:	**9-13-2010**
2nd AMENDMENT:	**8-2-2011**
3rd AMENDMENT:	**5-24-2012**
4th AMENDMENT:	**2-14-2013**

Version date 02.14.2013

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Principal Investigator:

Signature of Investigator | Date

Printed Name of Investigator

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, instructions from Celgene representatives, the Declaration of Helsinki, FDA Regulations, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

STUDY PERSONNEL

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1 Protocol Synopsis

PROTOCOL TITLE: A CONTROLLED, PARALLEL-GROUP, RANDOMIZED, OPEN-LABEL STUDY TO EVALUATE TWO LENALIDOMIDE DOSE REGIMENS WHEN USED IN COMBINATION WITH LOW DOSE DEXAMETHASONE FOR THE TREATMENT OF SUBJECTS WITH RELAPSED MULTIPLE MYELOMA

PROTOCOL NUMBER:	RV
DATE PROTOCOL FINAL:	9-17-2009
STUDY DRUG:	Revlimid®, lenalidomide
INDICATION:	15 mg and 25 mg of lenalidomide in conjunction with low dose dexamethasone
STUDY PHASE:	II

BACKGROUND AND RATIONALE: Several studies have shown that combination chemotherapy with addition of other alkylating agents such as cyclophosphamide or nitrosureas and anthracyclines does not improve the prognosis of subjects with multiple myeloma beyond results obtained with standard MP (Oken, 1994; Oken, *et al.* 1997). Notably, the median survival of subjects who achieve stable disease (lack of disease progression) is similar to that in subjects who respond to therapy and is superior to survival in subjects whose disease progresses (49 months *versus* 48 months *versus* 15 months) (Durie and Salmon, 1975). A recent trial conducted by Eastern Cooperative Oncology Group (ECOG) compared MP therapy to the combination treatment regimen of vincristine, carmustine, melphalan, cyclophosphamide, and prednisone (VBMCP) (Oken, *et al.* 1997). Although VBMCP resulted in a 72% objective response compared to 52% for MP, the median survivals of both Cohorts were not different. Interferon (IFN), either as part of induction treatment or as maintenance therapy, is only of marginal benefit (Ludwig, *et al.* 1995). Although subjects with progressive disease despite initial therapy or those who become resistant to initial therapy have a 50 to 75% response to salvage regimens such as vincristine, doxorubicin, and dexamethasone (VAD) (Barlogie, *et al.* 1984; Monconduit, *et al.* 1986), these responses are usually of short (months) duration. Myeloma, therefore, remains universally fatal, and the median survival of affected subjects is 3 to 4 years.

The primary rationale is to utilize Revlimid at dose that will be well tolerated and effective. We propose to use the need for dose reduction as a criterion to judge tolerability from various causes. In the veteran population which predominantly is in the older age category with number of co-morbidities, a lower dose regimen may be safer and advantageous. In a recent multi-institutional study, the 009 and 010 studies, patients were randomized to receive Revlimid with dexamethasone versus dexamethasone alone. A logistic regression was performed using dose reduction (i.e., whether or not having any lenalidomide dose reduction as the dependent variable). Treatment-emergent neutropenia and thrombocytopenia were the causes of the majority of dose reductions. Predictors analyzed included: age, prior transplant (yes vs. no), high vs. low risk (disease stage variable), previous thalidomide exposure (yes vs. no), previous lines of therapy (<=2 vs. 3+), prior medical history of neutropenia or thrombocytopenia. Among the 353 patients in the Revlimid/Dexamethasone groups, 131 (37.1%) had at least one dose reduction of

Revlimid. Age, whether used as a continuous variable or dichotomized one (<=65 vs. 66+), was the single significant predictor for dose reduction; 46% of the patients aged 66 or older required at least one dose reduction, as compared to 31% of the patients aged 65 or younger. Of interest, when the elderly population was specifically examined, the outcomes were similar for response rate, time to progression and overall survival than the younger group, suggesting that dose reduction had no significant effect on efficacy.

STUDY OBJECTIVES:

Primary:

- The primary objective of the study is to evaluate the frequency of dose reductions in two different lenalidomide dose regimens.

Secondary:

Secondary objectives are to:

- Evaluate the efficacy of two different lenalidomide dose regimens in patients with multiple myeloma using the EBMT and IMWG criteria.
- Evaluate the duration of response of 15 mg Lenalidomide and 25 mg of Lenalidomide when used in combination with Low Dose Dexamethasone.
- Evaluate the safety of 15 mg and 25 mg of Lenalidomide regiments when in combination with dexamethasone.
- Explore blood and cellular levels of angiogenic factors, cytokines, and adhesion molecules.

STUDY DESIGN:

This is a multi-center, controlled, open-label, randomized (1:1) parallel group study intended to select a tolerable dose regimen with acceptable efficacy of lenalidomide, when used in combination with dexamethasone.

Subjects will receive either oral lenalidomide 25 mg once daily for days 1-21 out of a 28 cycle or lenalidomide 15 mg once daily for 1-21 of a 28 day cycle. Subjects will be assessed before the start of treatment, and every 4 weeks while on therapy. Subjects will also receive 40 mg of dexamethasone once a week, (days 1,8,15, 22), and ASA (81 or 325 mg) will be given daily for anticoagulation prophylaxis. Lenalidomide will be reduced if patients develop grade 3 or greater toxicities. If patient has progressive disease after 2nd cycle, then the patient will be taken off the study. If at least a minimal response (MR) has not resulted after cycle 4 then the patient will be taken off the study. (see Section 5.7). Subjects who continue to show evidence of myeloma response will remain on the study and will be evaluated every 4 weeks for response and/or progression.

STUDY ENDPOINTS

Primary:

- Type, frequency, severity and timing of adverse events and their relationship to combination therapy with lenalidomide plus dexamethasone

Secondary:

- Duration of M-Protein response during combination therapy with lenalidomide plus dexamethasone
- Confirmed M-Protein response
- Expression of angiogenic factors, cytokines, adhesion molecules, and myeloma biomarker expression

STUDY DURATION: Subjects who respond to lenalidomide plus dexamethasone may continue on therapy until there is evidence of	**TOTAL SAMPLE SIZE:** Approximately 80 subjects will be enrolled.

progression or unacceptable toxicity. All subjects will be followed for survival indefinitely.	
DOSING REGIMEN(S): Depending on lenalidomide treatment assignment, subjects will receive either 15 mg p.o. q.d. or 25 mg p.o. q.d. for days 1-21 of a 28 day cycle.. In addition, dexamethasone (40 mg) will be added once a week (Days 1, 8, 15 and 22) to the Lenalidomide regimen, with a dose reduction on the same schedule if the patient cannot tolerate the higher dose of dexamethasone. ASA (81 or 325mg) will be given daily for anticoagulation prophylaxis.	**STUDY DRUG SUPPLIES:** Celgene Corporation will supply lenalidomide as 5 mg and 25 mg capsules.

2 Schedule of Study Assessments *

Procedure	Screening **≤ 14 days from Baseline (First day study drug administration)**	Cycle 1				**[12]Cycles 2, 4, 6, 8+**	**[12]Cycles 3, 5, 7, 9+**	**Discontinuation From Study Drug**
		Day **1**	Day **8**	Day **15**	Day **22**	Day **1**	Day **1**	
Record prior medications, treatments	X							
Record prior anti-cancer therapies	X							
Physical examination, vital signs	X	X				X	X	X
Weight	X							
ECOG performance status	X							
Chest x-ray [1]	X[1]							X[1]
ECG	X							
Register patient for RevAssist®[11]	X							
Pregnancy testing [2,3]	X[3]	X	X	X	X	X[3]	X[3]	X[3]
Education and counseling checklist [4]	X[4]	X[4]				X[4]	X[4]	
Skeletal Survey	X							X
Hematology • CBC, differential, platelets	X	X	X	X	X	X	X	X
Serum chemistry • Electrolytes, BUN, glucose, creatinine • Liver profile: SGOT, SGPT, alkaline phosphatase, total bilirubin , total protein, albumin • Calcium • CrCl ≥ 40 ml/min • Amylase ≤ 2.5x upper limit of normal	X X X X X	X X	X X	X X	X X	X X	X X	X X
Multiple Myeloma Disease Assessment: • β_2-microglobulin, C-reactive protein[5] • Serum protein electrophoresis with quantitated M-protein and Freelite	X[5] X					X	X	X
Serum Secretors: • Quantitative immunoglobulins • Serum immunofixation	X X					X X	X X	X X
Urine Secretors: • 24hr Urine total protein and urine protein electrophoresis and urine freelite • Immunofixation from 24hr urine	X[5] X[5]					X[6] X[6]	X[6] X[6]	X[5] X[5]

Procedure	Screening ≤ 14 days from Baseline (First day study drug administration)	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 1 Day 22	[12] Cycles 2, 4, 6, 8+ Day 1	[12] Cycles 3, 5, 7, 9+ Day 1	Discontinuation From Study Drug
Non-secretors: • Freelite™ • Bidemensional measurement of soft tissue plasmacytomas if present[7]	X X					X X[7]	X X[7]	X X[7]
Bone marrow aspirate and biopsy • Cytogenetics[8] • Morphology	X[8] X							X[9]
HIV Test	X							
Hep A,B,C titers (HAV, HBV, HCV)	X							
Dispense Cycle 1 study drug		X						
Response assessment[10]						X[10]	X[10]	X
Record adverse events		X	X	X	X	X	X	X
Record concomitant meds/procedures		X				X	X	X
Dispense study drug for next cycle					X	X	X	
Perform drug accountability					X	X		X

* An unscheduled visit can occur at any time during the study. Source must be maintained for these unscheduled visits. The date for the visit and any data generated must be recorded on the appropriate CRF. Source documents for these unscheduled visits must also be maintained.

[1] Not needed if Chest CT scan has been obtained.
[2] Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female 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., has had menses at any time in the preceding 24 consecutive months).
[3] Pregnancy tests must occur 10 – 14 days and again within 24 hours prior to initiation of lenalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 4 weeks and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 4 weeks and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods). All counseling will be done through RevAssist®
[4] Patients are required to complete counseling every 28 days during treatment with lenalidomide, follow the pregnancy testing and birth control requirements of the program that are appropriate for the patient and take telephone surveys regarding compliance with the program.
[5] Mandatory at the beginning and end of study
[6] Repeat every cycle only if protein present in urine at screening and/or 24hr IFE is positive.
[7] Repeat to verify response for response assessment and q 2 months and/or as clinically indicated for follow-up
[8] Cytogenetics only at screening; do not repeat if information available from an earlier bone marrow biopsy. (BMB).
[9] Repeat as clinically indicated or to confirm CR.
[10] If patient has progressive disease after 2nd cycle, then the patient will be taken off the study. If at least a minimal response (MR) has not resulted after cycle 4, then the patient will be taken off the study. Subjects who continue to show evidence of myeloma response will remain on the study and will be evaluated every 4 weeks for response/progression.

[11] All patients enrolled in the study must register through RevAssist® and must comply with all requirements of the RevAssist® program. Prescriptions must be filled within 7 days for females of childbearing potential and 14 days for all other risk categories. Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

[12] All subjects who respond to lenalidomide plus dexamethasone may continue on therapy until there is evidence of progression or unacceptable toxicity. All subjects will be followed for survival indefinitely.

3 Background and Rationale

3.1 Introduction

Lenalidomide, a thalidomide analog, belongs to a proprietary class of Celgene compounds called immunomodulatory drugs (IMiDs®). IMiDs® have both immunomodulatory and anti-angiogenic properties which could confer antitumor and antimetastatic effects.

Although the exact antitumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for lenalidomide's activity against multiple myeloma. Lenalidomide has direct activity against multiple myeloma and induces apoptosis or G1growth arrest in multiple myeloma cell lines and in multiple myeloma cells of patients resistant to melphalan, doxorubicin and dexamethasone [5]. Lenalidomide, a thalidomide analog, has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF.[1]. In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12 production.[2] Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity. [3]The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in multiple myeloma cell lysis [4].

3.2 Clinical experience in multiple myeloma with lenalidomide

In 2 phase I studies in multiple myeloma, a total of 41 patients have been treated with lenalidomide. In one study at the University of Arkansas, 15 patients who relapsed or were refractory to high dose melphalan therapy with stem cell transplant were treated for 4 weeks in an open-label safety study and were permitted to continue therapy in an extension phase of the trial. Patient cohorts were treated at the following daily doses: 5mg, 10mg, 25mg, and 50mg [9]. In a similar study at the Dana Farber Cancer Institute, 27 patients with rapidly advancing refractory multiple myeloma were enrolled [10].

Anti-myeloma activity was observed in each of these 2 phase I studies. Decreases in neutrophil and platelet counts were the dose-limiting toxicities associated with lenalidomide. The maximum tolerated dose (MTD) was not

reached within 28 days. Due to dose modifications associated with myelosuppression observed beyond Day 28 at the 25mg and 50mg daily dose levels, the dose schedule most widely used in future studies has been lenalidomide 25 mg on Days 1-21, repeated every 28 days.

Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in the phase I studies. Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood levels ranging from 0.7 to 2.0 hours at all dose levels (5mg, 10mg, 25mg, and 50mg). Plasma lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1 hours on both Day 1 and 28 at all 4 doses. No plasma accumulation was observed with multiple daily dosing. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg [(11)].

A multicenter, randomized, phase II trial compared 2 syncopated dose schedules of lenalidomide (15 mg B.D. vs. 30 mg O.D.) used alone or in combination with dexamethasone in the treatment of relapsed or refractory multiple myeloma. All patients were treated on Days 1-21 of a 28-day cycle. Patients treated with 15mg BID experienced more myelosuppression and dose reductions compared with patients treated with 30mg daily. Anti-myeloma activity was observed with each dose and schedule of single agent lenalidomide. The addition of dexamethasone to lenalidomide yielded responses in some patients who had not responded to lenalidomide alone [(12)].

Celgene Corporation sponsored 2 multicenter, randomized, double-blinded, placebo-controlled phase III trials [1 U.S. (MM-009) and 1 international (MM-010)] in patients with relapsed or refractory multiple myeloma [(14)]. More than 350 patients were enrolled into each of these studies. All patients had to be considered sensitive to dexamethasone and were treated with dexamethasone 40mg daily on Days 1-4, 9-12 and 17-20. In addition to receiving dexamethasone, patients were randomized to lenalidomide 25mg or placebo each given daily on Days 1-21. Cycles were repeated every 28 days. After 4 cycles, there was a predetermined reduction of the dexamethasone dose to 40mg daily on Days 1-4 repeated every 28 days. In both studies, a pre-specified interim analysis conducted by an Independent Data Monitoring Committee demonstrated that subjects receiving the combination of lenalidomide (Len) plus dexamethasone (Dex) had significantly longer times to progression and higher response rates (D 27% vs. 2D 61%, $p<0.001$) than those treated with single-agent dexamethasone. These studies led to the FDA approval of lenalidomide in combination with dexamethasone for the treatment of multiple myeloma in

patients that have received at least one prior therapy. Based on an excellent efficacy in relapsed patients, a recent phase II trial utilizing lenalidomide plus dexamethasone for newly diagnosed multiple myeloma patients was recently reported by the Mayo Clinic. Lenalidomide was given orally 25 mg daily on days 1-21 of a 28-day cycle. Dexamethasone was given orally 40 mg daily on days 1-4, 9-12, 17-20 of each cycle. Objective response was defined as a decrease in serum monoclonal protein by 50% or greater and a decrease in urine M protein by at least 90% or to a level less than 200 mg/24 hours, confirmed by two consecutive determinations at least 4 weeks apart. Thirty-one of 34 (91%) patients achieved an objective response, including 2 (6%) achieving complete response (CR), and 11 (32%) meeting criteria for both very good partial response and near complete response, resulting in an overall objective response rate of 91%. Of the 3 remaining patients not achieving an objective response, two had minor response (MR) and one stable disease. Forty-seven percent of patients experienced grade 3 or higher non-hematologic toxicity, most commonly fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%) and rash (6%). Revlimid®/dexamethasone is a highly active regimen with manageable side-effects in the treatment of newly diagnosed myeloma.(18)

3.3 Rationale

The primary rationale is to utilize Revlimid at dose that will be well tolerated and effective. We propose to use the need for dose reduction as a criterion to judge tolerability from various causes. In the veteran population which predominantly is in the older age category with number of co-morbidities, a lower dose regimen may be safer and advantageous. In a recent multi-institutional study, the 009 and 010 studies, patients were randomized to receive Revlimid with dexamethasone versus dexamethasone alone. A logistic regression was performed using dose reduction (i.e., whether or not having any lenalidomide dose reduction as the dependent variable). Treatment-emergent neutropenia and thrombocytopenia were the causes of the majority of dose reductions. Predictors analyzed included: age, prior transplant (yes vs. no), high vs. low risk (disease stage variable), previous thalidomide exposure (yes vs. no), previous lines of therapy (<=2 vs. 3+), prior medical history of neutropenia or thrombocytopenia. Among the 353 patients in the Revlimid/Dexamethasone groups, 131 (37.1%) had at least one dose reduction of Revlimid. Age, whether used as a continuous variable or dichotomized one (<=65 vs. 66+), was the single significant predictor for dose reduction; 46% of the patients aged 66 or older required at least one dose reduction, as compared to 31% of the patients aged 65 or younger. Of

interest, when the elderly population was specifically examined, the outcomes were similar for response rate, time to progression and overall survival than the younger group, suggesting that dose reduction had no significant effect on efficacy.

3.3.1 INDICATIONS AND USAGE:

Revlimid® is approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy. Revlimid® (lenalidomide) is also indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

3.4 Adverse Events

Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, spinal cord compression, disease progression, death not specified and fractures. Tumor flare reaction (TFR) has been reported frequently in CLL patients treated with lenalidomide. Tumor lysis syndrome (TLS) has been reported in CLL patients treated with lenalidomide. Precautions must be taken to prevent TLS including proper selection of patients with regard to renal function, correction of electrolyte abnormalities, and TLS prophylaxis and monitoring. Lenalidomide has been shown to increase the level of digoxin in the blood in some patients.

Second new cancers

According to researchers, patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer. In clinical studies of newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with induction therapy (treatment as first step to reducing number of cancer cells) and/or bone marrow transplant then lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant then placebo (a capsule containing no lenalidomide). Patients should make their doctors aware of their medical history

and any concerns they may have regarding their own increased risk of other cancers.

Complete and updated adverse events are available in the Investigational Drug Brochure and the IND Safety Letters.

4 Study Objectives and Endpoints

4.1 Objectives

4.1.1 Primary objectives

- Evaluate the frequency of dose reductions in two different lenalidomide dose regimens.

4.1.2 Secondary study objectives

- Evaluate efficacy of two different lenalidomide dose regimens in patients with multiple myeloma using the EBMT and IMWG criteria.
- Evaluate the duration of response of 15 mg lenalidomide and 25 mg lenalidomide when used in combination with low-dose dexamethasone
- Evaluate the safety of 15 mg and 25 mg lenalidomide regiments when in combination with dexamethasone
- Explore the blood and cellular levels of angiogenic factors, cytokines, and adhesion molecules

4.2 Endpoints

4.2.1 Primary Endpoint

- Type, frequency, severity and timing of adverse events and their relationship to combination therapy with lenalidomide plus dexamethasone.

4.2.2 Secondary Endpoints

- Duration of M-Protein response during combination therapy with Lenalidomide plus dexamethasone
- Confirmed M-Protein response
- Expression of angiogenic factors, cytokines, adhesion molecules, and myeloma biomarker expression

5 Investigational Plan

5.1 Overall design

This is a multi-center, controlled, open-label, randomized (1:1) parallel group study intended to select the dose regimen with the most promising efficacy of Lenalidomide, when used in combination with dexamethasone.

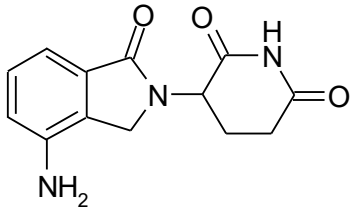
Subjects will receive either oral Lenalidomide 25 mg once daily for days 1-21 out of a 28 cycle or Lenalidomide 15 mg once daily for 1-21 of a 28 day cycle. Subjects will also receive 40 mg of dexamethasone once a week (Days 1, 8, 15 and 22) with a dose reduction on the same schedule if the patient cannot tolerate the higher dose of dexamethasone (refer to Section 5.5.3). ASA (81 or 325 mg will be given orally for anticoagulation prophylaxis. If patient has progressive disease after 2nd cycle, then the patient will be taken off the study. If at least a minimal response (MR) has not resulted after cycle 4, then the patient will be taken off the study. Subjects who continue to show evidence of myeloma response will remain on the study and will be evaluated every 4 weeks for response/progression.

5.1.1 Investigational Drug

5.1.1.1 Lenalidomide Description

REVLIMID® (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:

5.1.1.1.1.1.1 Chemical Structure of Lenalidomide



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

REVLIMID® (lenalidomide) is available in 5 mg and 25 mg capsules for oral administration.

5.1.1.2 CLINICAL PHARMACOLOGY

Mechanism of Action:

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro.

5.1.1.3 Pharmacokinetics and Drug Metabolism:

Absorption:

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. The pharmacokinetic disposition of lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic sampling in myelodysplastic syndrome (MDS) patients was not performed. In multiple myeloma patients maximum plasma concentrations occurred between 0.5 and 4.0 hours post-dose both on Days 1 and 28. AUC and Cmax values increase proportionally with dose following single and multiple doses. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Pharmacokinetic Parameters:

Distribution:

In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism and Excretion:

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged

through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

5.1.1.4 Supplier(s)

Celgene Corporation will supply Revlimid® (lenalidomide) to study participants at no charge through the RevAssist® program.

5.1.1.5 Dosage form

Lenalidomide will be supplied as 5 mg and 25 mg capsules for oral administration.

5.1.1.6 Packaging

Lenalidomide will be shipped to the pharmacy at the study site in individual bottles. Bottles will contain a sufficient number of capsules to last for one cycle of dosing. Study drug must be dispensed in the original packaging with the label clearly visible**. Only enough lenalidomide for 1 cycle of therapy may be provided to the patient each cycle.**

5.1.1.7 Labeling

Lenalidomide investigational supplies are dispensed to the patients in individual bottles of capsules. Each bottle will identify the contents as study medication. In addition, the label will bear Celgene's name, quantity contained and the standard caution statement as follows: Caution: New drug - Limited by Federal law to investigational use. The study drug label must be clearly visible. For appropriate drug accountability, it is recommended that the institution mark each bottle with the institutional protocol number or Celgene tracking number (**RV-PI-MM-0345)** upon receipt. Additional labels must not cover the Celgene label.

5.1.1.8 Receipt of study drug

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene or its representative.

5.1.1.9 Storage

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access.

The study drug should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

5.1.1.10 Unused study drug supplies

Celgene will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene. Patients will be instructed to return empty bottles or unused capsules.

5.1.1.11 Drug dispensing requirements

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the RevAssist® program of Celgene Corporation. Per standard RevAssist® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the RevAssist® program. Prescriptions must be filled within 7 days for females of childbearing potential and 14 days for all other risk categories. Drug will be shipped on a per patient basis by the contract pharmacy to the clinic sites. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle**.

Pregnancy Testing

Refer to Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods). All counseling will be done through RevAssist®.

5.2 Screening and Eligibility

The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form for entry into the study. All subjects will be screened for eligibility. Screening procedures are outlined in Section 2, Schedule of Study Assessments and unless otherwise specified, must take place within 14 days prior to initiation of therapy.

Approximately 80 of subjects with active multiple myeloma will be screened for enrollment and must meet the eligibility criteria below.

5.2.1 Inclusion Criteria

Subjects must meet the following inclusion/exclusion criteria to be eligible for the study.

Inclusion criteria

5.2.1.1 Subject was previously diagnosed with multiple myeloma based on standard diagnostic criteria as follows.

Diagnostic Criteria for Multiple Myeloma, Myeloma Variants, and Monoclonal Gammopathy of Unknown Significance

Monoclonal gammopathy of undetermined significance (MGUS)

- M-protein in serum <30 g/l
- Bone marrow clonal plasma cells <10%
- No evidence of other B-cell proliferative disorders
- No myeloma related organ or tissue impairment (no end organ damage, including bone lesions)

Asymptomatic myeloma (smoldering myeloma).

- M-protein in serum ≥ 30 g/l and/or
- Bone marrow clonal plasma cells ≥10%
- No myeloma related organ or tissue impairment (no end organ damage, including bone lesions) or symptoms

Symptomatic multiple myeloma.

- M-protein in serum and/or urine
- Bone marrow (clonal) plasma cells* or plasmacytoma
- Myeloma related organ or tissue impairment (end organ damage, including bone lesions)
- *If flow cytometry is performed, most plasma cells (> 90%) will show a 'neoplastic' phenotype.

Non-secretory myeloma.

- No M-protein in serum and/or urine with immunofixation
- Bone marrow clonal plasmacytosis ≥ 10% or plasmacytoma
- Myeloma-related organ or tissue impairment (end organ damage, including bone lesions)

Solitary plasmacytoma of bone.

- No M-protein in serum and/or urine*
- Single area of bone destruction due to clonal plasma cells
- Bone marrow not consistent with multiple myeloma
- Normal skeletal survey (and MRI of spine and pelvis if done)
- No related organ or tissue impairment (no end organ damage
- other than solitary bone lesion)*
- *A small M-component may sometimes be present.

Myeloma-related organ or tissue impairment (end organ damage) (ROTI)

- *Calcium levels increased: serum calcium > 0.25 mmol/l above the upper limit of normal or > 2.75 mmol/l
- *Renal insufficiency: creatinine >173 mmol/l

- *Anemia: haemoglobin 2 g/dl below the lower limit of normal or haemoglobin <10 g/dl
- *Bone lesions: lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)

Other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (> 2 episodes in 12 months)

5.2.1.1 Patients must have relapsed or refractory disease (refractory is defined as progression during treatment or within 60 days after the completion of treatment) requiring 2nd or 3rd line therapy (see Appendix C)

5.2.1.2 Patients may have received lenalidomide and/or dexamethasone

5.2.1.3 Patients with measurable disease defined as:

- Serum monoclonal protein > 0.5 g/dL and/or 0.2 g/24hr urine light chain excretion
- Patients with lower M-protein values or non-secretory myeloma will be eligible if measurable disease can be established, such as serum Freelite™ chain ratio > 5x normal limit, measurable soft tissue plasmacytoma > 2 cm by either physical exam and/or applicable radiographs (i.e. MRI, CT-scan) and/or bone marrow involvement > 30%

5.2.1.4 Age ≥18 years at the time of signing the informed consent form.

5.2.1.5 All necessary baseline studies for determining eligibility must be obtained within 14 days prior to enrollment. Serum pregnancy tests (sensitivity of at least 50 mIU/mL), for females of childbearing potential (WCBP) must be completed. The first test must be performed within 10-14 days, and the second test within 24 hours prior to initiation of lenalidomide.

5.2.1.6 Pre-study ECOG performance status 0-2. Patients with lower performance status based solely on bone pain will be eligible.

5.2.1.7 Patients must have adequate liver functions: AST and ALT ≤ 3x upper limit of normal, alkaline phosphatase ≤ 3.0x upper limit of normal, except if attributed to tumor, and bilirubin ≤ 2 x upper limit of normal.

5.2.1.8 Patients must have amylase ≤ 2.5x upper limit of normal

5.2.1.9 All study participants must be registered into the mandatory RevAssist® program, and be willing and able to comply with the requirements of RevAssist®.

5.2.1.10 Subject must be able to adhere to the study visit schedule and other protocol requirements

5.2.1.11 Subject must understand and voluntarily sign an informed consent document.

5.2.1.12 Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL 10 – 14 days prior to and again within 24 hours of starting Lenalidomide for Cycle 1 (prescriptions must be filled within 7 days as required by RevAssist) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure through the RevAssist® program. See Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods. All counseling will be done through RevAssist®.

5.2.1.13 Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation. Patients intolerant to ASA may use low molecular weight heparin. Lovenox is recommended. Coumadin will be allowed provided the patient is fully anticoagulate with INR 2.0 to 2.5.

† 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., has had menses at any time in the preceding 24 consecutive months).

5.2.1.14 Patients may receive a bisphosphonate.

5.2.2 Exclusion criteria

5.2.2.1 Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.

5.2.2.2 Pregnant or breast feeding females. (Lactating females must agree not to breast feed while taking lenalidomide).

5.2.2.3 Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.

5.2.2.4 Renal insufficiency of creatinine clearance < 40 mL/min

5.2.2.5 Known hypersensitivity to thalidomide or lenalidomide.

5.2.2.6 The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs.

5.2.2.7 Concurrent use of other anti-cancer agents or treatments.

5.2.2.8 Known seropositive for an active viral infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV). Patients who are seropositive because of hepatitis B virus vaccine are eligible.

5.2.2.9 Subjects with hemoglobin < 8.0 g/dL. The use of transfusion with pRBC to correct anemia and meet eligibility criteria will not be allowed.

5.2.2.10 Patient has an absolute neutrophil count < 1.0 x 10^9/L within 14 days before enrollment

5.2.2.11 Peripheral neuropathy of grade 3 or greater. Patients with painful grade 2 neuropathy are also excluded.

5.2.2.12 Patient has platelet count < 75 x 10^9/L within 14 days before enrollment.

5.2.2.13 Plasma cell leukemia at time of study entry.

5.3 Visit schedule and assessments

Screening Assessments and all on study scheduled visits and assessments are outlined in Section 2 Table of Study Assessments.

5.4 Drug Administration

5.4.1 Treatment assignments

Subjects who qualify for the study will be randomized to either Lenalidomide 15 mg p.o. q.d. days 1-21 of a 28 day cycle or Lenalidomide 25 mg p.o. q.d. for days 1-21 of a 28 day cycle. In addition, dexamethasone (40mg) will be added once a week (Days 1, 8, 15, 22) to the lenalidomide regimen

5.4.2 Dosing regimen

The planned dose of lenalidomide for investigation is either 15 or 25 mg/day, orally on days 1 - 21 followed by 7 days rest (28 day cycle). Dosing will be in the morning at approximately the same time each day. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.**

Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened.

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

Patients who take more than the prescribed dose of lenalidomide should be instructed to contact study staff immediately. Patients should be instructed on secondary contacts, such as a poison control center, should study staff be unavailable.

All subjects will receive dexamethasone 40 mg once a week (Days 1, 8, 15 and 22) with a dose reduction on the same schedule if the patient cannot tolerate the higher dose of dexamethasone (refer to Section 5.5.3).

ASA (81 or 325mg) will be given for anticoagulation prophylaxis. If unable to take ASA then other anticoagulation therapy should be given.

Subjects experiencing adverse events may need study treatment modifications (See section 5.5).

5.4.3 Special Handling Instructions

Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

5.4.4 Record of administration

Accurate records will be kept of all study drug administration (including dispensing and dosing) will be made in the source documents.

5.5 Dose Continuation, Modification and Interruption

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v3.0 (Appendix D: NCI CTCAE v3.0) used as a guide for the grading of severity.

5.5.1 Dose Reduction Steps

Table 1: LENALIDOMIDE Dose Reduction Steps		
Starting Dose	**25 mg daily for 21 days every 28 days**	**15 mg daily for 21 days every 28 days**
Dose Level – 1	15 mg daily for 21 days every 28 days	10 mg daily for 21 days every 28 days
Dose Level – 2	10 mg daily for 21 days every 28 days	5 mg daily for 21 days every 28 days
Dose Level – 3	Discontinue treatment	Discontinue treatment

5.5.2 Instructions for initiation of a New Cycle

A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is ≥ 1000/mm³
- The platelet count is ≥ 50000/mm^3
- Any drug-related rash, allergic reaction/hypersensitivity or sinus bradycardia/ other cardiac arrhythmia adverse event that may have occurred has resolved to ≤ grade 1 severity;
- Any other drug-related adverse events that may have occurred have resolved to ≤ grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above. If lenalidomide dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle**.** If lenalidomide dosing was omitted for the remainder of the previous cycle or if the new cycle is delayed due to toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction of lenalidomide. Treatment may be delayed upto 21 days from the original schedule but patients must follow the schedule for subsequent cycles.

5.5.3 Instructions for dose modifications or interruption during a cycle.

Table 2: Dose Modifications		
NCI CTC Toxicity Grade	**Onset Day 2-14 of Cycle**	**Onset ≥ Day 15 of Cycle**
Grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	• Hold (interrupt) lenalidomide dose. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained	• Omit lenalidomide for remainder of cycle • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level. Omitted doses are not made up. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained for the next cycle at the investigators discretion.
Thrombocytopenia ≥Grade 3 (platelet count < 50,000/mm³)	• Hold (interrupt) lenalidomide dose. • Follow CBC weekly. • If thrombocytopenia resolves to ≤ grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21 of the current cycle. • Hold prophylactic anti-coagulation, if applicable. • Restart prophylactic anti-coagulation when platelet count is ≥ 50,000/mm³.	• Omit lenalidomide for remainder of cycle • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • Hold prophylactic anti-coagulation, if applicable. • Restart prophylactic anti-coagulation when platelet count is ≥ 50,000/mm³.
Non-blistering rash **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue the cycle through Day 21 of the current cycle. • Discontinue lenalidomide. Remove patient from study.	• Omit lenalidomide for remainder of cycle. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • Discontinue lenalidomide. Remove patient from study.

Table 2: Dose Modifications		
NCI CTC Toxicity Grade	**Onset Day 2-14 of Cycle**	**Onset ≥ Day 15 of Cycle**
Desquamating (blistering) rash- any Grade	• Discontinue lenalidomide. Remove patient from study.	• Discontinue lenalidomide. Remove patient from study.
Neuropathy **Grade 3**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle.	• Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up.
Grade 4	• If Grade 4, discontinue lenalidomide. Remove patient from study.	• If Grade 4, discontinue lenalidomide. Remove patient from study.
Erythema multiforme ≥ Grade 3	• Discontinue lenalidomide. Remove patient from study.	• Discontinue lenalidomide. Remove patient from study.
Sinus bradycardia/ other cardiac arrhythmia **Grade 2**	• Hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21.	• Omit lenalidomide for the remainder of the cycle. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.
≥ Grade 3	• Discontinue lenalidomide. Remove patient from study.	• Discontinue lenalidomide. Remove patient from study.

Table 2: Dose Modifications		
NCI CTC Toxicity Grade	**Onset Day 2-14 of Cycle**	**Onset ≥ Day 15 of Cycle**
Allergic reaction or hypersensitivity **Grade 2-3**	• Hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21.	• Omit lenalidomide for the remainder of the cycle. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.
Grade 4	• Discontinue lenalidomide. Remove patient from study.	• Discontinue lenalidomide. Remove patient from study.
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) lenalidomide and start anticoagulation; restart lenalidomide at investigator's discretion (maintain dose level). See Anticoagulation Consideration (Section 5.6.1.2)	• Omit lenalidomide for remainder of cycle. See Anticoagulation Consideration (Section 5.6.1.2)
other non-hematologic toxicity ≥ Grade 3	• Hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to Day 21 restart lenalidomide and continue through the scheduled Day 21 of the current cycle.	• Omit lenalidomide for remainder of cycle. Omitted doses are not made up. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level when restarting Lenalidomide at the start of next cycle.
Hyperthyroidism or hypothyroidism	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.

Dexamethasone (40 mg) will be administered at a dose of 40mg once a week (Days 1, 8, 15 and 22) to the Lenalidomide regimen, with a dose reduction to 20mg on the same schedule if the patient cannot tolerate the higher dose of dexamethasone.

Grade 3 or 4 toxicity attributable to dexamethasone (e.g., proximal myopathy, glucose intolerance uncontrolled by insulin) may warrant dose modification of dexamethasone to 20 mg on the same schedule. If patient continues to have dexamethasone related toxicity then dexamethasone will be discontinued and lenalidomide will be continued as single agent as long as the response criteria are satisfied.

5.5.4 Treatment compliance

At all times, when dispensing study drug, research center personnel will review the dosing instructions, printed on the packaging, with subjects. Subjects will be asked to maintain a diary to record the drug administration. Subjects will be asked to bring any unused study drug to the research center at their next visit. Research personnel will count and record the number of used and unused study drug capsules at each visit and reconcile with the patient diary.

5.6 Concomitant therapy

5.6.1 Recommended concomitant therapy

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate.

5.6.1.2 Anticoagulation Consideration

Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide is combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (Doxil, Adriamycin) and erythropoietin the risk of thrombosis is increased.

Daily aspirin (81 or 325 mg) or some other form of prophylaxis as deemed appropriate is required. Low molecular weight heparin may be utilized in patients that are intolerant to ASA. Coumadin should be used with caution and close monitoring of INR.

5.6.2 Prohibited concomitant therapy

Concomitant use of sargramostim (GM-CSF), other anti-cancer therapies, including radiation, thalidomide, or other investigational agents is not permitted while subjects are receiving study drug during the treatment phase of the study.

5.7 Discontinuation of Study Treatment

Treatment will continue until the occurrence of any of the following events.

- Disease progression as defined in Appendix C
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of the treatment regimen.
- Discontinuation of lenalidomide for any reason.
- Major violation of the study protocol.
- Withdrawal of consent
- Lost to follow up
- Death
- Pregnancy
- Patient requests to be removed from study

5.8 Follow-Up

Subjects who discontinue treatment for any reason will not be followed. At treatment discontinuation, subjects will undergo a safety assessment approximately 28 days post the last dose of study drug. In addition, off study evaluations per the Schedule of Assessments, Section 2 will be done. All subjects who respond to treatment will be followed for survival indefinitely.

6 Adverse events

6.1 Serious Adverse Event (SAE) Definition

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

6.2 Adverse Drug Reaction Reporting

Toxicity will be scored using CTCAE Version 3.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP homepage (HTTP://CTEP.INFO.NIH.GOV). All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

SPMs are considered events of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report any second primary malignancies as serious adverse events regardless of causal relationship to lenalidomide, occurring at any time for the duration of the study For all subjects who develop second primary malignancies, sites will be required to submit all diagnostic reports (eg pathology, cytogenetics, flow cytometry results) from the indication diagnostic confirmation samples submitted at screening and all reports for the tumor samples from the SPM diagnosis. For SPMs diagnosed at another institution (outside the

investigational site), sites are to make every effort to obtain these reports for the SPM confirmation.

6.2.1 Pregnancies

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 lenalidomide or within 28 days after the subject's last dose of lenalidomide are considered immediately reportable events. If the subject is on lenalidomide, it is to be discontinued immediately and the subject is to be instructed to return any unused portion of lenalidomide to the Investigator. The pregnancy must be reported to Celgene Drug Safety immediately of the Investigator's knowledge of the pregnancy by phone and facsimile using the Pregnancy Initial Report Form.

The Investigator will follow the subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. 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 immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report 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 lenalidomide should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

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

6.2.2 Celgene Drug Safety Contact Information:

Celgene Corporation
Connell Corporate Park

300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922

Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

6.3 Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements.

IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder (or some such phrase), and a copy provided to Celgene Corporation as a supporter of this study as follows.

Celgene Corporation
Attn: Medical Affairs Operations
Connell Corporate Park
400 Connell Drive Suite 700
Berkeley Heights, NJ 07922

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to study drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for “serious” and as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described below.

6.3.1 Expedited reporting by investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day at the latest on the following working day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values

received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (**RV-PI-MM-0345)**, and the institutional protocol number, and the patient ID number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Any SAEs incurred at subsites must be reported immediately to the VA BOSTON office **and** to Celgene within 24 hours/1 business day at the latest on the following working day of awareness of the event.

6.3.2 Report of Adverse Events to the Institutional Review Board

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

6.3.3 Investigator Reporting to the FDA

Serious adverse events (SAEs) that are **unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) by telephone or by fax. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

Participating study sites should NOT report SAEs to the FDA. Participating sites should report SAEs to Celgene and the VA Boston site, and the VA Boston site will be responsible for reporting to FDA.

6.4 Adverse event updates/IND safety reports

Celgene shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

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 AE information, including correspondence with Celgene and the IRB/EC, on file (see Section 11.4 for records retention information).

7 Response Criteria

Efficacy assessments are scheduled to occur on day 1 of each even cycle (cycle 2, 4, 6, etc.).

All partial and complete responses must be confirmed with another efficacy assessment in no less than 4 weeks apart.

Response and progression will be evaluated in this study using the EBMT and IMWG criteria

Instructions for interpreting response criteria and best overall response may be found in Appendix C: Response Evaluation Criteria.

8 Protocol Amendments/Deviations

8.1 Protocol amendments

Any amendment to this protocol must be agreed to by the Principal Investigator and reviewed by Celgene. Amendments should only be submitted to IRB/EC after consideration of Celgene review. Written verification of IRB/EC approval will be obtained before any amendment is implemented.

8.2 Protocol deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the Investigator will notify the IRB/EC in writing of such deviation from protocol.

Non-emergency minor deviations from the protocol will be permitted with approval of the Principal Investigator.

9 Study Monitoring and Auditing

9.1 Investigator responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

Investigators must enter study data onto CRFs or other data collection system. The Investigator will permit study-related monitoring visits and audits by Celgene or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available to the Celgene representative so that the accuracy and completeness may be checked.

10 Biostatistical Analysis

10.1 Overview

This is a multi-center, controlled, open-label, randomized, parallel group study intended to select a tolerable dose regimen with acceptable efficacy of lenalidomide, when used in combination with dexamethasone. Patients will be randomized with 1:1 ratio to receive lenalidomide 25 mg + dexamethasone or lenalidomide 15mg + dexamethasone. The primary objective of the study is to evaluate the frequency of dose reductions in two different lenalidomide dose regimens. The study will help in selecting a safe lenalidomide dose for the elderly population.

10.2 Datasets to be analyzed

All analyses will be based on mITT population defined as below.

Modified Intent-to-treat (mITT) population: The mITT population will be defined as all subjects randomized into the trial who received at least one dose of lenalidomide. Treatment classification will be based on the randomized treatment.

Patients who did not receive any treatment of lenalidomide will not be included in the statistical analysis. Patients who have received at least one dose of lenalidomide will be considered evaluable for statistical analysis.

10.3 Statistical Methodology

Each treatment arm will be further stratified into those patients who received a reduction in dosage level and those who did not. As a first step, potential differences among the four groups on demographic variables will be tested. Those variables that are categorical will be analyzed by Chi Sq.; those variables that are quantitative will be analyzed by two-way between-groups Analyses of Variance. Any variable where a significant difference is established will be controlled by entry into future analyses as covariates.

The primary outcome variable is the proportion of patients in each treatment arm that received any dosage reduction, independent of when in the course of treatment this reduction occurred or how many subsequent reductions were introduced. These data will be analyzed by logistic regression with treatment arm as the main predictor and any variables found significant in the first step entered as covariates. A secondary analysis will consider the rate at which any dose reductions were introduced. For example, it is possible that the proportion of patients that receive a dose reduction may be equivalent in the two treatment arms, but that those patients in one arm may have received their reductions earlier. This will be examined by a Cox Proportional Hazard test, and, if necessary, with the same covariates identified above.

Power analysis shows that with a total N = 80 (40/group) power = .80 to detect an effect size difference in proportions of 32% (p=.05, 2-tail) (Borenstein M, Rothstein H and Cohen J. Power and Precision (2004). Englewood, NJ, Biostat).

This sample size provides adequate power to observe similar difference in dose reduction between the two groups for a range of dose reductions (10% - 40%) in 15mg dose group.

Secondary endpoints: Although this study is not powered to compare response as well as duration of response to the 2 dose regimen, we will collect and analyze both using power analysis. Objective response rate is defined as the proportion of randomized subjects who have evidence of either partial response or complete response as determined using the EBMT and IMWG criteria. One-sided 95% confidence limits on the lower limit of the percentage of responders will be established to determine if this lower bound exceeds 45%. Duration of response is computed among the subgroup of subjects whose best response is PR or better. It is defined as is the time from when measurement criteria are first met for objective response until the date of progression or death. A subject with an objective response who does not have a progression event will be censored at the same time as he or she was censored under the primary definition of PFS.

The data on growth factors and other markers will be collected. For each protein, the proportion of patients who are up or down-regulated will be reported along with the 90% CI. The Fisher's exact test (two sided significance level of 5%) will be used to compare the proportions of patients with CR+PR for those who are upregulated vs. those who are down-regulated.

10.4 Safety evaluation

Data from all subjects who receive any study drug will be included in the safety analyses. Subjects who entered the study and did not take any of the study drug(s) and had this confirmed, will not be evaluated for safety.

The severity of the toxicities will be graded according to the NCI CTCAE v3.0 whenever possible.

10.5 Sample size and power considerations

Assume the dose reduction rate for 25 mg arm is 50%, a sample size of 80 subjects (40 per arm) will provide a power of 81.6% to detect a difference of 30% (the rate of dose reduction assumed to be 20%) at significance level of 0.05.

11 Regulatory Considerations

11.1 Institutional Review Board/Ethics Committee approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki and FDA Regulations. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

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

11.2 Informed consent

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

11.3 Subject confidentiality

Celgene affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

Agents or designee of Celgene Corporation may visit and or meet the Principal Investigator and examine the facilities at any study location upon reasonable advance notice and with reasonable frequency, during normal business hours to observe the progress of the study and, review all documents, records, data (including study data) information, and materials relating to this study. The Principal Investigator will assist Celgene in scheduling such visits.

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

11.4 Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries

or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

The data collected from all sites will be transferred to an excel spread sheet by the coordinator and will be stored in a password protected VA computer housed in a locked office at the Boston VA. All information concerning the trial, including any PHI, will be securely protected in this password protected database or in a locked filing cabinet on VA campus.

11.6 Premature discontinuation of study

11.6.1 Single center

The responsible local clinical Investigator as well as Celgene have the right to discontinue this study at any time for reasonable medical or administrative reasons in any single center. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality.
- Inaccurate or incomplete data collection.
- Falsification of records.
- Failure to adhere to the study protocol.

11.6.2 Study as a whole

Celgene reserves the right to terminate this clinical study at any time for reasonable medical or administrative reasons.

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

12 References

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Appendices

Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature female 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 (i.e., has had menses at any time in the preceding 24 consecutive months).

Counseling

For a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide 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 lenalidomide, throughout the entire duration of lenalidomide treatment, including dose interruptions, and for 28 days after the end of lenalidomide 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 lenalidomide 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.
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

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, and acknowledge the aforementioned requirements
- Females NOT of childbearing potential acknowledge that she understands the hazards and necessary precautions associated with the use of lenalidomide
- Male patients taking lenalidomide acknowledge that he understands that traces of lenalidomide have been found in semen, that he understands the potential teratogenic risk if engaged in sexual activity with a female of childbearing potential, and that he understands the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP)[†] must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) while participating in the study; and 3) for at least 28 days after discontinuation from the study.

[†] 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., has had menses at any time in the preceding 24 consecutive months).

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method 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 patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective method 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 patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 50 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 lenalidomide:

Female Subjects:

FCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to starting lenalidomide . 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 patient may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.

Male Subjects:

Must agree to practice complete abstinence or agree to use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following discontinuation from the study:

Female Subjects:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of lenalidomide treatment, including dose interruptions, and then every 28 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 28 following lenalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days of lenalidomide treatment, including dose interruptions, and then every 14 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 14 and Day 28 following lenalidomide discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control at each visit during the time that birth control is required.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days throughout the entire duration of lenalidomide treatment, including dose interruptions.

- If pregnancy or a positive pregnancy test does occur in a study patient, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be temporarily discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after lenalidomide discontinuation.

Male Subjects:

- Must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.
- Counseling about the requirement for condom use during sexual contact with females of childbearing potential and the potential risks of fetal exposure must be conducted at a minimum of every 28 days throughout the entire duration of lenalidomide treatment, including dose interruptions.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

- Patients should be instructed never to give lenalidomide to another person and to return any unused capsules to the Investigator at the end of treatment.
- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.
- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.
- Only enough lenalidomide for one cycle of therapy may be dispensed with each cycle of therapy.

Appendix B – ECOG Performance Status Scale

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

Appendix C – Response Evaluation Criteria

Disease Response Criteria

Response	Criteria for Response
Complete Response (CR)	Requires all of the following: • Disappearance of the original monoclonal protein from the blood and urine on at least two determinations for a minimum of six weeks by immunofixation studies • < 5% plasma cells in the bone marrow on at least one determination • No increase in the size or number of lytic bone lesions (development of a compression fracture does not exclude response) • Disappearance of soft tissue plasmacytomas for at least six weeks.
Near CR	• Requires all of above except immunofixation remains positive • Or normal FLC ratio
Partial Response (PR)	Requires all of the following: • ≥ 50% reduction in the level of serum monoclonal protein for at least two determinations six weeks apart • If present, reduction in 24-hour urinary light chain excretion by either ≥ 90% or to < 200 mg for at least two determinations six weeks apart • ≥ 50% reduction in the size of soft tissue plasmacytomas (by clinical or radiographic examination) for at least six weeks • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response) • If the serum and urine M-protein are unmeasurable a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria
Minimal Response (MR)	Requires all of the following: • ≥ 25% to≤ 49% reduction in the level of serum monoclonal protein for at least two determinations six weeks apart • If present, a 50 to 89% reduction in 24 hour light chain excretion, which still exceeds 200 mg/24hr, for at least two determinations six weeks apart. • For patients with non-secretory myeloma only, a 25 to 49% reduction in plasma cells in the bone marrow for a minimum of six weeks • no increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
Stable Disease	Not meeting the criteria for CR, PR or PD

Response	Criteria for Response
Progressive Disease	Requires one or more of the following: • > 25% increase in the level of serum monoclonal paraprotein, which must also be an absolute increase of at least 5G/dL and confirmed on a repeat investigation • > 25% increase in 24-hour urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24hours and confirmed on a repeat investigation • > 25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10% • Only in patients without measureable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be <10mg/L) • Definite increase in the size of existing lytic bone lesions or soft tissue plasmacytomas or definite development of new bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.8 mmol/L not attributable to any other cause)
Relapse from CR	Requires at least one of the following: • Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis confirmed by at least one follow-up and excluding oligoclonal immune reconstitution • ≥ 5% plasma cells in the bone marrow aspirate or biopsy • Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (not including compression fracture). • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.8 mmol/L not attributable to any other cause).

***Note clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels:** CR in such patients a normal FLC ratio of 0.26-1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain FLC levels.

Based on the criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol. 102: 1998; 1115-1123. and International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group.
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10.1 Time to Treatment Failure
Time to treatment failure will be defined as the period of time, on study, from the first day of drug treatment to the time when progressive disease, treatment related toxicity resulting in discontinuation of treatment, or death (from any cause) is clearly documented.

10.2 Time to Disease Progression
Time to disease progression will be defined as the period of time, on study including follow-up, from the first day of drug treatment to the time when a disease progression or relapse is clearly documented

10.3 Duration of Response
Duration of response will be defined as the period of time, on study and including follow-up, from the first day of attainment of a response to treatment (CR or PR) to the time when a disease progression or relapse is clearly documented

Appendix D - NCI CTC Version 3.0

TOXICITY WILL BE SCORED USING NCI CTC VERSION 3.0 FOR TOXICITY AND ADVERSE EVENT REPORTING. A COPY OF THE NCI CTC VERSION 3.0 CAN BE DOWNLOADED FROM THE CTEP HOMEPAGE: (HTTP://CTEP.INFO.NIH.GOV**). ALL APPROPRIATE TREATMENT AREAS HAVE ACCESS TO A COPY OF THE CTC VERSION**