Phase I study of Pomalidomide in relapsed or refractory Waldenström macroglobulinemia

STUDY DRUG	**POMALIDOMIDE**
Celgene tracking Number:	**PO-WM-PI-0006**
DATE FINAL:	***8/25/2010***
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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Principal Investigator:

Signature of Investigator Date

Sheeba K. Thomas

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, 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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1.0 Protocol Synopsis

PROTOCOL TITLE: Phase I study of Pomalidomide in relapsed or refractory Waldenström macroglobulinemia	
PROTOCOL NUMBER:	PO-WM-PI-0006
DATE PROTOCOL FINAL:	
STUDY DRUG:	POMALIDOMIDE
INDICATION:	Relapsed or Refractory Waldenström Macroglobulinemia
STUDY PHASE:	I

BACKGROUND AND RATIONALE: Waldenström Macroglobulinemia is a low grade B-cell lymphoproliferative disorder characterized by bone marrow infiltration with lymphoplasmacytic cells, together with demonstration of a monoclonal gammopathy, as defined by the Revised European-American Lymphoma and WHO classification systems.[1] Patients with a disease-related hemoglobin level of less than 10 g/dL, a platelet count of less than 100 x 10^9/L, bulky adenopathy or organomegaly, symptomatic hyperviscosity, severe neuropathy, amyloidosis, cryoglobulinemia, cold agglutinin disease, or evidence of disease transformation should be considered for immediate therapy.[2] When treatment is initiated, overall response rates to frontline therapy with combinations of nucleoside analogs, alkylating agents and the anti-CD20 antibody, rituximab, have been high.[3] However, complete responses are infrequent, eventual relapse from disease is inevitable, and the disease remains incurable. Accordingly, novel strategies are needed to improve treatment of this disease.

Thalidomide is an immunomodulatory agent that induces the elaboration of immunostimulatory cytokines, including interleukin-2 and interferon-γ. Importantly, thalidomide induces the expansion of natural killer (NK) cells, and increases antibody-dependent, cell-mediated cytotoxicity (ADCC). As monotherapy, thalidomide has modest activity in WM patients, producing response rates of 25%, while the combination of thalidomide plus steroids and/or clarithromycin produces response rates of 40%.[4-6] Of further interest, a Phase II study that combined thalidomide with the anti-CD20 monoclonal antibody, rituximab, showed an overall response rate of 64%.[7]
Lenalidomide, a related immunomodulator (IMiD®), has also been studied with rituximab in Waldenström macroglobulinemia, but clinical investigation was halted before study completion due to the severity and frequency of anemia that was encountered (median hematocrit decrease of 4.8%).[8] All patients enrolled on this study received 25mg of lenalidomide on days 1-21 of every 28 days, as per standard treatment of multiple myeloma. However, in the absence of a phase I dose escalation study, the maximum tolerated dose of lenalidomide in patients with Waldenström macroglobulinemia remains unclear.
Pomalidomide is a new IMiD® that has shown promising preliminary results in a Phase II study of patients with relapsed multiple myeloma.[9] Accordingly, it merits investigation for the treatment of other plasma cell dyscrasias, including Waldenström

macroglobulinemia. In patients with relapsed myeloma, of whom 62% had received prior IMiD® therapy, pomalidomide combined with weekly dexamethasone produced an overall response rate of 63%.[9] While 35% of patients developed grade 3 neutropenia in this phase II study, the rate of grade 3 thrombocytopenia and anemia was modest at 3% and 5% respectively. Given these low rates of grade 3 thrombocytopenia and anemia, the lack of grade ≥3 peripheral neuropathy, and the moderate rates of grade ≤2 peripheral neuropathy (16%) in this study population, this agent hold the promise of both tolerability and efficacy in treating patients with Waldenström macroglobulinemia.

STUDY OBJECTIVES:

Primary: To determine the maximum tolerated dose of pomalidomide in patients with relapsed or refractory Waldenstrom Macroglobulinemia

Secondary: To evaluate the safety and toxicity profile of pomalidomide in patients with relapsed or refractory Waldenstrom Macroglobulinemia

To evaluate the efficacy of pomalidomide in patients with relapsed or refractory Waldenstrom Macroglobulinemia

STUDY DESIGN: This is a Phase 1, non-randomized, single institution study of pomalidomide in patients with symptomatic Waldenström macroglobulinemia (WM) whose disease has relapsed/and or is refractory to at least 1 prior line of therapy.

There are four predefined dose levels (1, 2, 3, and 4) for pomalidomide. The study also includes two alternative dosing schedules (A and B). With schedule A, patients will be treated with the study drug for 28 days within each cycle. With schedule B, patients will be treated for 21 days within each 28 day cycle. Schedule B will only be explored if the MTD is exceeded at dose level 1 (1 mg) within Schedule A. The first cohort of 3 patients will be treated at dose level 1 with schedule A (28-day dosing). If no dose limiting toxicities (DLTs) are observed then the next cohort of 3 patients will be treated at next higher dose level. If one DLT is observed then 3 more patients will be treated at the same dose level. At anytime if 2 or more DLTs are observed within 3 or 6 patients at dose level 1, then schedule A is considered too toxic and will be abandoned. Patient enrollment will then be resumed using dose level 1 of dosing schedule B (21-day dosing) to determine the MTD. The purpose of schedule B is to prepare for the scenario that dosing schedule A is not tolerable.

	Dosing Schedule A	**Dosing Schedule B**
Dose level 1	1 mg orally on days 1-28	1 mg orally on days 1-21
Dose level 2	2 mg orally on days 1-28	2 mg orally on days 1-21
Dose level 3	3 mg orally on days 1-28	3 mg orally on days 1-21
Dose level 4	4 mg orally on days 1-28	4 mg orally on days 1-21

Dose escalation will continue in 1 mg increments until the MTD is reached. Once the MTD has been determined, an additional 6 patients will be treated at this dose level.

Patients will continue receiving treatment until either disease progression or unacceptable toxicity develops.

STUDY ENDPOINTS

- **Primary:** 1) The primary endpoint is the maximum tolerated dose (MTD) of pomalidomide in patients with symptomatic Waldenström macroglobulinemia (WM) whose disease has relapsed/and or is refractory to at least 1 prior line of therapy. Tolerability of a given dose will be assessed after every 3 patients have been enrolled, until the maximum tolerated dose has been defined or, in the absence of dose limiting toxicities, the highest planned dose level is determined to have an acceptable toxicity profile.

- **Secondary:** 1)The safety and toxicity profile of pomalidomide will be evaluated after all patients to be enrolled have completed 1 cycle of therapy; patients who received at least 1 dose of pomalidomide will be eligible for evaluation.

  2) The efficacy of pomalidomide will be measured as best response to therapy. For each patient, this will be determined at the completion of their course of therapy. The collective data will be summed at study completion. Patients will be considered evaluable if they have completed at least 1 cycle of therapy.

STUDY DURATION: 3 years (expected)	**TOTAL SAMPLE SIZE:** maximum of 30
DOSING REGIMEN(S): **Schedule A:** Dose level 1 : 1 mg orally on days 1-28 Dose level 2 : 2 mg orally on days 1-28 Dose level 3 : 3 mg orally on days 1-28 Dose level 4 : 4 mg orally on days 1-28 **Schedule B:** Dose level 1: 1 mg orally on days 1-21 Dose level 2: 2 mg orally on days 1-21 Dose level 3: 3 mg orally on days 1-21 Dose level 4: 4 mg orally on days 1-21	**STUDY DRUG SUPPLIES:** Celgene Corporation will supply pomalidomide as 0.5 mg, 1.0 mg and 2.0 mg

2.0 Schedule of Study Assessments *

Procedure	Screening **≤ 28days from Baseline (First day study drug administration)**	Cycle 1				**Even Cycles**	**Odd Cycles starting at cycle 3**	**Discontinuation From Study Drug**	**End of Study safety assessment**	**Follow-Up Phase**
		Day **1**[19]	Day **8**[19]	Day **15**[19]	Day **22**[19]	Day **1**[15]	Day **1**[15]	**"End of Treatment"**	**30 days (+/- 1 week) post the last dose of study drug**	**Every 6 months**
Record prior medications, treatments	X									
Record prior anti-cancer therapies	X									
Physical examination, vital signs, weight *	X	X[10]				X	X	X[11]	X	
ECOG performance status *	X	X[10]				X	X	X[11]	X	
CT or MRI of the chest & abdomen / pelvis[8,9]	X						X[21]	X		
Chest x-ray [18]	X						X	X		
Bone survey [1]	X						X	X		
CT or MRI of the brain[2]	X						X	X		
Bone marrow aspirate and biopsy (unilateral)[17]	X									
ECG	X							X		
Hematology [3]	X	X[10]		X		X	X	X[11]	X	
Serum chemistry [4]	X	X[10]		X		X	X	X[11]	X	
Pregnancy testing [5]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]		
Pomalidomide Counseling[7]		X				X	X	X		
Baseline lesion assessment	X									
Dispense Cycle 1 study drug[12, 15]		X								
Response assessment labs[13, 14]	X	X				X	X	X		
Record adverse events [11]	X	X		X		X	X	X[11]	X	
Record concomitant therapies/procedures				X		X	X	X		
Dispense study drug for next cycle [12, 15]						X	X			
Perform drug accountability						X	X	X		
Obtain Follow-Up anti-cancer treatments[16]										X
Obtain Follow-Up survival information[16]										X
Hep B surface antigen [20]	X									
Hep C antibody [20]	X									

* If Physical examination, vital signs, weight and ECOG performance status were done within 7 days of Day 1, they do not need to be repeated at Study Day 1.
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]If subject had previously positive bone survey or if symptoms suggest metastases.
[2] This will only be performed if symptoms raise suspicion of CNS lesions.
[3] Complete blood count with differential, PT and PTT (within 5 days prior to Day 1 of each cycle); If PT and PTT are within normal limits at screening, and patient is not on anticoagulant therapy that affects these levels, they need only be repeated at discontinuation of study drug.
[4] Electrolytes, BUN, Creatinine, Calcium, Magnesium, Phosphorous, Albumin, Total Bilirubin (fractionated, if elevated), ALT, AST, Alkaline Phosphatase, Beta 2 microglobulin; A Thyroid Stimulating Hormone (TSH) level is to be drawn at Screening, and as clinically indicated. T3 and T4 levels may be assessed as clinically indicated. Cryocrit, Cold Agglutinin Titer and serum viscosity are to be drawn at screening; if abnormal on screening, they are to be repeated at treatment discontinuation (within 5 days prior to Day 1 of each cycle).
[5] Indicated 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).
[6] Pregnancy tests (either urine or serum ß HCG) must occur 10 – 14 days prior, and again within 24 hours prior to initiation of pomalidomide. 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 pomalidomide and at Day 28 post the last dose of pomalidomide. 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 pomalidomide and at Day 14 and Day 28 post the last dose of pomalidomide (see Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

[7] All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks. The counseling must be done on Day 1 of each cycle (or at a minimum of every 28 days) and at drug discontinuation. See Appendix A: Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods and Appendix B: Pomalidomide Education and Counseling Guidance Document

[8] If these CT/MRI assessments show no adenopathy or hepatosplenomegaly at screening, they will only be repeated at discontinuation of study drug. These imaging studies should be performed within 7 days prior to Day 1 of each odd cycle.
[9] All PRs and CRs must be confirmed by repeat scans no less than 6 weeks after the criteria for response are first met. The first response assessment will take place at completion of cycle 2.
[10] If screening assessments were done within 7 days of Cycle 1, Day 1, they do not need to be repeated on Cycle 1, Day 1.
[11] An additional safety assessment will be done 30 days (+/- 1 week) following the last dose of study drug.
[12] Only enough pomalidomide for 1 cycle of therapy may be provided to the patient each cycle.
[13] Serum and urine protein electrophoresis; Quantitative serum IgG, IgA, and IgM; Free serum kappa and lambda light chains; Serum and urine immunofixation studies will be performed at screening, and to evaluate for and confirm CR. Response assessment labs should be performed within 5 days prior to Day 1 of each cycle.
[14] All PRs and CRs must be confirmed by repeat Response Assessment labs no less than 6 weeks after the criteria for response are first met.
[15] Day 1 may be delayed up to 7 days to accommodate holidays/weekends/inclement weather and other unforeseen events.
[16] Information may be obtained without having the subject visit the study center (i.e. phone call).
[17] To be repeated if a complete remission is suspected

[18] Chest x-ray will only be performed as part of the screening evaluation and when CR/MRI of the chest is indicated as part of the patient's restaging evaluation.
[19] Assessments to be performed at Cycle 1 Days 1, 8, 15 and 22 may be performed +/- 2 business days from the planned date to accommodate holidays, inclement weather and other unforeseen events.
[20] Hep B -we will check Hep B surface antigen. If positive, we will check Hep B surface antibody and Hep B viral DNA. If Hep B surface antibody is negative and/or Hep B viral DNA shows circulating virus, patient will be excluded ; Hep C – we will check Hep C Antibody. If positive, we will check Hep C Viral PCR. If it shows circulating virus, patient will be excluded
[21] Starting with Cycle 3, CT scans will be performed every 4 months for the first 2 years, every 6 months for the next 2 years, and then once a year thereafter.

3.0 Glossary of Abbreviations

ADCC - antibody-dependent cytotoxic T-cell activity

AE - adverse event

CAS - Chemical Abstract Service

CFR - Code of Federal Regulations

CR - complete response

CRF - case report form

DLT - dose limiting toxicity

DMC - data monitoring committee

DVT - deep vein thrombosis

EC - ethics committee

EMEA - European Medicines Agency

FDA - Food and Drug Administration

FCBP - females of childbearing potential

GCP - Good Clinical Practice

ICH - International Conference on Harmonisation

IMiD - immunomodulatory agent

IND - Investigational New Drug

IRB - institutional review board

MM - multiple myeloma

MPT - melphalan-prednisone-thalidomide

MTD - maximum tolerated dose

NCI CTCAE v.4.0– National Cancer Institute Common Toxicity Criteria Adverse Events version 4.0

PD - progressive disease

PR - partial response

SAE - severe adverse event

TD - thalidomide-dexamethasone

TPP - Targeted Product Profile

UTMDACC – University of Texas M.D. Anderson Cancer Center

VGPR - very good partial response

WM - Waldenström Macroglobulinemia

WWDSS - Celgene Corporation World Wide Drug Safety Surveillance

4 Background and Rationale

4.1 Introduction

Waldenström Macroglobulinemia(WM) is a low grade B-cell lymphoproliferative disorder characterized by bone marrow infiltration with lymphoplasmacytic cells, together with demonstration of a monoclonal gammopathy, as defined by the Revised European-American Lymphoma and World Health Organization classification systems.[1] Patients with a disease-related hemoglobin level of less than 10 g/dL, a platelet count of less than 100 x 10^9/L, bulky adenopathy or organomegaly, symptomatic hyperviscosity, severe neuropathy, amyloidosis, cryoglobulinemia, cold agglutinin disease, or evidence of disease transformation should be considered for immediate therapy.[2] When treatment is initiated, overall response rates to frontline therapy with combinations of nucleoside analogs, alkylating agents and the anti-CD20 antibody, rituximab, have been high.[3] However, complete responses are infrequent, eventual relapse from disease is inevitable, and the disease remains incurable. Accordingly, novel strategies are needed to improve treatment of this disease.

The emergence of immunomodulatory agents such as thalidomide, lenalidomide and more recently pomalidomide, has altered the therapeutic paradigm for multiple myeloma (MM), a plasma cell dyscrasia related to WM.[4-9]

Thalidomide was initially developed as a sedative, but in the 1950s was found to be an effective anti-emetic for women with morning sickness. Because of its teratogenic effects (phocomelia), it was removed from the market in the early 1960s. However, in the 1980s, studies in erythema nodosum leprosy, Behcet's syndrome, and graft versus host disease led to subsequent approval of the drug by the United States Food and Drug Administration (1998) for the treatment of erythema nodosum leprosy.[10-15]

The in vitro anti-angiogenic properties of thalidomide led researchers at the University of Arkansas to evaluate thalidomide's clinical efficacy in patients with multiple myeloma. In a pilot study, one of five patients treated, achieved near complete remission.[16] A subsequent phase II clinical trial in patients with relapsing or refractory disease, confirmed a partial response rate of 25%.[17] Multiple studies have since confirmed single agent response rates between 24-36% in relapsed and/or refractory patients, and 34-36% in previously untreated patients with multiple myeloma. [18, 19]

Following the approval and establishment of thalidomide-containing regimens, such as melphalan-prednisone-thalidomide (MPT) and thalidomide-dexamethasone (TD), as standard first-line therapy for newly diagnosed MM, lenalidomide, a related IMiD, was

approved in combination with high-dose pulsed dexamethasone for the treatment of patients with previously treated MM.

Given thalidomide's activity in MM, it has also been studied in Waldenström's Macroglobulinemia, a related plasma cell dyscrasia. As monotherapy, thalidomide has modest activity in patients with WM, producing response rates of 25%; the combination of thalidomide plus steroids and/or clarithromycin produces response rates of 40%.[4-6] Treon et al. have also recently reported results of a Phase II study combining thalidomide with the anti-CD20 antibody, rituximab, which had an overall response rate of 64%.[7] Lenalidomide has also been studied in WM, but clinical investigation was halted before study completion due to the severity and frequency of anemia and thrombocytopenia that were encountered.[8]

Despite the success of these novel agents, MM and WM remain incurable and most patients will eventually relapse and progress after multiple lines of different therapeutic regimens.

4.2 POMALIDOMIDE

Pomalidomide is an IMiD analogue of thalidomide that, among other anti-tumor properties, on an equimolar basis *in vitro*, displays equivalent anti-angiogenic activity, about 8-fold greater activity in stimulation of apoptosis, at least 10-fold greater activity in inhibition of cellular COX-2 production and over 4,000-fold greater activity in inhibition of cellular TNF-alpha production relative to thalidomide.[20,21] Pomalidomide has also been shown to stimulate antibody-dependent cytotoxic T-cell activity (ADCC).[20]

At tolerated doses (MTD = 2 mg QD and 5 mg QOD), pomalidomide has been shown to be active in subjects with relapsed or refractory multiple myeloma (MM).[20,22,23] In 45 subjects who received doses of pomalidomide ranging, by cohort, up to 10 mg daily, the most commonly occurring dose-limiting toxicity (DLT) was reversible neutropenia. As with other IMiDs administered to subjects receiving concomitant systemic steroids, deep vein thrombosis (DVT) was seen (in 1 subject each in this study and in its subsequent named patient supply rollover program).[20,24]

Recently, efficacy and safety data from a phase II study, by Lacy et al., were published.[9] Sixty patients with relapsed or refractory multiple myeloma were enrolled. Pomalidomide was given orally at a dose of 2 mg daily on days 1-28 of a 28-day cycle and dexamethasone was given orally at a dose of 40 mg daily on days 1, 8, 15, 22 of each cycle. Patients also received aspirin 325 mg once daily for thromboprophylaxis. The study endpoints were the response rate in patients taking pomalidomide plus dexamethasone including patients with lenalidomide resistant refractory multiple myeloma, and safety of pomalidomide plus dexamethasone. Thirty eight patients achieved objective response (63%) including CR in 3 patients (5%), VGPR in 17 patients (28%), and PR in 18 patients (30%). The CR + VGPR rate was 33%. Grade 3 or 4 hematologic toxicity occurred in 23 patients (38%) and consisted of anemia in three patients (5%), thrombocytopenia in two patients (3%) and neutropenia in 21 (35%). Among those that developed grade 3/4 neutropenia, all first experienced the neutropenia in cycle 1-3; no new patients experienced grade 3/4 neutropenia in cycle 4 or later. The most common non-hematological grade 3/4

toxicities were fatigue (17%) and pneumonia (8%). Other grade 3/4 non-hematological toxicities that occurred in less than 5% included diarrhea, constipation, hyperglycemia, and neuropathy. One patient (1.6%) had a thromboembolic event of deep vein thrombosis.

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

4.3 Rationale for Treatment in this Setting

On the strength of the response rates and favorable toxicity profile seen in patients with relapsed and/or refractory MM, this study will evaluate the maximum tolerated dose of pomalidomide in patients with WM, whose disease has relapsed and/or is refractory to at least one line of prior therapy. The safety and toxicity profile of pomalidomide and preliminary data on efficacy will also be collected will also be assessed.

5 Study Objectives and Endpoints

5.1 Objectives

5.1.1 Primary objectives

- To determine the maximum tolerated dose (MTD) of pomalidomide in patients with relapsed or refractory Waldenstrom Macroglobulinemia

5.1.2 Secondary study objectives

- To evaluate the safety and toxicity profile of pomalidomide in patients with relapsed or refractory Waldenstrom Macroglobulinemia
- To evaluate the efficacy of pomalidomide in patients with relapsed or refractory Waldenstrom Macroglobulinemia

5.2 Endpoints

5.2.1 Primary Endpoint

- The primary endpoint of this study is to determine the maximum tolerated dose of pomalidomide in patients with symptomatic Waldenström macroglobulinemia (WM) whose disease has relapsed/and or is refractory to at least 1 prior line of therapy. Tolerability of a given dose will be assessed after every 3 patients have been enrolled, until the maximum tolerated dose has been defined or, in the absence of dose limiting toxicities, the highest planned dose level is determined to have an acceptable toxicity profile.

5.2.2 Secondary Endpoints

- The safety and toxicity profile of pomalidomide will be evaluated after all patients to be enrolled have completed 1 cycle of therapy; patients who received at least 1 dose of pomalidomide will be eligible for evaluation.

- The efficacy of pomalidomide will be measured by best response to therapy during. It will be assessed as the best response during each patient's course of therapy. The collective data will be summed at study completion. Patients will be considered evaluable if they have completed at least 1 cycle of therapy.

6 Investigational Plan

6.1 Overall design

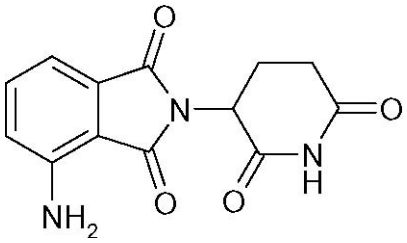
This is a Phase 1 study of single agent pomalidomide in patients with symptomatic Waldenström macroglobulinemia (WM) whose disease has relapsed/and or is refractory to at least 1 prior line of therapy.

To determine the maximum tolerated dose (MTD), patients will be enrolled in cohorts of 3, and the study will follow a standard 3+3 statistical dose-finding design as outlined in Section 11.0. Once the maximum tolerated dose has been determined, and additional 6 patients will be enrolled at that dose level to better assess the safety and toxicity profile of that dose and schedule.

6.1.1 Investigational Drug

6.1.1.1 Pomalidomide Description

Pomalidomide, 4-amino-2-(2, 6-dioxo-3-piperidyl) isoindoline-1'-one)-1, 3-dione, belongs to the IMiD class of compounds. The Chemical Abstract Service (CAS) registry number for Pomalidomide is 19171-19-8. The chemical structure of the active pharmaceutical ingredient (API) is as follows:



Pomalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S (-) and R (+). Pomalidomide has been developed as a racemate.

6.1.1.2 CLINICAL PHARMACOLOGY

Mechanism of Action:

Pomalidomide, a thalidomide analogue, is an immunomodulatory agent that, among other anti-tumor properties, on an equimolar basis in vitro, displays equivalent anti-angiogenic activity, about 8-fold greater activity in stimulation of apoptosis, at least 10-fold greater activity in inhibition of cellular COX-2 production and over 4,000-fold greater activity in inhibition of cellular TNF-alpha production relative to thalidomide [9,10]. Pomalidomide has also been shown to stimulate antibody-dependent cytotoxic T-cell activity (ADCC) [11].

6.1.1.3 Dose and tolerability:

Pomalidomide was safe at doses of up to 50 mg in a phase 1 single dose study in normal, healthy male volunteers and up to 5 mg QOD or 2 mg QD in a phase 1 multi-dose clinical study in subjects with relapsed or refractory multiple myeloma; DLTs seen in subjects receiving higher doses were predominantly hematopoetic (i.e., neutropenia), and lower grade, self-limited neutropenia was also seen in some of the 1 and 2 mg QD and 5 mg QOD recipients. In a multi-dose, phase 2 clinical study of subjects with prostate cancer, 2 mg QD dosing was well tolerated and, unlike the multiple myeloma subjects who received 1 and 2 mg QD doses, only an overall shift to lower neutrophil counts was noted. No clinically relevant neutropenic AEs were observed, and no grade 3 or 4 neutropenic events occurred. It is, therefore, likely that subjects with solid tumors that do not extensively involve the bone marrow will have a higher pomalidomide MTD than subjects with hematologic malignancies.

6.1.1.4 Supplier(s)

Celgene Corporation will supply pomalidomide.

6.1.1.5 Dosage form

Pomalidomide will be supplied as 0.5 mg, 1.0 mg, and 2.0 mg capsules for oral administration.

6.1.1.6 Packaging

Pomalidomide 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**.**

6.1.1.7 Labeling

Pomalidomide 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. Pomalidomide should not be handled by FCBP unless wearing gloves. All bottles will contain the following warning label: "WARNING: POTENTIAL FOR HUMAN BIRTH DEFECTS."

The study drug label must be clearly visible. Additional labels must not cover the Celgene label.

6.1.1.8 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.

6.1.1.9 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.

6.1.1.10 Unused study drug supplies

Any unused study drug is to be disposed of as per UTMDACC institutional policy. If any study drug is lost or damaged, its disposition should be documented in the source documents. Patients will be instructed to return empty bottles or unused capsules.

6.1.1.11 Drug dispensing requirements

In investigational studies, pomalidomide will be dispensed through a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). These healthcare professionals will be trained by Celgene in requirements specific to counseling of subjects. Once trained, these healthcare staff will counsel subjects prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the subject understands the risks associated with pomalidomide. This step will be documented with a completed Education and Counseling Guidance Document (Appendix B), and no drug will be dispensed until this step occurs. Counseling includes verification with the patient that required pregnancy testing was performed and results were negative.
A Pomalidomide Information Sheet (Appendix C) will be supplied to the patient each time that pomalidomide is dispensed.

Pomalidomide (POMALYST®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Pomalidomide will be provided in accordance with the Celgene Corporation's POMALYST REMS™ program. Per the standard **POMALYST REMS™** program requirements, all physicians who prescribe pomalidomide 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 **POMALYST REMS™** program.

Only enough pomalidomide capsules for 1 cycle of therapy may be provided to the patient each cycle.

6.2 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 28 days prior to initiation of therapy.

Approximately 21 subjects with symptomatic Waldenström Macroglobulinemia will be screened for enrollment and must meet the eligibility criteria below.

6.2.1 Inclusion Criteria

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

Inclusion criteria

1. Understand and voluntarily sign an informed consent form.
2. Age ≥18 years at the time of signing the informed consent form.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Waldenström's Macroglobulinemia that has relapsed and/or is refractory to at least one prior line of therapy
5. All previous cancer therapy, including radiation, hormonal therapy and surgery, must have been discontinued at least 4 weeks prior to treatment in this study.
6. ECOG performance status of ≤ 2 at study entry (see Appendix D).
7. Laboratory test results within these ranges:
   - Serum creatinine ≤ 2.0 mg/dL
   - Creatinine clearance ≥45 ml/min
   - Total bilirubin ≤ 3 x Upper Limit of Normal (ULN) or Direct Bilirubin ≤ 2 x ULN
   - AST (SGOT) and ALT (SGPT) ≤ 2 x ULN
   - Platelet count ≥ 20 K/μL
   - Absolute neutrophil count ≥ 500 K/μL
8. Disease free of prior malignancies for ≥ 5 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "*in situ*" of the cervix or breast.
9. Females of childbearing potential (FCBP)[†] must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days prior to

[†] 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).

starting pomalidomide 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 pomalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to practice complete abstinence or agree use a latex condom during sexual contact with a FCBP while participating in the study, during dose interruptions and for at least 90 days following study drug discontinuation, 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. See Appendix A Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, AND also Appendix B: Education and Counseling Guidance Document

10. Able to take aspirin (325mg) daily as prophylactic anticoagulation (patients intolerant to ASA may use therapeutic dose warfarin or low molecular weight heparin).
11. All study participants must be registered into the mandatory POMALYST REMS™ program, and be willing and able to comply with the requirements of the POMALYST REMS™ program.

6.2.2 Exclusion criteria

1. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.
2. Pregnant or breast feeding females. (Lactating females must agree not to breast feed while taking pomalidomide or for 28 days after stopping pomalidomide).
3. Any medical or psychiatric 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.
4. Use of any other experimental drug or therapy within 28 days of the first dose of study drug.
5. Known hypersensitivity to thalidomide or lenalidomide.
6. The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs.
7. Any prior use of pomalidomide.
8. Concurrent use of other anti-cancer agents or treatments.
9. Known positive for HIV or acute hepatitis A or acute or chronic active hepatitis B or C.
10. Grade >2 peripheral neuropathy

11. Neutrophil count <1000K/μL and/or platelet count <100K/μL unless infiltration by Waldenström's Macroglobulinemia equals or exceed 60% of bone marrow cellularity.

6.3 Visit schedule and assessments

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

At treatment discontinuation, subjects will undergo off study evaluations as per the *Schedule of Assessments*, Section 2. In addition, a safety assessment will be done approximately 30 days after the last dose of study drug. Subsequently, subjects will be contacted by the site study coordinator at a minimum of every 6 months, until death or 12 months from the last dose of study drug administration, whichever occurs first. At these follow-ups, the study coordinator will collect information about cancer therapies administered after participation in this study (including dates of treatment), and for survival unless the patient withdraws consent. The information on subsequent treatment and survival status may be obtained without having the subject visit the study center (i.e. phone call). If the information is obtained by phone call then written documentation of the communication must be available for review in the source documents.

6.4 Drug Administration

6.4.1 Treatment assignments

This is a Phase I non-randomized study. Eligible patients will be allocated to treatment in the order in which they sign the informed consent and that all documentation needed to confirm eligibility has been completed. A maximum of 30 subjects will be enrolled and treated with single agent pomalidomide. Starting at dose level 1 in Schedule A, the study will enroll patients in cohorts of 3, following a standard 3 +3 statistical design. (see Section 11.0).

Definition of Dose Limiting Toxicity (DLT):
Toxicity will be evaluated according to the NCI CTCAE version 4.0, (see Appendix E)
1) Non-hematologic dose limiting toxicity (DLT) is defined as any grade ≥3 non-hematological toxicity occurring during the first 28 days (first cycle) of treatment, with the specific exception of:

- Isolated Grade 3 elevation of liver function tests (LFTs) without associated clinical symptoms, lasting for ≤ 7 days in duration.
- Isolated Grade 3 elevation of amylase without associated clinical symptoms
- Grade 3 hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, or hypophosphatemia which responds to medical intervention.

2) Hematological dose limiting toxicity is defined as Grade ≥ 3 neutropenia with fever ≥ 38.5, Grade 4 neutropenia lasting for ≥ 7 days in duration, or any Grade 4 anemia or thrombocytopenia occurring during the first 28 days (first cycle) of treatment.

Definition of Maximum Tolerated Dose (MTD): MTD is defined as the highest dose level in which 6 patients have been treated with less than 2 instances of DLT.

6.4.2 Dosing regimen

There are four predefined dose levels (1, 2, 3, and 4) for pomalidomide, and two alternative dosing schedules (A and B). With schedule A, patients will be treated with the study drug for 28 days within each cycle. With schedule B, patients will be treated for 21 days within each 28 day cycle. Schedule B will only be explored if the MTD is exceeded at dose level 1 within Schedule A. The first cohort of 3 patients will be treated at dose level 1 with schedule A (28-day dosing). If no dose limiting toxicities (DLTs) are observed then the next cohort of 3 patients will be treated at next higher dose level. If one DLT is observed then 3 more patients will be treated at the same dose level. At anytime if 2 or more DLTs are observed within 3 or 6 patients at dose level 1, then schedule A is considered too toxic and will be abandoned. Patient enrollment will then be resumed using dose level 1 of dosing schedule B (21-day dosing) to determine the MTD. The purpose of schedule B is to prepare for the scenario that dosing schedule A is not tolerable.

Table 1

	Dosing Schedule A	**Dosing Schedule B**
Dose level 1	1 mg orally on days 1-28	1 mg orally on days 1-21
Dose level 2	2 mg orally on days 1-28	2 mg orally on days 1-21
Dose level 3	3 mg orally on days 1-28	3 mg orally on days 1-21
Dose level 4	4 mg orally on days 1-28	4 mg orally on days 1-21

Dose escalation will continue in 1 mg increments until the MTD is reached. Once the MTD has been determined, an additional 6 patients will be treated at this dose level.

An additional 6 patients will be treated at the MTD.

Dosing will be each night at approximately the same time. Pomalidomide should be taken with a glass of water on an empty stomach. **Only enough pomalidomide for one cycle of therapy will be supplied to the patient each cycle.**

Patients will continue receiving treatment with pomalidomide until disease progression or unacceptable toxicity develops.

Patients are to receive oral aspirin (325mg) as prophylactic anti-thrombotic treatment unless it is contraindicated, or the patient has a platelet count of less than 50,000. If the patient is intolerant of aspirin and has a platelet count of 50,000 or greater, the investigator is to prescribe therapeutic dose warfarin or low molecular weight heparin.

Pomalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. Pomalidomide should be taken without food, at least 2 hours before or 2 hours after a meal.

If a dose of pomalidomide 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, rather it should be taken at the next scheduled time point.

Patients who take more than the prescribed dose of pomalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

6.4.3 Special Handling Instructions

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

6.4.4 Record of administration

Accurate records of all study drug administration (including dispensing and dosing) will be made in the source documents. Accurate records of all prophylactic anti-thrombotic treatment compliance will also be made in the source documents.

6.4.5 Dose Modification or Interruption

Pomalidomide Dose Reductions

Dose reduction(s) will be allowed for any subject who develops a DLT during Cycle 1 or beyond Cycle 1 who develops a toxicity that, in the opinion of the Investigator, requires a dose-reduction.

For treatment interruptions during a cycle, the (28- or 21-day) schedule of each cycle will continue to be followed. Missed doses of pomalidomide are not made up.

For treatment interruptions that delay the scheduled start of a new cycle, when toxicity has resolved as required to allow the start of a new cycle (Section 6.5), the restart day of therapy becomes Day 1 of the next cycle.

The following table provides the dose reduction sequence for pomalidomide:

Table 2: Schedule of Pomalidomide Dose Reduction

	If the DLT/Toxicity occurred or recurred at --- (mg/dose/d 1-28 or d 1-21 depending on Schedule):	Reduce dose to --- (mg/dose/d 1-28 or d 1-21 depending on Schedule):
Pomalidomide	4	3
	3	2
	2	1
	1	0.5

Dosing interruptions and reductions are not permitted during Cycle 1 unless the subject experiences a DLT. Dose interruptions and reductions are permitted beyond Cycle 2. Examples of possible reasons for and extent of dose modification management are outlined in Table 3. The events listed are not all-inclusive and are based on observations pooled from studies with all compounds in the IMiD® class of drugs. Therefore, these events may occur but are not necessarily expected. The investigator may choose to modify pomalidomide dosing further downward or discontinue pomalidomide treatment for any adverse event.

Study drug may be held (up to 21 days) and subsequent dose reductions made as outlined in Table 3. If study drug needs to be held > 21 days, the patient is to be taken off study. Once a dose has been reduced, it cannot be re-escalated.

At the discretion of the Investigator, the use of G-CSF will be permitted to manage neutropenic fever or a Grade 4 neutropenia.

Table 3: Pomalidomide Dosage Modifications for cycles ≥ 2

Common Terminology Criteria (CTCAE) Version 4.0	Adverse Event	Dose Change for Pomalidomide
Allergy/Immunology	Allergic reaction/ hypersensitivity (including drug fever) Grade 2	Hold study drug until resolved to ≤ Grade 1; Decrease dose by 1 dose level
Allergy/Immunology	Allergic reaction/ hypersensitivity (including drug fever) Grade 3 or 4	Discontinue Study Drug

Common Terminology Criteria (CTCAE) Version 4.0	Adverse Event	Dose Change for Pomalidomide
Blood/Bone Marrow	Neutropenia (ANC) Grade 3 with fever or 4	**Day 2-14 of cycle:** Hold study drug. Follow CBC weekly; If neutropenia has resolved to ≤ grade 2 restart at next lower dose level until the end of the cycle. **Day ≥ 15 of cycle:** Hold study drug for remainder of cycle. Begin next cycle at next lower dose level
Blood/Bone Marrow	Thrombocytopenia Grade 3 or 4	**Day 2-14 of cycle:** Hold study drug. Follow CBC weekly; If thrombocytopenia resolves to ≤ grade 2 restart at next lower dose level and continue the cycle until Day 28 or Day 21 if previously reduced. Hold anticoagulation for platelet count < 50,000 **Day ≥ 15 of cycle:** Hold study drug. Begin next cycle at next lower dose. Hold anticoagulation for platelet count < 50,000
Blood/Bone Marrow	Anemia Grade 3 or 4	Hold study drug and treat anemia as needed until Hgb ≤ grade 2; Decrease dose by 1 dose level
Cardiac Arrhythmia	Grade 2	Hold study drug until resolved to ≤ Grade 1; Decrease dose by 1 dose level
Cardiac Arrhythmia	Grade 3 or 4	Discontinue study drug
Vascular	Thrombosis/embolism Grade 2, 3 or 4	Hold study drug and anticoagulate. Resume therapy at investigator's discretion.

Common Terminology Criteria (CTCAE) Version 4.0	Adverse Event	Dose Change for Pomalidomide
Dermatology/ Skin	Rash non-desquamation Grade 3	Hold study drug until resolved to ≤ Grade 1. Decrease dose by 1 dose level
Dermatology/ Skin	Rash non-desquamation Grade 4	Discontinue study drug
Dermatology/ Skin	Rash / desquamation Grade 3, 4	Discontinue study drug
	Grade 2	The dose may be modified or discontinued at the investigators discretion.
Dermatology/ Skin	Rash Erythema multiforme	Discontinue study drug
Endocrine	Elevated or Reduced Thyroid Function Test results without symptoms of hyper- or hypo-thyroidism	Confirm test results and if significant, refer for therapy; Do not alter study drug regimen
Endocrine	Elevated or Reduced Thyroid Function Test results with symptoms of hyper- or hypo-thyroidism	Hold study drug; Evaluate etiology and refer for appropriate therapy; Restart at the prior dose once symptoms have resolved and thyroid function has been stabilized with medical and/or surgical intervention
Neurology	Neuropathy cranial/motor/ sensory Grade 2 (unless baseline was grade 2)	Hold study drug; Restart at same or 1 dose level lower once event has resolved to ≤ Grade 1
Neurology	Neuropathy cranial/motor/ sensory Grade 3 or recurrence of Grade 2	Hold study drug until resolved to ≤ Grade 1 or baseline if baseline was grade 2; Decrease dose by 1 dose level
Neurology	Neuropathy cranial/motor/ sensory Grade 4	Discontinue study drug

Common Terminology Criteria (CTCAE) Version 4.0	Adverse Event	Dose Change for Pomalidomide
Other pomalidomide related toxicity	Grade 3 or Grade 4	Hold pomalidomide therapy; Decrease dose by 1 dose level and restart when resolved to ≤ Grade 2

6.5 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 ≥1.0K/μL, or ≥ the baseline ANC, if the baseline ANC was <1.0K/μL.
- The platelet count is ≥100K/μL, or ≥ the baseline platelet count, if the baseline platelet count was less than 100K/μL.
- Any drug-related rash, neuropathy or cardiac event that may have occurred has resolved to ≤ grade 1 severity or baseline.
- 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. A maximum delay of 21 days is allowed for any given cycle. If these conditions remain unmet on Day 21, the patient is to be taken off of the protocol.

If anti-thrombotic prophylaxis (aspirin, else warfarin or low molecular weight heparin) was held during a given cycle for a platelet count <50 K/μL, it should be resumed as soon as the platelet count recovers to ≥ 50 K/μL.

6.5.1 Treatment compliance

At all times, when dispensing study drug, research center personnel will review the 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 and empty study drug containers 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.

6.6 Concomitant therapy

6.6.1 Recommended concomitant therapy

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

6.6.1.1 Anticoagulation Consideration

Pomalidomide 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.

Patients are to receive oral aspirin (325mg) as prophylactic anti-thrombotic treatment unless it is contraindicated, or the patient has a platelet count of less than 50,000. If the patient is intolerant of low-dose aspirin and has a platelet count of at least 50,000, the investigator should prescribe therapeutic dose warfarin or low molecular weight heparin. If warfarin is used, close monitoring of the international normalized ratio (INR) is required.

6.6.2 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.

6.7 Discontinuation of Study Treatment

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

- Disease progression
- 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.
- Major violation of the study protocol.
- Withdrawal of consent
- Lost to follow up
- Death
- Pregnancy

6.8 Follow-Up

Subjects who discontinue treatment for any reason will be contacted by the site study coordinator at a minimum of every 6 months, until death or 12 months from the last dose of study drug administration, whichever occurs first. At these follow-ups, the study coordinator will collect information about cancer therapies administered after participation in

this study (including dates of treatment), and for survival unless the patient withdraws consent. The information on subsequent treatment and survival status may be obtained without having the subject visit the study center (i.e. phone call). If the information is obtained by phone call then written documentation of the communication must be available for review in the source documents.

At treatment discontinuation, subjects will undergo a safety assessment approximately 30 days (+/- 1 week) post the last dose of study drug. In addition, off study evaluations per the Schedule of Assessments, Section 2 will be done.

7 Adverse events

7.1 Serious Adverse Event (SAE) Definition

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical 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 (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last study treatment/intervention, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

7.2 Adverse Drug Reaction Reporting

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting (see Appendix E). A copy of the CTCAE Version 4.0 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 4.0. 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.

Abnormal laboratory results will be documented on adverse event worksheets. 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. Completed worksheets will be signed by the principal investigator and subsequently scanned into the electronic medical record upon completion of a patient's study participation.

7.3 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 pomalidomide, or within 4 weeks of the subject's last dose of pomalidomide, are considered immediately reportable events. Pomalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.
The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (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, or approved equivalent form.

All neonatal deaths that occur within -28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after28 days that the Investigator suspects is related to the *in utero* exposure to pomalidomide 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, or approved equivalent form .

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

7.4 Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
e-mail: drugsafety@celgene.com

7.5 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 with the UTMDACC IND Office, who will then forward it to the FDA. An additional copy should be placed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows:

Celgene Corporation
Attn: Medical Development
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Tel: (908) 673-9000

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.

7.5.1 Expedited reporting by investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator should 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. This form must be completed and supplied to the UTMDACC IRB, UTMDACC IND Office, and Celgene within 24 hours/1 business 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) if available. 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 M.D. Anderson Cancer Center SAE form.. A final report to document resolution of the SAE is required. The M.D. Anderson Protocol number (2009-0972) and the Celgene protocol number (PO-WM-PI-0006) should be included on SAE reports 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.

7.5.2 Report of Adverse Events to the Institutional Review Board

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

7.5.3 Investigator Reporting to the FDA

Adverse drug reactions that are **Serious, 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) in writing by each investigator/physician engaged in clinical research. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

Serious adverse events will be forwarded to the FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

7.6 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 12.4 for records retention information).

8 Response Criteria[25]

Baseline disease assessments must occur within ≤ 28 days of study drug administration.

Response assessments will be performed after each cycle of pomalidomide has been administered. Response will be assessed by either the principal investigator on a sub-investigator, and then documented in the UTMDACC protocol data management system (PDMS). Because of the IgM flare phenomenon[26], progressive disease cannot be confirmed until the response assessment performed after the second cycle of pomalidomide, has been reviewed. All partial and complete responses must be confirmed with a second efficacy assessment, performed at least 6 weeks later.

Definitions of response:

1. **Complete response (CR)**: categorized by the disappearance of serum and urine monoclonal protein determined by immunofixation, absence of malignant cells in the bone marrow determined by histologic evaluation, resolution of adenopathy/organomegaly (confirmed by computed tomography [CT] scan) and no signs or symptoms attributable to WM. Reconfirmation of the CR status is required ≥6 weeks later with a second immunofixation.
2. **Partial response (PR)**: categorized by ≥50% reduction of serum monoclonal IgM concentration determined by protein electrophoresis, ≥50% decrease in

adenopathy/organomegaly on physical examination or on CT scan and no new symptoms or signs of active disease.

3. **Minor response (MR)**: categorized by a ≥25% but <50% reduction of serum monoclonal IgM concentration determined by protein electrophoresis and no new symptoms or signs of active disease.
4. **Stable disease (SD)**: categorized by a <25% reduction and <25% increase of serum monoclonal IgM concentration determined by protein electrophoresis, without progression of adenopathy/organomegaly, cytopenias or clinically significant symptoms caused by disease and/or signs of WM.
5. **Progressive disease (PD)**: categorized by a ≥25% increase of serum monoclonal IgM concentration determined by protein electrophoresis confirmed by a second measurement or progression of clinically significant findings caused by disease (e.g. anemia, thrombocytopenia, leukopenia or bulky adenopathy/organomegaly) or symptoms (e.g. unexplained recurrent fever ≥38.4ºC, drenching night sweats, ≥10% weight loss, hyperviscosity, neuropathy or symptomatic cryoglobulinemia) attributable to WM.

Definition of Relapse/Progression after response:

1. **Relapse from CR**: categorized by the appearance of the monoclonal protein in serum or urine, confirmed by a second determination, recurrence of bone marrow involvement by lymphoplasmacytic cells, recurrence/development of lymphadenopathies/splenomegaly or symptoms/signs attributable to WM.

2. **Progression from PR**: categorized by ≥25% increase of serum monoclonal IgM concentration from the lowest attained response value determined by protein electrophoresis, confirmed by a second measurement or progression of clinically significant signs (anemia, thrombocytopenia, leukopenia, or bulky adenopathy/organomegaly) or symptoms (e.g. unexplained recurrent fever ≥38.4ºC, drenching night sweats, ≥10% weight loss, hyperviscosity, neuropathy, or symptomatic cryoglobulinemia) attributable to WM. An absolute increase of 5g/L (confirmed on a second determination) is required in order to define disease progression when the only criterion for progressive disease is the increase of M protein size. In a patient with a localized large mass and/or a high level of lactic dehydrogenase, at relapse or progression, a biopsy should be considered to assess the possibility that transformation to diffuse large B cell lymphoma has occurred.

9 Protocol Amendments/Deviations

9.1 Protocol amendments

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

10 Data Management

10.1 Analyses and Reporting

Data will be analyzed and reported after the maximum tolerated dose has been defined, and data regarding the safety and toxicity profile of the drug is available. All subsequent data collected will be analyzed and reported in a follow-up clinical report.

10.2 Data Monitoring Committee

The Data Monitoring Committee (DMC) will be composed of medical and statistical independent reviewers and will meet to review the efficacy and safety data and determine a risk/benefit analysis in this subject population. The purpose of the DMC is to advise on serious safety considerations, lack of efficacy and any other considerations within the charge to the Committee. The DMC may request additional meetings or safety reports as deemed necessary upon discussion with Celgene and its representatives. The DMC may stop the study following review of results from each interim analysis. Appropriate efficacy and safety data summaries will be provided to the DMC for the final analysis.

10.3 Study monitoring and auditing

10.3.1 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 UTMDACC's protocol data management system (PDMS). The Investigator will permit study-related monitoring visits and audits by the UTMDACC IND Office, 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 UTMDACC IND Office and the Celgene representative so that the accuracy and completeness may be checked.

11 Biostatistical Analysis

11.1 Overview

This is a Phase I study of single agent pomalidomide in patients with symptomatic Waldenström macroglobulinemia whose disease has relapsed and/or is refractory to at least one prior line of therapy.

The objectives of this phase I study are to assess the safety profile of pomalidomide in patients with relapsed Waldenström macroglobulinemia and to determine the maximum tolerated dose (MTD) of pomalidomide in this patient population.

There are four predefined dose levels (1, 2, 3, and 4) for pomalidomide. The study also includes two alternative dosing schedules (A and B). With schedule A, patients will be treated with the study drug for 28 days within each cycle. If the MTD is exceeded at dose level 1 of Schedule A, Schedule B will be explored. With schedule B, patients will be treated for 21 days within each cycle.

Non-hematologic dose limiting toxicity (DLT) is defined as any grade ≥3 non-hematological toxicity occurring during the first cycle (28 days on dosing schedule A and 21 days on dosing schedule B) of treatment, with the specific exception of:

- Isolated Grade 3 elevation of liver function tests (LFTs) without associated clinical symptoms, lasting for ≤ 7 days in duration.
- Isolated Grade 3 elevation of amylase without associated clinical symptoms
- Grade 3 hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, or hypophosphatemia which responds to medical intervention.

Hematological dose limiting toxicity is defined as Grade ≥4 neutropenia lasting for ≥ 7 days in duration, any Grade 4 anemia or thrombocytopenia, or any Grade 5 hematologic toxicity occurring during the first cycle (28 days on dosing schedule A and 21 days on dosing schedule B) of treatment.

The standard “3+3” design is applied with 4 pre-defined dose levels. The first cohort of 3 patients will be treated at dose level 1 with schedule A (28-day dosing). If no DLT is observed then the next cohort of 3 patients will be treated at next higher dose level. If one DLT is observed then 3 more patients will be treated at the same dose level. At anytime if 2 or more DLTs are observed within 3 or 6 patients at dose level 1, then schedule A is considered too toxic and will be abandoned. The trial will then be restarted at dose level 1 using dosing schedule B (21-day dosing) to determine the MTD. If dose level 1 with schedule A is well tolerated (less than 2 DLT), then the MTD will be determined with dosing schedule A, and dosing schedule B will not be used. The purpose of schedule B is to prepare for the scenario that dosing schedule A is not tolerable.

	Dosing Schedule A	Dosing Schedule B
Dose level 1	1 mg orally on days 1-28	1 mg orally on days 1-21
Dose level 2	2 mg orally on days 1-28	2 mg orally on days 1-21
Dose level 3	3 mg orally on days 1-28	3 mg orally on days 1-21
Dose level 4	4 mg orally on days 1-28	4 mg orally on days 1-21

The “3+3” algorithm is as follows: (1) If 0 out of 3 patients experiences DLT at the end of first cycle, the next cohort of 3 patients will be treated at the next higher dose level. (2) If 1 out of 3 patients develop a DLT, an additional 3 patients will be treated at the same dose level. If no more DLTs develop at this dose, i.e. 1 out of a total of 6 patients develops a DLT, the dose escalation will continue for the next cohort of 3 patients. (3) At any given dose, if more than 1 out 3 patients or 1 out of 6 patients experience DLT, the dose level exceeds the MTD and 3 more patients will be treated at the next lower dose if there are less than 6 patients already treated at that dose. Following the above scheme, MTD is defined as the highest dose level in which 6 patients have been treated with less than 2 instances of DLT.

Analysis Plan

Toxicity data will be summarized using frequency tables. The types and severity of toxicity will be evaluated.

11.2 Datasets to be analyzed

Data from all subjects who receive any study drug will be included in the determination of the maximum tolerated dose, unless they withdrew from the study before completing 1 cycle of therapy for reasons other than tolerability/toxicity.

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

Data from all subjects who received at least 1 cycles of therapy will be used in the analysis of drug efficacy.

11.3 Safety evaluation

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

The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible.

11.4 Interim analyses

11.4.1 Interim analysis strategy

Accrual will continue until maximum number of patients reaches or the trial is terminated according to the monitoring rules. No interim analyses are planned.

11.4.2 Efficacy

No interim analysis of efficacy will be performed.

11.5 Safety

Safety monitoring rules are detailed in Section 10.3.

11.6 Sample size and power considerations

Given 4 predefined dose levels and potential modification to dosing schedule B after treating 6 patients at dose level 1 with schedule A, it is anticipated that up to 30 eligible patients are required for the dose-finding portion of this phase I trial.

12 Regulatory Considerations

12.1 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. 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.

12.2 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.

12.3 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.

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.

12.4 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; SAE reports, 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.

12.5 Premature discontinuation of study

12.5.1 Single center

The responsible local clinical Investigator as well as Celgene has 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.

12.5.2 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.).

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Appendices

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

Risks Associated with Pregnancy

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

Criteria for females of childbearing potential (FCBP)

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

Counselling

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

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as pomalidomide 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 (Section 2).
- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The investigator must ensure that females of childbearing potential:

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

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

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

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

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

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) dose interruptions; and 4) for at least 28 days after study treatment discontinuation.

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 pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to another one of the effective methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

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

Pregnancy testing

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

Before starting study drug

Female Patients:

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

Male Patients:

Must practice complete abstinence or agree to use a condom during sexual contact with females of childbearing potential while participating in the study, during dose interruptions and for at least 90 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Patients:

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

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

Male Patients:

- Counselling 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.
- 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 this medicinal product to another person and to return any unused capsules to the Investigator at the end of treatment.
- Patients should not donate blood during therapy and for at least 28 days following discontinuation of pomalidomide.
- Male patients should not donate semen or sperm during therapy or for at least 90 days following discontinuation of pomalidomide.
- Only enough pomalidomide for one cycle of therapy may be dispensed with each cycle of therapy.

Appendix B: Pomalidomide Education and Counselling Guidance Document

Protocol Number: _____

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

Female: □

If female, check one:

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

† NOT FCBP

Male: □

To be completed prior to each dispensing of pomalidomide.

Do Not Dispense pomalidomide if:

- **The patient is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The patient states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual intercourse) [at least 28 days prior, while taking pomalidomide, during dose interruption, and 28 days after discontinuation of pomalidomide].**

FCBP:

1. I verified that the required pregnancy tests performed are negative.

2. I counselled FCBP regarding the following:

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

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

3. Provide Pomalidomide Information Sheet to the patient.

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

1. I counselled the female NOT of childbearing potential regarding the following:
    - Potential fetal harm (Refer to item #2 in FCBP)
    - NEVER share pomalidomide with anyone else.
    - Do not donate blood while taking pomalidomide and for 28 days after stopping pomalidomide.
    - Do not break, chew, or open pomalidomide capsules
    - Return used pomalidomide capsules to the Investigator.
2. Provide Pomalidomide Information Sheet to the patient.

MALE:

1. I counselled the Male patient regarding the following:
    - Potential fetal harm (Refer to item #2 in FCBP).
    - To engage in complete abstinence or use a condom when engaging in sexual intercourse (including those who have had a vasectomy) with a female of childbearing potential, while taking pomalidomide, during dose interruptions and for 90 days after stopping pomalidomide.
    - Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking pomalidomide should be advised to call their healthcare provider immediately if they get pregnant
    - NEVER share pomalidomide with anyone else.
    - Do not donate blood while taking pomalidomide and for 28 days after stopping pomalidomide.
    - Do not donate semen or sperm while taking pomalidomide and for 90 days after stopping pomalidomide.
    - Do not break, chew, or open pomalidomide capsules.
    - Return unused pomalidomide capsules to the investigator.

2. Provide Pomalidomide Information Sheet to the patient.

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

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

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

Appendix C: Pomalidomide Information Sheet

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

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

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

1. **Pomalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Pomalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Pomalidomide has not been tested in pregnant women but may also cause birth defects. Pomalidomide was found to cause birth defects when tested in pregnant rabbits. **If you are a female who is able to become pregnant:**
    - **Do not take pomalidomide if you are pregnant or plan to become pregnant**
        - for 28 days before starting pomalidomide
        - while taking pomalidomide
        - during dose interruptions of pomalidomide
        - for 28 days after stopping pomalidomide
    - **Stop taking pomalidomide if you become pregnant during pomalidomide treatment**
    - **Do not breastfeed while taking pomalidomide**
    - **You must have pregnancy testing done at the following times:**
        - within 10 – 14 days and again 24 hours prior to the first dose of pomalidomide
        - weekly for the first 28 days
        - every 28 days after the first month or every 14 days if you have irregular menstrual periods
        - if you miss your period or have unusual menstrual bleeding
        - 28 days after the last dose of pomalidomide (14 and 28 days after the last dose if menstrual periods are irregular)

- **You must either not have any sexual relations with a man or use two reliable, separate forms of effective birth control at the same time:**
    - for 28 days before starting pomalidomide
    - while taking pomalidomide
    - during dose interruptions of pomalidomide
    - and for 28 days after stopping pomalidomide
- The study doctor will be able to advise you where to get additional advice on contraception.
- If you suspect you are pregnant at any time during the study, you must stop pomalidomide immediately and immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation.

If you are a female not of childbearing potential:

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

If you are a male:

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

- Male patients must either **not have any sexual relations with a female who can become pregnant or a pregnant female** or must use a condom during sexual intercourse with a pregnant female or a female that can become pregnant (including those who have had a vasectomy):
    - While you are taking pomalidomide
    - During dose interruptions of pomalidomide
    - For 90 days after you stop taking pomalidomide
- **Male patients should not donate sperm or semen** while taking pomalidomide and for 90 days after stopping pomalidomide.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation.**

2. **Pomalidomide restrictions in sharing pomalidomide and donating blood:**

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

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

Appendix D – 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 E : National Cancer Institute Common Toxicity Criteria Version 4.0

TOXICITY WILL BE SCORED USING NCI CTC VERSION 4.0 FOR TOXICITY AND ADVERSE EVENT REPORTING. A COPY OF THE NCI CTC VERSION 4.0 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**