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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Saleh Ayache, MD
Review Completion Date	December 17, 2012
Established Name	Pomalidomide Capsules
(Proposed) Trade Name	Pomalyst
Therapeutic Class	Immunomodulatory agents (IMiD)
Applicant	Celgene
Formulation(s)	1 mg, 2 mg, 3 mg, and 4 mg capsules
Dosing Regimen	4 mg daily on days 1-21 of 28-day cycle until disease progression
Indication(s)	Treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and (b) (4) and have demonstrated disease progression on or within 60 days of completion of the last therapy.
Intended Population(s)	Adult patients ≥ 18 years of age

Template Version: March 6, 2009

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ASCT	Autologous Stem Cell Transplant
BM	Bone marrow
CI	Confidence interval
CR	Complete Remission
CSR	Clinical Study Report
DLT	Dose Limiting Toxicity
DSI	Division of Scientific Investigations
ECOG	Eastern Cooperative Oncology Group
EBMT	European Group for Blood and Marrow Transplantation
LD-DEX/DEX	Low Dose Dexamethasone/Dexamethasone
MGUS	Gammopathy of undetermined significance
IgG	Immunoglobulin G
IgM	IgM Immunoglobulin
IEC	Independent Ethics Committee
IRAC	Independent Response Adjudication Committee
ITT	Intent to treat
HL	Hodgkin's Lymphoma
HR	Hazard ratio
MM	Multiple myeloma
NCI	National Cancer Institute
NDA	New drug application
NHL	Non Hodgkin's Lymphoma
NME	New Molecular Entity
ORR	Overall Response Rate
OS	Overall survival
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
POM	Pomalidomide
PR	Partial Response
PS	Performance status
RCT	Randomized Control Trial
SAE	Serious Adverse Event
SEER	Surveillance epidemiology and end results
TEAE	Treatment emergent adverse event
VGPR	Very Good Partial Response
WHO	World health organization

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1 Recommendations/Risk Benefit Assessment

The clinical reviewer recommendation is to grant accelerated approval for the proposed indication and agree with the applicant's proposed restricted distribution to mitigate the risk of fetal exposure.

1.1 Recommendation on Regulatory Action

The recommendation for accelerated approval is based on the two Phase 2 clinical trials, CC-4047-MM-002 and IFM-2009-02, in which pomalidomide and dexamethasone showed overall response responses rate of 29% and 34%, respectively. The efficacy of single-agent pomalidomide in CC-4047-MM-002 was 7%.

1.2 Risk Benefit Assessment

The clinical reviewer finds a favorable benefit-risk profile for pomalidomide and dexamethasone for the proposed indication (for treatment of relapsed refractory multiple myeloma who received at least two prior therapies) for the following reasons:

- The efficacy results showed an overall response rate of 29% in trial CC-4047-MM-002 and 34% in trial IFM-2009-02 for the combination of pomalidomide and dexamethasone. These are supported by a median duration of overall response of 7.4 months and 10.5 months, respectively. The efficacy of single-agent pomalidomide in CC-4047-MM-002 was 7%, and the median duration of response was not reached. The efficacy results demonstrate a treatment effect on a surrogate endpoint that is likely to predict clinical benefit.

- The clinical trial population represented a population with a serious and life-threatening illness. The median overall survival (OS) was 71.7 weeks. The median progression free survival (PFS) was 16.6 weeks. This was a heavily pretreated population who received a median of 5 of prior therapies (range of 2 to 13). In addition, none of the FDA-approved therapies for multiple myeloma have substantial evidence of efficacy and safety in this population.

- The safety profile for pomalidomide appeared to be similar to thalidomide and lenalidomide. Safety issues identified in 20% or more of patients included myelosuppression, infections, neuropathy, dizziness, gastrointestinal (GI) toxicity, and fatigue.

However, we identified the following limitations in this application. First, the safety population was small, consisting of 303 patients with multiple myeloma. Second, the study design included pomalidomide on all treatment arms, and hence the trial results do not adequately isolate the treatment effect of pomalidomide.

To address these limitations, the Applicant proposed the following confirmatory trials:

1. Clinical trial CC-4047-MM-003 is an ongoing Phase 3 randomized controlled trial in patients with multiple myeloma (MM), treated with 2 prior therapies. The treatment arms in CC-4047-MM-003 are pomalidomide plus low dose dexamethasone (POM+LD-dex) versus high dose dexamethasone (HD-dex). The primary endpoint for this clinical trial is PFS. This trial is fully accrued as of August 30, 2012.

2. Clinical trial CC-4047-MM-007 is a planned Phase 3 randomized controlled trial in patients with multiple myeloma MM treated with 1-3 prior therapies. The treatment arms in CC-4047-MM-007 are pomalidomide plus velcade plus dexamethasone (POM+ Velcade-Dex) versus velcade plus dexamethasone (Velcade-Dex). The primary endpoint for this clinical trial is PFS. This trial is expected to start enrollment in December 2012.

Below is a separate analysis which was carried out using the Benefit-Risk Assessment Framework Tool. This analysis is provided below in Table 1.

Table 1: Benefit-Risk Assessment Framework

Decision Factor	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition: MM Clinical Manifestations Overall Response Rate Duration of response	 Bone pain and damage, hypercalcemia, renal failure, recurrent infection, and anemia 29% and 34% (pom-dex) 7% (pom without dex) 7.4 months	MM is a serious, life-threatening condition. The median overall survival (OS) in CC-4047-MM-002 was 71.7 weeks. The median progression free survival (PFS) was 16.6 weeks. This was a heavily pretreated population who received a median of 5 prior therapies (range of 2 to 13) with no approved therapy
Unmet Medical Need: There is no approved therapy in this population who are heavily pretreated (median of 5 prior therapies).		There is an unmet medical need in MM who is relapsed refractory to two approved prior therapies.
Clinical Benefit: Two randomized phase 2	Patients treated with pomalidomide and	The combination of pomalidomide and

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
trials were conducted with reproducible results.	dexamethasone showed an ORR of 29% and 34%. Patients treated with pomalidomide alone had an ORR of 7%. However, the design of the trials did not isolate the effects of pomalidomide.	dexamethasone showed an acceptable response rate in heavely pretreated patients with relapsed refractory multiple myeloma. The median duration of response was 7.4 months.
Risks: Hematological toxicities include neutropenia, thrombocytopenia and anemia. Non-hematologic toxicies include infection, dyspnea, neuropathy, dizziness, gastrointestinal (GI) toxicity, and fatigue. Fetal risk	Increased in ≥ 20% of subjects Increased in ≥ 20% of subjects Pomalidomide is teratogenic	The risks associated with the pomalidomide and dexamethasone treatment are comparable to those reported in other drugs in the same class IMiDs (thalidomide or lenalidomide) Pregnant patients should not receive the drug. Women with childbirth potential should use two type of contraceptives.
Risk Management: REMS Need confirmatory trials for efficacy (effect on overall all survival or progression free survival) and safety (toxicity).	To mitigate the fetal risk. Two phase II trials showed clinical benefit on overall response rate. Need PMRs to confirm the efficacy and safety of the drug on OS or PFS. Need PMRs for further study the pharmakinetecs, pharmacodynamics and effect in renal and hepatic impaired patients.	REMS program is designed to mitigate the risks of fetal exposure with the use of the drug. PMRs: To confirm the efficacy and the safety, and further study the effects of the pomalidomide in subpopulation such as renal and hepatic impaired, and pharmacodynamics.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies (REMS)

The applicant submitted REMS for restriction distribution to mitigate the risk of fetal exposure. Please refer to the Office of Surveillance and Epidemiology (OSE) review for details.

1.4 Recommendations for Postmarket Requirements and Commitments

Please refer to the Cross-Discipline Team Leader (CDTL) review and approval letter for details of the recommended postmarketing requirements and commitments. At the time of completion of this review, negotiations of postmarketing requirements and commitments are ongoing.

2 Introduction and Regulatory Background

Multiple myeloma is a neoplastic plasma cell disorder characterized by clonal proliferation of malignant plasma cells in the bone marrow, monoclonal immunoglobulins (called M-protein) in the blood or urine, and associated organ dysfunction. These diseases are all associated with a monoclonal protein (M protein). They include monoclonal gammopathy of undetermined significance (MGUS), isolated plasmacytoma of the bone, extramedullary plasmacytoma, and multiple myeloma. Plasma cells accumulate in the bone marrow resulting in destruction of boney structures and marrow failure. Symptoms and signs of the disease include bone pain and bone damage, hypercalcemia, renal failure, recurrent infection, and anemia. Affected individuals may also have frequent infections, weight loss, and weakness or numbness. Loss of function of visceral organs due to deposition of light chains and infiltration by neoplastic plasma cells can occur as well. Multiple myeloma is a disease primarily of older individuals.

The National Cancer Institute estimates that 21,700 of new cases will be diagnosed and 10,710 patients will die of multiple myeloma in the United States in 2012. MM is a disease of older adults. The median age at diagnosis is 66 years; only 10 and 2 percent of patients are younger than 50 and 40 years, respectively. Disease behavior varies among patients and the median survival is about 4-5 years.

The current treatment for multiple myeloma focuses on therapies that decrease the clonal plasma cell population resulting in an improvement in the signs and symptoms of the disease. The treatment chosen for patients with multiple myeloma depends on the age and performance status of the patient, as well as on the stage of the disease. High-dose chemotherapy with autologous hematopoietic stem-cell transplantation (ASCT) has become a standard treatment for patients under the age of 65 years with

symptomatic multiple myeloma. Conventional dose combination chemotherapy is given as initial therapy prior to the use of autologous stem cell transplant. Common conventional dose induction chemotherapy regimens include: bortezomib based chemotherapy regimens, thalidomide/dexamethasone based chemotherapy regimens, and lenalidomide/dexamethasone based chemotherapy regimens. Autologous stem cell transplantation (ASCT) is the most common type of stem cell transplantation used to treat patients with multiple myeloma.

For patients over the age of 65 years with multiple myeloma and patients with significant pre-treatment organ comorbidities which would preclude the administration of any of the regimens described in the previous paragraph, treatment might include melphalan and prednisone with or without a proteasome inhibitor or an IMiD.

Treatment options for relapsed or refractory MM (relapsed MM refers to patients treated to the point of maximal response but experienced disease progression, whereas refractory MM refers to patient is either unresponsive to current therapy or progresses within 60 days of last treatment) include hematopoietic cell transplantation (HCT), a re-challenge of chemotherapeutic agents used previously, or a trial of new agents. In patients with multiple myeloma who have relapsed following initial therapy, the choice of subsequent treatment depends on patient specific features, the duration of the response to the initial therapy, and the type of therapy used in the beginning. There are no established care pathways for patients with multiple myeloma who have relapsed following initial response or who are primary refractory.

Treatment approaches for patients who have been shown to progress following a response to initial therapy include retreatment with the drugs used for the initial therapy, as well as treatment with a different conventional dose chemotherapy regimen consisting of other available agents. These agents may include bortezomib, lenalidomide, thalidomide, cyclophosphamide, and melphalan. Treatment of patients with multiple myeloma who have relapsed or are primary refractory can also include a second stem cell transplant if that treatment has already been delivered and the response was significant. A final option is protocol therapy. The overall survival of patients with multiple myeloma who have relapse or who are no longer responding to therapy is usually less than a year.

2.1 Product Information

- Pomalidomide (CC-4047) is a thalidomide derivative, the third in the class of immunomodulatory agents (after thalidomide and lenalidomide).
- Pomalidomide was found to be teratogenic in animals when administered during the period of major organogenesis. Pomalidomide teratogenic effects if administered during pregnancy in humans can not be ruled out.
- Pomalidomide has a chemical name (RS)-4-Amino-2- (2, 6-dioxo-piperidin-3-yl)-isoindoline-1,3-dione.

- Pomalidomide has an empirical formula is $C_{13}H_{11}N_3O_4$ and molecular weight of 273.4 grams.
- Pomalidomide carries both of the functional groups which distinguish thalidomide from lenalidomide on a multi-ring scaffold that is identical among the three IMiDs. Pomalidomide chemical structure is similar to lenalidomide and thalidomide (as shown in Figure 1).

Figure 1: Pomalidomide chemical structure

- Pomalidomide is an immunomodulatory agent from IMiDs class of drugs with anti-angiogenic and anti-neoplastic properties.
- Pomalidomide is provided in capsules each of which contains pomalidomide as the active ingredient in addition to inactive ingredients (mannitol, pregelatinized starch and sodium stearyl fumarate).
- Pomalidomide is a yellow solid powder. It has limited to low solubility in organic solvents and it has low solubility at all pH (about 0.01 mg/mL). Pomalidomide has a chiral carbon atom which exists as a racemic mixture of the R (+) and S (-) enantiomers.
- Pomalidomide has an empirical formula C13H11N3O4 and the gram molecular weight is 273.24.
- Pomalidomide is available in 1 mg, 2 mg, 3 mg and 4 mg capsules for oral administration.

Applicant's Proposed Indication: Pomalidomide in combination with dexamethasone is indicated for patients with relapsed and refractory multiple myeloma who have received at least two prior regimens of established benefit, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

Proposed Dose and Schedule: The recommended dose of pomalidomide is 4 mg orally once daily on Days 1-21 of every (b) (4) cycle. (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

There are multiple FDA-approved drugs for the treatment of patients with multiple myeloma (Table 2). Typically, the approved drugs are used in combination in initial and subsequent therapies. Combination regimens often include corticosteroids such as dexamethasone or prednisone.

Table 2: FDA approved drugs for treatment of Multiple Myeloma

Drug	Year of Approval	Approved MM Indication	Type of Approval
Cyclophosphamide	1959	MM	Regular
Melphalan	1964	Palliative treatment of MM	Regular
Carmustine	1977	MM–in combination with prednisone	Regular
Bortezomib	2003	MM, two prior therapies	Accelerated
	2005	MM, one prior therapy	Regular
	2008	MM	Regular
Thalidomide	2006	MM, newly diagnosed	Subpart H (restricted distribution and surrogate EP)
Lenalidomide	2006	MM, one prior therapy	Subpart H (restricted distribution)
Liposomal doxorubicin	2007	MM, in combination with bortezomib, one prior therapy	Regular
Carfilzomib	2012	MM, 2 prior therapies including bortezomib and an immunomodulatory agent	Accelerated

Source: reviewer table.

2.3 Availability of Proposed Active Ingredient in the United States

Pomalidomide is not presently marketed in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

Pomalidomide is a thalidomide analogue from the IMiDs class and has immunomodulatory effects. Class effects include myelosuppression, thromboembolic events, hemorrhage, neuropathy, and renal events.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The pomalidomide original IND 066188 was submitted on November 13, 2002. In a pre-phase 3 meeting which was held on March 19, 2010, the FDA discussed the clinical and

regulatory development plan for a proposed Phase 3 study. On February 15, 2011 a second meeting was held with the applicant to discuss the clinical and regulatory development plan for an alternative Phase 3 study.

A pre-NDA meeting held on September 13, 2011. The FDA discussed the possibility of submitting clinical trials CC-4047-MM-002 and IFM-2009-02 in support of an accelerated approval under 21 CFR Part 314 Subpart H. A follow up meeting to discuss items remaining from the pre-NDA meeting was held on February 2, 2012.

On April 10, 2012, the Applicant submitted NDA 204026 for accelerated approval.

The expanded access protocol was submitted on May 17, 2012 entitled "Open-Label Treatment Use Program for Pomalidomide (POM) in Combination with Low Dose Dexamethasone (LD-DEX) in Subjects with Relapsed or Refractory Multiple Myeloma who received ≥4 prior therapies."

2.6 Other Relevant Background Information

Table 3 lists the U.S. FDA approvals for new molecular entities (NMEs) for multiple myeloma indications for the period 2003 to 2012. Accelerated approval for the pomalidomide NDA would be consistent with the prior action taken for bortezomib and carfilzomib, where the basis for the approval was similarly-sized phase 2 single-arm trials as shown in Table 3.

To confirm the efficacy and safety of pomalidomide, the Applicant has two Phase 3 trials in the multiple myeloma population.

Table 3: Approvals for NMEs based on single arm clinical trials, 2003 to 2012 (Multiple Myeloma)

Drug	Year of AA	Safety Database at Time of AA	Converted to Regular approval?	Proposed Safety Database at Time of RA
Bortezomib	2003	N=228, single-arm Phase 2	Yes	N=669, Phase 3 randomized control trial (RCT)
Carfilzomib	2012	N=526, single-arm Phase 2	No	N=792, Phase 3 RCT
Pomalidomide	2013	N=303, Phase 2	No	N=456, Phase 3 RCT N=782, Phase 3 RCT

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains all required components of the electronic Common Technical Document (eCTD). The overall quality and integrity of the application appear reasonable.

The initial filing review of the submission revealed the following:

- The trials submitted to support clinical efficacy did not clearly isolate the drug effect.
- The safety population consisted of a relatively small number of patients, and had a short follow-up time for safety assessment.

3.2 Compliance with Good Clinical Practices

Prior to study initiation, the protocol, informed consent form, and any advertisements for patient recruitment were approved by each site's institutional review board (IRB) or independent ethics committee (IEC) as required by the U.S. Code of Federal Regulations, Title 21 CFR, Part 56 and/or other applicable regional legal requirements. Amendments to the protocol were approved by the IRB/IEC before changes were implemented.

Table 4 shows the sites which are chosen to be inspected. The basis of the selection was the number of enrolled patients and response rates.

Table 4: Sites inspected by FDA

Site # (Name, Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
SITE # 101 **David Siegel, MD** Hackensack University Medical Center 30 Prospect Avenue Hackensack, NJ 07601	CC-4047-MM-002	30	MM
SITE # 108 **Craig Hofmeister, MD** James Cancer Hospital 300 West 10th Avenue Columbus, OH 43210	CC-4047-MM-002	14	MM
SITE # 102 **Paul Gerard Guy Richardson MD** Dana-Farber Cancer Institute 44 Binney Street Boston, MA 02115	CC-4047-MM-002	36	MM

The Division of Scientific Investigations review concluded that the study data collected appear generally reliable in support of the requested indication.

3.3 Financial Disclosures

In accordance with 21 CFR 54.4, the applicant submitted the required financial disclosure requirements and certification for study CC-4047-MM-002 and study IFM-2009-02.

Financial conflict of interest information was collected from all principal investigators and sub investigators participated in trials CC-4047-MM-002 and IFM-2009-02. All investigators claimed no financial conflict of interest except for (b) (6) (b) (6) who received more than $US 680,000 of grants from the applicant during the period from 2005 to 2012. (b) (6) participated as the principal investigator for the Phase 2 portion of study CC-4047-MM-002 and recruited a total of (b) (6) patients into the study.

The following steps were taken by the applicant to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

- The trial design of Study CC-4047-MM-002 eliminated the introduction of bias by any primary investigator or sub-investigator. The investigator had no influence on the primary efficacy endpoint of progression-free survival (PFS).
- Assessment of the primary endpoint was conducted by an Independent Response Adjudication Committee (IRAC) who reviewed myeloma response

data as well as dates of progressive disease for each study subject in a blinded manner.

- Prior to the final analysis of the study all Celgene analyses were performed using aggregated data and not by treatment arm. Interim analysis results using aggregated data provided by Celgene and analysis by treatment arm was performed by an independent statistician for the data monitoring committee (DMC).
- Key secondary endpoints included objective response via European Group for Blood and Marrow Transplantation (EBMT) criteria; duration of response; time to response and overall survival. The assessments of these secondary key endpoints were also evaluated by IRAC. The independent reviewers were blinded to the treatment assignment and the investigator assessment of response.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Pomalidomide belongs to the Immunomodulatory drugs (IMiDs) class of compounds and has antiangiogenic and antineoplastic properties. Pomalidomide has an empirical formula of C13H11N3O4 and the molecular weight of 273.24. The active ingredient is pomalidomide (CC-4047) Pomalidomide is a yellow solid powder. It has limited to low solubility into organic solvents and it has low solubility in all pH solutions (about 0.01 mg/mL). Pomalyst is available in 1 mg, 2 mg, 3 mg and 4 mg capsules for oral administration. Each capsule contains pomalidomide as the active ingredient and the following inactive ingredients: mannitol, pregelatinized starch and sodium stearyl fumarate. Commercial drug product lots will be manufactured by Celgene International Sarl or (b) (4)

Two starting materials will be used in the synthesis of pomalidomide (b) (4) The manufacturing steps will be monitored by routine inprocess controls (IPC) testing.

4.2 Clinical Microbiology

The Clinical Microbiology reviewer (Steven P. Donald, M.S.) recommended approval of NDA 204026 from the standpoint of product quality microbiology. The drug product is a capsule for oral administration. (b) (4) The drug provided with 1 mg, 2 mg, 3 mg and 4 mg dose. No deficiencies were found through the product quality microbiology review.

Refer to clinical microbiology review for details.

4.3 Preclinical Pharmacology/Toxicology

Refer to the Pharmacology-Toxicology Review for details.

In pharmacology safety studies conducted in rats, monkeys and anesthetized dogs to assess the effects of pomalidomide on neurological, pulmonary, and cardiovascular functions. The results showed that there are no dose-dependent effects of pomalidomide observed on neurological function in rats, cardiac function in telemeterized monkeys or anesthetized dogs, or pulmonary function in conscious rats.

Pomalidomide produced < 1% inhibition of hERG at concentrations of 7.9 or 87.5 µM, in an *in vitro* hERG channel assay in HEK293 cells. The results revealed a low potential to block *in vivo* cardiac I_{Kr}. This finding is supported by the absence of QT prolongation in the *in vivo* animal studies with electrocardiographic measurement.

In the rat studies, pomalidomide was well tolerated and did not produce any clear toxicity at doses up to 2000 mg/kg/day (12,000 mg/m^2/day) for 28 days, 1500 mg/kg/day (9000 mg/m^2/day) for 90 days, or 1000 (6000 mg/m^2/day) for 180 days (6 months). Immunomodulatory effects of pomalidomide were observed in the cynomologus monkeys including decreases in platelets, white blood cell count, and lymphocytes in serum, lymphoid hypocellularity in the bone marrow, and lymphoid depletion or atrophy of various lymphoid tissues (mandibular and mesenteric lymph noses, Peyer's patch, spleen and thymus).

Pomalidomide was tested for mutagenicity in an *in vitro* reverse mutation (Ames) assay and an *in vitro* mouse lymphoma assay and tested for clastogenicity in an *in vitro* chromosomal aberrations assay in cultured human peripheral blood lymphocytes and an *in vivo* rat bone marrow micronucleus assay. At the concentrations and doses tested, pomalidomide was not mutagenic or clastogenic.

In the fertility and early embryonic development study conducted in rats, pomalidomide had no effect on premating estrous cyclicity, reproductive performance, or fertility. In pomalidomide treated females paired with treated males, the number of viable embryos was significantly decreased and the post-implantation loss and total number of resorptions (early + late) were significantly increased compared to controls at all doses (≥150 mg/m^2/day). There were no effects of pomalidomide on embryo viability in untreated females paired with the same treated males, indicating that the increase in post-implantation loss seen in the pairing with treated males and treated females was not attributable to the treatment of the males.

The embryo-fetal development effects of pomalidomide were studied in the rat and rabbit. Visceral malformations of absent urinary bladder and absent thyroid were

observed at all doses. Increases in aortic arch malformations (right-sided aortic arch, dilated arch, retroesophageal arch, extra azygous vein, and small pulmonary trunk) were observed at the highest dose of 6000 mg/m^2/day. Skeletal malformations included fused centra, fused neural arches, and misaligned neural arches of the lumbar and thoracic vertebrae.

Carcinogenicity studies have not been conducted.

Pomalidomide was not mutagenic in bacterial and mammalian mutation assays, and did not induce chromosomal aberrations in human peripheral blood lymphocytes or micronuclei formation in polychromatic erythrocytes in bone marrow of rats administered doses up to 2000 mg/kg/day.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Pomalidomide is immunomodulatory drug (IMiD) and structurally similar to both thalidomide and lenalidomide. Pomalidomide exhibits greater potency than thalidomide regarding immune modulation, anti-inflammatory and anti-proliferative activity, and has greater potency than lenalidomide at anti-proliferative effects in MM cell lines, augmentation of CD4+ and CD8+ T-cell proliferation, Th1 cytokine production and natural killer and natural killer T cell activation. Pomalidomide inhibits the proliferation of MM cell lines in vitro.

The combination of lenalidomide and dexamethasone is synergistic in cell lines that are sensitive to lenalidomide. The combination of lenalidomide with dexamethasone is noted to be clinically more effective than lenalidomide alone in MM patients.

4.4.2 Pharmacodynamics

No formal assessments of pomalidomide pharmacodynamics have been conducted.

4.4.3 Pharmacokinetics

Pomalidomide pharmacokinetics were evaluated in in vitro and in vivo studies. Pomalidomide is orally absorbed and was found to have low to moderate plasma protein binding in animals and humans, ranging from approximately 12% to 59% at concentrations between 30 and 1000 ng/mL. The metabolism of pomalidomide was found to be similar in rats, monkeys, and humans with no unique or disproportionate metabolites observed in humans.

Following a single 2 mg radio-labeled dose of pomalidomide, it was determined that the predominant (approximately 70%) circulating radioactive entity was pomalidomide. Renal excretion is the main mode of pomalidomide excretion with approximately 73% of administered pomalidomide excreted through the kidneys, and 2.2% excreted as unchanged drug in urine. Approximately 15.5% of administered dose was excreted via the fecal route. CYP dependent metabolites accounted for 43% of the excreted radioactivity in humans. Circulating metabolites accounted for less than 10% of the total radioactivity. Pomalidomide is primarily metabolized by CYP3A4 and CYP1A2, with some contribution from CYP2C19 and CYP2D6.

Refer to the Clinical Pharmacology review for additional details.

Absorption
In multiple myeloma patients who received pomalidomide 4 mg daily alone or in combination with dexamethasone, pomalidomide steady-state drug exposure was characterized by AUC(T) of 400 ng.hr/mL and maximum plasma concentration (C_{max}) of 75 ng/mL.

In a single oral dose of pomalidomide administration, pomalidomide was absorbed with a C_{max} occurring between 2 and 3 hours. The systemic exposure (AUC) of pomalidomide increased in an approximately dose proportional manner. There was minimal to no accumulation of pomalidomide observed.

The co-administration of pomalidomide with a high-fat and high-calorie meal revealed slower rate of absorption and a decreasing in plasma C_{max} by approximately 25%. However, there were minimal effects on the overall extent of absorption (AUC decreased by 8%).

Distribution
Pomalidomide has a mean volume of distribution (Vd/F) between 62 and 138 L at steady state. Pomalidomide is distributed in semen of healthy subjects at a concentration of approximately 67% of plasma level at 4 hours post-dose (~T_{max}) after 4 days of once daily dosing at 4 mg. In vitro binding of pomalidomide enantiomers to proteins in human plasma ranges from 12% to 44% and is not concentration dependent.

Metabolism
In healthy subjects trial received a single oral dose of [14C]-pomalidomide (2 mg) showed that pomalidomide account for approximately 70% of plasma radioactivity in circulation. No metabolites were present at >10% relative to parent or total radioactivity in plasma.

The predominant metabolic pathways of excreted radioactivity are hydroxylation with subsequent glucuronidation, or hydrolysis. In vitro, CYP1A2 and CYP3A4 were identified as the primary enzymes involved in the CYP-mediated hydroxylation of

pomalidomide. It is not anticipated that inhibition of any one of these CYPs by co-administered drugs will have a significant impact on pomalidomide pharmacokinetics.

Elimination
Pomalidomide is eliminated with a median plasma half-life of approximately 9.5 hours in healthy subjects and approximately 7.5 hours in patients with multiple myeloma. Pomalidomide has a mean total body clearance (CL/F) of 7-10 L/hr.

Following a single oral administration of [^{14}C]-pomalidomide (2 mg) to healthy subjects, approximately 73% and 15% of the radioactive dose was eliminated in urine and feces, respectively, with approximately 2% and 8% of the dosed radiocarbon eliminated as pomalidomide in urine and feces.

Pomalidomide is extensively metabolized prior to excretion, with the resulting metabolites eliminated primarily in the urine. There are three predominant metabolites in urine account for approximately 23%, 17%, and 12%, respectively, of the dose in the urine.

Special Populations: The effects of renal impairment and hepatic impairment on the pharmacokinetics of pomalidomide have not been studied.

The effects of age, gender or race on the pharmacokinetics of pomalidomide have not been studied.

Pediatric: No pharmacokinetic data are available in patients below the age of 18 years.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical trials included in this NDA submission are summarized in the Table 5 below.

Table 5: Studies that most relevant to this review.

Study ID	Design	Site	Regimen	Number of Patients
CC-4047-MM-002 phase 1 Multiple sites in US and Canada	A phase 1 multicenter, randomized, open label, dose-escalation study to determine the MTD, safety, and efficacy alone and in combination with dexamethasone. Subjects with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide and bortezomib	3 Sites in US	POM 2, 3, 4, or 5 mg QD Days 1-21 of each 28-day cycle Dex QD on Days 1, 8, 15, and 22 of each 28-day cycle for subjects who develop PD (40 mg for subjects ≤ 75 y 20 mg for subjects > 75 y)	38 subjects
CC-4047-MM-002	A Phase 2 multicenter, randomized, open label study to evaluate the safety and efficacy of pomalidomide alone and in combination with low dose dexamethasone in patients with relapsed refractory multiple myloma	Multiple sites in US and Canada	Pomalidomide: 4 QD on Days 1-21/28 day cycle. versus Pomalidomide: 4 mg QD on Days 1-21/28 + dexamethasone (20 mg >75 yr) or (40 mg ≤ 75 yr) once weekly	221
MMM-001 Multiple sites in US and EU	Multicenter double-blind, active control, parallel-group, safety and efficacy in subjects with myelofibrosis with myeloid metaplasia			88 Subjects
IFM 2009-02	Phase 2, multicenter, randomized, open label study to evaluate the safety and efficacy of two regimens of oral pomalidomide in combination with low dose dexamethasone	22 sites (France)	Arm A: Pomalidomide at 4 mg QD Days 21/28 + 40 mg dexamethasone Every week Arm B: Pomalidomide at 4 mg QD continuous + 40 mg dexamethasone	84
MM-002	A phase 1 multicenter, randomized, open label, dose-escalation study to determine the MTD, safety, and efficacy alone and in combination with dexamethasone	Multiple sites in US and EU	Doses of 2, 3, 4 mg QD + 40 mg Dexamethasone	38
MM-001 (CDC-407-00-001)	A phase 1 single-center, open-label, safety and efficacy in subjects with relapsed or refractory multiple myeloma	1 UK	Cohort 1: Doses of 1 mg, 2 mg, 5 mg and 10 mg QD* Cohort 2: Doses of 1 mg, 2 mg, 5 mg and 10 mg QOD**	Cohort 1: 24 Cohort 2: 21

*QD: Daily
** QOD: every other day
Source: Applicant NDA 204026, Tabular listing of clinical studies

For the purposes of this review, the safety and efficacy analyses were conducted on the two phase 2 clinical trials. 1) Study CC-4047-MM-002 which was a multicenter, randomized, open label, dose- escalation study designed to determine the MTD, safety, and efficacy alone and in combination with low-dose dexamethasone in patients with relapsed/refractory multiple myeloma who had received prior treatment that includes lenalidomide and bortezomib.
2) Study IFM-2009-02 which was a multicenter, randomized, open label study designed to evaluate the safety and efficacy of two regimens of pomalidomide in combination with low dose dexamethasone in subjects with relapsed/refractory multiple myeloma who had received prior treatment with lenalidomide and bortezomib.

5.2 Review Strategy

This review is focused on safety and efficacy evidence that the applicant provided to support the proposed indication. Therefore, this review is driven by the proposed indication, including:

- Review focused on the two phase 2 randomized trials (CC-4047-MM-002 and IFM-2009-02) for efficacy and safety.
- Examination of the study population eligibility to enter the trials and for prior therapy received.
- Reproduction or auditing of major efficacy and safety analyses.
- Survey of current literature on diagnosis, classification and treatment of multiple myeloma, using standard textbooks, reviews, references submitted by the sponsor and publications listed in PubMed.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study CC-4047-MM-002

5.3.2.1 Overview

Title: A Phase 1/2, multicenter, randomized, open-label, dose-escalation study to determine the MTD, safety and efficacy of CC-4047 alone or in combination with low dose oral dexamethasone in patients with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide and bortezomib.

Study objectives:
The primary objective is to determine the efficacy of pomalidomide alone and in combination with low dose dexamethasone as treatment for patients with relapsed and refractory multiple myeloma.
The secondary objectives are to evaluate the safety of pomalidomide alone and in combination with low-dose dexamethasone as treatment for patients with relapsed and refractory multiple myeloma.

Endpoints:
The primary efficacy endpoint was progression-free survival (PFS) defined as the time from randomization to the first documentation of disease progression or death from any cause during study, whichever occurs earlier.

The secondary endpoints were objective response (EBMT); duration of response; time to response; overall survival; response (IMWG Uniform Response criteria); relationship between response and cytogenetic abnormalities.

Study Design:
The trial was a phase 1/2, international, multicenter, randomized, open-label, dose-escalation study designed to evaluate the safety and efficacy of oral pomalidomide alone and in combination with low dose oral dexamethasone in patients with relapsed and refractory MM. Eligible subjects must have received at least 2 prior therapies and all subjects must have received at least 2 cycles of prior treatments that included lenalidomide and bortezomib and were refractory to their last myeloma therapy. Subjects must also have had measurable disease.

The phase 1 trial was designed as an open label, multicenter, dose escalation study to determine the MTD of pomalidomide. Thirty eight subjects with MM were treated with pomalidomide at doses of 2, 3, 4 or 5 mg daily on days 1 to 21 of each 28 days cycle administered with 40 mg dexamethasone on days 1, 8, 15, and 22 of each cycle. The MTD was determined to be 4 mg/day administered daily in the first 21 days on 4 weeks cycle.

The phase 2 design was an open label randomized trial with crossover design (allowing subjects in pomalidomide alone arm with progressive disease to crossover to combination treatment arm). Up to 192 subjects were planned to be entered and a total of 221 eligible subjects with relapsed MM were enrolled and randomized in 1:1 ratio to treatment arm A (n=112) or arm B (n=109). Figure 1 below shows the trial design. Subjects underwent a screening assessment for protocol eligibility within 28 days of randomization. Randomization was accomplished by an Interactive Voice Response System (IVRS). At randomization, subjects were stratified by age (≤ 75 vs. > 75), prior number of treatments (2 vs. > 2), and prior thalidomide exposure (yes vs. no).

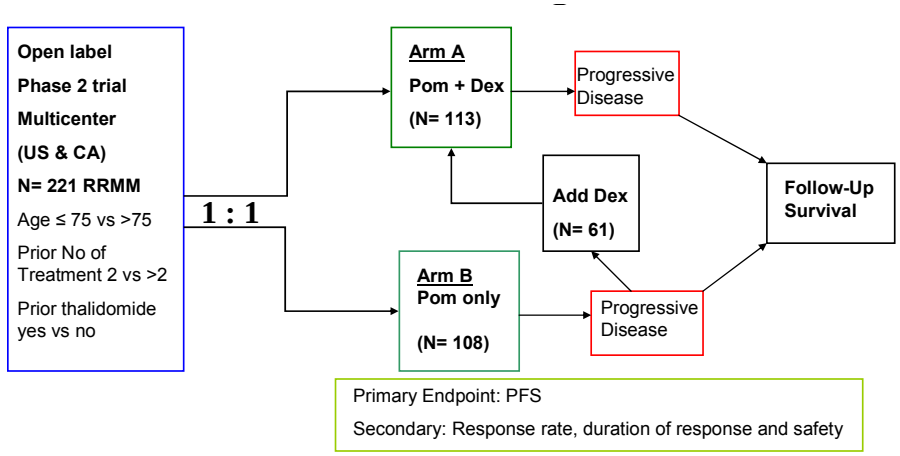
One hundred and twelve subjects randomized to treatment arm (A) received pomalidomide 4 mg daily for the first 21 days in 4 weeks cycle and 40 mg dexamethasone weekly for subjects who were ≤ 75 years of age (20 mg of dexamethasone for subjects > 75 years of age).

One hundred and nine subjects who were randomized to arm B received pomalidomide only 4 mg daily for the first 21 days in 4 weeks cycle. Subjects in Arm B who had confirmed progressive disease (PD) at any time had the option to receive concurrent commercial low-dose oral dexamethasone in addition to their prespecified dose of

pomalidomide and continue study treatment until PD developed again. Subjects with PD who choose to not add dexamethasone to pomalidomide therapy were discontinued from study treatment.

All subjects received prophylactic anti-thrombotic treatment (aspirin 81-100 mg daily or other anticoagulants).

Figure 2: Phase 2 trial design (CC-4047-MM-002)



Source: Applicant NDA 204026, CSR CC-4047-MM-002 study figure 1 (p.28)

5.3.1.2 Eligibility:

Inclusion criteria: Subjects were eligible to enroll in the trial if they met the following:

- Adults 18 years of age or older who had a documented diagnosis of MM and had relapsed and had refractory disease. Subjects must have received at least 2 prior therapies.
- Subjects must have relapsed after having achieved at least stable disease for at least one cycle of treatment to at least one prior regimen and then developed progression of disease (PD).
- Subjects must also have had documented evidence of PD during or within 60 days (measured from the end of the last cycle) of completing treatment with the last anti-myeloma drug regimen used just prior to study entry (refractory disease).
- Subjects must have also undergone prior treatment with at least 2 cycles of lenalidomide and at least 2 cycles of bortezomib (either in separate regimens or within the same regimen).
- Measurable levels of myeloma para-protein in serum (≥ 0.5 g/dL) or urine (≥ 0.2 g/24 hours).
- Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.

- Females of childbearing potential (FCBP) must have agreed to refrain from becoming pregnant for 28 days prior to initiation of study drug, while on study drug, and for 28 days after discontinuation from the study drug.
- Males must have agreed to use a latex condom during any sexual contact with FCBP while participating in the study and for 28 days following discontinuation from this study even if he had undergone a successful vasectomy.
- Males must also have agreed to refrain from donating semen or sperm while on study drug and for 28 days after discontinuation from this study.
- All subjects must have agreed to refrain from donating blood while on study drug and for 28 days after discontinuation from this study.
- All subjects must have agreed not to share medication with another person.

Exclusion Criteria:

- Pregnant or lactating females.
- Any of the following laboratory abnormalities:
  - ANC < 1,000/μL.
  - Platelet count < 75,000/μL for subjects in whom < 50% of BM nucleated cells were plasma cells; or a platelet count < 30,000/μL for subjects in whom ≥ 50% of BM nucleated cells were plasma cells.
  - Serum creatinine > 3.0 mg/dL.
  - Serum SGOT/asparate transaminase (AST) or SGPT/ alanine aminotransaminase (ALT) > 3.0 x upper limit of normal (ULN).
  - Serum total bilirubin > 2.0 mg/dL.
- Prior history of malignancies, other than MM, unless the subject had been free of the disease for ≥ 3 years. Exceptions included the following:
  - Basal or squamous cell carcinoma of the skin.
  - Carcinoma in situ of the cervix or breast.
  - Incidental histological finding of prostate cancer (TNM stage of T1a or T1b).
- Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) and/or
- Hepatitis C Virus (HCV) infection.
- Hypersensitivity to thalidomide, lenalidomide, or dexamethasone.
- Peripheral neuropathy ≥ Grade 2.
- Use of any anti-myeloma drug therapy within 14 days of the initiation of study drug treatment or use of any experimental drug therapy within 28 days of the initiation of study drug treatment.
- Radiation therapy within 14 days of initiation of study drug treatment.
- Inability or unwillingness to comply with birth control requirements.

5.3.1.3 Treatment:

Trial CC-4047-MM-002 was conducted in two phases. The phase 1 of the CC-4047-MM-002 trial was conducted in 38 subjects with relapsed refractory MM and designed in

a 3+3 design to define the MTD for single-agent pomalidomide among the 2, 3, 4, and 5 mg daily dose levels. The MTD was 4 mg when delivered as a single agent and administered once per day orally on Days 1-21 of each 28-day cycle. Neutropenia was the most commonly reported DLT.

The pomalidomide dose used in the phase 2, CC-4047-MM-002 trial, was based on data from part 1 of study CC-4047-MM-002 where the MTD was determined to be 4 mg. Subjects were randomized into two arms:

> Arm A: Subjects received oral pomalidomide at 4 mg/day on Days 1-21 of each 28-day treatment cycle and low-dose dexamethasone. The starting dose of dexamethasone was 40 mg once per day on Days 1, 8, 15 and 22 of each 28-day cycle for subjects who were ≤ 75 years of age. For subjects who were > 75 years of age, the starting dose of dexamethasone was 20 mg once per day on Days 1, 8, 15 and 22 of each 28-day cycle.
>
> Arm B: Subjects received oral pomalidomide at 4 mg/day on Days 1-21 of each 28-day treatment cycle. Subjects in this arm who had confirmed PD at any time had the option to cross over to arm A and receive low dose oral dexamethasone in addition to their current dose of pomalidomide. Patients who crossed over, received the same starting dose as the starting dose stated in arm A. Subjects who chose to receive dexamethasone in addition to pomalidomide therapy could continue study treatment until PD developed again. Subjects with PD who choose to not add dexamethasone to pomalidomide therapy were discontinued from study treatment.

Subjects continued study treatment until disease progression or intolerable toxicity developed or until discontinuation for any other reason.

All subjects were given a prophylactic anti-thrombotic treatment of aspirin 81-100 mg daily unless contraindicated. If aspirin was contraindicated, subjects were to receive another form of anti-thrombotic therapy according to hospital guidelines or physician preference. In addition, all subjects were to be monitored for signs and symptoms of venous thromboembolism (VTE) while on pomalidomide.

The use of biphosphonates and hematopoietic growth factors was permitted.

Treatment with myeloid growth factors was encouraged when the absolute neutrophil counts (ANC) was less than 1,000/μL. Dose reduction steps for pomalidomide and dexamethasone were provided for dose limiting toxicities (DLT).

Upon discontinuation from study treatment for PD or any other reason, subjects were to be assessed three times per year (every 4 months or as deemed necessary by Celgene), for up to five years, for survival and subsequent anti-myeloma therapies.

Dose Modifications:

Pomalidomide: The dose reduction of pomalidomide was based on evaluation of subjects at each visit for adverse events using the NCI CTCAE version 3.0. Table outlines the dose reduction steps used for pomalidomide. The criteria for dose reductions and interruptions are outlined in Table 5.

Table 6: Pomalidomide Dose Reduction Steps by Dose level

Starting Dose Level (Days 1-21 of each 28-day cycle)	Dose Reduction (Days 1-21 of each 28-day cycle)
5 mg[a]	4 mg
4 mg	3 mg
3 mg	2 mg
2 mg	1 mg
1 mg	Discontinue study drug

[a] A 5 mg dose was not administered in this study.

Source: Applicant NDA 204026, CSR CC-4047-MM-002 study table 2 (p.34)

Table 7: Dose modification due to pomalidomide toxicities:

Toxicity	**Dose Modification**
Neutropenia Grade 4 neutropenia (ANC < 500/μL) or febrile neutropenia (fever ≥38.5 ^{0}C and ANC < 1,000/μL)	Hold the dose for remainder of cycle. If the subject was not receiving GCSF therapy, initiate GCSF therapy. On Day 1 of next cycle, continue GCSF as needed and maintain dose of pomalidomide if neutropenia was the only toxicity. Otherwise, decrease by one dose level at start of next cycle.
Grade 4 Thrombocytopenia (Platelets <25,000/μL)	Hold the dose for remainder of cycle. Decrease by one dose level when dosing is resumed at next cycle.
Rash = Grade 3	Hold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (rash must resolve to ≤ Grade 1).
Rash = Grade 4 or Blistering	Discontinue study drug and discontinue subject from study.
Constipation ≥ Grade 3	Hold dose for remainder of cycle. Initiate bowel regimen. Decrease by one dose level when dosing restarted at next cycle (constipation must resolve to ≤ Grade 2).
VTE ≥ Grade 3	Hold dose for remainder of cycle. Initiate anticoagulation treatment. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.
Hypo/hyperthyroidism ≥ Grade 2	Hold dose for remainder of cycle. Initiate appropriate medical therapy. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.
Peripheral Neuropathy = Grade 3	Hold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (neuropathy must resolve to ≤ Grade 1).
Peripheral Neuropathy = Grade 4	Discontinue study drug and discontinue subject from study.
Other ≥ Grade 3 CC-4047-related AEs	Hold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (AE must resolve to ≤ Grade 2).

Source: Applicant NDA 204026, CSR, CC-4047-MM-002, Table 4 (p.35)

Dexamethasone: The dose reductions for dexamethasone were based on the subject's age. The starting dose for subjects age 75 years or older was 40 mg on Days 1, 8, 15, and 22 of each cycle which will reduced to 20 mg.

Monitoring and Assessment:

This study was designed to have one interim analyses performed, which was to occur when approximately 70 subjects from both treatment arms developed PD or died during the treatment phase (ie, 50% information for the primary endpoint of PFS).

An Independent Response Adjudication Committee (IRAC) determined the date of progression and the myeloma response achieved for each subject according to the categories as specified in the Blade/EBMT (Blade, 1998) response criteria and to the VGPR category as defined by the International Myeloma Working Group (IMWG) myeloma response determination criteria by reviewing M-protein, plasmacytoma, bone marrow, lytic bone lesions, and serum calcium data.

Based on the IRAC review on December 15, 2010, 141 PFS events for both arms had occurred by October 29, 2010 (data cutoff date for the interim analysis at 50% information for PFS). The median follow-up time for PFS was 9.6 weeks, and the median follow-up time for survival was 20.3 weeks (data on file).

The DMC met on January 31, 2010 to review the results of the first interim analysis. The PFS Kaplan-Meier estimate curves demonstrated a highly significant difference in favor of Arm A (pomalidomide and dexamethasone) when compared with Arm B (pomalidomide). The DMC recommended unblinding the study based on the superior efficacy results of pomalidomide and dexamethasone as compared to pomalidomide.

Final unblinded analyses of the data with April 01, 2011 cutoff were performed after the database lock on June 10, 2011.

Efficacy assessment:

Myeloma para-protein and serum immunoglobulins: The date of randomization and start of study drug was designated as Study Day 1. Serum M-protein levels by electrophoresis (PEP), urine M-protein levels (UPEP), and serum immunoglobulin levels were obtained at screening, at Study Day 1, and then every 28 days (4 weeks) thereafter and performed by central laboratory. Serum and urine immunofixation (IFE) tests were performed at screening to identify the immunoglobulin subtype of MM and thereafter were triggered to be performed by the central laboratory whenever M-protein was undetectable in both serum and urine by protein electrophoresis studies to confirm complete response (CR). Response was assessed using the EBMT criteria and the International Myeloma Working Group criteria.

Bone marrow aspiration: A bone marrow aspirate was to be performed at screening and when clinically indicated to confirm CR at the discretion of the treating physician. A biopsy was needed only if the marrow was unable to be aspirated.

Radiographic assessments of lytic bone lesions: Radiographic assessment of the bones was performed at screening, discontinuation and when clinically indicated at the

discretion of the treating physician and performed by the site investigator/radiologist. These assessments were performed by the site investigator/radiologist.

Extramedullary plasmacytoma assessments: Plasmacytomas that could be assessed clinically were to be assessed every 28 days. Plasmacytomas that were assessed by radiography were assessed at screening, discontinuation, and to assess best response.

Assessment of response: Objective overall best response using the EBMT was to be assessed every 28 days (4 weeks) and at discontinuation from study drug. An assessment of response by the International Myeloma Working Group Response criteria was also to be performed as a secondary endpoint. Overall response rates utilizing either or both criteria were to be reported in the clinical study report.

Overall survival: All subjects were to be followed for survival for up to 5 years. Subjects were to be assessed three times per year (approximately every 4 months) to determine survival status. Cause of death was to be recorded in the CRF and the subject's medical record.

5.3.1.4 Efficacy Evaluations:

Planned Analyses:
The applicant conducted as planned an interim analysis at 50% and final analysis at 100% of study data collected. The boundary for declaring superiority of Arm A over Arm B was based on an alpha-spending function of the O'Brien-Fleming type with overall $\alpha = 0.025$, one-tailed. However, no futility boundary was used to stop the trial for lack of difference between the treatment groups.

Several modifications were implemented beyond the original planned analyses with the following are the major ones:

- Additional analyses for subjects who had at least two dose reductions/interruptions of pomalidomide and time to second dose reduction/interruption;
- Additional efficacy subgroup analysis for subject who were refractory to both Lenalidomide and Bortezomib, previously treated with Bone Marrow Transplant or Stem Cell Transplant;
- Additional subgroup analyses for TEAEs, Grade 3/4 TEAEs, SAEs, and death
- Additional analyses for AEs of special interest
- Grade 5 AE by treatment arm were summarized instead of AEs leading to death since no AE leading to death information was available
- Death was not summarized by relationship to the study drug (suspected to be related to pomalidomide, suspected to be related to dexamethasone, or non-study drug related) since such information was not collected in the eCRF.

As of the data cutoff date, there were three protocol amendments; with only Amendment 3 was implemented (April 28, 2010) during Phase 2 of this study.

Subsequent to the implementation of Amendment 3, 183 subjects were enrolled in Phase 2. Key changes implemented under Amendment 3 were:

- Revised pomalidomide dose reduction table
- Added a Pomalidomide Pregnancy Risk Minimization Plan
- Established timeline for a follow-up period of up to 5 years
- Updated inclusion/exclusion criteria to include reference to Pomalidomide Pregnancy Risk Minimization Plan

Response Criteria

The criteria for determining relapsed and refractory disease were defined as follow:

Relapsed Disease: defined as previously treated myeloma patients who, after a period of being off-therapy, require salvage therapy but do not meet criteria for "primary refractory" or "relapsed-and-refractory" categories.

Refractory Disease: defined as disease that is non-responsive while on therapy or progresses within 60 days of last therapy.

- Relapsed-and-refractory myeloma is defined as relapse of disease in patients who either become non-responsive while on salvage therapy, or progress within 60 days of last therapy.
- Primary refractory myeloma refers to refractory disease in patients who have never achieved a minimal response (MR) with any therapy, and includes two sub-categories:
    - Patients who never achieved MR or better in whom there is no significant change in M protein and no evidence of clinical progression.
    - Primary refractory, progressive disease.

The criteria for determining disease response and progression were defined in the protocol as follows:

The primary efficacy endpoint was progression free survival (PFS). Primary efficacy analysis was based on responses assessed by the Independent Response Adjudication Committee (IRAC) based on the European Group for Blood and Marrow Transplantation (EBMT) criteria.

Progression free survival was defined as the time from randomization to the first documentation of disease progression or death from any cause during study, whichever occurs earlier.

Overall survival was defined as the time from randomization to death from any cause.

In addition, the IRAC assessed the responses using the International Myeloma Working Group (IMWG) criteria, and the response data based on the IMWG criteria were analyzed as a supportive response analysis.

Complete response (CR): Complete response (CR) requires all of the following:

1. Absence of the original monoclonal para-protein in serum and urine by immunofixation, maintained for a minimum of 42 days (6 weeks). The presence of oligo-clonal bands consistent with oligo-clonal immune reconstitution does not exclude CR.
2. < 5% plasma cell in a bone marrow aspirate and also on bone marrow biopsy, if biopsy is performed. However, if absence of monoclonal protein is sustained for at least 42 days (6 weeks), it is not necessary to repeat the bone marrow, except in patients with non-secretory myeloma where the marrow examination must be repeated after an interval of at least 42 days (6 weeks) to confirm CR.
3. No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response). If absence of monoclonal protein is sustained for at least 42 days (6 weeks), it is not necessary to repeat the skeletal survey.
4. Disappearance of soft tissue plasmacytomas.

Partial response (PR): Partial response (PR) requires all of the following:

1. ≥50% reduction in the level of serum monoclonal para-protein, maintained for a minimum of 42 days (6 weeks).
2. Reduction in 24-hour urinary light chain extraction by ≥ 90% or to <200 mg, maintained for a minimum of 42 days (6 weeks).
3. For patients with non-secretory myeloma, ≥ 50% reduction in plasma cells in bone marrow aspirate and on bone marrow biopsy, if a biopsy is performed, maintained for a minimum of 42 days (6 weeks).
4. ≥50% reduction in the size of the soft tissue plasmacytomas (by radiography or clinical examination)
5. No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response). If the reduction of the monoclonal protein required for PR is sustained for at least 42 days (6 weeks), it is not necessary to repeat the skeletal survey.

Minimal Response (MR): Minimal response requires all of the following:

1. 25-49% reduction in the level of serum monoclonal para-protein, maintained for a minimum of 42 days (6 weeks).
2. Reduction in 24-hour urinary light chain extraction by 50-89%, which still exceeds 200 mg per 24 hours, maintained for a minimum of 42 days (6 weeks).
3. For patients with non-secretory myeloma, 25-49% reduction in plasma cells in bone marrow aspirate and on bone marrow biopsy, if a biopsy is performed, maintained for a minimum of 42 days (6 weeks).
4. 25-49% reduction in the size of the soft tissue plasmacytomas (by radiography or clinical examination).

5. No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response). If the reduction of the monoclonal protein required for MR is sustained for at least 42 days (6 weeks), it is not necessary to repeat the skeletal survey.

Stable Disease: Not meeting the criteria for either MR or PD

Progressive disease (for patients who relapse from CR requires at least one of the following):

1. Reappearance of serum or urine monoclonal para-protein on electrophoresis or immunofixation studies, confirmed by at least one consecutively repeated investigation. Oligo-clonal immune reconstitution must be excluded.
2. ≥5% plasma cells in bone marrow aspirate or biopsy.
3. Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in size of residual bone lesions (development of a compression fracture does not exclude continued response and may not indicate PD).
4. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL [2.8 mmol/L]) not attributable to any other cause.

Progressive disease for patients not in CR: One or more of the following:

1. > 25% increase in the level of the serum monoclonal para-protein, which must also be an absolute increase of at least 5 g/l and confirmed by at least one repeated investigation
2. > 25% increase in the 24 h urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 h and confirmed by at least one repeated investigation
3. > 25% increase in plasma cells in a bone marrow aspirate or biopsy, which must also be an absolute increase of at least 10%
4. Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
5. Development of new lytic bone lesions or soft tissue plasmacytomas (development of a compression fracture does not exclude continued response and may not indicate PD).
6. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL [2.8 mmol/L]) not attributable to any other cause.

<u>Schedule of Assessment:</u>
The schedule of assessments consists of screening period, treatment period and follows up periods.

Table 8: Schedule of assessment used in CC-4047-MM-002 trial

Procedure	Screening	MTD and Open Label Treatment						Follow Up	
	Screen/Baseline (Within 28 Days of Randomization)	Cycle 1 Day 1	Cycle 1 Days 8, 15, 22	Subsequent Cycles incl Day 1	Every 28 Days[1] (regardless of Cycle Day)	Disease Progression (Arm B only)	Disease Progression Treatment Disc	30 Days After Study Treatment Disc	April August December
Visit Window			± 2 Days	± 3 Days	± 2 Days	± 3 Days		± 3 Days	± 7 Days
Informed consent	X	--	--	--	--	--	--	--	--
Inclusion/exclusion criteria	X	--	--	--	--	--	--	--	--
Confirmation of diagnosis	X	--	--	--	--	--	--	--	--
Prior antimyeloma therapies	X	--	--	--	--	--	--	--	--
Medical and surgical history	X	--	--	--	--	--	--	--	--
Randomization (Phase 2)	--	X	--	--	--	--	--	--	--
Review concomitant medications	X	X	X	X	X	X	X	--	--
Performance status	X	X	--	X	X	X	X	--	--
Measurement of vital signs[2]	X	X	--	X	X	X	X	--	--
Bone marrow aspiration and/or biopsy[3] (diagnosis, cytogenetics, and biomarkers)	X	--	--	--	--	--	--	--	--
Serum biochemistry[4]	X	--	--	X	--	--	X	--	--
Haematology[5]	X	X	X	X[5]	--	X	X	--	--
Thyroid function tests[6]	X	--	--	--	X[6]	--	X[6]	--	--
Quantitative serum immunoglobulin levels	X	X	--	--	X	--	X	--	--
Protein electrophoresis (serum and 24-hour urine)	X	X	--	--	X	--	X	--	--

Procedure	Screening	MTD and Open Label Treatment						Follow Up	
	Screen/Baseline (Within 28 Days of Randomization)	Cycle 1 Day 1	Cycle 1 Days 8, 15, 22	Subsequent Cycles incl Day 1	Every 28 Days[1] (regardless of Cycle Day)	Disease Progression (Arm B only)	Disease Progression Treatment Disc	30 Days After Study Treatment Disc	April August December
Visit Window			± 2 Days	± 3 Days	± 2 Days	± 3 Days		± 3 Days	± 7 Days
Immunofixation studies (serum and 24-hour urine)[7]	X	X	--	--	X	--	X	--	--
Urinalysis[8]	X	--	--	X	--	--	X	--	--
Pregnancy test for FCBP[9]	X	X	X[9]	--	X	--	X	X	--
Pregnancy counseling[10]	X	X	--	X	X	--	X	X	--
Skeletal survey[11]	X	--	--	--	--	--	X	--	--
Extramedullary plasmacytoma assessment[12]	X	X	--	--	X[12]	--	X[12]	--	--
12-Lead electrocardiograph[13]	X	--	--	--	X[13]	--	X	--	--
Assessment of response[14]	--	--	--	--	X	--	X	--	--
VTE monitoring	--	X	X	X	X	--	X	--	--
Adverse events[15]	X	X	X	X	X	X	X	X[15]	--
Study drug dispensing[16]	--	X	--	X	--	--	--	--	--
Study drug return[16]	--	--	--	X	--	--	X	--	--
Dexamethasone[17]	--	--	--	--	--	X	--	--	--
Survival[20]	--	--	--	--	--	--	--	X	X

Procedure	Screening	MTD and Open Label Treatment						Follow Up	
	Screen/Baseline (Within 28 Days of Randomization)	Cycle 1 Day 1	Cycle 1 Days 8, 15, 22	Subsequent Cycles incl Day 1	Every 28 Days[1] (regardless of Cycle Day)	Disease Progression (Arm B only)	Disease Progression Treatment Disc	30 Days After Study Treatment Disc	April August December
Visit Window			± 2 Days	± 3 Days	± 2 Days	± 3 Days		± 3 Days	± 7 Days
Subsequent myeloma therapies	--	--	--	--	--	--	--	X	X
PK blood sampling[18]		X	Day 8						
PK urine sampling[19]			Day 8 only						

ALC = absolute lymphocyte count; ALT/SGPT = alanine transaminase/serum glutamate pyruvic transaminase; ANC = absolute neutrophil count; AST/SGOT = asparate transaminase/serum glutamic oxaloacetic transaminase; ECG = electrocardiogram; FCBP = females of childbearing potential; GGT = gamma-glutamyl transferase; incl = including; PD = progressive disease; PK = pharmacokinetic; RBC = red blood cell; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; VTE = venous thromboembolism; WBC = white blood cell

1. Efficacy measurements were to be performed every 28 days (± 2-day window) while on study treatment regardless of current Cycle day (ie, for the first 48 weeks efficacy measurements were to be performed on Study Days 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337).
2. Vital signs include weight, height (Screening visit only), blood pressure, temperature, and heart rate.
3. A bone marrow aspirate and/or at least a unilateral biopsy was to be performed at screening and when clinically indicated.
4. Serum chemistry (total protein, albumin, calcium, phosphorous, glucose, uric acid, total bilirubin, alkaline phosphatase, AST/SGOT, ALT/SGPT, GGT, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, lactate dehydrogenase, creatine kinase and magnesium).
5. Hematology included WBC, hemoglobin, hematocrit, differential, platelet count, ANC, ALC, mean corpuscle volume and reticulocyte count. Hematology has to be performed every 14 days during Cycle 2 than at a minimum of Cycle Day 1 of each cycle beginning with Cycle 3.
6. Serum TSH level, T3 and T4 levels was to be monitored every 84 days (3 months) and at discontinuation visit.
7. To be done at screening and to confirm complete response (undetectable M-protein by protein electrophoresis in urine and serum will trigger Central Lab to perform immunofixation studies in urine and serum).
8. Urinalysis (specific gravity, pH, glucose, bilirubin, protein, ketones, and microscopic analysis [casts, RBCs, and WBCs]).
9. FCBP must have had a medically supervised pregnancy test (serum or urine with sensitivity of at least 25 mIU/mL). FCBP must have had two negative pregnancy tests prior to starting the study drug. The first pregnancy test had to be performed within 10-14 days prior to the start of study drug and second test within 24 hours prior to starting study drug. Pregnancy test were to be performed every 7 days (weekly) during the first 28 days (4 weeks) of therapy, then every 28 days (4 weeks) (every 14 days [2 weeks] in women with irregular cycles) while on study drug, at study drug discontinuation, and then 28 days after study discontinuation. Study drug was not to be dispensed for FCBP until the investigator verified that the result of the pregnancy test was negative. See Protocol Section 21.7.
10. Counseling about pregnancy precautions and the potential risks of fetal exposure had to be conducted at a minimum of every 28 days.
11. Skeletal survey was to be performed at screening (or within 60 days of Study Day 1), discontinuation, and when clinically indicated.

Source: Applicant NDA 204026, CSR, CC-4047-MM-002 table 4 (p.39-41)

5.3.1.5 Safety evaluations:

Safety was monitored by the investigators and, independently, by a data monitoring committee. All toxicities observed will be graded according to the NCI CTCAE v3.0.

5.3.1.6 Statistical Plan:

Populations:
ITT population (n=221) is defined as all patients enrolled in the trial.

Efficacy evaluable (EE) population (n=191) are all subjects who enrolled who met the efficacy evaluable eligibility criteria, received at least 1 dose of study treatment, and had baseline and at least one post-baseline efficacy assessment.

Safety Population (n=219) defined as all randomized subjects who received at least 1 dose of either pomalidomide or dexamethasone.

Efficacy analysis: The primary analysis was based on the ITT population and used myeloma responses determined based on EBMT criteria and were also analyzed using the new IMWG criteria.

Progression free survival (PFS) was determined as the time from randomization to the first documentation of disease progression or death from any cause during study, whichever occurred earlier.

Overall survival (OS) was defined as the time from randomization to death from any cause.

A responder was any subject who showed at least a partial response (PR) at any time within the first 6 cycles of study treatment.
Time to response was defined as the time from randomization to the first documentation of response (either PR or CR).

Duration of response was the time from the first PR or complete response (CR) to the first documentation of disease progression.

For time to event analyses, the Kaplan-Meier method was used to estimate the distribution functions for each treatment arm. For comparison of treatment arms, the log rank test was used (two-sided, alpha =0.05). The trial had an 85% power to detect a 40% reduction in PFS or OS (median PFS of 6 and 10 months in the pomalidomide [monotherapy arm) vs the pomalidomide + dexamethasone (combination arm)]. Planned accrual was 192 and the actual accrual was 221 patients (113 to the combination arm and 108 to the monotherapy arm). The planned final analysis was at 129 events, and the final analysis was conducted at 167 events.

Response rates together with 95% confidence intervals (CI) were provided for each treatment arm. A 2-sided continuity-corrected chi-square test was used to compare response rates.

One interim analysis of PFS was planned at 50% (70 PFS events). The Lan-DeMets spending function based on O'Brien-Fleming boundary was used: first interim analysis alpha = 0.003 and final analysis alpha=0.049.

Based on projection, interim analysis was scheduled with a cutoff data of October 29, 2010 (141 events). Since the results of the interim analysis (April 1, 2011) demonstrated a highly significant difference in favor of combination therapy, the IRAC recommended unblinding the study. An updated analysis of OS was performed based on the cutoff date of September 16, 2011.

Safety analyses were performed on the safety population.

Adverse events were classified using the MedDRA classification system (Version 14.0). The severity of the toxicities was graded according to the NCI CTCAE version 3.0 whenever possible.

The frequency of AEs was tabulated by MedDRA system organ class, preferred term, and dose cohort/treatment arm. In the by-subject analysis, a subject having the same event more than once was counted only once. Adverse events were summarized by NCI CTCAE version 3.0 grade. Adverse events leading to discontinuation from treatment, events classified as NCI CTCAE version 3.0 Grade 3 or higher, study drug related events, and serious adverse events were tabulated and listed separately. By-subject listings of all adverse events, serious adverse events, and their attributes were provided.

Clinical laboratory data (including TSH, T3 and T4 levels) was summarized by dose regimen/treatment arm. Laboratory data was graded according to NCI CTCAE version 3.0 criteria wherever possible. The frequencies of the worst severity grade observed during treatment were displayed in cross-tabulations by baseline status for each dose regimen. In addition, clinically notable laboratory values were summarized by cycle.

Planned Subgroup analyses (exploratory in nature):
The applicant planned to analyzed the results of the effect of treatment on the efficacy endpoints of PFS, OS, and ORR between treatment arms within subgroups based on gender (male, female), age group (≤ 75, > 75 years); number of prior anti-myeloma regimens (2, >2); and prior thalidomide exposure (yes, no).

In addition an exploratory subgroup analysis (post hoc analysis) conducted by the applicant was based on the subjects' prior anti-myeloma regimens, selected efficacy endpoints. These post hoc analyses were summarized by treatment arms within the following subgroup of subjects:

- Refractory to lenalidomide
- Refractory to bortezomib
- Refractory to both lenalidomide and bortezomib
- Refractory to both lenalidomide and bortezomib, previously treated with bone marrow transplant or stem cell transplant, and with previous thalidomide exposure
- Previously Treated with carfilzomib
- Number of prior anti-myeloma regimens (=2 or =3, >3, >=5)
- Cytogenetic abnormality (High risk, non-high risk)

5.3.1.7 Study Amendments:

There were a total of three protocol amendments as follow:

- Amendment 1 & 2 was applicable to the phase 1 of the trial.

- Amendment 3: By the time of implementation 183 subjects were enrolled in the phase 2 trial. Key changes include:
    - Revised pomalidomide dose reduction table
    - Added Pomalidomide Pregnancy Risk Minimization Plan
    - Established timeline for follow-up period of up to 5 years
    - Updated inclusion/exclusion criteria to include reference to Pomalidomide Pregnancy
    - Risk Minimization Plan

5.3.1 Study IFM 2009-02

5.3.2.1 Overview

Title: A multicenter randomized open label phase II study of pomalidomide and dexamethasone in relapse and refractory multiple myeloma patients who are progressive and did not achieve at least a partial response to bortezomib and lenalidomide.

Endpoints:

Primary endpoint: The primary endpoint was the response rate (PR+CR) to pomalidomide and dexamethasone in the studied population using International Myeloma Working Group (IMWG) response.

Secondary Endpoints:

- Response rate of two dosing regimens of pomalidomide using IMWG response criteria
- Safety (type, frequency, severity, and relationship of adverse events to study treatment). Incidence of treatment emergent adverse events (TEAE), serious adverse events (SAE) and laboratory abnormalities using NCI-CTCAE criteria (version 3.0)
- Time to response (from the date of inclusion to the date of the first observation of response) and response duration (time between first documentation of response and disease progression).
- Time to disease progression (from the date of the first dose to the date of the first observation of disease progression)
- Overall survival (from the date of inclusion to the date of the last news).
- To determine response in both arms with regards to cytogenetic of the bone marrow tumor plasma cells. Analysis of cytogenetic study of bone marrow plasma cells is a key test in myeloma. The following cytogenetic FISH studies (deletion 13q, deletion 17p, translocation 4; 14) were to be performed for

patients with myeloma that had not been previously screened for cytogenetic (performed by [redacted](b) (4)

Study Design: The study was a randomized, multicenter, open label, two-stage phase II study of pomalidomide and dexamethasone in relapsed and refractory MM patients with progressive and did not achieve at least a partial response to bortezomib and lenalidomide.

Patients were randomized in 1:1 ratio into two arms:

- Arm A were treated with pomalidomide 4 mg daily for 21 days every 4 weeks cycle and dexamethasone 40 mg on Days 1, 8, 15, and 22 of each 28-day cycle
- Arm B: 4 mg/day pomalidomide on Days 1 to 28 and dexamethasone 40 mg on Days 1, 8, 15, and 22 of each 28-day cycle.

5.3.2.2 Eligibility:

Inclusion criteria:

- Age ≥ 18 years with life expectancy > 6 months
- Symptomatic patients with progressive myeloma following bortezomib and/or lenalidomide treatment, defined as follows:
    - Patients must have undergone prior treatment with at least 2 cycles of lenalidomide and at least 2 cycles of bortezomib:
        - At diagnosis or at relapse
        - Either in separate regimens or within the same regimen
        - Any number of prior therapies
        - Course of treatment with bortezomib and/or lenalidomide did not need to be the very last line of therapy administered
    - Patients were to have progressive disease as defined by the IMWG, one of the following:
    - 25% increase in the level of the serum monoclonal para-protein (5g/L increase minimum)
    - 25% increase in the 24h urinary light chain excretion (200 mg/24h increase minimum)
    - 25% increase in the serum Free Light chain (sFLC) levels (with an absolute value ≥100 mg/L and an abnormal sFLC K/λ ratio (<0.26 and >1.65) in the absence of renal failure), only in patients without measurable serum and urine M-protein levels.
    - Increase in plasma cells in a bone marrow aspirate (>10%)
    - Increase in the size of existing bone lesions or soft tissue plasmacytomas
    - New bone lesions or soft tissue plasmacytomas (not including compression fracture)
    - Onset of hypercalcemia not attributable to any other cause
- Patients were to have had at best a stable disease as per IMWG response criteria (i.e. not achieving a partial response), with the last course of bortezomib

and lenalidomide administered to the patient during any line of anti-myeloma therapy. Patients might have responded initially to either bortezomib and/or lenalidomide but did not respond again at re-challenge with bortezomib and/or lenalidomide.

- Patients were to have a clearly detectable and quantifiable monoclonal M component value:
  - IgG (serum M-component > 10g/L)
  - IgA (serum M-component > 5g/L)
  - IgD (serum M-component > 0.5g/L)
  - Light chain (serum M-component >1g/L or Bence Jones > 200mg/24h)
  - Without measurable serum and urine M-protein levels and in the absence of renal failure when the absolute serum Free Light chain (sFLC) was ≥100 mg/L and an abnormal sFLC K/λ ratio (<0.26 and >1.65) was found.
- Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2
- Adequate bone marrow function, documented within 72 hours prior to treatment without transfusion or growth factor support, defined as:
  - Absolute neutrophils ≥ 1000/mm3,
  - Platelets ≥ 75000/mm3
  - Hemoglobin ≥ 8.5g/dL.
- Adequate organ function defined as:
  - Serum SGOT/AST or SGPT/ALT < 3.0 X upper limit of normal (ULN)
- Wash out period of at least 2 weeks from previous antitumor therapy or any investigational treatment
- Able to take antithrombotic medicines such as low molecular weight heparin or aspirin 75mg.
- Patients affiliated with an appropriate social security system
- Agree to abstain from donating blood while taking study drug therapy and for one week following discontinuation of study drug therapy
- Female patients of childbearing potential should use effective methods of contraceptive. Also agree to have supervised pregnancy test.

<u>Exclusion criteria:</u>

1. Pregnant or breast feeding females
2. Use of any other experimental drug or therapy within 15 days of screening
3. Known positive for HIV or infectious hepatitis, type A, B or C.
4. Patients with non-secretory MM
5. Prior history of malignancies, other than multiple myeloma, unless the patient had been free of the disease for ≥3 years. Exceptions included the following:
   - Basal or squamous cell carcinoma of the skin
   - Carcinoma in situ of the cervix or breast
   - Incidental histological finding of prostate cancer (TNM stage of T1a or T1b)
6. Prior local irradiation within two weeks before screening
7. Evidence of central nervous system (CNS) involvement

8. Any >grade 2 toxicity unresolved
9. Peripheral neuropathy ≥ grade 2
10. Known hypersensitivity to thalidomide, lenalidomide or dexamethasone
11. Ongoing active infection, especially ongoing pneumonitis
12. Ongoing cardiac dysfunction
13. Inability or unwillingness to comply with birth control requirements
14. Unable to take antithrombotic medicines at study entry
15. Unable to take corticosteroid therapy at study entry
16. Refusal to participate in the study
17. Persons protected by a legal regime (guardianship, trusteeship)

5.3.2.3 Treatment:

Eighty four patients were randomized in 1:1 ratio into two arms:

- Arm A: 4 mg/day pomalidomide on Days 1 to 21, plus dexamethasone 40 mg on Days 1, 8, 15, and 22 of each 28-day cycle
- Arm B: 4 mg/day pomalidomide on Days 1 to 28 plus dexamethasone 40 mg on Days 1, 8, 15, and 22 of each 28-day cycle.

Dose modifications:
A new course of treatment could begin on the scheduled Day 1 of a new cycle if:

• The neutrophil count was ≥ 1 x109/L
• The platelet count was ≥ 50 x109/L
• Any pomalidomide-related allergic reaction/hypersensitivity or sinus bradycardia/ other cardiac arrhythmia adverse event that may have occurred and has resolved to ≤ grade 1 severity;
• Any other pomalidomide-related adverse event that may have occurred had resolved to ≤ grade 2 severity

6 Review of Efficacy

Efficacy Summary

The efficacy of Pomalidomide was evaluated in 305 patients with relapsed or refractory multiple myeloma who were randomized in the two Phase 2 trials. A summary of the important efficacy results from these clinical trials are listed below.

- The contribution of pomalidomide to the combination therapy can not be evaluated, since the effect of pomalidomide was not isolated in both trials supporting this NDA application.
- The overall response rate (CR+PR) in CC-4047-MM-002 trial was 29.2% with median duration of 7.4 months among subjects who received pomalidomide plus

low-dose dexamethasone, and 7.4% with median duration not achieved yet among subjects who received pomalidomide alone.

- The overall response rate (CR+PR) in IFM 2009-02 trial was 34.9% with median duration of response of 10.5 months among subjects who received intermittent pomalidomide plus dexamethasone, and 34.1% with median duration of 7.3 months among subjects who received continuous pomalidomide plus dexamethasone.
- The overall response rate results by subgroups of refractory status to prior bortezomib and lenalidomide treatment are consistent with the ORR results for all patients.

6.1 Indication

Applicant's Proposed Indication: Pomalidomide in combination with dexamethasone is indicated for patients with relapsed and refractory multiple myeloma who have received at least 2 prior regimens of established benefit, including both lenalidomide and bortezomib and have demonstrated disease progression on the last treatment.

6.1.1 Methods

The efficacy review for pomalidomide was performed by review of the following items submitted by the Applicant (Celgene Inc.):

- Summary of Clinical Efficacy
- Protocol and Statistical Analysis Plan for CC-4047-MM-002 and IFM-2009-02
- Clinical study report for CC-4047-MM-002 and IFM-2009-02
- Raw and derived datasets for CC-4047-MM-002 and IFM-2009-02
- Case report forms for CC-4047-MM-002 and IFM-2009-02
- Response to Information Requests
- Proposed labeling for Pomalidomide

6.1.2 Demographics

CC-4047-MM-002 Trial:

Study CC-4047-MM-002 enrolled a total of 221 subjects in multiple sites in U.S and Canada. The majority of subjects were male 119 (54%), white 178 (81%), age 75 years or younger 194 (88%) with an ECOG status score of 1 or less 195 (88%) at baseline. The median age was similar between the two arms with overall population median age of 63 (34, 88) years. The two arms of the trial were balanced for subjects age, sex, race and ECOG performance status score at base line.

Refer to Table 9 for the summary of baseline demographics and disease characteristics in clinical trial CC-4047-MM-002.

Table 9: Baseline characteristics of subjects by treatment arm: CC-4047-MM-002 Phase 2

	Pom + Dex (N = 113)	POM only (N = 108)	Overall (N = 221)
Age (years)			
Mean (SD)	64.4 (9.24)	62.9 (10.35)	63.7 (9.80)
Median (Min, Max)	64.0 (34.0, 88.0)	61.0 (37.0, 88.0)	63.0 (34.0, 88.0)
	n (%)	n (%)	n (%)
Age Distribution, n (%)			
Age ≤ 75	99 (87.6)	95 (88.0)	194 (87.8)
Age > 75	14 (12.4)	13 (12.0)	27 (12.2)
Sex, n (%)			
Female	51 (45.1)	51 (47.2)	102 (46.2)
Male	62 (54.9)	57 (52.8)	119 (53.8)
Race, n (%)			
White	92 (81.4)	86 (79.6)	178 (80.5)
Black or African American	17 (15.0)	16 (14.8)	33 (14.9)
Asian	2 (1.8)	3 (2.8)	5 (2.3)
Other	2 (1.8)	3 (2.8)	5 (2.3)
ECOG Performance Status Score, n (%)			
0	32 (28.3)	24 (22.2)	56 (25.3)
1	68 (60.2)	71 (65.7)	139 (62.9)
2	13 (11.5)	11 (10.2)	24 (10.9)
3	0 (0.0)	2 (1.9)	2 (0.9)

Source: Applicant NDA 204026, 2.7.4 Summary of Clinical Safety, Table 5 (page 42).

The cytogenetic abnormalities present at baseline were similar between the two arms with 37% and 35% of subjects had a high risk cytogenetic abnormality in pomalidomide and dexamethasone, and pomalidomide, respectively.

Trial IFM-2009-02:

A total of 84 subjects enrolled in trial IFM-2009-02 which was conducted in France. Most of the subjects where male and had ECOG score of 1 or less. The median age of patients at study entry was 60 (range: 42 to 83) years which was similar between the two arms. Patients had a median interval between diagnosis and randomization of 5.1(0.9-18.7) years in pomalidomide plus dexamethasone (POM+DEX) 21/28 arm which shorter than 6.5 (0.8-23.1) years in POM+DEX 28/28 arm.

Refer to Table 10 for the summary of the baseline characteristics of subjects in IFM-2009-02 trial.

Table 10: Baseline characteristics of subjects by treatment arm: IFM-2009-02 Phase 2

	POM+DEX (21/28) (N=43)	**POM+DEX (28/28) (N=41)**	**Total (N=84)**
Median age, years (Min- Max)	60 (45- 81)	60 (42- 83)	60 (42- 83)
	n (%)	n (%)	n (%)
Sex, n (%), male	30 (70)	27 (66)	57 (68)
ECOG score, n (%)			
- 0	16 (37)	17 (42)	33 (39)
- 1	18 (42)	16 (39)	34 (41)
- 2	8 (19)	8 (20)	16 (19)
Median time from diagnosis, years	5.1 (0.9- 18.7)	6.5 (0.8- 23.1)	5.9 (0.8- 23.1)

Source: Applicant NDA 204026, 2.7.4 Summary of Clinical Safety, Table 7 (page 26).

Baseline Disease Characteristics:

The majority 148 (67%) of subjects had prior exposure to thalidomide with similar exposure between the two arms. The median time from first diagnosis to enrolment in the study was 5.6 years (95% CI, 1, 19.3). However, the length of time from diagnosis was longer in POM+DEX arm 6.0 (1.0, 19.3) than POM only arm 5.3 (1.1, 18.1).

The majority of subjects had Stage III 147 (66.5%) with slightly higher incidence among subjects in arm A (67.3%) than arm B (65.7%).

One hundred sixty six subjects (75%) of subjects received prior stem cell transplant which was similar between the two arms. Approximately 40% (88/221) received prior radiation therapy, and 9.5% (21/221) had prior cancer surgery.

Table 11 shows the baseline disease characteristics by treatment arm.

Table 11: Baseline disease characteristics by treatment arm (Study MM-02, Cut off April 01, 2011)

	Pom + Dex (N = 113)	**Pomalidomide (N = 108)**	**Overall (N = 221)**
Number of subjects (%)	**n (%)**	**n (%)**	**n (%)**
Prior Thalidomide Exposure			
No	37 (32.7)	36 (33.3)	73 (33.0)
Yes	76 (67.3)	72 (66.7)	148 (67.0)
Time From First Pathologic Diagnosis (years)			
Mean (SD)	6.2 (3.58)	6.2 (3.39)	6.2 (3.48)
Median (Min, Max)	5.3 (1.1, 18.1)	6.0 (1.0, 19.3)	5.6 (1.0, 19.3)
Baseline Multiple Myeloma Stage			
I	8 (7.1)	8 (7.4)	16 (7.2)
II	29 (25.7)	29 (26.9)	58 (26.2)
III	76 (67.3)	71 (65.7)	147 (66.5)
Prior Stem Cell Transplant			
No	29 (25.7)	26 (24.1)	55 (24.9)
Yes	84 (74.3)	82 (75.9)	166 (75.1)
Prior Radiation Therapies			
No	71 (62.8)	62 (57.4)	133 (60.2)
Yes	42 (37.2)	46 (42.6)	88 (39.8)
Prior Cancer Surgeries			
No	104 (92.0)	96 (88.9)	200 (90.5)
Yes	9 (8.0)	12 (11.1)	21 (9.5)
Prior Anti-Myeloma Therapies given			
Yes	113 (100)	108 (100)	221 (100)

Source: Applicant NDA 204026 submission, CC-4047-MM-002 CSR, Table 14, P. 71.

Prior Anti-myeloma Therapy:

All subjects in the CC-4047-MM-002 trial had received prior anti-myeloma therapy. The median number of prior anti-myeloma regimens was 5 regimens. All patients had received lenalidomide, bortezomib and corticosteroid treatment prior to trial entry.

Two thirds of subjects received thalidomide prior to trial entry. Approximately 90% of subjects enrolled in the CC-4047-MM-002 trial had received melphalan and three quarters of patients in both trials had received autologous stem cell transplant.

Table 12 shows the prior anti-myeloma therapies by therapeutic class.

Table 12: Prior Anti-myeloma Therapies CC-4047-MM-002

	POM+DEX (N = 113)	POM only (N = 108)
	n (%)	n (%)
Prior Anti-Myeloma Therapies	113 (100)	108 (100)
Median No. of MM therapy (Min, Max)	5.0 (2.0, 13.0)	5.0 (2.0, 12.0)
Corticosteroids	113 (100)	108 (100)
Dexamethasone	112 (99.1)	107 (99.1)
Prednisone	39 (34.5)	50 (46.3)
IMiD	113 (100)	108 (100)
Lenalidomide	113 (100)	108 (100)
Thalidomide	77 (68.1)	72 (66.7)
Proteasome inhibitor	113 (100)	108 (100)
Bortezomib	113 (100)	108 (100)
Alkylators	105 (92.9)	103 (95.4)
Melphalan	102 (90.3)	97 (89.8)
Cyclophosphamide	56 (49.6)	66 (61.1)
Anthracycline	55 (48.7)	54 (50.0)
Doxorubicin HCl	29 (25.7)	25 (23.1)
Pegylated Liposomal Doxorubicin HCl	22 (19.5)	25 (23.1)
Doxorubicin	15 (13.3)	16 (14.8)
NU	2 (1.8)	5 (4.6)
Bendamustine	2 (1.8)	2 (1.9)
Carmustine	0 (0)	3 (2.8)
ASCT	84 (74.3)	82 (75.9)

Source: Applicant NDA 204026, CC-4047-MM-002 CSR, Table 16 (page 74).

Trial IFM-2009-02:

Consistent with the CC-4047-MM-002 trial, all subjects in IFM-2009-02 received prior anti-myeloma therapy. The median number of prior anti-myeloma regimens was 5 regimens. All patients received lenalidomide, bortezomib and corticosteroid treatment prior to trial entry.

Table 13: Prior Anti-myeloma Therapies IFM-2009-02

Prior Anti-Myeloma Agents	**POM+DEX (21/28) (N=43)**	**POM+DEX (28/28) (N=41)**
Number of subjects	n (%)	n (%)
Prior Anti-Myeloma Therapies, n (%)	43 (100)	41 (100)
Median No. of MM therapy (Min, Max)	5 (1- 13)	5 (2- 10)
Bortezomib, n (%)	43 (100)	41 (100)
Lenalidomide, n (%)	43 (100)	41 (100)
Thalidomide, n (%)	29 (67)	32 (78)
Alkylating agents, n (%)	33 (77)	28 (68)
Nitrosourea, n (%)	6 (14)	7 (17)
Anthracyclines, n (%)	31 (72)	33 (81)
Glucocorticoids (Dex), n (%)	43 (100)	41 (100)
Autologous stem cell transplant	33 (77)	35 (85)

Source: Applicant NDA 204026, IFM 2009-02 CSR, Table 26 (page 113).

Medical History: Sixty seven (31%) of a total of subjects (35 subjects in POM+DEX arm and 32 subjects in POM only arm) had a history of malignancy prior enrollment in this trial. The most common prior malignancies were plasmacytoma which was reported in 10 (5 %) of subjects (4 subjects in arm A and 6 subjects in arm B), followed by basal cell carcinoma in 7 (3%) subjects. There were 4 (2%) subjects who had a medical history of breast cancer and 3 subjects in each arm who had a medical history of malignant melanoma and prostate cancer. Other prior malignancies occurred in ≤ 2 subjects each including cervical carcinoma, colon cancer, squamous cell carcinoma, thyroid cancer, bladder cancer and endometrial cancer.

History of thrombosis: A total of 67 (31%) of subjects had a history of thrombosis (35 subjects in POM+DEX arm and 32 subjects in POM only arm). Most of the subjects had a history of venous thrombosis (30 in POM+DEX arm and 26 in POM only arm). Table 14 shows a summary of thrombosis history by treatment arm.

Table 14: Summary of Thrombosis History by Treatment Arm (safety population)

	Pom + Dex (N=112)	**Pom only (N=107)**
No. of subjects with at least one thrombosis, n (%)	35 (31%)	32 (30%)
Venous thrombosis	30 (27%)	26 (24%)
Deep venous thrombosis	27 (24%)	23 (22%)
Pulmonary embolism	5 (5%)	8 (8%)
Other venous thrombosis	3 (3%)	4 (4%)
Arterial thrombosis	6 (5%)	8 (8%)
Coronary artery thrombosis	4 (4%)	3 (3%)
Cerebral artery thrombosis	2 (2%)	4 (4%)
Peripheral artery thrombosis	0 (0%)	1 (1%)

Source: Applicant NDA 204026, CC-4047-MM-002 CSR, Table 14.1.12 page # 305.

Baseline Laboratory Data:

Clinical laboratory values were graded according to NCI CTCAE version 3.0 for applicable tests. The hematological laboratory data showed that most of subjects had Grade 1 or 2 low hemoglobin level with a similar incidence (81%) in both arms. Other hematological laboratory data such as lymphocyte count, neutrophil count, and platelet count were normal in more than two thirds of patients in two arms at baseline. However, none of subjects had grade 4 hematologic laboratory value at baseline.

Liver and renal function tests (AST, ALT and alkaline phosphatase) were within normal limits or grade one abnormalities in the majority of patients in both arms at baseline. However, in 10% of subjects in POM+DEX arm and 7% of subjects in POM only arm, had creatinine values of Grade 2 abnormalities at baseline.

Glucose values were abnormal (mostly Grade 1) in approximately half of patients at baseline.

Table 15 summarizes the available laboratory tests results at baseline.

Table 15: Laboratory tests values at baseline (CC-4047-MM-002 trial)

Baseline Lab test	**Pomalidomide & Dexamethasone (N=111)**					**Pomalidomide (N=101)**				
	Normal	Grade 1	Grade 2	Grade 3	Grade 4	Normal	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	13 (12)	51 (46)	39 (35)	8 (7)	0 (0)	12 (12)	32 (32)	50 (49)	7 (7)	0 (0)
Lymphocytes	86 (78)	2 (2)	18 (16)	5 (4)	0 (0)	75 (74)	3 (3)	18 (18)	5 (5)	0 (0)
Neutrophils	75 (68)	19 (17)	15 (13)	2 (2)	0 (0)	75 (74)	14 (14)	11 (11)	1 (1)	0 (0)
Platelets	71 (65)	27 (25)	6 (5)	5 (5)	0 (0)	67 (67)	22 (22)	6 (6)	5 (5)	0 (0)
	Pomalidomide & Dexamethasone (N= 102)					**Pomalidomide (N=95)**				
	Normal	Grade 1	Grade 2	Grade 3	G- 4	Normal	Grade 1	Grade 2	Grade 3	Grade 4
ALT	93 (91)	9 (9)	0 (0)	0 (0)	0 (0)	89 (94)	4 (4)	2 (2)	0 (0)	0 (0)
Alkaline Phosphatase	94 (94)	6 (6)	0 (0)	0 (0)	0 (0)	89 (94)	5 (5)	1 (1)	0 (0)	0 (0)
AST	87 (85)	14 (14)	1 (1)	0 (0)	0 (0)	88 (93)	5 (5)	2 (2)	0 (0)	0 (0)
Bilirubin	102 (100)	0 (0)	0 (0)	0 (0)	0 (0)	94 (99)	0 (0)	1 (1)	0 (0)	0 (0)
Blood Urea Nitrogen	102 (100)	0 (0)	0 (0)	0 (0)	0 (0)	95 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Creatinine	71 (70)	21 (20)	10 (10)	0 (0)	0 (0)	67 (71)	21 (22)	7 (7)	0 (0)	0 (0)
Calcium	87 (85)	10 (10)	3 (3)	1 (1)	1 (1)	87 (92)	6 (6)	0 (0)	2 (2)	0 (0)
Glucose	52 (51)	45 (44)	5 (5)	0 (0)	0 (0)	42 (44)	48 (51)	4 (4)	1 (1)	0 (0)

Source: Applicant NDA 204026, CC-4047-MM-002 CSR, Tables 14.3.4.1.1.1 and 14.3.4.1.1.2 (P. 2528-33).

6.1.3 Subject Disposition

CC-4047-MM-002 Trial:

At the time of cutoff date of April 01, 2011, a total of 176 (80%) subjects have been discontinued from the study. The percentage of subjects discontinued trial CC-4047-MM-002 was similar between the two arms (80%). The primary reasons for discontinuation were disease progression reported in 50- 58% of subjects. However, approximately 7 to 12% of subjects discontinued due to adverse events and 7-8% as a result of death.

Table 16 summarizes the reason for discontinuation by treatment arm in CC-4047-MM-002 trial.

Table 16: Discontinuation by treatment arm in CC-4047-MM-002 trial

Reason for discontinuation	**POM+DEX (N=112)**	**POM Only (N=107)**
Subjects discontinued study, n (%)	90 (80)	86 (80)
Disease Progression, n (%)	65 (58)	53 (50)
Adverse Event, n (%)	8 (7)	13 (12)
Death, n (%)	8 (7)	9 (8)
Withdrew Consent, n (%)	5 (4)	7 (7)
Lost To Follow Up, n (%)	0 (0)	1 (1)
Other, n (%)	4 (4)	3 (3)

IFM-2009-02 Trial:

At the time of the cut-off date of March 01, 2011, a total of 61(73%) randomized patients had discontinued from the study. Disease progression was the most common reason for disease progression.

Table 17 summarizes the reason for discontinuation by treatment arm in IFM-2009-02 trial.

Table 17: Discontinuation by treatment arm in IFM—2009-02 trial as of cut of date (4/1/2011)

Reason for discontinuation	**POM+DEX (21/28) (n=43)**	**POM+DEX (28/28) (n=41)**
Subjects discontinued study, n (%)	29 (67)	32 (78)
Disease progression, n (%)	24 (56)	27 (66)
Death, n (%)	3 (7)	3 (7)
Discontinue due to adverse events, n (%)	0 (0)	2 (5)
Lost to follow-up, n (%)	1 (2)	0 (0)
Consent withdrawn, n (%)	1 (2)	0 (0)

6.1.4 Analysis of Primary Endpoint(s)

CC-4047-MM-002 trial:

The primary efficacy endpoint of Study CC-4047-MM-002 was progression free survival (PFS) defined as the time from date of randomization to the date of progression or death due to any cause, whichever occurred first. If no baseline or post-baseline disease assessment available, the PFS time was censored at the date of randomization. Otherwise, in the absence of an event, the PFS time was censored at the last date with adequate disease assessment.

Secondary endpoints included:

- Overall response rate (ORR) is defined as partial response (PR) or better which is maintained for at least 6 weeks,
- Duration of response (DOR),
- Overall survival (OS)
- Time to response (TTR)

Primary efficacy analysis was based on response assessment by the Independent Response Adjudication Committee (IRAC) based on EBMT criteria. The IRAC was blinded as to which arm each patient was assigned.

Based on one-sided $\alpha = 0.025$; an 85% power to detect a 40% reduction in progression or death risk (median PFS of 6 and 10 months in the monotherapy vs. combination therapy arms respectively) and 12-month accrual and additional 12-month follow-up. The applicant planned to enroll 192 patients. The final analysis was determined to be conducted when 139 events of primary endpoints occur. In addition, one interim analysis of PFS for futility was planned at 50% information (~70 events). The Lan-

DeMets α spending function based on O'Brien-Fleming boundary for the interim analysis was an alpha α = 0.0015.

The actual accrual was a total of 221 patients randomized to pomalidomide + dexamethasone (n=113) and pomalidomide alone (n=108). The final analysis conducted at 167 events happened.

The scheduled interim analysis at a cut off date October 29, 2010, 141 events occurred. The analysis demonstrated a highly significant difference in favor of pomalidomide + dexamethasone arm; therefore, the DMC recommended unblinding the study.

The analysis results submitted in this NDA application were based on cutoff date of April 01, 2011. For overall analysis, an updated analysis was performed based on the cutoff date of September 16, 2011.

The results of the efficacy analysis of PFS are presented below in Table 18.

Table 18: PFS Results of CC-2027-MM-002

	Pom + Dex (N=113)	**Pom (N=108)**
Number of subjects censored, n (%)	27 (23.9)	27 (25.0)
Patients with events, n (%)	86 (76.1)	81 (75.0)
Median PFS (months) (95% CI)	3.8 (3.2, 4.9)	2.5 (1.9, 3.7)

Reviewer Comment: Because this study did not isolate the effect of pomalidomide, no P-value from testing of PFS difference between the two treatment arms was presented. The time to event endpoint of PFS is inevaluable since there is no active comparator arm that isolates the effect of pomalidomide. In addition, there were 7 patients who were switched from pomalidomide to pomalidomide with dexamethasone prior to documentation of progression on pomalidomide.

Overall Response Rate:

CC-4047-MM-002 Trial:
Given the inadequate control arm in this trial, the ORR was used by the IRC to evaluate the efficacy for each treatment arm separately and will be used in this review. As of the cut off date of April 1, 2011, there were 33 patients from POM+DEX and 8 patients from POM only arm experienced response to treatment (CR or PR). The overall response rates were 29.2% in the Pom + Dex arm and 7.4% in the pomalidomide arm. The median duration of response was 7.4 months in the POM+DEX arm and unable to evaluate in the POM only arm.

Table 19 summarizes the results of the ORR analysis as reported by the applicant and confirmed by FDA.

Table 19: Overall Response Rate Results of CC-4047-MM-002 per IRC (Cutoff date 4/1/2011)

	Pom + Dex (N=113)	**Pom (N=108)**
Overall response rate (CR + PR), n (%)	33 (29.2)	8 (7.4)
Complete Response (CR), n (%)	1 (0.9)	0 (0)
Partial Response (PR), n (%)	32 (28.3)	8 (7.4)
Duration of response (DOR)	33	8
Number of subjects progressed or died, n (%)	22 (66.7)	1 (12.5)
Median Duration of Response (months)	7.4 (5.1, 9.2)	NE* (NE, NE)

NE: not evaluable

Reviewer comments: As we see from Table 19 is the response rate is 29% among patients who received POM+DEX and response had a median duration of 7.4 months. The results were slightly differ from the Applicant results (ORR 30.1% in POM+DEX and 9.3% in POM arm), because there were two patients CC-4047-MM-002-105-3001, CC-4047-MM-002-111-3007 from the Pom arm and one patient CC-4047-MM-002-113-3006 from the POM (21/28) + Dex arm who had a partial response with a duration less than 6 weeks, and should not be considered as having achieved PR. In addition, our d*uration of response differed from the applicant, since it was based on 41 instead of 44 responders.*

IFM-2009-02 Trial:
As of the cut off date of March 1, 2011, there were 29 patients had a response to study treatment which include 15 patients in POM+DEX 21/28 arm and 14 patients in the POM+DEX 28/28 arm. The overall response rate (PR or better) was similar in the both arms (34.9% in 21/28 POM+DEX arm versus 34.1% in the 28/28 POM+DEX arm). The median duration of response was longer in 21/28 POM+DEX arm (10.5 months) than in 21/28 POM+DEX arm (7.3 months).

Table 20 summarized the results of the ORR analysis.

Table 20: Efficacy analysis results in MM-2009 Trial (Cutoff date 3/1/2011)

	POM+DEX (21/28) (n=43)	**POM+DEX (28/28) (n=41)**
Overall response rate (CR + PR), n (%)	15 (34.9)	14 (34.1)
Complete Response (CR), n (%)	1 (2.3)	1 (2.4)
Partial Response (PR), n (%)	14 (32.5)	13 (31.7)
Duration of response (DOR)	15	14
Number of subjects progressed or died, n (%)	6 (40.0)	9 (64.3)
Median Duration of Response (months)	10.5 (3.5, 12.6)	7.3 (3.7, NE)

NE: not evaluable

Reviewer's comment: The overall response rate and median duration of response observed in the study IFM 2009-02 were slightly better than those observed in the POM+DEX arm in the CC-4047-MM-002 trial.

6.1.5 Analysis of Secondary Endpoints(s)

Overall survival: A total of 121 patients (59 in the POM+DEX and 62 in the POM only arm) died as of the cutoff date of 4/1/2011. The median duration of overall survival was longer in the POM+DEX arm (14.4 months) than in the POM only arm (13.6 months).

Time to response: There were 33 patients in the POM+DEX arm and 8 patients in the POM arm who showed a response to treatment as defined by the protocol (at least PR lasting a minimum of 6 weeks).

Table 21 summarized the results of the OS and TTR analysis.

Table 21: OS and TTR Analysis Results of CC-4047-MM-002 (Cutoff date 4/1/2011)

	Pom + Dex (N=113)	**Pom (N=108)**
Overall Survival (OS)		
Number (%) of subjects censored	69 (61.1)	61 (56.5)
Number of Patients died, n (%)	44 (38.9)	47 (43.5)
Median OS (months) (95% CI)	14.4 (12.3, NE)	13.6 (9.6, NE)
Time to response (TTR)		
Number of responders, n (%)	33	8
Mean (SD)	2.5 (2.6)	4.0 (3.8)
Median (Min, Max)	1.9 (0.9, 10.4)	2.0 (1.0, 11.4)

Reviewer comments: The FDA analysis of OS showed the same results as the Applicant. However, the FDA, TTR analysis results were slightly different from those the applicant because of exclusion of 3 patients (2 from POM+DEX and 1 from POM) who did not meet the criteria of responders (<6 weeks duration).

6.1.6 Other Endpoints

N/A

6.1.7 Subpopulations

6.1.7.1 Refractoriness to lenalidomide or bortezomib

The majority of subjects in CC-4047-MM-002 were refractory to lenalidomide (77.8%) or bortezomib (71%) and 60.2% were refractory to both lenalidomide and bortezomib Table 22.

Table 22: Summary of refractory status, ITT population (CC-4047-MM-002)

	Pom + Dex N=113	Pom N=108	Total N=221
Refractory to lenalidomide, n (%)			
Yes	87 (77.0)	85 (78.7)	172 (77.8)
No	26 (23.0)	20 (18.5)	46 (20.8)
Missing	0 (0.0)	3 (2.8)	3 (1.4)
Refractory to bortezomib, n (%)			
Yes	82 (72.6)	75 (69.4)	157 (71.0)
No	31 (27.4)	30 (27.8)	61 (27.6)
Missing	0 (0.0)	3 (2.8)	3 (1.4)
Refractory to both lenalidomide and bortezomib, n (%)			
Yes	69 (61.1)	64 (59.3)	133 (60.2)
No	44 (38.9)	40 (37.0)	84 (38.0)
Missing	0 (0.0)	4 (3.7)	4 (1.8)

Source: NDA 204026 application, CSR CC-4047-MM-002 trial, Pages 76 Table 18.

In study IFM 2009-02, the majority of subjects were refractory to lenalidomide (89.3%) or bortezomib (85.7%) and 81.0% were refractory to both lenalidomide and bortezomib Table 23.

Table 23: Summary of refractory status, ITT population (IFM 2009-02)

	Pom+ Dex (21/28) N=43	**Pom+ Dex (28/28) N=41**	**Total N=84**
Refractory to lenalidomide, n (%)			
Yes	36 (83.7)	39 (95.1)	75 (89.3)
No	7 (16.3)	2 (4.9)	9 (10.7)
Refractory to bortezomib, n (%)			
Yes	35 (81.4)	37 (90.2)	72 (85.7)
No	8 (18.6)	4 (9.8)	12 (14.3)
Refractory to both lenalidomide and bortezomib, n (%)			
Yes	33 (76.7)	35 (85.4)	68 (81.0)
No	10 (23.2)	6 (14.6)	16 (19.0)

Source: FDA Statistical reviewer's analysis

Table 24 summarizes the subgroup analyses of ORR by refractory status to prior treatments for the study CCC-4047-MM-002 and IFM 2009-02. The ORR results by subgroups of refractory status to prior treatment are consistent with the ORR results for all patients.

Table 24: ORR Per IRC – Subgroup Analyses By Refractory Status, ITT Population

Subgroup	Study CC-4047-MM-002		Study IFM 2009-02	
	Pom +Dex (28/28) N=113 r/n (%)	Pom N=108 r/n (%)	Pom+Dex (21/28) N=43 r/n (%)	Pom +Dex (28/28) N=41 r/n (%)
Refractory to lenalidomide				
Yes	22/87 (25.3)	6/85 (7.1)	13/36 (36.1)	14/39 (35.9)
No	11/26 (42.3)	2/20 (10.0)	2/7 (28.6)	0/2 (0)
Missing	0/0 (0)	0/3 (0)		
Refractory to bortezomib				
Yes	23/82 (28.0)	6/75 (8.0)	12/35 (34.3)	11/37 (29.7)
No	10/31 (32.3)	2/30 (6.7)	3/8 (37.5)	3/4 (75.0)
Missing	0/0 (0)	0/3 (0)		
Refractory to both lenalidomide and bortezomib				
Yes	19/69 (27.5)	4/64 (6.3)	12/33 (36.4)	11/35 (31.4)
No	14/44 (31.8)	4/40 (10.0)	3/10 (30.0)	3/6 (50.0)
Missing	0/0 (0)	0/4 (0)		

r: number of response, n: number of subjects in a subgroup
Source: FDA Statistical reviewer's analysis

Reviewer comments: Approximately two thirds and three quarters of subjects in the two phase 2 trials were refractory to the lenalidomide and bortezomib treatment. The overall response rates were similar to that seen in the trial and range from 27.5% in the CC-4047-MM-002 trial to 36.4% in IFM 2009-02 trial.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant conducted two dose finding trials:

CC-4047-MM-001 was phase 1b trial conducted in relapsed/refractory MM consisted of two cohorts of subjects. The primary endpoint was the determination of the maximum tolerated dose (MTD) of pomalidomide.

The first cohort consisted of 24 subjects who were treated with pomalidomide at dose levels of 1, 2, 5, and 10 mg once daily (QD). The MTD for this cohort was determined to be 2 mg QD. Thirteen subjects (54%) had a response of PR or greater, the median progression free survival was 5.6 months and the median OS was 12.9 months. The second cohort consisted of 21 subjects who were treated with pomalidomide at dose levels of 1, 2, 5, and 10 mg on alternate days. The MTD for this cohort was determined to be 5 mg on alternate days. Ten subjects (50%) had a PR or greater response rate. Progression free survival was 10.5 months and median OS was 35.9 months. The dose limiting toxicity of CC-4047 in this phase 1 study is myelosuppression: Grade 4 neutropenia observed at the 10 mg dose level in both Cohort I and Cohort II and the 5 mg level in Cohort I.

The CC-4047-MM-002 trial was phase I/II multi-national, multicenter, randomized open label dose escalation study in patients with relapsed and refractory multiple myeloma who were refractory to their last myeloma therapy and had received lenalidomide and bortezomib. In the first phase of trial was conducted in 38 patients with relapsed refractory MM in 3+3 design to define the MTD for single agent of pomalidomide. Oral pomalidomide was administered in escalating dose of 2 mg, 3 mg, 4mg, 5, 6, 8, 10, and 12 mg once per day on Days 1-21 of a 24-day cycle. The maximum tolerated dose (MTD) of pomalidomide capsules was determined to be 4 mg/day, given on 21/28 days until disease progression. The DLT was determined to be 5 mg dose level and the most common DLT was Grade 4 neutropenia.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Please see duration of response analysis.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

The safety of Pomalidomide was evaluated in 303 patients with relapsed or refractory multiple myeloma who received at least two prior therapies in the two Phase 2 trials. A summary of the important safety results from this clinical trial are listed below.

- Pomalidomide dose was 4 mg orally administered daily for 21 days in 28-day cycle. The median duration of treatment per patient with pomalidomide was 5 cycles (range 1 to 17).
- There were 57 (19%) deaths within 30 days of the last dose in both trials.
- Two third (67%) of patients experienced serious adverse events (SAE). Infection was the most common SAE.
- Sixteen percent discontinued treatment due to treatment emergent adverse events.
- Eighty-nine percent of patients experienced a Grade 3 or Grade 4 treatment-emergent adverse event (TEAE). Neutropenia and pneumonia were most common TEAEs.
- Safety issues in ≥ 20% of patients include myelosuppression, infections, neuropathy, dizziness, GI toxicity, and fatigue.
- The safety profile for pomalidomide is similar to thalidomide and lenalidomide.
- No new safety signals were detected in the analysis of 120-day safety update data.
- Review of the adverse events of special interest revealed:
    - The combination of POM+DEX is myelosuppressive and manifested as neutropenia, anemia and thrombocytopenia
    - Infection occurred in two third of the patients. Pneumonia was the most common infections.
    - The incidence of hemorrhagic events occurred in quarter of the patients. The majority of the hemorrhagic events were grade 2 or less and epistaxis was the most common hemorrhagic event.
    - Thromboembolic events occurred in 3% of the patients. Patients enrolled in the clinical trials were required to use prophylactic anticoagulation.
    - Approximately 17% of patients experienced neurologic adverse events and peripheral neuropathy was the most common neurologic AE. All neurologic events were grade 2 or less.
    - Renal events of Grade 3 or 4 occurred in 9-10% of patients and acute renal failure was the most common renal event.
    - Other common TEAEs are dizziness, asthenia and fatigue, pyrexia and confusional state.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The two phase 2 clinical trials (Study CC-4047-MM-002 and Study IFM-2009-02) were used to analyze the safety data. The safety population (defined as all subjects who

received at least one dose of pomalidomide in phase 2 trials) consisted of a total of 303 patients (219 subjects in CC-4047-MM-002 trial and 84 subjects in IFM-2009-02).

Table 25 summarized the safety population analyzed in this application.

Table 25: Safety population analyzed

	CC-4047-MM-002		**IFM 2009-02**	
Trial arms	POM+DEX	POM only	POM+DEX (21/28)	POM+DEX (28/28)
No. of patients	N=112	N= 107	N= 43	N= 41
Total No. of patients	N= 219		N= 84	

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0. The intensity of AEs was graded according to the NCI-CTCAE version 3.0. Treatment-emergent AEs (TEAEs) are defined as any AE occurring or worsening on or after the first dose of the study medication and within 30 days after the last dose

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety population analyzed across the two phase 2 trials consisted of a total of 303 patients. Since the IFM 2009-02 trial is small the review will discuss the safety results from the two phase 2 trials (CC-4047-MM-002 and IFM 2009-02) separately. However, the safety results from trial IFM 2009-02 were consistent with safety results from CC-4047-MM-002.

7.2 Adequacy of Safety Assessments

The data submitted to this NDA is adequate to perform the safety review. Inspections were conducted at three clinical sites and DSI concluded that the study data appear reliable, which include adverse event reporting (Refer to Section 3.2 for the summary of DSI findings).

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.1.1 Dose Exposure

As of the data cutoff date (April 01, 2011), subjects were exposed to pomalidomide for a median of 100 (2, 357) days. The median daily dose exposure was similar between the two arms: pomalidomide 4.0 (1.6, 4.2) mg/day.

Table 26: Summary of dose exposure for pomalidomide by treatment arm (MM-02 trial)

	POM & DEX (N = 112)	**POM only (N = 107)**	**Overall (N = 219)**
Pomalidomide Dose Exposure (Days)			
Mean (SD)	123.0 (89.3)	119.5 (94.8)	121.2 (91.8)
Median (Min, Max)	99 (3, 336)	105 (2, 357)	100 (2, 357)
Average Daily Dose of Pomalidomide (mg/day)			
Mean (SD)	3.8 (0.43)	3.8 (0.35)	3.8 (0.39)
Median	4.0 (1.6, 4.2)	4.0 (2.8, 4.0)	4.0 (1.6, 4.2)

Source: Applicant NDA 204026, CC-4047-MM-002 CSR, Table 46 (page 143).

The median treatment duration overall was 21.6 (0.3, 70.4) weeks with a median exposure of 21.8 (0.6, 70.4) weeks in the POM+DEX arm versus 20.6 (0.3, 69.0) weeks in POM arm. However, the median duration of treatment in the POM only arm prior to add dexamethasone was 9.7 (0.3, 69.0).

Please note that 61 subjects had dexamethasone added to their regimen of single-agent pomalidomide during the study. Of these 61 subjects, a total of 17 subjects had dexamethasone added to their pomalidomide only regimen, for patients were assessed by the adjudication review committee as not having progression of disease. The median treatment duration of pomalidomide alone prior to the addition of dexamethasone was 57 days.

Table 27 summarizes the dexamethasone exposure during the MM-02 trial.

Table 27: Summary of dose information for dexamethasone by treatment arm (MM-02 trial)

	POM & DEX (N = 112)	POM only (N = 61)
Dexamethasone Dose Exposure (days)		
Mean (SD)	22.5 (17.05)	14.8 (11.32)
Median (Min, Max)	18.0 (1.0, 64.0)	13.0 (1.0, 51.0)
Average Daily Dose of Pomalidomide (mg/day)		
Mean (SD)	34.1 (8.37)	37.1 (6.59)
Median (Min, Max)	40.0 (13.9, 40.0)	40.0 (16.6, 40.0)

Source: Applicant NDA 204026, CC-4047-MM-002 CSR, Table 14.3.1.2 (page 1319).

The median number of cycles was 5.0 (1.0, 17.0). The median number of cycle was similar between the two arms. However, the median number of cycles received by patients in POM only arm prior to receiving dexamethasone was 2.0 (1.0, 17.0) cycles.

Table 28: Summary of treatment duration by treatment arm (CC-4047-MM-002 Trial)

	Pom + Dex (N = 112)	Pom Prior to Dex (N = 107)	Overall Pom (N = 107)	Overall (N = 219)
Treatment Duration (Weeks),				
Mean (SD)	25.3 (17.77)	15.1 (14.88)	24.3 (18.75)	24.8 (18.22)
Median (Min, Max)	21.8 (0.6, 70.4)	9.7 (0.3, 69.0)	20.6 (0.3, 69.0)	21.6 (0.3, 70.4)
Treatment Duration (Weeks) n (%)				
Less than 1 week	1 (0.9)	3 (2.8)	3 (2.8)	4 (1.8)
1 to < 4 weeks	8 (7.1)	11 (10.3)	9 (8.4)	17 (7.8)
4 to < 8 weeks	9 (8.0)	25 (23.4)	13 (12.1)	22 (10.0)
8 to < 12 weeks	15 (13.4)	22 (20.6)	13 (12.1)	28 (12.8)
12 to < 16 weeks	9 (8.0)	12 (11.2)	9 (8.4)	18 (8.2)
16 to < 20 weeks	8 (7.1)	11 (10.3)	3 (2.8)	11 (5.0)
20 to < 24 weeks	10 (8.9)	2 (1.9)	7 (6.5)	17 (7.8)
24 to < 28 weeks	9(8.0)	2 (1.9)	8 (7.5)	17 (7.8)
28 to < 32 weeks	4 (3.6)	4 (3.7)	4 (3.7)	8 (3.7)
32 to < 36 weeks	7 (6.3)	1 (0.9)	8 (7.5)	15 (6.8)
36 to < 40 weeks	3 (2.7)	3 (2.8)	5 (4.7)	8 (3.7)
40 to < 44 weeks	10 (8.9)	3 (2.8)	4 (3.7)	14 (6.4)
44 to < 48 weeks	3 (2.7)	3 (2.8)	6 (5.6)	9 (4.1)
48 to < 52 weeks	4 (3.6)	1 (0.9)	4 (3.7)	8 (3.7)
52 to < 56 weeks	5 (4.5)	1 (0.9)	2 (1.9)	7 (3.2)
56 to < 60 weeks	1 (0.9)	0 (0.0)	3 (2.8)	4 (1.8)
60 to < 64 weeks	3 (2.7)	2 (1.9)	3 (2.8)	6 (2.7)
≥ 64 weeks	3 (2.7)	1 (0.9)	3 (2.8)	6 (2.7)
Number of Cycles on Study Medications				
Mean (SD)	6.3 (4.21)	3.7 (3.54)	6.1 (4.46)	6.2 (4.33)
Median (Min, Max)	5.0 (1.0, 16.0)	2.0 (1.0, 17.0)	5.0 (1.0, 17.0)	5.0 (1.0, 17.0)

Source: Applicant NDA 204026, CC-4047-MM-002 CSR, Table 45 (page 142).

7.2.1.2 Dose modification:

There were 71 (64%) subjects in POM+DEX arm and 63 (59%) in POM only arm who had at least one dose interruption during the trial. The number of subjects who had their dose reduced at least once during treatment was two times higher in the POM+DEX arm as compared to subjects in the POM only arm 39% vs 17%, respectively. However, the percentage of subjects had a dose modification during treatment was less than 10% of subjects during the trial.

Table 29: Dose modification in CC-4047-MM-002 trial (safety population)

	POM+DEX (N = 112) n (%)	POM only (N = 107) n (%)
Subjects with ≥1 TEAEs leading to dose interruption	71 (64)	63 (59)
Subjects with ≥1 TEAEs leading to dose reduction	44 (39)	36 (17)
Subjects with ≥1 TEAEs leading to discontinuation	8 (7)	13 (12)

Source: Applicant NDA 204026, CC-4047-MM-002 CSR, Table 47 (page 144).

7.2.2 Explorations for Dose Response

The trial CC-4047-MM-002 was designed as a phase 1 and 2 trial. The phase 1 portion of the study was conducted as a multicenter, randomized, open label, dose-escalation study in a 3+3 design to determine MTD and evaluate safety and efficacy of CC-4047 alone and in combination with low-dose dexamethasone (LD-Dex) in patients with relapsed refractory MM.

Thirty eight subjects with relapsed/refractory multiple myeloma were enrolled in the phase 1 segment to define the MTD for single-agent pomalidomide among the 2, 3, 4, and 5 mg/day dose levels. The MTD was defined as the highest dose level at which no more than one of six subjects experienced a dose-limiting toxicity (DLT) within the first 28-day cycle. The MTD was determined as 4 mg and neutropenia was the most commonly reported DLT.

7.2.3 Special Animal and/or In Vitro Testing

In vitro studies show that pomalidomide displays anti-proliferative activity against myeloma cell lines that exhibit increased resistance to lenalidomide and thalidomide. Pomalidomide has been shown to exhibit synergistic activity when combined with dexamethasone as measured by inhibition of myeloma cell proliferation and induction of apoptosis of a lenalidomide-resistant myeloma cell line.

Refer to the Pharmacology-Toxicology review for details.

7.2.4 Routine Clinical Testing

Refer to Sections 7.4.2, 7.4.3, and 7.4.4.

Routine clinical assessments in Study CC-4047-MM-002 included medical history, physical exam, laboratory exams, and procedures (bone marrow evaluation, electrocardiogram). Refer to Section 5.3.1.4 for detailed schedule of safety assessments.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to Clinical Pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The pharmacology-toxicology review noted of immunomodulatory and antineoplastic effects for pomalidomide similar to IMiDs drugs (thalidomide and lenalidomide). The safety profile for pomalidomide is notable for the similarity to other IMiDs. These similar features include myelosuppression (neutropenia, thrombocytopenia and anemia), infections, neuropathy, dizziness, GI toxicity, confusional state and fatigue. The following listing includes FDA-approved IMiDs drugs.

REVLIMID

BOXED WARNING: FETAL RISK, HEMATOLOGIC TOXICITY, and DEEP VEIN THOMBOSIS AND PULMONARY EMBOLISM

MM: Most common adverse reactions (≥20%) include fatigue, neutropenia, constipation, diarrhea, muscle cramp, anemia, pyrexia, peripheral edema, nausea, back pain, upper respiratory tract infection, dyspnea, dizziness, thrombocytopenia, tremor and rash.

THALOMID

BOXED WARNING: FETAL RISK AND VENOUS THROMBOEMBOLIC EVENTS

MM: The most common adverse reactions (≥ 20%) are fatigue, hypocalcemia, edema, constipation, neuropathy-sensory, dyspnea, muscle weakness, leukopenia, neutropenia, rash/desquamation, confusion, anorexia, nausea, anxiety/agitation, asthenia, tremor, fever, weight loss, thrombosis/embolism, neuropathy-motor, weight gain, dizziness, and dry skin.

7.3 Major Safety Results

7.3.1 Deaths

Trial CC-4047-MM-002:

There were a total of 41 (19%) subjects who died during the trial at the time of cut off (April 01, 2011). Twenty (18%) subjects in the POM and Dex arm and 21 (20%) subjects in the POM arm died during the treatment or within 30 days after the last dose. Most of the deaths were attributed to disease progression and the incidence was similar between the two arms.

The most common causes of deaths, excluding death due to disease progression, were attributed to treatment-emergent adverse events. Most of the deaths attributed to AEs were due to infections (9 subjects) of which pneumonia was the most common (three subjects in the pomalidomide and dexamethasone arm and two subjects in the pomalidomide arm).

Table 30 summarizes the deaths occurred during the trial as of cut off date April 01, 2012.

Table 30: Cause of death in clinical trial CC-4047-MM-002

	POM + Dex (N=112)	POM Only (N= 107)	Total (N=219)
Death during trial n (%)	20 (18)	21 (20)	41 (19)
- Disease Progression, n (%)	11 (10)	12 (11)	23 (11)
- Death due to TEAE, n (%)	6 (5)	7 (7)	13 (6)
Pneumonia	3 (3)	2 (2)	5 (2)
Sepsis	1 (1)	4 (4)	5 (2)
Cerebral or subarachnoid hemorrhage	2 (2)	1 (1)	3 (2)
- Acute respiratory distress syndrome	1 (1)	0 (0)	1 (1)
- Cardio-respiratory arrest	0 (0)	1 (1)	1 (1)
- Others or Unknown, n (%)	2* (3)	1 (1)	5 (2)

* One subject committed suicide

Trial IFM 2009-02:

There were a total of 16 (19%) subjects who died during the trial at the time of cut off (March 01, 2011). Seven (16%) subjects in the 21/28 POM+DEX arm and 9 (22%) subjects in the 28/28 POM+DEX arm died during the treatment or within 30 days after the last dose. Most of the deaths were attributed to disease progression. Death due to TEAE was similar between the two arms (7%).

Table 31 summarizes the cause of death occurred during treatment in IFM 2009-02 trial as of cut off date March 01, 2011.

Table 31: Cause of death in clinical trial IFM-2009-02 (Safety Population)

	POM+DEX (21/28) (N=43)	POM+DEX (28/28) (N=41)	Total (N=84)
Total Death, n (%)	7 (16)	9 (22)	16 (19)
Disease Progression, n (%)	4 (9)	6 (15)	10 (12)
Death during treatment due to TEAE, n (%)	3 (7)	3 (7)	6 (7)
- Pneumonia	2 (5)	2 (5)	5 (6)
- Cerebrovascular hemorrhage	1 (2)	0 (0)	1 (1)
- Renal failure	0 (0)	1 (2)	1 (1)

7.3.2 Nonfatal Serious Adverse Events

Trial CC-4047-MM-002:
The incidence of serious treatment emergent adverse events was similar between the two arms in CC-4047-MM-002 trial. There were 69 (62%) subjects in POM+DEX and 71 (66%) in the POM only arm experienced at least one serious adverse event during the trial. Infection was the most common serious TEAE which was higher in POM+DEX arm than that in POM only arm (46% vs. 36%). Pneumonia was the most common serious adverse event with a similar incidence between the two arms (21% in POM+DEX versus 19% in POM only arm).

Table 32 summarizes the serious treatment-emergent adverse events occurring in ≥ 2 subjects in CC-4047-MM-002 trial.

Table 32: Serious treatment-emergent AEs occurring in ≥ 2 subjects (CC-4047-MM-002)

System Organ Class and Preferred Term	**POM+DEX (N= 112)**	**POM only (N= 107)**
No. of patients with at least SAE, n (%)	**69 (62)**	**72 (67)**
Blood and lymphatic system disorders	**6 (5)**	**10 (9)**
Anemia	2 (2)	2 (2)
Febrile neutropenia	1 (1)	5 (5)
Neutropenia	2 (2)	2 (2)
Thrombocytopenia	2 (2)	2 (2)
Cardiac disorders	**9 (8)**	**3 (3)**
Angina pectoris & Myocardial ischemia	3 (3)	0 (0)
Atrial fibrillation	3 (3)	2 (2)
Cardiac failure congestive	3 (3)	0 (0)
Gastrointestinal disorders	**7 (6)**	**8 (7)**
Constipation	3 (3)	1 (1)
Nausea	1 (1)	2 (2)
Vomiting	0 (0)	2 (2)
General disorders and administration site	**10 (9)**	**7 (7)**
Pyrexia	5 (5)	3 (3)
Fatigue & Asthenia & Malaise	2 (2)	3 (3)
General physical health deterioration	2 (2)	0 (0)
Chest pain & non-cardiac chest pain	1 (1)	2 (2)
Infections and infestations	**38 (34)**	**29 (27)**
Pneumonia*	24 (21)	17 (16)
Sepsis	3 (3)	6 (6)
Urinary tract infection	6 (5)	0 (0)
Urosepsis	2 (2)	0 (0)
Gastroenteritis & Clostridium difficile colitis	2 (2)	1 (1)
Bacteremia & Escherichia bacteremia	2 (2)	0 (0)
Device related infection	2 (2)	0 (0)
Viral infection	0 (0)	2 (2)
Investigations	**3 (3)**	**3 (3)**
Blood creatinine increased	1 (1)	2 (2)
Hemoglobin decreased	0 (0)	2 (2)
Metabolism and nutrition disorders	**7 (6)**	**13 (12)**
Dehydration	3 (3)	5 (5)
Failure to thrive	0 (0)	2 (2)
Hypercalcemia	3 (3)	5 (5)
Musculoskeletal and connective tissue disorders	**5 (4)**	**9 (8)**
Back pain & Bone Pain	3 (3)	5 (5)
Nervous system disorders	**4 (4)**	**7 (7)**

System Organ Class and Preferred Term	**POM+DEX (N= 112)**	**POM only (N= 107)**
Psychiatric disorders	**5 (4)**	**5 (5)**
Confusional state	2 (2)	2 (2)
Mental status changes	2 (2)	2 (2)
Renal and urinary disorders	**9 (8)**	**11 (10)**
Renal failure	7 (6)	10 (9)
Respiratory, thoracic and mediastinal disorders	**12 (11)**	**9 (8)**
Bronchospasm	2 (2)	0 (0)
Dyspnea & Hypoxia	7 (6)	5 (5)
Pulmonary embolism	2 (2)	0 (0)
Respiratory failure	2 (2)	0 (0)
Vascular disorders	**3 (3)**	**3 (3)**
Deep vein thrombosis & Thrombosis	1 (1)	2 (2)

* Pneumonia included pneumonia, lobar pneumonia, pneumonia respiratory syncytial viral, pneumonia streptococcal, and pneumonia viral

Reviewer comments: Serious adverse events were reported in two thirds of the patients and infection (pneumonia) was the most common SAE.

Trial IFM 2009-02:

The incidence of serious adverse events during the IFM 2009-02 trial was reported in a total of 62 (74%) patients with similar incidence between the two arms. Pneumonia was the most common serious adverse events reported during the IFM 2009-02 trial. Thirteen patients (30%) in 21/28 POM+DEX arm and 10 patients (24%) developed pneumonia during the trial.

Table 33 summarizes the serious treatment-emergent adverse events occurring in ≥ 2 subjects in IFM 2009-02 trial.

Table 33: Serious TEAEs reported in ≥ 2 subjects (IFM 2009-02 trial)

SAEs by organs system class	**POM+DEX (21/28) (N=43)**	**POM+DEX (28/28) (N=41)**
All Serious TEAEs, n (%)	**32 (74)**	**30 (73)**
Infections and infestations	**15 (35)**	**15 (37)**
Pneumonia*	13 (30)	10 (24)
Bronchitis	1 (2)	1 (2)
Bronchopneumonia	1 (2)	1 (2)
Blood and lymphatic system disorders	**2 (5)**	**3 (7)**
Anemia	1 (2)	1 (2)
Respiratory, thoracic and mediastinal disorders	**6 (14)**	**5 (12)**
Dyspnea	2 (5)	1 (2)
General disorders and administration site conditions	**9 (21)**	**5 (12)**
General physical health deterioration	3 (7)	1 (2)
Hyperthermia	2 (5)	1 (2)
Pyrexia	1 (2)	1 (2)
Renal and urinary disorders	**4 (9)**	**3 (7)**
Renal failure	3 (7)	3 (7)
Metabolism and nutrition disorders	**4 (9)**	**1 (2)**
Hypercalcemia	2 (5)	1 (2)
Musculoskeletal and connective tissue disorders	**6 (14)**	**3 (7)**
Bone pain	2 (5)	1 (2)
Nervous system disorders	**3 (7)**	**3 (7)**

* Pneumonia included lung infection and pneumocystis jiroveci pneumonia

Reviewer comments: Serious adverse events reported in three quarters of the patients in the IFM-2009-02 trial with infection (pneumonia) were the most common which was consistent with the pivotal trial.

7.3.3 Dropouts and/or Discontinuations

Trial CC-4047-MM-002:

At the time of cut off date of April 1, 2011, 80% of subjects in each arm discontinued the trial. Fifty eight percent in POM+DEX arm and 50% in POM only subjects discontinued the study due to disease progression. Seven to 12% of subjects discontinued due to adverse events and 7-8% as a result of death.

Table 34 summarizes the reason for discontinuation in CC-4047-MM-002 trial as of cut off date of April 01, 2011.

Table 34: Reason for discontinuation (trial CC-4047-MM-002)

Reason for discontinuation	**POM+DEX (n=112)**	**POM only (n=107)**
No. of subjects discontinue trial, n (%)	90 (80)	86 (80)
Disease Progression, n (%)	65 (58)	53 (50)
Treatment Emergent Adverse Event, n (%)	8 (7)	13 (12)
Death, n (%)	8 (7)	9 (8)
Withdrew Consent, n (%)	5 (4)	7 (7)
Lost To Follow Up, n (%)	0 (0)	1 (1)
Other*, n (%)	4 (4)	3 (3)

* Included investigator decision, deterioration of patient condition, access to treatment and lack of response
Source: Applicant NDA 204026, CC-4047-MM-002 CSR, Table 10 (page 64).

Trial IFM 2009-02:
A total of 61 (73%) patients discontinue the IFM 2009-02 trial at the time of cut off date of March 01, 2011 with a similar incidence between the two arms. Progression of disease was the most common cause for treatment discontinuation which was reported in 56% of patients in 21/28 POM+DEX arm and in 66% in 28/28 POM+DEX arm.

Table 35 summarized the reason for discontinuation during trial IFM 2009-02 trial.

Table 35: Reason for discontinuation (IFM 2009-02 trial)

Reason for discontinuation	**POM+DEX (21/28) (N=43)**	**POM+DEX (28/28) (N=41)**
No. of subjects discontinue trial, n (%)	29 (67)	32 (78)
Disease progression, n (%)	24 (56)	27 (66)
Discontinue due TEAEs, n (%)	0 (0)	2 (5)
Death, n (%)	3 (7)	3 (7)
Consent withdrawn, n (%)	1 (2)	0 (0)
Lost to follow-up, n (%)	1 (2)	0 (0)

7.3.4 Significant Adverse Events

Trial CC-4047-MM-002:
The incidence of Grade 3 or Grade 4 TEAEs occurred during the trial was similar between the two arms (88% in POM+DEX arm vs. 90% in POM only arm). The most frequently occurring grade 3 or 4 TEAEs were neutropenia, anemia, thrombocytopenia, pneumonia, asthenia and fatigue.

Table 36 summarizes the incidence of Grade 3 or 4 TEAEs occurred during CC-4047-MM-002 trial.

Table 36: TEAEs with NCI CTCAE Grade 3 or Grade 4 occurred in ≥5% subjects (CC-4047-MM-002 Trial)

TEAE by body system class and preferred term	**POM+DEX (n=112)**	**POM only (n=107)**
Number of Subjects with Grades 3 or 4 TEAEs, n (%)	**99 (88)**	**96 (90)**
Blood and lymphatic system disorders	**59 (53)**	**71 (66)**
Neutropenia	43 (38)	50 (47)
Anemia	23 (21)	24 (22)
Thrombocytopenia	21 (19)	24 (22)
Leukopenia	11 (10)	6 (6)
General disorders and administration site conditions	**20 (18)**	**18 (17)**
Asthenia & fatigue	14 (13)	12 (11)
Infections and infestations	**42 (38)**	**29 (27)**
Pneumonia**	24 (21)	16 (15)
Urinary tract infection	9 (8)	2 (2)
Metabolism and nutrition disorders	**25 (22)**	**29 (27)**
Hypercalcemia	1 (1)	10 (9)
Musculoskeletal and connective tissue disorders	**16 (15))**	**25 (23)**
Back pain	10 (9)	11 (10)
Renal and urinary disorders	**9 (8)**	**11 (10)**
Renal failure acute	5 (5)	8 (7)
Respiratory, thoracic and mediastinal disorders	**18 (16)**	**13 (12)**
Dyspnea	14 (13)	7 (7)

Source: Applicant NDA 204026, CC-4047-MM-002 CSR, Table 53 (P. 153).

Trial IFM 2009-02:

Table 37 summarizes the incidence of Grade 3 or 4 TEAEs occurred in ≥5% patients during IFM 2009-02 trial.

Ninety one percent of patients treated with 21/28 POM+DEX and 83% of patient treated with 28/28 POM+DEX experienced Grade 3 or Grade 4 treatment emergent adverse events. The most frequently occurring Grade 3 or 4 TEAEs were neutropenia, anemia, thrombocytopenia, pneumonia, and asthenia.

Table 37: Grades 3 or 4 Treatment emergent adverse events reported in ≥5% patients (IFM 2009-02 Trial)

	POM+DEX (21/28) (N=43)	POM+DEX (28/28) (N=41)
TEAEs by System Class/Preferred Term	**n (%)**	**n (%)**
No. of Subjects with TEAEs Grade 3 or Grade 4	**39 (91)**	**34 (83)**
Blood and lymphatic system disorders	**31 (72)**	**29 (71)**
Neutropenia	27 (63)	23 (56)
Anemia	14 (33)	13 (32)
Thrombocytopenia	12 (28)	10 (24)
General disorders and administration site conditions	**10 (23)**	**11 (27)**
Bone pain	6 (14)	3 (7)
Asthenia	6 (14)	2 (5)
Pain	2 (5)	2 (5)
General physical health deterioration	1 (2)	3 (7)
Infections and infestations	**7 (16)**	**11 (27)**
Pneumonia*	4 (9)	6 (15)
Bronchitis	2 (5)	2 (5)
Renal and urinary disorders	**5 (12)**	**2 (5)**
Renal failure	4 (9)	2 (5)
Musculoskeletal and connective tissue disorders	**9 (21)**	**7 (17)**
Muscle spasms	1 (2)	2 (5)
Respiratory, thoracic and mediastinal disorders	**9 (21)**	**0 (0)**
Dyspnea	4 (9)	1 (2)
Metabolism and nutrition disorders	**7 (16)**	**4 (10)**
Hyperglycemia	3 (7)	0 (0)
Hypercalcemia	2 (5)	2 (5)
Gastrointestinal disorders	**0 (0)**	**2 (5)**
Diarrhea	0 (0)	2 (5)
Nervous system disorders	**2 (5)**	**4 (10)**

* Pneumonia included pneumococcal pneumonia, pneumocystis jiroveci pneumonia and lung infection
Source: Applicant NDA 204026, CSR IFM-2009-02, Table 114 (P. 293)

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Hematological Toxicity

Hematological adverse events were reported in three quarters of patients with a similar incidence in both arms. The drug is myelosuppressive as reflected in the data presented in Table 38. Grade 3 and Grade 4 adverse events due to anemia and thrombocytopenia were observed at nearly equal frequencies on both arms: 21% of the patients on the pomalidomide with dexamethasone arm, whereas 22% of the patients on the pomalidomide alone arm experienced Grade 3 and Grade 4 adverse events due to anemia and thrombocytopenia. In contrast, the percentage of patients experiencing Grade 3 and Grade 4 adverse events due to neutropenia was lower on the combined arm (38%) as compared to the monotherapy arm (47%).

Table 38: Hematological adverse events

TEAE (Hematological Toxicity)	**POM+DEX (N=112)**			**POM Only (N=107)**		
	Any Grade, n (%)	Grade 3 or 4, n (%)	SAE, n (%)	Any Grade, n (%)	Grade 3 or 4, n (%)	SAE, n (%)
Blood and lymphatic disorder	**85 (76)**	**59 (53)**	**6 (5)**	**81 (76)**	**71 (66)**	**10 (9)**
Neutropenia	53 (47)	43 (38)	2 (2)	56 (52)	50 (47)	2 (2)
Anemia	44 (39)	23 (21)	2 (2)	41 (38)	24 (22)	2 (2)
Thrombocytopenia	26 (23)	21 (19)	2 (2)	27 (25)	24 (22)	2 (2)
Febrile neutropenia	3 (3)	2 (2)	1 (1)	5 (5)	5 (5)	5 (5)

7.3.5.2 Infection Events

As shown in the Table 39, the incidences of infectious TEAEs, Grade 3 or 4 and Serious AEs reported in the trial (CC-4047-MM-002) were similar between the two arms. Pneumonia was the most common treatment emergent adverse event which accounts for approximately 50% of all infection AEs.

Table 39: TEAEs due to infections on CC-4047-MM-002

	POM+DEX (N=112)			POM Only (N=107)		
	Any Grade, n (%)	Grade 3 or 4, n (%)	SAE, n (%)	Any Grade, n (%)	Grade 3 or 4, n (%)	SAE, n (%)
Infections and infestations	**79 (71)**	**42 (38)**	**38 (34)**	**71 (66)**	**29 (27)**	**29 (27)**
Pneumonia *	32 (29)	27 (24)	24 (21)	26 (24)	18 (17)	17 (16)
Upper respiratory tract infection	23 (21)	1 (1)	0 (0)	27 (25)	0 (0)	0 (0)
Urinary tract infection	18 (16)	9 (8)	6 (5)	8 (8)	2 (2)	0 (0)
Sepsis	4 (4)	4 (4)	3 (3)	7 (7)	6 (6)	6 (6)

* Pneumonia included lobar pneumonia, lower respiratory tract infection, pneumocystis jiroveci pneumonia, pneumonia respiratory syncytial viral, pneumonia streptococcal, pneumonia fungal, pneumonia parainfluenza viral and pneumonia viral.

7.3.5.3 Hemorrhagic Events

While the incidence of hemorrhagic TEAEs trended higher on the monotherapy arm as compared to the combined therapy arm of CC-4047-MM-002, as shown in Table 40, the incidence of clinically significant hemorrhagic events was low on both arms, in spite of the prevalence of thrombocytopenia on both arms of the study.

Most of the hemorrhagic adverse events were grade 2 or less with epistaxis being the most common TEAE.

Table 40: Hemorrhagic TEAEs on CC-4047-MM-002

	POM + Dex (n=112)		**POM only (n=107)**	
TEAE Grade	All Grades n (%)	Grades 3- 5 n (%)	All Grades n (%)	Grades 3 - 5 n (%)
Subjects with at least one hemorrhagic event, n (%)	**23 (21)**	**5 (5)**	**29 (27)**	**4 (4)**
Epistaxis	12 (11)	0 (0)	16 (15)	2 (2)
Ecchymosis & Contusion	6 (5)	0 (0)	8 (8)	0 (0)
Cerebral Hemorrhage	1 (1)	1 (0)	1 (1)	1 (1)
Petechiae	1 (1)	1 (1)	3 (3)	0 (0)
Subdural Hematoma	1 (1)	1 (1)	1 (1)	1 (1)
Hemoptysis	0 (0)	0 (0)	2 (2)	
Gingival bleeding	1 (1)	0 (0)	1 (1)	0 (0)
Rectal hemorrhage	0 (0)	0 (0)	2 (2)	0 (0)
Hemorrhoid hemorrhage	1 (1)	0 (0)	2 (2)	0 (0)
Hematuria	2 (2)	1 (1)	2 (2)	0 (0)
Infusion Site Hematoma	1 (1)	0 (0)	1 (1)	0 (0)
Hematoma	0 (0)	0 (0)	2 (2)	0 (0)

7.3.5.4 Thromboembolic Events

A total of 7 (3%) subjects experienced 9 venous thromboembolic (VTE) adverse events during the CC-4047-MM-002 trial. As seen in the Table 41, three of these subjects were in the Pom + Dex arm and 4 in the POM only arm. As shown in Table 42, three of these subjects had a history of (VTE) and were all in the POM only arm. Three of 4 VTEs in the POM only arm occurred in the first cycle of therapy.

Please note that all subjects received prophylactic anti-thrombotic treatment (Aspirin 81-100 mg daily or other anticoagulant).

Table 41: Subjects with reported thromboembolic events (TE)

Subjects	Arm	TE type	AE Grade	Cycle
CC-4047-MM-002-101-3028	POM	Thrombosis arm	3	Cycle 1
CC-4047-MM-002-101-3033	POM	Deep vein thrombosis leg	3	Cycle 1
CC-4047-MM-002-103-3014	POM	Deep vein thrombosis leg	3	Cycle 14
CC-4047-MM-002-111-3001	POM POM	Deep vein thrombosis Venous thromboembolism	3 1	Cycle 3 Cycle 1
CC-4047-MM-002-102-3058	POM+Dex	DVT	3	Cycle 4
CC-4047-MM-002-111-3015	POM+Dex	Pulmonary embolism	4	Cycle 12
CC-4047-MM-002-113-3005	POM+Dex POM+Dex	DVT of legs Pulmonary embolism	3	Cycle 10

Source: Applicant NDA 204026 submission, CC-4047-MM-002 CSR, Table 64 (P. 172)

Table 42: Thromboembolic events

	Pom + Dex (N= 112)		Pom only (N= 107)	
	VTE History (n=26)	No VTE History (n= 86)	VTE History (n=22)	No VTE History (n= 85)
No. of Patients with at least one VTE	0 (0)	3 (4)	2 (9)	1 (1)

Reviewer comments: The low incidence rate of VTE in this trial in comparison to that reported in thalidomide trials (13%) may be due to a requirement for the prophylactic use of anticoagulant during this most recent trial.

7.3.5.4 Neuropathy Events

The incidence of TEAEs associated with neuropathy is presented in Table 43. A total of 39 (18%) of subjects experienced TEAEs of neuropathy with similar incidence between the two arms. All subjects experienced a Grade 2 or less neuropathy adverse events.

Table 43: Subjects with reported neuropathy in CC-4047-MM-002 trial

	POM+Dex N=112	POM only N=107
Subjects with ≥ 1 TEAE of Neuropathy, n (%)	**17 (15)**	**22 (21)**
Neuropathy peripheral, n (%)	8 (7)	11 (10)
Paresthesia, n (%)	4 (4)	5 (5)
Hypoesthesia, n (%)	2 (2)	6 (6)
Peripheral sensory neuropathy, n (%)	5 (5)	2 (2)
Hyperesthesia, n (%)	0 (0)	1 (1)

Reviewer comments: The TEAEs reported in the trial CC-4047-MM-002 is consistent with that reported with thalidomide trials. There were no cases of grade 3 or higher neuropathy reported in the MM-02 trial which was similar to the 3% risk of Grade 3 or higher neuropathy observed with thalidomide.

7.3.5.5 Renal Events

The TEAEs associated with altered renal function are presented in Table 44. A total of 30 (14%) subjects experienced renal TEAEs. Twenty seven events of acute renal failure were reported in the trial (11 in POM+Dex arm and 16 in POM only arm). The majority of the renal TEAEs were grade 3 or 4 with similar incidence between the two arms.

Table 44: TEAEs Associated with Altered Renal Function on CC-4047-MM-002 trial

	POM+Dex (n=112)			POM only (n=107)		
TEAE Grade	All Grades n (%)	Grade 3 or 4 n (%)	Serious TEAE n (%)	All Grades n (%)	Grade 3 or 4 n (%)	Serious TEAE n (%)
Subjects with at least one renal TEAE	**12 (10)**	**10 (9)**	**7 (6)**	**18 (17)**	**11 (10)**	**11 (10)**
Acute renal failure	11 (9)	8 (7)	7 (6)	16 (15)	10 (9)	9 (8)
Chronic renal failure	1 (1)	1 (1)	0 (0)	1 (1)	1 (1)	1 (1)
Renal impairment	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)

Reviewer comments: The high incidence of grade 3 or 4 renal failure is hard to attribute to treatment because renal failure may be related to the underlying disease of multiple myeloma and lack of control.

7.3.5.5 Other Adverse Events

The incidence of dizziness and confusional state was similar between the treatment arms and mostly grade 2 or less. The incidence of dizziness and confusional state reported in this trial was comparable to that reported with Thalidomide.
Other common treatment emergent adverse events were GI toxicity (constipation, diarrhea and nausea), asthenia and fatigue and pyrexia which were mostly grade 2 or less. There were no pregnancies reported during this trial.

Table 45: Other TEAEs of clinical significant occurred in CC-4047-MM-002 trial

	POM+Dex (n=112)			**POM only (n=107)**		
	All Grade n (%)	Grade 3 or 4 n (%)	SAE n (%)	All Grade n (%)	Grade 3 or 4 n (%)	SAE n (%)
Dizziness	19 (17)	1 (1)	0 (0)	21 (20)	2 (2)	1 (1)
Confusional state	15 (13)	3 (3)	0 (0)	11 (10)	4 (4)	0 (0)
GI Toxicity						
Constipation	39 (35)	3 (3)	3 (3)	38 (36)	2 (2)	1 (1)
Diarrhea	37 (33)	2 (2)	0 (0)	36 (34)	1 (1)	0 (0)
Nausea	25 (22)	3 (3)	1 (1)	38 (36)	5 (5)	2 (2)
Other Common Toxicity						
Asthenia & fatigue	70 (63)	14 (13)	1 (1)	59 (55)	12 (11)	2 (2)
Pyrexia	34 (30)	2 (2)	6 (5)	20 (19)	3 (3)	3 (3)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

CC-4047-MM-002 Trial:
All subjects in the CC-4047-MM-002 trial experienced at least one treatment emergent adverse event of any grade in both arms. The most frequently occurring TEAEs ≥ 15% in the CC-4047-MM-002 trial were neutropenia, anemia, thrombocytopenia, GI toxicity, pneumonia, fatigue and asthenia, dizziness and confusional state. The incidence of TEAEs of any grade was similar between the two arms.

Table 46 summarized the TEAEs of any grade reported in at least 15% of the subjects in any of the treatment arms in trial MM-02.

Table 46: Treatment Emergent Adverse Events ≥ 15% of subjects (CC-4047-MM-002 trial)

TEAEs by preferred term and body system class	**POM+DEX (N=112)**	**POM (N=107)**
Any Grade TEAEs, n (%)	**112 (100)**	**107 (100)**
Blood and lymphatic system disorders	**85 (76)**	**81 (76)**
Neutropenia	53 (47)	56 (52)
Anemia	44 (39)	41 (38)
Thrombocytopenia	26 (23)	27 (25)
Leukopenia	20 (18)	12 (11)
Lymphopenia	17 (15)	4 (4)
Cardiac disorders	**20 (18)**	**19 (18)**
Eye disorders	**18 (16)**	**20 (19)**
Gastrointestinal disorders	**80 (71)**	**78 (73)**
Constipation	39 (35)	38 (36)
Diarrhea	37 (33)	36 (34)
Nausea	25 (22)	38 (36)
Abdominal pain*	22 (20)	17 (16)
Vomiting	15 (14)	15 (14)
General disorders and administration site conditions	**87 (78)**	**80 (75)**
Asthenia & fatigue	70 (63)	59(55)
Edema peripheral	20 (18)	25 (23)
Pyrexia	34 (30)	20 (19)
Infections and infestations	**79 (71)**	**71 (66)**
Pneumonia**	32 (29)	26 (24)
Upper respiratory tract infection	23 (21)	27 (25)
Urinary tract infection	18 (16)	8 (7)
Injury, poisoning and procedural complications	**28 (25)**	**23 (21)**
Investigations	**62 (55)**	**44 (41)**
Blood creatinine increased	12 (11)	16 (15)
Weight decreased	10 (9)	15 (14)
Metabolism and nutrition disorders	**72 (64)**	**64 (60)**
Decreased appetite	20 (18)	23 (21)
Hypercalcemia	14 (13)	22 (21)
Hyperglycemia	17 (15)	13 (12)
Musculoskeletal and connective tissue disorders	**77 (69)**	**71 (66)**
Back pain	34 (30)	34 (32)
Musculoskeletal chest pain	22 (20)	23 (22)
Arthralgia	17 (15)	17 (16)
Muscle spasms	21 (19)	20 (19)

TEAEs by preferred term and body system class	POM+DEX (N=112)	POM (N=107)
Musculoskeletal pain	17 (15)	12 (11)
Nervous system disorders	**65 (58)**	**57 (53)**
Dizziness	19 (17)	21 (20)
Psychiatric disorders	**53 (47)**	**40 (37)**
Confusional state	15 (13)	11 (10)
Insomnia	16 (14)	7 (7)
Renal and urinary disorders	**23 (20)**	**29 (27)**
Respiratory, thoracic and mediastinal disorders	**77 (69)**	**59 (55)**
Dyspnea & Dyspnea exertion	50 (45)	36 (34)
Cough	23 (21)	15 (14)
Epistaxis	12 (11)	16 (15)
Skin and subcutaneous tissue disorders	**65 (58)**	**54 (50)**
Rash	18 (16)	23 (22)
Hyperhidrosis	18 (16)	6 (6)
Pruritus***	12 (11)	16 (15)
Vascular disorders	**21 (19)**	**21 (20)**

* Abdominal Pain: included abdominal pain, abdominal pain upper, abdominal pain lower and gastrointestinal pain.
** Pneumonia included pneumonia, lobar pneumonia, pneumonia streptococcal, pneumonia viral, pneumonia parainfluenza viral, pneumonia respiratory syncytial viral and pneumocystis jiroveci pneumonia.
*** Pruritus included pruritus generalized and pruritus allergic.

IFM 2009-02 Trial:
All treated patients in IFM 2009-02 trial experienced at least one treatment-emergent adverse event (TEAE) of any grade. The most frequent TEAEs of any grade reported were neutropenia, anemia, thrombocytopenia, pyrexia, pneumonia and bronchitis.

Table 47 summarized the TEAEs of any grade reported in at least 15% of the subjects in any of the treatment arms in trial IFM 2009-02.

Table 47: TEAEs of any grade reported in ≥15% patients, by treatment arm (IFM 2009-02)

TEAEs by Organ System Class/Preferred Term	**POM+DEX (21/28) (N=43)**	**POM+DEX (28/28) (N=41)**
No. of Patients with any Grade TEAEs, n (%)	**43 (100)**	**41 (100)**
Blood and lymphatic system disorders	**35 (81)**	**33 (81)**
Neutropenia	29 (67)	24 (59)
Anemia	19 (44)	20 (49)
Thrombocytopenia	17 (40)	11 (27)
General disorders and administration site conditions	**33 (77)**	**32 (78)**
Asthenia	20 (47)	20 (49)
Pyrexia	11 (26)	8 (20)
Edema peripheral	5 (12)	9 (22)
Pain	5 (12)	5 (12)
Infections and infestations	**29 (67)**	**31 (76)**
Pneumonia*	12 (28)	12 (28)
Bronchitis	12 (28)	12 (29)
Musculoskeletal and connective tissue disorders	**25 (58)**	**29 (71)**
Bone pain	13 (30)	7 (17)
Back pain	5 (12)	10 (24)
Muscle spasms	8 (19)	15 (37)
Respiratory, thoracic and mediastinal disorders	**16 (37)**	**20 (49)**
Dyspnea and Dyspnea exertional	6 (14)	10 (24)
Gastrointestinal disorders	**24 (56)**	**21 (51)**
Constipation	9 (21)	11 (27)
Nausea	11 (26)	8 (20)
Diarrhea	9 (21)	8 (20)
Renal and urinary disorders	**12 (28)**	**7 (17)**
Renal failure	9 (21)	7 (17)
Nervous system disorders	**21 (49)**	**19 (46)**
Dizziness	7 (16)	3 (7)
Tremor	3 (7)	8 (20)
Metabolism and nutrition disorders	**13 (30)**	**12 (29)**
Psychiatric disorders	**11 (26)**	**13 (32)**
Insomnia	5 (12)	6 (15)
Cardiac disorders	**5 (12)**	**6 (15)**
Skin and subcutaneous tissue disorders	**14 (33)**	**16 (39)**
Vascular disorders	**8 (19)**	**4 (10)**

* Pneumonia included lung infection and pneumocystis jiroveci pneumonia

7.4.2 Laboratory Findings

During the CC-4047-MM-002 trial the shifts in laboratory data analysis showed the following:

- The majority of subjects experience a decrease in hemoglobin value with similar incidences in both arms. However, approximately one third of subjects in both arms had a hemoglobin value decrease to grade 3 or 4.
- Approximately half of the subjects in both arms experienced a decreased of neutrophils count of grade 3 or 4 during the trial.
- Approximately 20% of subjects experienced a grade 3 or 4 decrease in platelet counts during the trial with similar incidence between the two arms.
- Approximately 30% of subjects had grade 3 or 4 decrease in lymphocytes counts during the trial with similar incidence between the two arms.
- Liver enzymes did not show any significant shifts during the trial.
- Approximately half of the subjects' creatinine values increased during the trial with mostly grade 1 or 2 with similar incidence between the two arms.
- The majority of subjects had their glucose value increased during the trial, mostly grade 2 or less with similar incidence between the two arms.

Table 48 summarizes shifts in laboratory parameters from baseline to a worst grade during the CC-4047-MM-002 trial.

Table 48: Shifts Laboratory Parameters from baseline in CC-4047-MM-002 Trial

Changes in Lab tests	**Pomalidomide & Dexamethasone (N=111)**					**Pomalidomide (N=101)**				
	Normal n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Normal n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hemoglobin	0 (0)	27 (24)	59 (53)	24 (22)	1 (1)	4 (4)	13 (13)	54 (53)	28 (28)	2 (2)
Lymphocytes	31 (28)	8 (7)	39 (35)	31 (28)	2 (2)	38 (37)	3 (3)	32 (32)	23 (23)	5 (5)
Neutrophils	16 (14)	15 (14)	25 (23)	47 (42)	8 (7)	16 (16)	7 (7)	26 (26)	34 (33)	18 (18)
Platelets	39 (36)	29 (27)	18 (16)	19 (17)	4 (4)	32 (32)	28 (28)	20 (20)	15 (15)	5 (5)
	Pomalidomide & Dexamethasone (N= 102)					**Pomalidomide (N=95)**				
	Normal n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Normal n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Alanine Aminotransferase	73 (72)	24 (23)	4 (4)	1 (1)	0 (0)	69 (73)	21 (22)	4 (4)	1 (1)	0 (0)
Alkaline Phosphatase	85 (83)	15 (15)	2 (2)	0 (0)	0 (0)	77 (81)	17 (18)	1 (1)	0 (0)	0 (0)
Aspartate Aminotransferase	80 (79)	18 (18)	3 (3)	0 (0)	0 (0)	77 (81)	15 (16)	2 (2)	1 (1)	0 (0)
Bilirubin	97 (96)	4 (4)	0 (0)	0 (0)	0 (0)	91 (96)	3 (3)	1 (1)	0 (0)	0 (0)
Blood Urea Nitrogen	102 (100)	0 (0)	0 (0)	0 (0)	0 (0)	95 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Calcium	67 (65)	15 (15)	15 (15)	3 (3)	2 (2)	60 (63)	18 (19)	13 (14)	4 (4)	0 (0)
Creatinine	56 (55)	29(28)	12 (12)	5 (5)	0 (0)	47 (49)	23 (24)	21 (22)	4 (4)	0 (0)
Glucose	10 (10)	63 (62)	25 (24)	4 (4)	0 (0)	7 (7)	65 (68)	15 (16)	8 (8)	0 (0)

7.4.3 Vital Signs

Analysis of vital signs (systolic blood pressure, diastolic blood pressure, and temperature) was limited due to reporting as normal or abnormal. However, no notable shifts in any of the vital signs parameters were reported to have occurred during the study (except in 1 subject).

7.4.4 Electrocardiograms (ECGs)

Only 148 subjects in the trial had baseline and post-baseline ECG data. Assessment of ECGs in this study was classified as “Normal”, “Abnormal not clinically significant” and “abnormal clinically significant.”

The analysis of shifts of ECG data from baseline to worst post-baseline reading revealed that 45% of the subjects had normal ECG values at baseline and 55% had “abnormal not clinically significant” baseline values. The majority of shifts in ECGs in both treatment arms from baseline were from normal to “abnormal not clinically significant” and had a similar incidence in both treatment arms.

Please refer to QT/IRT review for details.

7.4.5 Special Safety Studies/Clinical Trials

None

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Analysis was not performed due to the small size of the safety population.

7.5.2 Time Dependency for Adverse Events

Analysis was not performed due to the small size of the safety population.

7.5.3 Drug-Demographic Interactions

Analysis was not performed due to the small size of the safety population.

7.5.4 Drug-Disease Interactions

Analysis was not performed due to the small size of the safety population.

7.5.5 Drug-Drug Interactions

Refer to clinical pharmacology review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Refer to Pharmacology-Toxicology review. Evaluation for human carcinogenicity in clinical trials CC-4047-MM-002 or IFM-2009-02 is confounded by the absence of a control arm, small safety population, short duration of follow-up, and prior cytotoxic therapies.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women. However, pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of organogenesis.

Since pomalidomide is an analogue of thalidomide, a known human teratogen, no studies were conducted on pregnant women to identify the effects of pomalidomide on human reproduction and pregnancy.

Therefore, pomalidomide is contraindicated in pregnant women and women capable of becoming pregnant. Females of childbearing potential may be treated with pomalidomide provided adequate precautions are taken to avoid pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

Pomalidomide has not been studied in patients younger than 18 years of age.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Pomalidomide doses as high as 50 mg as a single dose in healthy volunteers, and 10 mg as once-daily multiple doses in MM patients have been studied without reported serious adverse events related to overdose. No specific information is available on the treatment of overdose with pomalidomide and it is unknown whether pomalidomide or its metabolites are dialyzable.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

Pomalidomide is a new molecular entity in the United States. No U.S. postmarketing information is available. Pomalidomide is not marketed outside of the U.S.

9 Appendices

9.1 Literature Review/References

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Wildes TM, Vij R, Petersdorf SH, Medeiros BC, Hurria A. New Treatment Approaches for Older Adults with Multiple Myeloma. J Geriatr Oncol. 2012 Jul;3(3):279-290. Epub 2012 Feb 28.

9.2 Labeling Recommendations

The applicant was requested to update AE tables to include AEs regardless of attribution to pomalidomide.

9.3 Advisory Committee Meeting

This application was not taken for an Advisory Committee Meeting.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SALEH AYACHE
12/20/2012

ALBERT B DEISSEROTH
12/20/2012

CLINICAL FILING CHECKLIST FOR NDA 204026

NDA/BLA Number: 204026 **Applicant: Celgene** **Stamp Date: April 10, 2012**

Drug Name: Pomalidomide **NDA/BLA Type: NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505(b)(1)			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Phase 1b study CC-4047-MM-001 (alone) Study Title: An open-label study of the safety and efficacy of CC-4047 treatment for patients with relapsed MM Sample Size: 45 (two cohorts) Cohort 1: in 24 subjects MTD= 2 mg QD. Cohort 2: in 21 subjects MTD 5 mg on alternative days Study Number: phase 1 of CC-4047-MM-002 (+Dex) Study title: A Phase 1/2 Multi-center, Randomized, Open Label, Dose-Escalation Study to Determine the Maximum Tolerated Dose, Safety, And Efficacy of CC-4047 Alone or in Combination with Low-dose Dexamethasone in subjects	X			

	Content Parameter	Yes	No	NA	Comment
	with Relapsed and Refractory Multiple Myeloma who Have Received Prior Treatment that Includes Lenalidomide and Bortezomib. The Phase 1 conducted in 3 US centers, dose-escalation study to determine MTD of pomalidomide dosing schedule in 38 subjects. MTD = 4 mg daily on days 1-21 every 28 days cycle Location in submission: Module 5				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? CC-4047-MM-002 (Phase 2): Open label randomized trial evaluated the efficacy of Pomalidomide alone and in combination with Low dose Dexamethasone IFM 2009-02 (PO-MM-PI-0024): Phase 2 randomized open label trial evaluated response rate to Pomalidomide and Dex in subjects with relapsed and refractory MM who have PD and did not achieve at least a PR to bortezomib and Lenalidomide.	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?		X		Final determination will be based on the full review of the application.
16.	Do the endpoints in the pivotal studies confirm to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	The Agency and the Applicant did not have previous agreements regarding primary/ secondary endpoints.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			Most of the patients are from North America (N=221).
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?		X		Clin pharm will request additional information.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA 204026

	Content Parameter	Yes	No	NA	Comment
	exposed as requested by the Division?				
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Orphan designation was granted 1/15/03.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial	X			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 204026

	Content Parameter	Yes	No	NA	Comment
	Disclosure information?				
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None. The clinical review team will send information requests as needed during the review.

Saleh Ayache, M.D. June 1, 2012

Reviewing Medical Officer Date

Albert Deisseroth, M.D., Ph.D. June 1, 2012

Clinical Team Leader Date

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/s/

SALEH AYACHE
06/06/2012

ALBERT B DEISSEROTH
06/06/2012