CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204026Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 21, 2012
From	Albert Deisseroth, MD, PhD
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA#	NDA 204026
Applicant	Celgene
Date of Submission	April 10, 2012
PDUFA Goal Date	February 10, 2013
Trade Name (Non-proprietary name)	Pomalyst (Pomalidomide)
Dosage forms / Strength	1, 2, 3, and 4 mg capsules
Applicant's Proposed Indication	For patients with multiple myeloma who have received at least two prior therapies including bortezomib (b) (4) and have demonstrated disease progression on or within 60 days of completion of the last therapy.
Recommended:	Approval

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Saleh Ayache, MD, and Angelo De Claro, MD
Statistical Review	Yun Wang, PhD, Mark Rothmann, PhD
Pharmacology Toxicology Review	Pedro Del Valle, PhD, Brenda Gehrke, PhD and Haleh Saber, PhD
ONDQA-CMC Reviews	William Adams, PhD, and Janice Brown, PhD
ONDQA-Biopharm Review	Tien Mien Chen, PhD, and Angelica Dorantes, PhD
Microbiology	Steven Donald, PhD, and David Hussong, PhD
Clinical Pharmacology Review	Rachelle Lubin, PharmD, Bahru Habtemariam, PharmD, and Julie Bullock, PharmD
OSI/DGCPC Review	Anthony Orencia, MD, and Susan D. Thompson, MD
Regulatory Program Manager	Amy Baird
OSE-DRISK	Joyce Weaver, PhD and Cynthia La Civita, PhD

1. Introduction

On April 10, 2012, Celgene submitted a New Drug Application (NDA) for pomalidomide in combination with dexamethasone for the treatment of patients with relapsed or 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 therapy.

Executive Summary. This application is based upon the results of two studies:

1. Study CC-4047-MM-002, which is a Phase 1/2 randomized open label trial, is designed to determine the MTD, safety and efficacy of CC-4047 (pomalidomide) alone or in combination with low-dose dexamethasone in 221 patients with refractory or relapsed multiple myeloma who have received at least 2 prior therapies that included a proteasome inhibitor and an immunomodulatory agent (IMiD). Data from several other Phase 1 and 2 trials was included in the submission;

2. IFM2009-02, which is a Phase 2 randomized open label study, compares the effect of pomalidomide (given for 21 days of each 28 day cycle as compared to 28 days of each 28 day cycle) when combined with dexamethasone in 84 patients with relapsed and refractory multiple myeloma who are progressive and did not achieve at least a partial response to bortezomib and lenalidomide.

Benefit Risk Discussion

Efficacy Results of CC-4047-MM-002. The Applicant reported an overall response rate (ORR) for monotherapy with pomalidomide of 7%, and an ORR for the combination of pomalidomide with dexamethasone of 29% (only 1 CR). The median duration of response was 7.4 months for the combination. Notably, the 29% ORR was in a population of patients all of whom must have undergone at least 2 cycles of lenalidomide and bortezomib therapy and have been shown to have relapsed and refractory disease within 60 days of completing therapy. Importantly, the ORR of 9% and 29% obtained with pomalidomide and the combination of pomalidomide with dexamethasone, was obtained in a population to whom a median of 5 prior regimens had been administered and 65% of which had received intensive therapy followed by stem cell transplant rescue. The ORR rate to the combination of pomalidomide with dexamethasone in the supportive trial (IFM-2009-02) was 34%. The median duration of response was 10.5 months.

Safety. The results of the pivotal trial (CC-4047-MM-002) show that the incidence of Grade 3 or greater neutropenia was between 40-50% but the incidence of febrile neutropenia was between 1-5%. The incidence of Grade 3 anemia or thrombocytopenia is 20% but the incidence of Grade 3 or greater hemorrhagic TEAEs was no greater than 5%. The incidence of thromboembolic TEAEs on CC-4047-CC-002 was less than 3%. There were no instances of Grade 3 neuropathy on either arm of CC-4047-CC-002. There were no new safety signals from IFM-02 that were not expected on the basis of the knowledge of the safety profile of thalidomide and lenalidomide. It is noted that the dose proposed for pomalidomide (4 mg po qd X21) is one tenth of that recommended for thalidomide, and also lower than that recommended for lenalidomide.

Summary. The benefit risk is favorable.

CDTL Recommendation. Accelerated approval for patients with multiple myeloma who have received at least two prior therapies including bortezomib (b) (4) and have demonstrated disease progression on or within 60 days of completion of the last therapy.

2. Background

Pomalidomide

Pomalidomide is the third in the class of immunomodulatory agents (after thalidomide and lenalidomide) which carries both of the functional groups which distinguish thalidomide from lenalidomide on a multi-ring scaffold that is identical among the three IMiDs (as shown below in Figure 1). Pomalidomide has pharmacologic properties that suggest that this IMiD will be more potent than either of its predecessors in terms of tumoricidal activity, immunomodulatory activity, anti-angiogenesis, and anti-inflammatory activity (see Table 1).

Figure 1: Chemical Structures of Thalidomide, Lenalidomide and Pomalidomide

Table 1: Pharmacologic Properties of Pomalidomide, Lenalidomide and Thalidomide, and Relative Potency (EC50 [µM])

Parameter	Thalidomide	Lenalidomide	Pomalidomide
Tumoricidal (MM1.S)	>100	0.1-1	0.01-0.1
Immunomodulation (T-cell IL-2)	>100	0.15	0.01
Anti-angiogenesis (human explant)	0.17	1.8	0.33
Anti-inflammatory (TNF-α)	60	0.03	0.01

These efficacy properties may be the differences that will allow the administration of pomalidomide at lower relative doses as compared to thalidomide or lenalidomide. 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 synergism when combined with dexamethasone as measured by inhibition of myeloma cell proliferation and induction of apoptosis of a lenalidomide-resistant myeloma cell line.

Multiple Myeloma

Multiple myeloma is a malignancy of plasma cells. These 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, hypercalcaemia, renal failure, 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.

FDA Approved Agents for Multiple Myeloma

There are 8 drugs that are currently approved for the treatment of multiple myeloma in multiple drug classes (Table 2). Six of these drugs have received regular approval, while one of these drugs (thalidomide) was approved under the accelerated approval pathway and has not received regular approval for multiple myeloma. Dexamethasone is approved for the treatment of hematologic malignancies.

Table 2: FDA Approved Drugs for Multiple Myeloma

Class	Drug	FDA Approval
Alkylating agents	Melphalan Cyclophosphamide	Regular Regular
Anthracyclines	Liposomal doxorubicin (Doxil™)	Regular
Nitrosureas	Carmustine	Regular
IMiDs	Thalidomide Lenalidomide	Accelerated Regular
Proteasome Inhibitors	Bortezomib Carfilzomib	Regular Accelerated

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 has become a standard treatment for patients under the age of 65 years. Conventional dose combination chemotherapy is given as initial therapy prior to the use of myeloablative therapy/autologous stem cell transplant. Common conventional dose induction chemotherapy regimens include: bortezomib/dexamethasone based chemotherapy regimens, thalidomide/dexamethasone based chemotherapy regimens, and lenalidomide/dexamethasone based chemotherapy regimens. Autologous stem cell transplantation is the most common type of stem cell transplantation used to treat patients with multiple myeloma. None of the above cited treatments are curative. Allogeneic stem cell transplantation is the only therapy for multiple myeloma that has the potential for a cure, but only a minority of patients is eligible for this treatment.

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.

Recurrent Disease

In patients with multiple myeloma who have relapsed following initial therapy, the choice of subsequent treatment depends on patient specific features, disease 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 relapsed or who are no longer responding to therapy is usually less than a year.

Regulatory

Applicant's Proposed Indication

For patients with multiple myeloma who have received at least two prior therapies including bortezomib (b) (4) and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Accelerated Approval

Accelerated approval is a regulatory pathway that applies to certain new drug products that have been studied for their safety and effectiveness and treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to or intolerant of available therapy, or improved patient response over available therapy (CFR 314.500)).

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity (CFR 314.510).

Approval under this section will be subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome (CFR 314.510).

Pomalidomide Regulatory History

A summary of the regulatory interactions between the FDA and the Sponsor are outlined below in Table 3.

At the pre-NDA meetings held on September 13, 2011 and February 2, 2012, FDA requested that Celgene: 1. provide a development program that meets the regulatory criterion of "meaningful therapeutic benefit to patients over existing treatments" necessary for review under the accelerated approval regulations; 2. provide an explanation of the ability of the pomalidomide clinical development program to demonstrate the effect of pomalidomide in the subjects studied; and 3. Provide data demonstrating the adequacy of the pomalidomide safety database.

Table 3: Regulatory History

November 12, 2002	Submission IND 066188
February 15, 2011	Pre-Phase 3 Meeting
September 13, 2011	Pre-NDA Meeting
October 21, 2011	Fast Track Designation
February 2, 2012	Second Pre-NDA Meeting
February 9, 2012	No SPA Agreement Letter for CC-4047-007
April 10, 2012	Submission of NDA 204026

3. CMC

3. A. ONDQA-CMC Reviews (This Section was excerpted from the review of William Adams, PhD, and Janice Brown, PhD).

Elucidation of Structure and other Characteristics

Molecular Formula/Molecular Weight: $C_{13}H_{11}N_3O_4$ / 273.24 g/mol

(b) (4)

(b) (4) (b) (4)

(b) (4)

Physicochemical (PC) Characterization

(b) (4)

Evaluation

Structure Elucidation. Elemental analysis, NMR, IR and MS studies are adequate to establish molecular formula, molecular weight and structural groups in the proposed molecule.

(b) (4)

(b) (4)

Impurities

Residual Solvents

(b) (4)

Residual Metals

(b) (4)

Related Substances

(b) (4)

(b) (4)

Table 4: Impurities

Chemical Name / Descriptor, Celgene Code	Structure	Molecular Weight (g/mole)	Origin	Characterization	Maximum Level Observed in the API Batches	Qualified Level (see Section 4.2.3.7.6)
(b) (4)						

Recommendation of ONDQA-CMC: Approval of the NDA.

3.B. ONDQA-Biopharmaceutics Review. (This Section was excerpted from the review of Tien Mien Chen, PhD, and Angelica Dorantes, PhD).

Recommendation of OND-Biopharm Review. Approval of the NDA.
Pomalidomide is an NME (new molecular entity), which was developed by Celgene under IND 66,188. Pomalidomide is an analog of thalidomide, an agent which is a known human teratogen that can cause severe life-threatening birth defects. Pomalidomide has demonstrated teratogenic activity in both rats and rabbits when administered during the period of major organogenesis.

The 1 and 2 mg capsule formulations (b) (4) have been tested in major clinical studies. They are the same as the TBM (to-be-marketed) formulations except for the differences in capsule shell dye components. The two higher capsule strengths, 3 and 4 mg, (b) (4)), the same as the TBM formulations, and employed in the BE (bioequivalence) study only. (b) (4) The BE study (No. CC-4047-CP-007) provides the link for the 1 and 2 mg capsule strengths vs. the 3 and 4 mg capsule strengths.

Current Submission
On 04/10/12, Celgene submitted the original NDA 204026 for pomalidomide IR capsules, 1, 2, 3, and 4 mg. The NDA included CMC information, comparative dissolution profile data/information, and a BE study No. CC-4047-CP-007.

Upon request, the Applicant submitted:

- On 12/03/12, a biowaiver request with supporting dissolution data in order to bridge the two proposed manufacturing sites for the TBM drug products, i.e., Celgene International

Sarl site and the [redacted] site. The TBM drug products manufactured at Celgene International Sarl site have never been tested clinically.

- On 12/12/12, additional analyses on the relationship of [redacted] for the drug substance (DS) lots made for clinical supplies and drug product (DP) batches made at both proposed manufacturing sites.

Biopharmaceutics Review. The Biopharmaceutics review is focused on the evaluation and acceptability of (1) the proposed dissolution method and acceptance criterion, (2) the comparative dissolution profile data supporting the biowaiver request, and (3) the relationship between [redacted]
ONDQA-Biopharmaceutics has evaluated the information included in NDA 204026 and has the following comments:

1. The dissolution method proposed by the Applicant and the acceptance criterion are acceptable.

2. The Applicant's request for a waiver of the BE study between the two proposed drug product manufacturers sites for the TBM drug products at Celgene International Sarl site and at [redacted] site is acceptable.

3. The results from the additional analyses submitted on 12/12/12 showed that there is no relationship between [redacted] for the DS lots manufactured for clinical use or the DP batches made from both manufacturing sites.

Recommendation from QNDQA-Biopharmaceutics. From the ONDQA-Biopharmaceutics perspective, NDA 204-026 for Pomalidomide IR Capsules is recommended for approval.

4. Nonclinical Pharmacology/Toxicology (This section was excerpted from the review of Haleh Saber, PhD).

Pomalidomide is an immune-modulator and analogue of thalidomide, developed to treat patients with relapsed/refractory multiple myeloma. Thalidomide and lenalidomide (also a thalidomide analogue) have been approved for treatment of multiple myeloma.

Thalidomide, lenalidomide, and pomalidomide are structurally related. Previously the mechanisms of action of thalidomide and lenalidomide were not fully characterized, as also mentioned in the label for these drugs. The Applicant conducted studies to characterize the pharmacology of pomalidomide, while using thalidomide and lenalidomide as comparators in several pharmacology studies. Pomalidomide targets the protein cereblon, which is involved in poly-ubiquitination of proteins. The activity of pomalidomide was dependent on the presence of cereblon. Expression of cereblon in activated human T cells was needed for induction of interleukin-2 (IL-2) and tumor necrosis factor-alpha (TNF-α) by pomalidomide. In cell based assays, pomalidomide modulated the production of several cytokines, e.g. decreased the production of IL-12, IL-6, TNF-α, and GM-CSF and increased the production of IL-10. Pomalidomide inhibited the expression of COX-2 in the assay tested.

Safety pharmacology, pharmacokinetic/ADME (absorption, distribution, metabolism and excretion), and toxicology studies were also conducted. Animal toxicology studies were conducted in appropriate species, using the administration route and dosing regimens that adequately addressed safety concerns in humans. Pomalidomide-related toxicities were more evident in monkeys and included: reduction in platelet and WBC counts, lymphoid depletion, inflammation in the GI tract, and infection (likely related to lymphoid depletion). In the chronic toxicology study, one of the 12 monkeys in the high-dose arm developed acute myeloid leukemia (AML) when animals were treated for 9 months. An association between pomalidomide treatment and development of AML cannot be ruled out at this time. While pomalidomide was negative in the battery of genetic toxicology studies, secondary malignancies with immune-modulatory agents have been reported.

The following statement is from the label from Revlimid (lenalidomide), a thalidomide analogue: Patients with multiple myeloma treated with lenalidomide in studies including melphalan and stem cell transplantation had a higher incidence of second primary malignancies, particularly acute myelogenous leukemia (AML) and Hodgkin lymphoma, compared to patients in the control arms who received similar therapy but did not receive lenalidomide.

Pomalidomide was teratogenic in rats and rabbits. In the embryo-fetal developmental study conducted in rabbits, thalidomide was used as a comparator. Teratogenic and embryo-fetal toxic effects of pomalidomide were similar to those seen with thalidomide.

A pregnancy Category X has been assigned to pomalidomide because of the teratogenic effects of this drug in animals and to be consistent with thalidomide and lenalidomide labels. Pomalidomide did not affect the fertility index in male or female rats, when tested in a fertility and early embryonic study. However, the number of viable embryos was reduced, which is likely secondary to the increase in post-implantation loss and the increase in resorption, as described in this study. This effect was seen when male and female rats treated with pomalidomide were mated. The reduction in the number of embryos was attributed to the exposure of females to pomalidomide, since treating male rats with pomalidomide and mating them with untreated females did not affect the viability of embryos.

The pharmacologic class assigned to pomalidomide is “thalidomide analogue”. This is consistent with the pharmacologic class assigned to lenalidomide and is also based on similarities between pomalidomide and thalidomide in regard to chemical structures, and pharmacologic/ toxicologic effects.

The nonclinical studies were reviewed by Dr. Brenda Gehrke and Dr. Pedro Del Valle. The nonclinical findings are summarized in the “Executive Summary” of the NDA review and reflected in the product label.

Recommendation of Nonclinical Pharmacology/Toxicology. I concur with Drs. Gehrke and Del Valle that from a nonclinical perspective, POMALYST may be approved for the following indication: for patients with multiple myeloma who have received at least two prior therapies including bortezomib [redacted] (b) (4) and have demonstrated disease

progression on or within 60 days of completion of the last therapy. No additional nonclinical studies are needed to support approval of POMALYST for this indication.

5. Clinical Pharmacology (This summary was excerpted from the review of Rachelle Lubin, PharmD, Bahru Habtemariam, PharmD, and Julie Bullock, PharmD).

Pomalidomide is immunomodulatory drug (IMiDs® class) and structurally similar to both thalidomide and lenalidomide, which is being developed as a capsule formulation for the treatment of multiple myeloma (MM). 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. (Clinical overview P.19)

To support the MM indication, the sponsor conducted two pivotal phase 2 studies in patients with relapsed and refractory MM who were previously treated with lenalidomide and bortezomib. Study 1 had two arms where patients received either pomalidomide (4 mg per day) or pomalidomide plus low dose dexamethasone (40 mg per day). The ORR in Study 1 was 7% or 29% in the monotherapy and combination arms respectively. In Study 2, patients were on pomalidomide plus dexamethasone for 21 Days out of a 28 Day cycle or patients received treatment for 28 Days out of a 28 Day cycle. The overall response rate (primary endpoint) in Study 2 was approximately 34%, which was similar regardless of the length of regimen (21/28 days vs. 28/28 days) for pomalidomide plus dexamethasone. No exposure-response relationship assessment was conducted.

The ADME properties of pomalidomide were evaluated following a single 2 mg radiolabeled dose. It was determined that the predominant (~70%) circulating radioactive entity was pomalidomide. Pomalidomide is eliminated primarily through the kidneys (~73% of administered dose), with 2.2% of dose 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 contributions from CYP2C19 and CYP2D6.

The Applicant conducted a food effect study to assess the influence of food on the PK of pomalidomide. However, the food effect study was conducted using a capsule formulation that failed to achieve bioequivalence with the to-be-marketed formulation. Therefore, the food effect study results were deemed unreliable to properly evaluate the food effect on the PK of pomalidomide.

Population PK analysis, exposure-response analysis, organ impairment studies, and a thorough QT study have not been provided to the Agency for review.

Recommendations of the Division of Clinical Pharmacology 5

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 204026. This NDA is considered acceptable from a clinical pharmacology perspective provided that the applicant and the FDA come to an agreement regarding the labeling language and the identified clinical studies to be conducted as PMR or PMC.

6. Clinical Microbiology (This section excerpted from the review of Stephen Donald).

The composition of the pomalidomide capsules is given below in Table 5.

Table 5: Batch formula and batch size for the Celgene International location (batch-formula-celg-int.pdf, pg. 1/1)

Strength (label claim)			1 mg Capsules	2 mg Capsules	3 mg Capsules	4 mg Capsules
Target Batch Size (approximate number of dosage units)			(b) (4)			
Component and Grade	Quality Standard	Function	Quantity per batch (kg)	Quantity per batch (kg)	Quantity per batch (kg)	Quantity per batch (kg)
Pomalidomide (CC-4047)	In-house	Active ingredient	(b) (4)			
Mannitol	USP-NF/Ph. Eur.					
Starch, pregelatinized	NF/Ph. Eur.					
Sodium stearyl fumarate	NF/Ph. Eur.					

The Applicant proposed not to include microbial limits in the specifications of pomalidomide drug product as they say they have demonstrated a well-controlled manufacturing process at both manufacturing locations. They state that the study and exhibit batches of the drug product were monitored according to USP <61> and USP <62> and were found to comply. However, microbial limits specifications or data were not provided. They also stated that the drug substance lots were also monitored according to the same standards but specifications and data were not provided. They stated that excipients are controlled according to NF standards but only one of the excipients had a microbial limits specification according to the NF.

Comment of CMC Reviewer (Stephen Donald of Microbiology):

The Agency acknowledges the microbial limits testing of product samples placed on stability, including both registration batch and validation batch samples. The applicant proposes to omit microbial limits testing for the annual production batches. Because of the historical bioburden data submitted to date and the future submission of the stability results (which will

include bioburden testing) in the annual reports, this reviewer feels the omission of bioburden testing in the annual production batches is justified, (b) (4) .

Recommendation. Approval of the NDA.

7. Clinical/Statistical/Efficacy (This section has been excerpted from the report of Jun Wang of Biostatics).

Overview

Pomalidomide is an IMiDs compound with a dual mechanism of action, including of both tumoricidal and immunomodulatory effects. Pomalidomide was active at inhibiting proliferation in multiple myeloma (MM) cells lines selected for resistance to either dexamethasone, melphalan, doxorubicin, or mitoxantrone. Pomalidomide is still cytotoxic in cell lines that have been resistant to lenalidomide. The combination of pomalidomide and dexamethasone is synergistic at inhibiting cell proliferation and inducing apoptosis in both lenalidomide-sensitive and lenalidomide-resistant cell lines.

It has been reported that the clinical efficacy of low-dose dexamethasone (40 mg weekly) as a single agent in a heavily pretreated population is likely to be minimal. The subjects enrolled in MM studies of pomalidomide have routinely received this agent in combination with dexamethasone. These subjects have generally received multiple prior courses of corticosteroid treatment and have demonstrated refractoriness to corticosteroids. Thus, the efficacy observed with pomalidomide-dexamethasone combination therapy can be attributed substantially to pomalidomide and its synergistic effects when used in combination. Pomalidomide represents a promising new agent for MM treatment in patients when alkylators, anthracyclines, proteasome inhibitors, and corticosteroids are no longer effective.

The proposed indication submitted in this NDA application is for the treatment of patients with MM who have received at least 2 prior regimens of established benefit, including both lenalidomide and bortezomib and have demonstrated disease progression on the last therapy.

Pomalidomide is a novel agent that belongs to the IMiDs series of compounds and has direct anti-myeloma tumoricidal activity, immunomodulatory activities, and inhibitory effects on stromal cell support for multiple myeloma (MM) tumor cell growth. In this NDA submission, the applicant seeks the approval of pomalidomide in combination with low-dose dexamethasone for the treatment of relapsed or refractory multiple myeloma patients who received at least two prior regimens of established benefit, including both lenalidomide and bortezomib and have demonstrated disease progression on the last therapy.

This NDA is based on four clinical studies in 552 subjects in which pomalidomide was evaluated as a single agent, as well as in combination with low-dose dexamethasone. Among the four studies, two studies (Study CC-4047-MM-002 [Phase 2] and Study IFM 2009-02) are considered primary for the evaluation of efficacy and form the basis for this statistical review. CC-4047-

MM-002 is a Phase I/II, randomized, open-label, multi-center study of pomalidomide plus low-dose dexamethasone versus pomalidomide alone for patients with relapsed or refractory MM. The Phase I part was designed to determine the maximum tolerated dose (MTD) of pomalidomide in combination with low-dose dexamethasone (40 mg weekly). The Phase II part of the study was designed to evaluate the efficacy and safety of pomalidomide alone (4 mg daily on days 1-21 of a 28-day cycle) and in combination with low-dose dexamethasone (40 mg weekly) in the target population. This statistical review only considered phase II part of the study for efficacy evaluation.

Study IFM 2009-02 was a non-comparative study comprising two groups of subjects treated with pomalidomide 4 mg daily plus low-dose dexamethasone (40 mg weekly). Pomalidomide was administered on days 1-21 of a 28-day cycle in one group and continuously (once daily over 28 days) in another group. This study, although conducted by a cooperative group, is considered primary for evaluation of efficacy and supporting this NDA application as it includes similar study populations, similar dosing paradigms, and efficacy endpoints as Phase II of Study CC-4047-MM-002.

In Study CC-4047-MM-002, the overall response rate (ORR) was 29.2% with median duration of response (DOR) of 7.4 months (95% CI [5.1, 9.2] months) for patients in pomalidomide plus low-dose dexamethasone group, and 7.4% with median DOR not achieved yet for patients in pomalidomide alone group.

In Study IFM 2009-02, all patients received pomalidomide plus low-dose dexamethasone, the ORR was 34.9% with median DOR of 10.5 months (95% CI [3.5, 12.6] months) for patients in intermittent treatment group (treated 21 days out of a 28-day cycle), and 34.1% with median DOR of 7.3 months (95% CI [3.7, NE] months) for patients in continuous treatment group (treated 28 days out of a 28-day cycle).

Although both studies CC-4047-MM-002 and IFM 2009-02 were designed as randomized studies, the treatment effect of pomalidomide was not isolated. Therefore, no formal statistical comparisons were performed between two treatment arms in both studies. The response data from CC-4047-MM-002 and IFM 2009-02 demonstrate some treatment effect of pomalidomide plus low-dose dexamethasone for relapsed and refractory multiple myeloma patients, although the contribution of pomalidomide to the combination therapy cannot be evaluated in this NDA application.

7.A. Design of Study CC-4047-MM-002

The Phase II part of the Study CC-4047-MM-002 was designed to evaluate the efficacy and safety of pomalidomide alone (4 mg daily on days 1-21 of a 28-day cycle) and in combination with low-dose dexamethasone (40 mg weekly) in the target population (see Figure 2 below). The original primary efficacy endpoint was progression-free survival (PFS) based on independent review committee (IRC) assessments. However, since this study was randomized but uncontrolled, which did not isolate the treatment effect of pomalidomide, PFS was not comparable between two treatment arms, the applicant proposed ORR per IRC using European

Group for Blood and Marrow Transplantation (EBMT) criteria was more appropriate and used primarily to evaluating efficacy in this study.

The secondary efficacy endpoints are duration of response (DOR), time to response (TTR), overall survival (OS). A total of 221 patients with MM were randomized between 01 December 2009 and 22 September 2010 from 18 sites in the US and Canada. The data cut-off date was 01 April 2011, and an updated analysis of overall survival was performed based on the cutoff date of 16 Sep 2011.

The original protocol for study CC-4047-MM-002 was dated 20 September 2007, and the last version was Amendment 4 dated 27 July 2011.

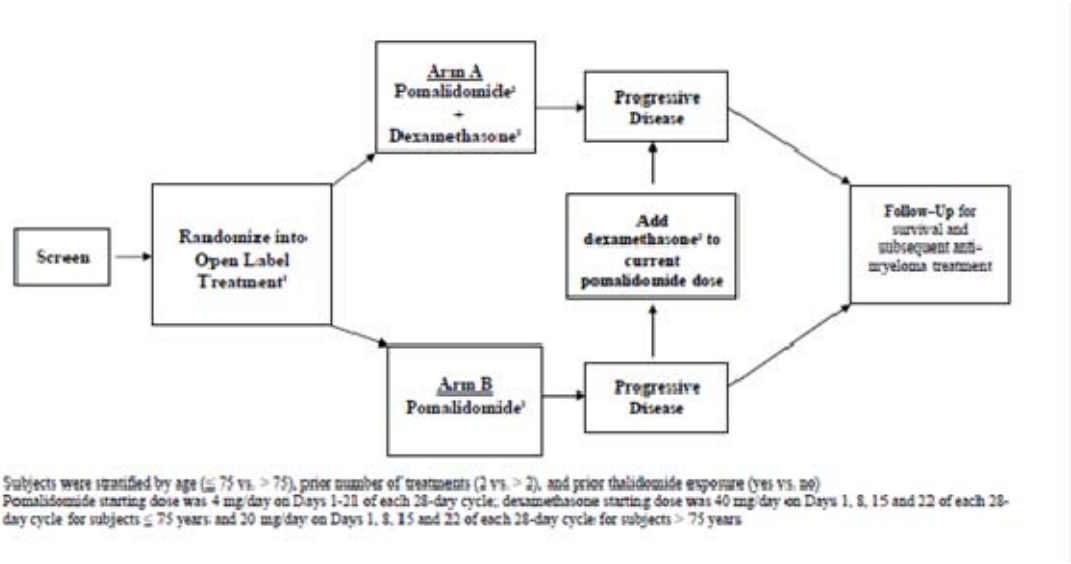

Figure 2: Treatment Arms on CC-4047-MM-002

Throughout this review, for study CC-4047-MM-002, patients randomized to receive pomalidomide alone are referred as "Pom" arm in the text, the tables/figures, whereas patients randomized to receive pomalidomide plus low-dose dexamethasone are referred as "Pom(21/28) + Dex" arm in the text, the tables and figures.

7.B. Design of Study IFM 2009-02

The Study IFM 2009-02 is an open-label, multicenter, randomized, Phase II study designed to evaluate the efficacy and safety of pomalidomide with low-dose dexamethasone in relapse and refractory MM patients who are progressive and did not achieve at least a partial response to Bortezomib and Lenalidomide. Patients received pomalidomide 4 mg daily on days 1-21 of a 28-day cycle plus dexamethasone 40 mg weekly in one arm, and pomalidomide 4 mg daily on 28 days continuously of a 28-day cycle plus dexamethasone 40 mg weekly in another arm. The primary efficacy endpoint is ORR per IRC using International Myeloma Working Group (IMWG) response criteria.

The secondary efficacy endpoints are TTR, time to disease progression (TTP) and OS. A total of 84 patients with MM were randomized between 16 October 2009 and 28 July 2010 from 22 sites in France. The data cut-off date was March 1, 2011. The original protocol for study IFM 2009-02 was dated June 11, 2009, and the latest version was Amendment 3 dated January 27, 2010.

Throughout this review, for study IFM 2009-02, patients randomized to receive pomalidomide intermittent (21 days out of 28-day cycles) plus low-dose dexamethasone are referred as "Pom(21/28) + Dex" arm in the text, the tables/figures, whereas patients randomized to receive pomalidomide continuously (28 days out of 28-day cycles) plus low-dose dexamethasone are referred as "Pom(28/28) + Dex" arm in the text, the tables and figures.

7.C. Results from the Study CC-4047-MM-002

Based on projection, interim analysis of PFS was scheduled with a cutoff date of October 29, 2010. However, 141 PFS events have actually occurred at the time of interim analysis. The DMC concluded that interim analysis results demonstrated a highly significant difference in favor of Pom (21/28) + Dex arm versus Pom arm, and recommended to unblind the study. The final analysis was performed based on a cutoff date of April 1, 2011 and the analysis results were submitted to support this NDA application.

Although PFS was the primary efficacy endpoint in study CC-4047-MM-002, the study was not correctly controlled, ORR per IRC was used to evaluating efficacy for each treatment arm separately in the CSR and this review. The analysis results of ORR are summarized in Table 6. Overall response rate was 7.4% with median duration not achieved yet among subjects who received pomalidomide alone, and 29.2% with median duration of 7.4 months among subjects who received pomalidomide plus low-dose dexamethasone.

Table 6: Study CC-4047-MM-002 analysis results of ORR per IRC, ITT population

	Pom(21/28) + Dex		**Pom**	
	N=113	**(%)**	**N=108**	**(%)**
Overall response rate (CR + PR), n (%)	33	(29.2)	8	(7.4)
Complete response (CR), n (%)	1	(0.9)	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 DOR (Months)	7.4	(5.1, 9.2)	NE	(NE, NE)

[Source: Study CC-4047-MM-002 CSR Page 78 Tables 19 and Statistical reviewer's analysis]

Reviewer's Comment. *The study protocol defined that response should have a minimum duration of 42 days (6 weeks). 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 had a partial response with duration less than 6 weeks, and should not be considered as having achieved PR. Therefore, number of responders in this statistical review was 3 less than what was reported in the study CSR. The duration of response was summarized based on 41 instead of 44 responders. Two patients CC-4047-MM-002-101-3033 and CC-4047-MM-002-*

101-3047 from the Pom arm and one patient CC-4047-MM-002-113-3005 from Pom(21/28) + Dex arm were counted as responders although their calculated DOR were less than 6 weeks, since the patients were censored with PR at the last assessment.

The analysis results of time to response (TTR), PFS and OS endpoints are summarized in Table 7 for study CC-4047-MM-002). In addition to the analysis of OS done at the cutoff of April 1, 2011, the applicant performed an updated analysis of OS at the cutoff of September 16, 2011. The estimated median OS was longer for the Pom (21/28) + Dex arm at the later cutoff, while the median OS for the Pom arm were the same.

Reviewer's Comment. *No valid comparisons were made between two treatment arms for any efficacy endpoints since this study was randomized but uncontrolled. Three patients CC-4047-MM-002-105-3001, CC-4047-MM-002-111-3007, CC-4047-MM-002-113-3006 were counted as non-responders in this statistical review, so they were excluded from the estimation of TTR.*

Table 7: Study CC-4047-MM-002 summary of other efficacy endpoints, ITT population

Endpoints	Statistic	Pom(21/28) + Dex N=113 (%)	Pom N=108 (%)
PFS (Months)			
	Number (%) of subjects censored	27 (23.9)	27 (25.0)
	Number of subjects progressed/died	86 (76.1)	81 (75.0)
	Median (95% CI)	3.8 (3.2, 4.9)	2.5 (1.9, 3.7)
TTR (Months)			
	Number of responders	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)
OS (Months) 01 Apr 2011 cutoff			
	Number (%) of subjects censored	69 (61.1)	61 (56.5)
	Number of subjects died	44 (38.9)	47 (43.5)
	Median (95% CI)	14.4 (12.3, NE)	13.6 (9.6, NE)
OS (Months) 16 Sep 2011 cutoff			
	Number (%) of subjects censored	54 (47.8)	46 (42.6)
	Number of subjects died	59 (52.2)	62 (57.4)
	Median (95% CI)	16.5 (12.4, NE)	13.6 (9.6, 17.2)

[Source: Study CC-4047-MM-002 CSR Page 78 Tables 19 and Statistical reviewer's analysis]

7.D. Results from the Study IFM 2009-02

The primary analysis results of ORR are summarized in Table 8 for study IFM 2009-02. The overall response rate 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.

Table 8: Study IFM 2009-02 analysis results of ORR per IRC, ITT population

	Pom(21/28) + Dex N=43	(%)	Pom 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 DOR (Months)	10.5 (3.5, 12.6)		7.3 (3.7, NE)	

NE: not achieve yet.
[Source: Study IFM 2009-02 CSR Page 123 Tables 34, Page 131 Table 42 and Statistical reviewer's analysis]

Reviewer's Comment. *The study protocol specified that all response required two consecutive assessments made at any time before the institution of any new therapy, and there was no need for a 6-week wait time to confirm response. One patient IFM-2009-02-029-01 had many assessments of partial response or very good partial response and achieved complete response at the last assessment, he/she should only be counted to have partial response not complete response. Therefore, number of partial response in this statistical reviewer was 1 more and the number of complete response was one less than what were reported in the study CSR. The overall response rate and median duration of response observed in the study IFM 2009-02 were slightly better than what were observed in the study CC-4047-MM-002.*

The analysis results of time to response (TTR), PFS and OS endpoints are summarized in Table 9 for study IFM 2009-02.

Reviewer's Comment. *No valid comparisons were made between two treatment arms for any efficacy endpoints since this study was randomized but uncontrolled study.*

Table 9: Study IFM 2009-02 Summary of Other Efficacy Endpoints, ITT Population

Endpoints	Statistic	Pom(21/28) + Dex N=43	(%)	Pom N=41	(%)
PFS (Months)					
	Number (%) of subjects censored	14	(32.6)	9	(22.0)
	Number of subjects progressed/died	29	(67.4)	32	(78.0)
	Median (95% CI)	5.8 (3.7, 9.6)		5.8 (3.1, 8.3)	
TTR (Months)					
	Number of responders	15		14	
	Mean (SD)	3.9	(3.3)	2.1	(2.3)
	Median (Min, Max)	2.7 (0.8, 9.5)		1.1 (0.6, 8.3)	
OS (Months)					

Number (%) of subjects censored	24	(55.8)	23	(56.1)
Number of subjects died	19	(44.2)	18	(43.9)
Median (95% CI)	13.4 (8.9, 13.9)		15.3 (9.2, NE)	

[Source: Study IFM 2009-02 CSR Page 133 Table 43, Page 134 Table 44, and Page 140 Tables 47]

Conclusions for Efficacy

The study CC-4047-MM-002 and IFM 2009-02 demonstrated consistent treatment benefit of pomalidomide plus low-dose dexamethasone for relapsed and refractory multiple myeloma patients, although the contribution of pomalidomide to the combination therapy cannot be evaluated in this NDA application.

Recommendation of Biostatistics Review. Approval of NDA.

8. Safety (The following is excerpted from the Safety Review of Dr. Saleh Ayache and Dr. R. Angelo DeClaro).

8.A. Overview of the Safety Population

The safety population, which is displayed in Table 10 below, is comprised of 107 patients who received pomolidomide alone and 112 patients who received both dexamethasone and pomalidomide on clinical trial CC-4047-MM-002 clinical trial, and 43 patients who received dexamethasone with pomalidomide on a 21/28 day schedule, and 41 patients who received dexamethasone with pomalidomide on a 28/28 day schedule.

Table 10: Safety Population

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

Abbreviations: POM=pomalidomide; DEX=dexamethasone

8.B. Significant Adverse Events

8.B.i. Trial CC-4047-MM-002. Table 11 summarizes the Grade 3 or 4 treatment emergent adverse events (TEAEs) which occurred in the CC-4047-MM-002 trial. The incidence of Grade 3 or Grade 4 TEAEs 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 11: TEAEs with NCI CTCAE Grade 3 or Grade 4 Which 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)**
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, MM-002 CSR, Table 53 (P. 153).

8.B.ii. Trial IFM-2009-02.
Table 12 summarizes the Grade 3 or 4 TEAEs which occurred in ≥5% patients during the 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 a 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 12: Grades 3 or 4 Treatment Emergent Adverse Events Reported in ≥5% Patients in the IFM-2009-02 Trial

TEAEs by System Class/Preferred Term	POM+DEX (21/28) (N=43)	POM+DEX (28/28) (N=41)
Subjects with TEAEs of Grade 3 or 4, n(%)	**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)	0 (0)
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 pneumonia and lung infection

Source: Applicant NDA 204026, CSR IFM-2009-02, Table 114 (P. 293)

8.C. Submission Specific Primary Safety Concerns

8.C.i. 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 Table 13. Grade 3 and Grade 4 adverse events due to anemia and thrombocytopenia were observed at nearly equal frequencies on both arms: Twenty-one percent (21%) of the patients on the pomalidomide with dexamethasone arm, and 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 13: 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	29 (26)	21 (19)	2 (2)	27 (25)	24 (22)	2 (2)
Febrile neutropenia	3 (3)	2 (2)	1 (1)	5 (5)	5 (5)	5 (5)

8.C.ii. Adverse Events Associated with Infection

As shown in Table 14, the incidence of infectious TEAEs, Grade 3 or 4 and serious adverse events (SAEs) reported in the trial (CC-4047-MM-002) were similar between the two arms. Pneumonia was the most common infectious treatment emergent adverse event which accounts for approximately 50% of all infectious AEs.

Table 14: TEAEs Due to Infections on CC-4047-MM-002

	POM+DEX (N=112)			**POM Only (N=107)**		
	All Grades n (%)	**Grades 3 or 4 n (%)**	**SAE n (%)**	**All Grades n (%)**	**Grades 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)	27 (24)	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)	4 (4)	7 (7)	6 (6)	6 (6)

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

8.C.iii. 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 15, 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 15: Hemorrhagic TEAEs on CC-4047-MM-002

	POM + Dex (n=112)		**POM only (n=107)**	
TEAE Grade	**All Grades**	**Grades 3- 5**	**All Grades**	**Grades 3 – 5**
	n (%)	**n (%)**	**n (%)**	**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)

8.C.iv. Thromboembolic Events. A total of 7 (3%) subjects experienced 9 venous thromboembolic (VTE) adverse events during the MM-002 trial. As seen in Table 16, three of these subjects were in the Pom + Dex arm and 4 in the POM only arm. As shown in Table 17, three of these subjects had a history of (VTE) and were all in the POM only arm. Three of the 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 16: 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-	POM	Deep vein thrombosis	3	Cycle 1

3033		leg		
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, MM-002 CSR, Table 64 (P. 172)

Table 17: Thromboembolic Events

	Pom + Dex (N= 112)		**Pom only (N= 107)**	
	VTE History (N=26) n (%)	No VTE History (N= 86) n (%)	VTE History (N=22) n (%)	No VTE History (N= 85) n (%)
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 (13%) may be due to the prophylactic use of anticoagulant during this trial.*

8.C.v. Neuropathy Adverse Events. The incidence of TEAEs associated with neuropathy is presented in Table 18. 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 18: Subjects with Reported Neuropathy

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

Reviewer Comments. *The TEAEs reported in the trial MM-002 is consistent with that reported with thalidomide. 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.*

Safety Summary

The safety of Pomalidomide was evaluated in 303 patients with relapsed 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/kg orally administered daily for 21 days in 28-day cycle. The median duration of treatment per patient with pomalidomide was 5.0 cycle (range 1.0, 17.0).
- 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) with infection was the most common.
- Approximately (16%) discontinued treatment due to treatment emergent adverse events.
- Approximately (89%) of patients experienced a Grade 3 or Grade 4 treatment-emergent adverse event (TEAE) with neutropenia and pneumonia were most common.
- Safety issues in ≥ 20% of patients include myelosuppression, infections, neuropathy, dizziness, GI toxicity, and fatigue.
- Safety profile for pomalidomide is similar to thalidomide and lenalidomide.
- No new safety signal 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 as apparent of neutropenia, anemia and thrombocytopenia.
    - Infection occurred in two third of the patients and pneumonia was the most common.
    - The incidence of hemorrhagic events occurred in quarter of the patients with the majority were grade 2 or less and epistaxis was the most common.
    - The thromboembolic events were low with only 3% of patients experienced VTE. The low incidence of VTE may be due to the use of prophylactic anticoagulant.
    - Approximately 17% of patients experienced neurologic adverse events with peripheral neuropathy was the most common. All neurologic events were grade 2 or less.
    - Renal events of Grade 3 or 4 occurred in 9- 10% of patients with acute renal failure was the most common cause. It is hard to attribute renal failure to treatment because renal failure may be related underlying disease of MM.
    - Other common TEAEs are dizziness, asthenia and fatigue, pyrexia and confusional state.

Safety Analysis of CC-4047-MM-002 Trial
All subjects in the study experienced at least one treatment emergent adverse event of any grade in both arms. The most frequently occurring TEAEs ≥ 15% in 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.

CDTL Comment. *The pivotal trial does not isolate the effect of pomalidomide, and therefore final conclusions about the safety of pomalidomide will await the results of phase III trials to be conducted by the Applicant. On the other hand, assessment of both arms of the pivotal trial shows that the toxicity profile of pomalidomide or pomalidomide are not very different from each other, and not very different from the toxicity profile of thalidomide or lenalidomide, the two other drugs of this class to be approved for refractory relapsed myeloma.*

Recommendation of the Medical Reviewer. Approval of the NDA.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

There is no comparable disease in pediatric oncology to the proposed indication.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP).** Issues resolved as described above.
- **Exclusivity or Patent Issues of Concern.** None
- **Financial Disclosures**. Adequate and complete.
- **Other GCP Issues**. None
- **Office of Scientific Investigation (OSI) Audits.** This section was excerpted from the review of Dr. Anthony Orencia.

The OSI carried out investigations of three clinical sites for the pivotal trial MM002 as shown below.

a. **Assessment of data integrity of David Siegel Site in Hackensack, NJ (site #101).** Data submitted by this clinical site appear acceptable for this specific indication.

b. **Assessment of data integrity of Paul Richardson, M.D. in Boston, MA (site #102).** Data submitted by this clinical site appear acceptable for this specific indication**.**

c. **Assessment of data integrity of Craig Hofmeister, M.D. in Columbus, OH (site #101).** Data submitted by this clinical site appear acceptable for this specific indication.

d. **Assessment of data integrity of Celgene in Summit, NJ.** The study appears to have been conducted adequately. Data submitted by this Sponsor appear acceptable in support of the respective indication

Summary Conclusion of OSE. Based on review of inspectional findings for these clinical investigators, the study data collected appear generally reliable in support of the requested indication.

12. Labeling

The labeling is currently under negotiation between the Applicant and the FDA.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**. Approval
- **Risk Benefit Assessment, Benefit-Risk Discussion**
- **Efficacy.** The Applicant reported an ORR for monotherapy with pomalidomide of 9% but the FDA analysis suggests that the ORR may be as low as 7% for monotherapy with pomalidomide.
- Although the contribution of pomalidomide to ORR was not isolated in the pivotal clinical trial (CC-4047-MM-002), the ORR of the combination of dexamethasone with pomalidomide, the proposed indication, was 29% (only 1 CR). Notably, the 29% ORR was in a population of patients all of whom must have undergone at least 2 cycles of lenalidomide and bortezoib therapy and have been shown to have relapsed and refractory disease within 60 days of completing therapy. Importantly, the ORR of 7% and 29% obtained with pomalidomide and the combination of pomalidomide with dexamethasone,

was obtained in a population to whom a median of 5 prior regimens had been administered and 65% of which had received intensive therapy followed by stem cell transplant rescue.

- **Safety.** The results of the pivotal trial (CC-4047-MM-002) show that the incidence of Grade 3 or greater neutropenia is between 40-50% but the incidence of febrile neutropenia is between 1-5%. The incidence of Grade 3 anemia or thrombocytopenia is 20% but the incidence of Grade 3 or greater hemorrhagic TEAEs is no greater than 5%. The incidence of thromboembolic TEAEs on CC-4047-CC-002 was less than 3%. There were no instances of Grade 3 neuropathy on either arm of CC-4047-CC-002.
- There were no new safety signals from IFM-02 that were not expected on the basis of the knowledge of the safety profile of thalidomide and lenalidomide. It is noted that the dose proposed for pomalidomide (4 mg po qd X21) is one tenth of that recommended for thalidomide, and one fifth of that recommended for lenalidomide.
- **Summary.** The risk benefit analysis is favorable for patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.

CDTL Recommendation. The recommendation of the CDTL reviewer is accelerated approval for the indication listed in the previous paragraph.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  None

- Recommendation for Other Postmarketing Commitments

  PMC #1: Smoking (CYP1A2 Inducer) Study: The relative contribution of CYP1A2 to pomalidomide metabolism is approximately 54%. Cigarette smoking may reduce pomalidomide AUC due to CYP1A2 induction; therefore reduced pomalidomide efficacy may be seen. The intent is to confirm whether cigarette smoking can impact pomalidomide exposure. Pomalidomide is metabolized by CYP1A2. Information on the effect of CYP1A2 induction on pomalidomide exposure was not submitted in the NDA. Patients who smoke cigarettes may be at greater risk of reduced pomalidomide efficacy. Propose and carry out a smoking induction study.

- Recommendation for Other Postmarketing Requirements

1. PMR #1: CYP3A Induction Study: In vitro studies suggest that pomalidomide is a substrate of CYP3A. The relative contribution of CYP3A to pomalidomide metabolism is approximately 30%. Based on these findings, patients on strong or moderate CYP3A inducers may have decreased pomalidomide exposure. Therefore studies are needed to determine the clinical impact of CYP3A inducers. Appropriate labeling recommendations (e.g. dose adjustments) maybe needed for patients taking drugs that are inducers of CYP3A. Pomalidomide is a substrate of CYP3A. Information on the effect of CYP3A induction on pomalidomide exposure was not submitted in the NDA. Concomitant use of CYP3A inducers may decrease the exposure of Pomalidomide.

Propose and carry out a CYP3A Induction Study.

2. PMR #2: CYP3A Inhibition Study: In vitro studies suggest that pomalidomide is a substrate of CYP3A. The relative contribution of CYP3A to pomalidomide metabolism is approximately 30%. Based on these findings, patients on CYP3A inhibitors may have increased pomalidomide exposure. Therefore studies are needed to determine the clinical impact of CYP3A inhibitors. Appropriate labeling recommendations (e.g. dose adjustments) may be needed for patients taking drugs that are inhibitors of CYP3A. Pomalidomide is a substrate of CYP3A. Information on the effect of CYP3A inhibition on pomalidomide exposure was not submitted in the NDA. Concomitant use of CYP3A inhibitors may increase the exposure of Pomalidomide.

Propose and carry out a CYP3A Inhibition Study

3. PMR #3: Renal Impairment Trial in patients with Baseline Renal Impairment and those on Chronic Dialysis: Human ADME study results showed that pomalidomide and metabolites are excreted via the kidneys. Approximately 73% of radiolabeled pomalidomide dose was recovered in the urine. Based on these findings, patients with baseline renal impairment may have a decrease in pomalidomide clearance; therefore the safety and PK properties of pomalidomide needs to be evaluated in a post marketing setting. Pomalidomide is excreted via the kidneys. The influence of renal impairment on the safety, efficacy and pharmacokinetics of pomalidomide has not been provided in the NDA

Provide and carry out a renal impairment trial in patients with baseline renal impairment.

4. PMR #4: Hepatic Impairment Trial in Patients with Baseline Hepatic Impairment: A human ADME study showed that pomalidomide is metabolized hepatically. Based on these findings, patients with baseline hepatic impairment maybe at an increased risk of liver toxicity, therefore the safety and PK properties of pomalidomide needs to be evaluated in a post marketing setting. Pomalidomide is metabolized in the liver. The influence of

hepatic impairment on the safety, efficacy and pharmacokinetics of pomalidomide has not been provided in the NDA.

Provide and carry out an hepatic impairment trial in patients with baseline hepatic impairment.

5. PMR #5: Food Effect Study: Food effect was assessed as a secondary objective in a clinical study with 2 mg of pomalidomide. However, that study was not sufficient because the sponsor used a failed test formulation to assess food effect. Food effect was not evaluated with the final market formulation. The proposed PMR will determine whether the effect of food alters the pharmacokinetics of pomalidomide. This data is pertinent for labeling purposes. The effect of food on pomalidomide exposure has not been addressed. Food-effect studies should be conducted to guide the decisions to administer the drug with or without food.

Propose and carry out a food effect study.

6. PMR #6: QT Prolongation Study: Studies to assess QT prolongation potential of pomalidomide have not been performed. The intent of this study is to determine whether patients taking pomalidomide are at greater risk of QT/QTc interval prolongation. A QT study designed to assess whether there are any effects of pomalidomide on QT interval was not performed.

Propose and carry out an AT prolongation study.

7. PMR (Subpart H): Conduct a randomized controlled trial (MM-007) that isolates the efficacy and safety of pomalidomide in patients with previously treated multiple myeloma: The goal of the clinical trial would be to demonstrate the efficacy and safety of pomalidomide using a controlled trial designed to (1) show superiority (e.g., add-on design, active-control) and (2) isolates the treatment effect of pomalidomide. The Applicant has a current ongoing clinical trial that meets the design, MM-007. Clinical trial MM-007, titled "A Phase 3, Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Pomalidomide, Bortezomib and Low-Dose Dexamethasone versus Bortezomib and Low-Dose Dexamethasone in Subjects with Relapsed or Refractory Multiple Myeloma" received SPA agreement on December 14, 2012. Patients with previously treated multiple myeloma have an incurable disease that confers a poor prognosis. The results of clinical trial MM-002, one of the trials submitted to support the NDA, showed a median overall survival of 14 months in a patient population that was heavily pretreated (median of 5 prior therapies).

Propose and carryout a confirmatory trial in which the benefit of pomalidomide is demonstrated.

8. PMR#8: (FDAAA Safety): Conduct a randomized controlled trial (MM-003) of the combination of pomalidomide and dexamethasone in patients with previously treated multiple myeloma:

The Applicant should submit the results of a recently completed Phase 3 trial, MM-003, titled "A Phase 3, Multicenter, Randomized, Open-label Study to Compare the Efficacy and Safety of Pomalidomide in Combination with Low-Dose Dexamethasone versus High-Dose. Dexamethasone in Subjects with Refractory or Relapsed and Refractory Multiple Myeloma". Justification for FDAAA PMR: Previous clinical trials did not have an acceptable control arm to adequately describe the safety of pomalidomide. Patients with previously treated multiple myeloma have an incurable disease that confers a poor prognosis. The results of clinical trial MM-002, one of the trials submitted to support the NDA, showed a median overall survival of 14 months in a patient population that was heavily pretreated (median of 5 prior therapies).

Propose and carry out a RCT of the combination of pomalidomide and dexamethasone in patients with previously treated myeloma.

9. PMR#9: PMR (FDAAA Safety): Conduct an epidemiologic study to address the questions detailed below:

1. What is the failure rate for each of the different types of thromboembolic prophylaxis (e.g., antiplatelet or anticoagulant therapy) for multiple myeloma patients treated with a pomalidomide-containing regimen?
2. What is the failure rate for each type of Deep Vein Thrombosis (DVT) treatment (e.g., dose-adjusted heparin, low molecular weight heparin, coumadin, or other oral anticoagulants) for those patients with multiple myeloma and a DVT who continue to receive ongoing treatment with pomalidomide?
3. What is the failure rate for each type of post-DVT thromboembolic prophylaxis for those patients with multiple myeloma and a DVT who continue to receive ongoing treatment with pomalidomide?

This prospective epidemiologic study will enroll select patients identified in the (b) (4) program, and collect the necessary additional data on these patients to further evaluate occurrences of thrombosis and anticoagulant use.

Justification for FDAAA PMR: Immunomodulatory class of drugs are associated with an increased risk of venous thromboembolic events. The clinical trials to support pomalidomide approval do not adequately characterize the risk of venous thromboembolic events and most appropriate prophylaxis regimen. Patients with previously treated multiple myeloma have an incurable disease that confers a poor prognosis. The results of clinical trial MM-002, one of the trials submitted to support the NDA, showed a median overall survival of 14 months in a patient population that was heavily pretreated (median of 5 prior therapies).

Propose and carry out the epidemiological study outlined above.

- Recommended Comments to Applicant

None

Appears this way on original

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

/s/

ALBERT B DEISSEROTH
12/21/2012