CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 204026
Supplement #:	
Drug Name:	Pomalidomide
Indication(s):	Relapsed or refractory multiple myeloma
Applicant:	Celgene Inc.
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Statistical Reviewer:	Yun Wang, PhD
Concurring Reviewers:	Mark Rothmann, PhD, Team Leader
	Rajeshwari Sridhara, PhD, Division Director
Medical Division:	Office of Hematology and Oncology Product
Clinical Team:	Saleh Ayache, MD
	Albert Deisseroth, MD
Project Manager:	Amy Baird, MPH

Keywords: Multiple Myeloma, Overall response rate, Duration of response

Table of Contents

LIST OF TABLES

1 EXECUTIVE SUMMARY

In this NDA submission, the applicant seeks the approval of pomalidomide in combination with (b) (4) dexamethasone for the treatment of relapsed or refractory multiple myeloma (MM) 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 considers the phase II part of the study. 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 part of Study CC-4047-MM-002.

In Study CC-4047-MM-002, the overall response rate (ORR) was 7.4% with median DOR not achieved yet for patients in pomalidomide alone group, and 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. 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 can not be evaluated in this NDA application.

2 INTRODUCTION

2.1 Overview

Pomalidomide is an IMiDs compound with a dual mechanism of action, including of both tumoricidal and immunomodulatory effects. 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 may be attributed substantially to pomalidomide and its synergistic effects when used in combination. Pomalidomide may represent 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.

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. 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, based on IRC assessments 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.

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/figures.

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 01 Mar 2011.

The original protocol for Study IFM 2009-02 was dated 11 June 2009, and the latest version was Amendment 3 dated 27 January 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/figures.

TABLE 1: LIST OF ALL STUDIES INCLUDED IN ANALYSIS

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Enrollment period Geographic region
CC-4047-MM-002 Phase 2	Phase I/II, multicenter, randomized (1:1), open-label, dose-escalation study to determine the MTD and evaluate safety and efficacy of pomalidomide alone and in combination with dexamethasone	Treatment until progressive disease (PD), therapy is discontinued permanently for any reason, or death	After treatment discontinuation, subjects were followed 3 times per year, up to five years, for survival, subsequent anti-myeloma therapies and monitoring of secondary primary malignancies.	Pom (N=108) Pom-Dex (N=113)	01 December 2009 – 22 September 2010 18 sites in the US and Canada
IMF 2009-02	Phase II, multicenter, randomized (1:1), open-label study to evaluate the safety and efficacy of two regimens of pomalidomide with low-dose dexamethasone	Treatment until PD, therapy is discontinued permanently for any reason, or death	After treatment discontinuation, subjects were followed for PD monthly until PD or until start of further myeloma therapy, after that, patients will be followed every 28 days until end of the study	Pom(21/28)+Dex (N=43) Pom(28/28)+Dex (N=41)	07 January 2009 – 08 July 2010 22 sites in France

2.2 Data Sources

Analysis datasets, SDTM tabulations, and software codes are located on network with network path: \\CDSESUB1\EVSPROD\NDA204026\204026.enx

3 STATISTICAL EVALUATION

This statistical evaluation is based on data from the Phase II part of the Study CC-4047-MM-002 and Study IFM 2009-02.

3.1 Data and Analysis Quality

The overall response data for Study CC-4047-MM-002 were derived and saved in analysis dataset "ADRS" for both IRC and investigator assessments. The overall response data for Study IFM 2009-02 were derived and saved in analysis datasets "ORR_D", "ORRINV_D" for IRC and investigator assessments respectively. This NDA application provided source data for deriving overall response from individual disease assessments. The statistical reviewer could verify overall response for most patients, except that in Study CC-4047-MM-002, number of responses (CR + PR) derived by the statistical reviewer was 3 less than what was derived by the applicant. The overall responses derived by the statistical reviewer were used in this statistical review.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

3.2.1.1.1 Study CC-4047-MM-002

The study CC-4047-MM-002 is Phase I/II, multicenter, randomized, open-label, dose-escalation study to determine the MTD and evaluate safety and efficacy of pomalidomide alone and in combination with 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.

The randomization was conducted via Interactive Voice Response System (IVRS) and stratified by age (≤75 vs. >75), prior number of treatments (2 vs. >2), and prior thalidomide exposure (yes vs. no). Approximately 192 patients were planned to be enrolled in the study. The final analysis of PFS was planned when 139 events occurred.

The primary objective of the study was to determine the efficacy of pomalidomide alone and in combination with low-dose dexamethasone as treatment for patients with relapsed and refractory multiple myeloma. PFS per IRC assessments was originally used as primary efficacy endpoint. However, since the study was not controlled for isolating the effect of pomalidomide, ORR per IRC was actually used to evaluating efficacy for each treatment arm separately in the CSR and this review.

One interim analysis was planned with 50% information (~70 PFS events). The superiority boundaries were calculated using alpha-spending function of the O'Brien-Fleming type with overall two-sided Type I error of 0.05 (Table 2).

The sample size was calculated based on log-rank test of PFS at a significance level of 5% (two-sided). With a 12-month accrual period and 12-month follow-up after the study closes to accrual, assuming a 10% drop-out rate, a sample size of 192 will have 85% power to detect a PFS HR

ratio of 0.6, i.e. median PFS of 10 months for Pom(21/28) + Dex arm versus 6 months for Pom arm, when approximately 139 PFS events occur.

TABLE 2: INTERIM ANALYSIS INFORMATION TIME AND BOUNDARIES

Analysis	# Event	Information time	Critical 2-sided P value
Interim analysis (50% information)	70	0.50	0.003
Final Analysis	139	1	0.0245

3.2.1.1.2 Study IFM 2009-02

The study IFM 2009-02 is a Phase II, multicenter, randomized, open-label study of pomalidomide and dexamethasone in relapsed or refractory MM patients who are progressive and did not achieve at least a partial response to lenalidomide and bortezomib. This study is a non comparative study investigating two modalities of administration.

The randomization was accomplished by the sponsor clinical research monitor according to the randomization list provided by the trial statistician. Randomization was only stratified by center.

The primary objective of the study was to determine the response rate to pomalidomide in combination with low-dose dexamethasone as treatment for the target population.

One initial interim analysis was planned when 6 patients had been randomized in each arm and completed at least one cycle to verify the safety of pomalidomide plus low-dose dexamethasone. A second interim analysis was planned when approximately 34 subjects had been enrolled across both treatment arms (17 per arm) in the first stage of the study and received at least two cycles of treatment. If a minimum of five responses (PR/CR) were observed in at least one treatment arm, the study will continue to the second stage.

The sample size was calculated according to the two stages binomial design for primary endpoint ORR. The null hypothesis H_0 is $p \leq 0.25$ (considered as an uninteresting level of response), against the alternative hypothesis H_1: $P \geq 0.45$ (where one can consider that the regimen would be sufficiently promising for further studies). For a two-sided type I error of 0.05 and power of 80%, the first stage will enroll 17 patients into each treatment arm. If 4 or fewer responses are observed from a treatment arm, that arm will be stopped early. Otherwise, additional 19 patients will be enrolled into that arm. Therefore, up to 36 patients will be enrolled into each treatment arm, and the whole study will enroll up to 72 patients. By expecting a 15% non-evaluable rate, 84 patients was planned to be randomized into the study.

3.2.1.2 Efficacy Endpoints

3.2.1.2.1 Study CC-4047-MM-002

The primary efficacy endpoint was progression-free survival, 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.

The secondary efficacy endpoints included:

- Overall response rate (ORR)
- Overall survival (OS)
- Duration of response (DOR)
- Time to response (TTR)

3.2.1.2.2 Study IFM 2009-02

The primary efficacy endpoint was overall response rate based on IRC assessments using IMWG criteria.

The secondary efficacy endpoints included:

- Overall response rate (ORR) based on investigator assessments
- Duration of response (DOR)
- Time to response (TTR)
- Time to progression (TTP)
- Progression-free survival (PFS)
- Overall survival (OS)

3.2.2 Statistical Methodologies

3.2.2.1.1 Study CC-4047-MM-002

According to the statistical analysis plan, PFS will be compared between Pom(21/28) + Dex arm and Pom arm using log-rank test. The hazard ratio and corresponding 95% confidence interval (CI) will be estimated using the un-stratified Cox proportional hazard model. Median PFS with 95% CI and survival curves will be estimated using Kaplan-Meier method.

One-sided one-sample binomial test for ORR in each arm will be performed with α=1.25%. The hypotheses of interest for each test are:

H_0: $p \leq 0.12$ vs. H_1: $p > 0.12$

Comparisons of ORR between treatment arms will be performed using a 2-sided Fisher's exact test with $\alpha = 5\%$.

However, the comparisons of PFS or ORR across two arms were not performed and HR for PFS with corresponding 95% CI was not calculated in this statistical review since CC-4047-MM-002 was a randomized but uncontrolled study.

3.2.2.1.2 Study IFM 2009-02

Efficacy results will be summarized descriptively by treatment arms. Comparisons of ORR between treatment arms will be made in an exploratory manner.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Analysis population

The intent-to-treat (ITT) population was the primary analysis population for all efficacy analyses, and was used for descriptions of disposition, demographics, and baseline disease characteristics.

Study CC-4047-MM-002 randomized 221 subjects with relapsed or refractory MM, 113 to the combination arm and 108 to the monotherapy arm respectively, from 18 sites in US and Canada. Two subjects (one from each arm) were randomized but never received study drug.

Study IFM 2009-02 randomized 84 subjects with relapsed or refractory MM, 43 to the intermittent treatment arm, and 41 to continuous treatment arm respectively, from 22 sites in France. All randomized subjects received at least one dose of study treatment.

Subject disposition

In study CC-4047- MM-002, at the time of study cutoff of 01 April 2011, 45 of 221 subjects remained active in the study. The most common reason for discontinuation in both arms was disease progression (57.5% in the Pom(21/28) + Dex arm and 49.1% in the Pom arm, respectively). The second most common reason for treatment discontinuation was adverse event (7.1% in the Pom(21/28) + Dex arm and 12.0% in the Pom arm, respectively).

TABLE 3: STUDY CC-4047-MM-002 SUBJECT DISPOSITION, ITT POPULATION

	Pom(21/28) + Dex N=113 n (%)	**Pom N=108 n (%)**
Subject still on treatment	23 (20.4)	22 (20.4)
Subject discontinued study tretament	90 (79.6)	86 (79.6)
Primary reason for discontinuation		
Disease progression	65 (57.5)	53 (49.1)
Adverse event	8 (7.1)	13 (12.0)
Death	8 (7.1)	9 (8.3)
Withdrew consent	5 (4.4)	7 (6.5)
Other*	4 (3.5)	3 (2.8)
Lost to follow-up	0 (0.0)	1 (0.9)

*: Other reasons included investigator decision, deterioration of patient condition, access to treatment, lack of response

[Source: study CC-2047-MM-002 CSR Pages 64 Table 10]

Reviewer's comment: In the applicant's Table 10, there is a category of "disease progression (unconfirmed)", the reviewer combined that category with "disease progression" category in Table 3.

In study IFM-2009-02, at the time of study cutoff of 01 March 2011, 23 of 84 subjects remained active in the study. The most common reason for discontinuation in both arms was disease progression (55.8% in the Pom(21/28) + Dex arm and 65.9% in the Pom(28/28) + Dex arm, respectively). The second most common reason for treatment discontinuation was death (7.0% in the Pom(21/28) + Dex arm and 7.3% in the Pom(28/28) + Dex arm, respectively).

TABLE 4: STUDY IFM 2009-02 SUBJECT DISPOSITION, ITT POPULATION

	Pom(21/28) + Dex N=43 n (%)	**Pom (28/28) + Dex N=41 n (%)**
Subject still on treatment	14 (32.6)	9 (22.0)
Subject discontinued study treatment	29 (67.4)	32 (78.0)
Primary reason for discontinuation		
Disease progression	24 (55.8)	27 (65.9)
Death	3 (7.0)	3 (7.3)
Toxicity	0 (0)	2 (4.9)
Consent withdrawn	1 (2.3)	0 (0)
Lost to follow-up	1 (2.3)	0 (0)

*: Other reasons included investigator decision, deterioration of patient condition, access to treatment, lack of response

[Source: study IFM 2009-02 CSR Pages 93 Table 10]

Reviewer's comment: In applicant's table 10, percentages for each discontinuation reason were calculated using number of subjects discontinued from study treatment as the denominator. To present subject disposition results consistently across studies CC-4047-MM-002 and IFM 2009-02, percentages for each discontinuation reason in Table 4 were calculated using number of subjects randomized to that treatment arm as the denominator.

Subject demographics and baseline disease characteristics

Baseline disease characteristics for study CC-4047-MM-002 are summarized in Table 5. Subject demographics appeared to be balanced between the Pom(21/28) + Dex arm and the Pom arm, except that more patients were < 65 years old in the Pom arm(60.2% vs. 53.1%), a higher percentage of subjects had normal baseline ECG in the Pom(21/28) + Dex arm (46.9% vs. 40.7%), a higher percentage of subjects had ECOG performance status of 0 in the Pom(21/28) + Dex arm (28.3% vs. 22.2%), more patients had cytogenetic risk measurements missing in Pom arm (32.4% vs. 23.0%).

TABLE 5: STUDY CC-4047-MM-002 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, ITT POPULATION

	Pom(21/28) + Dex N=113	Pom N=108	Total N=221
Age (years)			
Mean (SD)	64.4 (9.2)	62.9 (10.4)	63.7 (9.8)
Median (Min, Max)	64.0 (34, 88)	61.0 (37, 88)	63.0 (34, 88)
Category, n (%)			
< 65	60 (53.1)	65 (60.2)	125 (56.6)
≥ 65	53 (46.9)	43 (39.8)	96 (33.4)
Sex, n (%)			
Male	51 (45.1)	51 (47.2)	102 (46.2)
Female	62 (54.9)	57 (52.8)	119 (53.8)
Race, n (%)			
White	92 (81.4)	86 (79.6)	178 (80.5)
Black or Africa 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)
Baseline ECG, n (%)			
Normal	53 (46.9)	44 (40.7)	97 (43.9)
Abnormal, not clinically significant	56 (49.6)	59 (54.6)	115 (52.0)
Abnormal, clinically significant	0 (0.0)	1 (0.9)	1 (0.5)
Missing	4 (3.5)	4 (3.7)	8 (3.6)
ECOG performance Status, 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)	13 (12.1)	26 (11.8)
Cytogenetic abnormality, n (%)			
High risk	42 (37.2)	36 (33.3)	78 (35.3)
Non-high risk	45 (39.8)	37 (34.3)	82 (37.1)
Missing	26 (23.0)	35 (32.4)	61 (27.6)

SD: standard deviation; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group
[Source: Study CC-2047-MM-002 CSR Page 69 Table 13 and statistical reviewer's analysis]

Reviewer's comment: The applicant categorized age to "≤ 75" vs. "> 75" in the study CC-4047-MM-002. To present demographics consistently across two studies CC-4047-MM-002 and IFM 2009-02, age was presented as "< 65" vs. "≥ 65" in Table 5 and Table 16 for subgroup analysis of ORR by age.

Baseline disease characteristics for study IFM 2009-02 are summarized in Table 6. Subject demographics appeared to be balanced between the Pom(21/28) + Dex arm and the Pom(28/28) + Dex arm, except that more subjects in the Pom(21/28) + Dex arm (74.4% vs. 63.4%) were younger than 65 years of age. Compared to Study CC-4047-MM-002, patients in study IFM 2009-02 were slightly younger, more were male, and more had ECOG performance status of 0 or ≥ 2.

TABLE 6: STUDY IFM 2009-02 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, ITT POPULATION

	Pom(21/28) + Dex N=43	**Pom (28/28) + Dex N=41**	**Total N=84**
Age (years)			
Mean (SD)	60.5 (9.3)	60.41 (9.1)	60.4 (9.2)
Median (Min, Max)	60.0 (45, 81)	60.0 (42, 83)	60.0 (42, 83)
Category, n (%)			
< 65	32 (74.4)	26 (63.4)	58 (69.0)
≥ 65	11 (25.6)	15 (36.6)	26 (31.0)
Sex, n (%)			
Male	30 (69.8)	27 (65.9)	57 (67.9)
Female	13 (30.2)	14 (34.1)	27 (32.1)
ECOG performance Status, n (%)			
0	16 (37.2)	17 (41.5)	33 (39.3)
1	18 (41.9)	16 (39.0)	34 (40.5)
≥ 2	9 (20.9)	8 (19.5)	17 (19.0)

SD: standard deviation; ECOG: Eastern Cooperative Oncology Group
[Source: Study IFM 2009-02 CSR Page 100 Table 14]

Table 7 and 8 summarize the baseline disease characteristics for study CC-4047-MM-002 and IFM 2009-02 respectively. The two studies were similar in the distribution of baseline disease characteristics.

TABLE 7: STUDY CC-4047-MM-002 BASELINE DISEASE CHARACTERISTICS, ITT POPULATION

	Pom(21/28) + Dex N=113	**Pom N=108**	**Total N=221**
Prior anti-myeloma therapy given, n(%)			
Yes	113 (100)	108 (100)	221 (100)
Number of prior anti-myeloma regimen			
Mean (SD)	5.6 (2.37)	5.5 (2.47)	5.6 (2.42)
Median (Min, Max)	5.0 (2.0, 13.0)	5.0 (2.0, 12.0)	5.0 (2.0, 13.0)
Prior thalidomide exposure, n (%)			
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 MM stage, n (%)			
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, n (%)			
No	29 (25.7)	26 (24.1)	55 (24.9)
Yes	84 (74.3)	82 (75.9)	166 (75.1)
Prior radiation therapy, n (%)			
No	71 (62.8)	62 (57.4)	133 (60.2)
Yes	42 (37.2)	46 (42.6)	88 (39.8)
Prior cancer surgery, n (%)			
No	104 (92.0)	96 (88.9)	200 (90.5)
Yes	9 (8.0)	12 (11.1)	21 (9.5)

SD: standard deviation;

[Source: Study CC-4047-MM-002 CSR Pages 71 Table 14]

TABLE 8: STUDY IFM 2009-02 BASELINE DISEASE CHARACTERISTICS, ITT POPULATION

	Pom(21/28) + Dex N=43	**Pom (28/28) + Dex N=41**	**Total N=84**
Prior anti-myeloma therapy given, n(%)			
Yes	43 (100)	41 (100)	84 (100)
Number of prior anti-myeloma regimen			
Mean (SD)	5.9 (3.8)	6.2 (3.4)	6.1 (5.1)
Median (Min, Max)	6.0 (3.0, 8.0)	6.0 (3.0, 8.0)	6.0 (3.0, 8.0)
Prior thalidomide exposure, n (%)			
No	14 (32.7)	9 (22.0)	23 (27.4)
Yes	29 (67.4)	32 (78.0)	61 (72.6)
Time from first pathologic diagnosis (years)			
Mean (SD)	6.4 (4.7)	7.0 (4.0)	6.7 (4.4)
Median (Min, Max)	5.1 (0.9, 18.7)	6.5 (0.8, 23.1)	5.9 (0.8, 23.1)

SD: standard deviation;

[Source: Study IFM 2009-02 CSR Pages 100 Table 14, Page 113 Table 26 and statistical reviewer's analysis]

Summary of refractory status

In study CC-4047-MM-002, the majority of subjects were refractory to lenalidomide (77.8%) or bortezomib (71%) and 60.2% were refractory to both lenalidomide and bortezomib.

TABLE 9: STUDY CC-4047-MM-002 SUMMARY OF REFRACTORY STATUS, ITT POPULATION

	Pom(21/28) + Dex	**Pom**	**Total**
	N=113	**N=108**	**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: Study CC-4047-MM-002 CSR 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 10: STUDY IFM 2009-02 SUMMARY OF REFRACTORY STATUS, ITT POPULATION

	Pom(21/28) + Dex N=43	**Pom(28/28) + Dex 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: Statistical reviewer's analysis]

Reviewer's comment: In IFM 2009-02 study CSR, the applicant only summarized refractory status to last prior regimen containing lenalidomide or bortezomib or both. To present refractory status consistently across two studies CC-4047-MM-002 and IFM 2009-02, the statistical reviewer summarized the refractory status to all prior regimens containing lenalidomide or bortezomib or both in Table 10 and Table 17 for subgroup analysis of ORR by refractory status.

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Protocol deviation

In study CC-4047-MM-002, a total of 27 subjects [12.2%] (7 [6.2%] in the Pom(21/28) + Dex arm and 20 [18.5%] in the Pom arm) had major protocol deviations defined in the study protocol.

TABLE 11: STUDY CC-4047-MM-002 SUBJECTS WITH MAJOR PROTOCOL VIOLATIONS, ITT POPULATION

	Pom(21/28) + Dex (N=113) n (%)	**Pom (N=108) n (%)**
Subjects with at least 1 major protocol violation	7 (6.2)	20 (18.5)
Entered study but did not satisfy entry criteria	2 (1.8)	8 (7.4)
Study treatment were not discontinued per protocol	1 (0.9)	0 (0.0)
Received wrong medication or incorrect dose	3 (2.7)	9 (8.3)
Missing visit or assessment	1 (0.9)	0 (0.0)
Other	0 (0.0)	5 (4.6)

[Source: Study CC-4047-MM-002 CSR Page 67 Table 11]

In study IFM 2009-02, 5 patients were reported to have major eligibility criteria deviations and 4 patients had major protocol deviation of either receiving wrong treatment in wrong schedule or incorrect dose.

3.2.4 Results and Conclusions

3.2.4.1 Results from the Study CC-4047-MM-002

3.2.4.1.1 Results of Overall response

Based on projection, interim analysis of PFS was scheduled with a cutoff date of 29 October 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 01 April 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 controlled to isolate the effect of pomalidomide, ORR per IRC was used to evaluating efficacy for each treatment arm separately in the CSR and this review. This review's analysis results of ORR are summarized in Table 12. 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. Differences between the applicant's analysis and FDA analysis are provided below table 12 in "Reviewer's comments".

TABLE 12: STUDY CC-4047-MM-002 ANALYSIS RESULTS OF ORR PER IRC, ITT POPULATION (FDA ANALYSIS)

	Pom(21/28) + 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
Partial Response (PR), n (%)	32 (28.3)	8 (7.4)
95% CI for ORR (%)	(21.0, 38.5)	(3.3, 14.1)
Duration of response (DOR)	33	8
Number of subjects progressed or died, n (%)	22 (66.7)	1 (12.5)
Median DOR (Months) (95% CI)	7.4 (5.1, 9.2)	NE (NE, NE)

CI: confidence interval;

[Source: Statistical reviewer's analysis]

Reviewer's comments:

- 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 summarized in Table 12 was based on 41 not 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. Formally, it is unknown whether these three patients were responders with respect to the protocol definition of response.

3.2.4.1.2 Analysis results for other efficacy endpoints

The analysis results of time to response (TTR), PFS and OS endpoints are summarized in Table 13 for study CC-4047-MM-002. In addition to the analysis of OS done at the cutoff of 01 April 2011, the applicant performed an updated analysis of OS at the cutoff of 16 September 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.

TABLE 13: STUDY CC-4047-MM-002 SUMMARY OF OTHER EFFICACY ENDPOINTS, ITT POPULATION (FDA ANALYSIS)

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: Statistical reviewer's analysis]

Reviewer's comment:

- In this review, no comparisons were made between two treatment arms for any efficacy endpoints since study CC-4047-MM-002 was uncontrolled relative to isolating the effect of pomalidomide.
- 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.

3.2.4.2 Results from the Study IFM 2009-02

3.2.4.2.1 Results of Overall response

The primary analysis results of ORR are summarized in Table 14 for study IFM 2009-02. The overall response rates were 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 14: STUDY IFM 2009-02 ANALYSIS RESULTS OF ORR PER IRC, ITT POPULATION

	Pom(21/28) + Dex	**Pom (28/28) + Dex**
	N=43	**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)
95% CI for ORR (%)	(21.0, 50.9)	(20.1, 50.6)
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)

CI: confidence interval; 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.

3.2.4.2.2 Analysis results for other efficacy endpoints

The analysis results of time to response (TTR), PFS and OS endpoints are summarized in Table 15 for study IFM 2009-02.

Reviewer's comment:

- In this review, no comparisons were made between two treatment arms for any efficacy endpoints since study IFM 2009-02 was uncontrolled relative to isolating the effect of pomalidomide.

TABLE 15: STUDY IFM 2009-02 SUMMARY OF OTHER EFFICACY ENDPOINTS, ITT POPULATION

Endpoints	**Statistic**	**Pom(21/28) + Dex** N=43	**Pom (28/28) + Dex** 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]

3.2.4.3 Conclusions for efficacy

The studies 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 can not be evaluated in this NDA application.

3.3 Evaluation of Safety

Please refer to clinical review of this application for safety results and conclusions for safety.

3.4 Benefit-risk assessment

Since both studies supporting this NDA application are uncontrolled, the benefit/risk can not be assessed based on comparative analyses. Whether the submission demonstrated an overall favorable risk-benefit profile on pomalidomide alone or pomalidomide plus low-dose dexamethasone is deferred to the clinical team reviewing this submission.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age, Race and Region

Table 16 summarizes the subgroup analyses of overall response rate by gender, age, race and region for the study CC-4047-MM-002 and IFM 2009-02 when applicable. The ORR results by subgroups of gender, age, race and region are consistent with the ORR results for all patients.

TABLE 16: ORR PER IRC – SUBGROUP ANALYSES BY GENDER, AGE, RACE, AND REGION, ITT POPULATION (FDA ANALYSIS)

Subgroup	**Study CC-4047-MM-002**		**Study IFM 2009-02**	
	Pom(21/28) + Dex	**Pom**	**Pom(21/28) + Dex**	**Pom(28/28) +Dex**
	N=113	**N=108**	**N=43**	**N=41**
	r/n (%)	**r/n (%)**	**r/n (%)**	**r/n (%)**
Gender				
Male	17/51 (33.3)	6/51 (11.8)	11/30 (36.7)	10/27 (37.0)
Female	16/62 (25.8)	2/57 (3.5)	4/13 (30.8)	4/14 (28.6)
Age				
< 65 yrs	17/60 (28.3)	3/65 (4.6)	13/32 (40.6)	9/26 (34.6)
≥ 65 yrs	16/53 (30.2)	5/43 (11.6)	2/11 (18.2)	5/15 (33.3)
Race				
White	26/92 (28.3)	6/86 (7.0)	NA	
Other	7/21 (33.3)	2/22 (9.1)		
Region				
USA	29/94 (30.9)	8/84 (9.5)	N/A	
Canada	4/19 (21.1)	0/24 (0)		

r: number of response, n: number of subjects in a subgroup

NA: Not available.

[Source: Study IFM 2009-02 CSR Page 153 Table 54 and statistical reviewer's analysis]

Reviewer's comments:

- Race information was not collected in the study IFM 2009-02, therefore results of ORR by race are not provided for that study.
- All patients in the study IFM 2009-02 were enrolled in France; therefore results of ORR by region are not provided either for that study.
- In study CC-4047-MM-002, number of responses (CR/PR) is slightly different based on statistical reviewer's and applicant's derivations respectively, the subgroup analyses results presented in Table 16 were based on statistical reviewer's derivations.
- The subgroup analyses results of ORR were consistent with those from the primary analyses of ORR for all patients.

4.2 Refractory status to prior treatment

Table 17 summarizes the subgroup analyses of overall response rate 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 17: ORR PER IRC – SUBGROUP ANALYSES BY REFRACTORY STATUS, ITT POPULATION

Subgroup	**Study CC-4047-MM-002**		**Study IFM 2009-02**	
	Pom(21/28) + Dex	**Pom**	**Pom(21/28) + Dex**	**Pom(28/28) +Dex**
	N=113	**N=108**	**N=43**	**N=41**
	r/n (%)	**r/n (%)**	**r/n (%)**	**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	0/3 (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	0/3 (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	0/4 (0)		

r: number of response, n: number of subjects in a subgroup

[Source: Statistical reviewer's analysis]

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The treatment effect of pomalidomide can not be isolated and the contribution of pomalidomide to the treatment benefit of pomalidomide plus low-dose dexamethasone can not be evaluated in both studies CC-4047-MM-002 and IFM 2009-02.

5.2 Collective evidence

Based on the overall response data from both studies CC-4047-MM-002 and IFM 2009-02, pomalidomide plus low-dose dexemethasone provided durable treatment effect for relapsed or refractory multiple myeloma patients. However, both studies CC-4047-MM-002 and IFM 2009-02 were uncontrolled studies, no statistical comparisons between treatment arms can be performed to evaluate the contribution of pomalidomide to the treatment benefit of the combination therapy of pomalidomide plus low-dose dexamethasone.

5.3 Conclusions and Recommendations

This NDA application was based on two multicenter Phase II studies (CC-4047-MM-002 and IFM 2009-02) to evaluate the treatment effect of pomalidomide plus low-dose dexamethasone for 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. Both studies demonstrated durable overall response benefit of pomalidomide plus low-dose dexamethasone, although the contribution of pomalidomide was not evaluable. The final decision on the benefit-risk evaluation of pomalidomide alone or pomalidomide plus low-dose dexamethasone is deferred to the clinical review team.

5.4 Labeling recommendations

Reviewer's comment:

- Since there is no controlled comparison that isolated the effect of pomalidomide, PFS results, p values or any comparative statements between treatment arms should not be included in the labeling.
- Overall response rate and duration of response results for study CC-4047-MM-002 should be revised based on statistical reviewer's analyses.
- Due to the small number of responders in the subgroups, overall response results by refractory status to lenalidomide and/or bortezomib should not be included in the labeling.

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

/s/

YUN WANG
12/17/2012

MARK D ROTHMANN
12/17/2012
I concur

RAJESHWARI SRIDHARA
12/17/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

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

Drug Name: Pomalidomide plus dexamethasone **NDA/BLA Type:** 505(b)(2)

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.				Additional information is being requested on the interim analysis
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			X	

File name: 5_Statistics Filing Checklist for a New NDA_BLA

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Comment:

1. Please provide the details on how the interim analysis was performed, such as the efficacy boundaries that were used, and the closed report for DMC and DMC meeting minutes.

Yun Wang **12Jun2012**

Reviewing Statistician Date

Supervisor/Team Leader Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA

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

/s/

YUN WANG
06/13/2012

MARK D ROTHMANN
06/13/2012