

## 2. SYNOPSIS

<b>Name of Sponsor/Company:</b> Celgene Corporation	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Revlimid®	Volume:	
<b>Name of Active Ingredient:</b> Lenalidomide (CC-5013)	Page:	
<p><b>Title of Study:</b> A Phase III, Multicentre, Randomised, Double-blind, Placebo-controlled, 3-Arm Parallel-group Study to Determine the Efficacy and Safety of Lenalidomide (Revlimid®) in Combination With Melphalan and Prednisone Versus Placebo Plus Melphalan and Prednisone in Subjects With Newly Diagnosed Multiple Myeloma Who are 65 Years of Age or Older</p>		
<p><b>Coordinating Principal Investigator:</b> [REDACTED]</p> <p><b>Investigators:</b> Appendix 16.1.4 contains a list of investigators who participated in this study.</p>		
<p><b>Study centers:</b> Subjects were randomized at 82 sites (70 in Europe; 8 in Australia; and 4 in Israel).</p>		
<p><b>Publications (reference):</b> Dimopoulos MA, Palumbo A, Hajek R, Kropff M, Petrucci MT, Lewis P, et al. Factors that influence health-related quality of life in newly diagnosed multiple myeloma patients aged ≥ 65 years treated with melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance: results of a randomized trial. <i>Leuk Lymphoma</i>. 2013 Oct 21 [Epub ahead of print].</p> <p>Dimopoulos MA, Delforge M, Hájek R, Kropff M, Petrucci MT, Lewis P, et al. Lenalidomide, melphalan, and prednisone, followed by lenalidomide maintenance, improves health-related quality of life in newly diagnosed multiple myeloma patients aged 65 years or older: results of a randomized phase III trial. <i>Haematologica</i>. 2013;98(5):784-8.</p> <p>Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. <i>N Engl J Med</i> 2012;366(19):1759-69. Erratum in: <i>N Engl J Med</i>. 2012;367(3):285.</p> <p>Palumbo A, Dimopoulos MA, Delforge M, Kropff M, Foa R, Yu Z, et al. A phase III study to determine the efficacy and safety of lenalidomide in combination with melphalan and prednisone (MPR) in elderly patients with newly diagnosed multiple myeloma. <i>Blood</i> 2009;114:Abstract 613.</p>		
<p><b>Studied period (years):</b></p> <p><b>Date first patient randomized:</b> 01 Feb 2007</p> <p><b>Date last patient randomized:</b> 19 Sep 2008</p>		<p><b>Phase of development:</b></p> <p>3</p>
<p><b>Objectives:</b></p> <p><b>Primary:</b></p> <p>To determine the efficacy of melphalan/prednisone/lenalidomide (MPR) compared with placebo plus MP in subjects with newly diagnosed multiple myeloma (NDMM) who are 65 years of age or older.</p> <p><b>Secondary:</b></p> <p>To assess the safety of MPR compared with placebo plus MP in subjects with NDMM who are 65 years of age or older.</p>		
<p><b>Methodology:</b></p> <p>This is an ongoing, multicenter, randomized, double-blind, placebo-controlled, 3-arm parallel-group study that investigates the use of standard-dose melphalan/prednisone (MP) plus lenalidomide (R; 10 mg daily dose) in</p>		

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subjects with newly diagnosed MM who are 65 years of age or older. This study consists of 3 periods/phases for each study subject: a treatment period (induction therapy period followed by maintenance therapy period), an open-label extension phase, and a follow-up phase. Since Protocol Amendment 3, all subjects were unblinded and could either continue with lenalidomide treatment (Arm MPR+R) or stopped placebo and were observed until PD (Arms MPR+p and MPp+p). Subjects who met all eligibility criteria were randomized (1:1:1) by a double-blind procedure utilizing a validated interactive voice response system (IVRS) to 1 of 3 treatment arms:

- Induction therapy with MPR (up to 9 cycles) followed by maintenance therapy with single-agent lenalidomide (herein referred to as Arm MPR+R)
- Induction therapy with MPR (up to 9 cycles) followed by maintenance therapy with placebo (herein referred to as Arm MPR+p)
- Induction therapy with MP plus placebo (up to 9 cycles) followed by maintenance therapy with placebo (herein referred to as Arm MPp+p)

Subjects were stratified at randomization by age ( $\leq 75$  years versus  $> 75$  years) and stage (International Staging System [ISS]; Stages I and II versus Stage III).

The start of the treatment phase (Day 1 of study treatment) was to occur on the same day that the subject was randomized. Each subject continued the treatment phase until: 1) progressive disease (PD) occurred; or 2) lenalidomide/placebo therapy was discontinued permanently for any reason. All subjects were to be followed in this study for at least 5 years from randomization.

**Number of patients (planned and analyzed):**

**Planned:** 450 subjects randomized in a 1:1:1 ratio to Arms MPR+R, MPR+p, or MPp+p  
**Enrolled:** 459 subjects – 152 in Arm MPR+R, 153 in Arm MPR+p, and 154 in Arm MPp+p  
**Analyzed:** 459 subjects (intent-to-treat population) and 455 subjects (safety population)

**Diagnosis and main criteria for inclusion:**

Newly diagnosed with symptomatic MM as defined by monoclonal plasma cells in the bone marrow  $\geq 10\%$  and/or presence of a biopsy-proven plasmacytoma, monoclonal protein present in the serum and/or urine, and myeloma-related organ dysfunction (at least 1 of the following)

- [C] Calcium elevation in the blood (serum calcium  $>10.5$  mg/dL or  $\geq$  upper limit of normal)
- [R] Renal insufficiency (serum creatinine  $> 2$  mg/dL)
- [A] Anemia (hemoglobin  $< 10$  g/dL or  $2$  g  $<$  normal)
- [B] Lytic bone lesions or osteoporosis

AND have measurable disease as defined by the following;

- Immunoglobulin G (IgG) MM: Serum monoclonal paraprotein (M-protein) level  $\geq 1.0$  g/dL or urine M-protein level  $\geq 200$  mg/24 hours
- Immunoglobulin A (IgA) MM: Serum M-protein level  $\geq 0.5$  g/dL or urine M-protein level  $\geq 200$  mg/24 hours
- Immunoglobulin D (IgD) MM: Serum M-protein level  $\geq 0.05$  g/dL or urine M-protein level  $\geq 200$  mg/24 hours
- Light chain MM: Serum M-protein level  $\geq 1.0$  g/dL or urine M-protein level  $\geq 200$  mg/24 hours
- Immunoglobulin M (IgM) multiple myeloma (IgM M-protein plus lytic bone disease documented by skeletal survey plain films): Serum M-protein level  $\geq 1.0$  g/dL or urine M-protein level  $\geq 200$  mg/24 hours

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<b>Name of Active Ingredient:</b> Lenalidomide (CC-5013)		
<b>Test product, dose and mode of administration, batch number:</b>		
<p><u>Treatment period:</u> Lenalidomide capsules for oral administration were supplied by Celgene International Sàrl as 2.5- and 5-mg capsules in 21-day blister packs. Each blister pack contained 42 capsules (ie, 2 x 5-mg capsules for 21 days of dosing) of active lenalidomide.</p>		
<p><b>Batch numbers for lenalidomide:</b> 06F0180, 07F0220, 08F0089, 09F0604 (2.5-mg capsule); 06F0180, 07F0220, 08F0089, 09F0604 (5-mg capsule); 06F0118.1, 06F0180, 07F0220, 08F0089, 09F0604 (1 x 2.5-mg capsule plus 1 x 5-mg capsule = 7.5 mg); 06F0117.1, 06F0117.2, 06F0179, 07F0221, 08F0100, 09F0604 (2 x 5-mg capsules = 10 mg).</p>		
<p><u>Open-label extension phase:</u> Lenalidomide capsules for oral administration were supplied by Celgene International Sàrl as 2.5-, 5-, 10-, 15-, and 25-mg capsules in bottles packaged for 21 days of dosing.</p>		
<p><b>Batch numbers:</b> 09F0294, 10F0240, 11F0296, 12F0286 (2.5-mg capsules); 07F0231, 09F0295, 10F0241, 11F0297 (5-mg capsules); 06F0148, 08F0333, 10F0242, 11F0298, 12F0313 (10-mg capsules); 06F0149, 09F0296, 11F0299, 12F1004 (15-mg capsules); 06F0150, 08F0095, 09F0118, 09F0297, 11F0300 (25-mg capsules).</p>		
<b>Duration of treatment:</b>		
<p>During the treatment period, all subjects were to receive up to 9 cycles of MPR (or MP plus placebo therapy) during the induction therapy period followed by treatment with either lenalidomide or placebo during the maintenance therapy period until disease progression or treatment discontinuation. Each cycle of the treatment period was a 28-day (4-week) cycle.</p>		
<b>Reference therapy, dose and mode of administration, batch number:</b>		
<p><u>Treatment period:</u> Matching placebo capsules for oral administration were supplied by Celgene International Sàrl as 2.5- and 5-mg capsules in 21-day blister packs. Each blister pack contained 42 capsules (ie, 2 x 5-mg capsules for 21 days of dosing) of matching placebo capsules.</p>		
<p>Commercial supplies of Alkeran® (melphalan 2-mg tablets) and prednisone (1-, 5-, 10-, 20-, and 50-mg tablets) for oral administration, were labeled as clinical trial supplies and provided by Celgene International Sàrl.</p>		
<p><b>Batch numbers for matching placebo capsules:</b> 07F0220, 08F0089, 09F0604 (2.5-mg capsule); 06F0180, 07F0220, 08F0089, 09F0604 (5-mg capsule); 06F0118.2, 06F0180, 07F0220, 08F0089, 09F0604 (1 x 2.5-mg capsule plus 1 x 5-mg capsule = 7.5 mg); 06F0117.2, 06F0179, 07F0221, 08F0100, 09F0604, 09F0624 (2 x 5-mg capsules = 10 mg).</p>		
<p><b>Batch numbers for melphalan 2-mg tablets:</b> 06F0119, 06F0181, 07F0041, 08F0160, 08F0190</p>		
<p><b>Batch numbers for prednisone:</b> 06F0120, 06F0182, 08F0321 (1-mg tablet); 06F0121, 06F0183, 08F0322 (5-mg tablet); 06F0122, 06F0184, 08F0323 (10-mg tablet); 06F0123, 06F0185, 08F0324 (20-mg tablet); 06F0124, 06F0186, 07F0167, 08F0159, 08F0262 (50-mg tablet).</p>		
<p><u>Other recommended medications:</u> Other recommended medications such as aspirin for oral administration were provided by the hospital.</p>		
<p><u>Open-label extension phase:</u> Dexamethasone for oral administration was provided by the hospital.</p>		
<b>Criteria for evaluation:</b>		
<p><b>Efficacy:</b> <u>Protocol-planned primary efficacy endpoint</u> – progression-free survival (PFS)  <u>Secondary efficacy endpoints:</u> time to progression (sensitivity analysis for PFS), myeloma response rate, time to response, duration of response, time to next antimyeloma therapy (AMT), overall survival (OS), and quality of life  <u>Additional efficacy endpoint:</u> progression-free survival on next-line therapy (PFS2)</p>		

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<b>Name of Active Ingredient:</b> Lenalidomide (CC-5013)		
<p align="center"><u>Exploratory endpoint:</u> cytogenetic abnormalities</p>		
<p><b>Safety:</b> Adverse events, clinical laboratory assessments, vital sign measurements, and electrocardiograms (ECGs).</p>		
<p><b>Statistical methods:</b></p> <p>The primary efficacy analyses for all endpoints were performed based on the intent-to-treat (ITT) population. For the efficacy analysis of all endpoints, the primary comparison was Arms MPR+R versus MPP+p.</p> <p>Progression-free survival was calculated as the time from randomization to the first documentation of progressive disease based on the Bladé response criteria [EBMT/IBMTR/ABMTR], or death due to any cause during the treatment period, whichever occurred earlier. Subjects who withdrew for any reason, or received another AMT without documented PD were censored on the date of their last adequate response assessment, before receiving any other AMT. Subjects who were still active at the time of the data cutoff date without PD were censored on the date of their last adequate response assessment. These rules were based on Food and Drug Administration (FDA) guidance for cancer trial endpoints (Guidance for Industry – Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007).</p> <p>The Kaplan-Meier method was used to estimate the survival distribution functions for each treatment arm. The median PFS along with the 2-sided 95% confidence intervals (CIs) for the median were estimated. In addition, the event rates at specific time points (eg, 26, 52, 78, and 104 weeks) were computed, along with the standard errors (Greenwood’s formula; Klein, 2003). The plots of survival curves using the Kaplan-Meier method were presented. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.</p> <p>For the primary efficacy variable, PFS, a 50% improvement in median TTP, from 15 months in Arm MPP+p to 22.5 months in Arm MPR+R, was considered clinically relevant and, therefore, the target difference. Based on prior clinical experience, the median survival in Arm MPR+R was estimated at 54 months, while that in Arm MPP+p was 36 months.</p> <p>For the primary analysis, the comparison of PFS between Arms MPR+R and MPP+p using the unstratified log-rank test, the overall 2-sided significance level was 5%. This 5% was spread over 3 analyses (2 interim analyses and 1 final analysis) by an O’Brien-Fleming alpha spending function (DeMets, 1994). The significance of efficacy was claimed if the p-value was less than or equal to the significance level as calculated based on the specified alpha spending function and the observed number of events. To account for the stratified randomization, a log-rank test stratified by the 2 strata used in the randomization (age and ISS score) was performed as a secondary analysis for PFS, in addition to the unstratified analysis described above. Sensitivity analyses for PFS were performed using different censoring rules to support the robustness of the primary PFS results, including censoring subjects who discontinued due to reasons other than progressive disease, or censoring subjects according to the EMA anticancer guidelines on hematologic malignancies (Appendix 1 to the Guideline on the Evaluation of Anticancer Medicinal Products in Man on Haematological Malignancies; CHMP, 2012).</p> <p>Overall survival was defined as the time between randomization and death. Subjects who died, regardless of the cause of death, were considered to have had an event. All subjects who were lost to follow-up before the end of the trial, or who were withdrawn from the trial, were censored at the time of last contact. Subjects who were still being treated were censored at the last available date available, or clinical cutoff date, if it was earlier.</p> <p>Time to progression (TTP) was calculated as the time between the randomization and disease progression as determined by the Central Adjudication Committee (CAC) based on the Bladé response criteria [EBMT/IBMTR/ABMTR]. Subjects who withdrew consent for any reason, or received another AMT without documented PD, were censored at the date of their last adequate response assessment, before receiving any other AMT. Subjects who were still ongoing on study at the time of the data cutoff date without PD were censored on the date of their last adequate response assessment. This rule, based on FDA for cancer trial endpoints (Guidance for Industry – Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, FDA/CDER/CBER, May</p>		

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<b>Name of Finished Product:</b> Revlimid®	Volume:	
<b>Name of Active Ingredient:</b> Lenalidomide (CC-5013)	Page:	

2007), which specifies the application of the FDA guidance for various common situations, were also applied to TTP except that progression, instead of death, was considered as an event.

The response rate was based on the response assessments. The European Group for Blood and Marrow Transplantation (EBMT) criteria (Bladé, 1998), also referred to as the IBMTR/ABMTR criteria, including PD, were used to determine the myeloma responses.

The overall response rate (ORR) was calculated as the number of confirmed responders (at least a PR and maintained for at least 6 weeks) divided by the number of subjects in the ITT population for the primary analysis of the response rate. The ORR, together with the relative proportions in each response category based on the EBMT criteria (ie, CR, PR, SD, and PD), was examined. Confirmed responses that were documented after the subjects received other antimyeloma treatment were not counted as responses; however, these subjects were included in the denominator. Comparisons of ORR between treatment arms were performed using a 2-sided Fisher’s exact test with  $\alpha = 5\%$ . The distribution of subjects over the response categories (excluding the “Response Not Evaluable” [NE] category) was compared between treatment groups using the Wilcoxon rank sum test.

Summary statistics were used to summarize the time to response (defined as the time from randomization to the time when the response criteria for a CR, VGPR, or PR were first achieved) by treatment arm, and the time to response was compared between treatment arms using the Wilcoxon rank sum test. Subjects who were nonresponders were excluded from this analysis.

Duration of myeloma response was defined as the time from when the response criteria for CR or PR were first achieved to the time when the response criteria for PD were met, or until the subject died from any cause, whichever occurred first. Duration of response for subjects last known to be alive with no progression after a CR or PR was censored at the date of last adequate response assessment. Subjects with confirmed responses that occurred after receiving any other AMT, including radiation therapy initiated after baseline, were censored at the last adequate assessment before the initiation of such treatment. Subjects who were nonresponders were excluded from this analysis.

Time to the next AMT was defined as time from randomization to the start of another non-protocol AMT. Subjects who did not receive other AMT were censored at the last assessment or follow-up visit known to have received no new therapy.

Progression-free survival on next-line therapy (PFS2) was defined as the time from randomization to the start of 3<sup>rd</sup>-line AMT or death, whichever came first. Subjects who did not receive 3<sup>rd</sup>-line AMT or who were survivors were censored as of the data cutoff date (30 Apr 2013).

The effect of treatment on the efficacy endpoints PFS, OS, PFS2, and ORR were compared between treatment arms within subgroups defined by the following variables:

- Age group ( $\leq 75$  versus  $> 75$  years)
- Baseline International Staging System (stages I or II versus stage III)
- Gender (male versus female)

The quality of life (QoL) outcomes assessments included EORTC QLQ-C30 and QLQ-MY24.

Changes from baseline in Karnofsky performance status scores were summarized by treatment group and by cycle, and compared between treatment groups using 2-sample t-test.

An IDMC was convened for the study. The IDMC was composed of medical hematologists/oncologists with experience in treating subjects with multiple myeloma and a statistician, all of whom were not otherwise involved in the study. An independent unblinded statistician performed the interim analyses. The IDMC reviewed the safety data, including AEs and clinical laboratory data, at regular time intervals on an ongoing basis in closed sessions. During the study, the IDMC reviewed the efficacy data in accordance with the guidelines for the

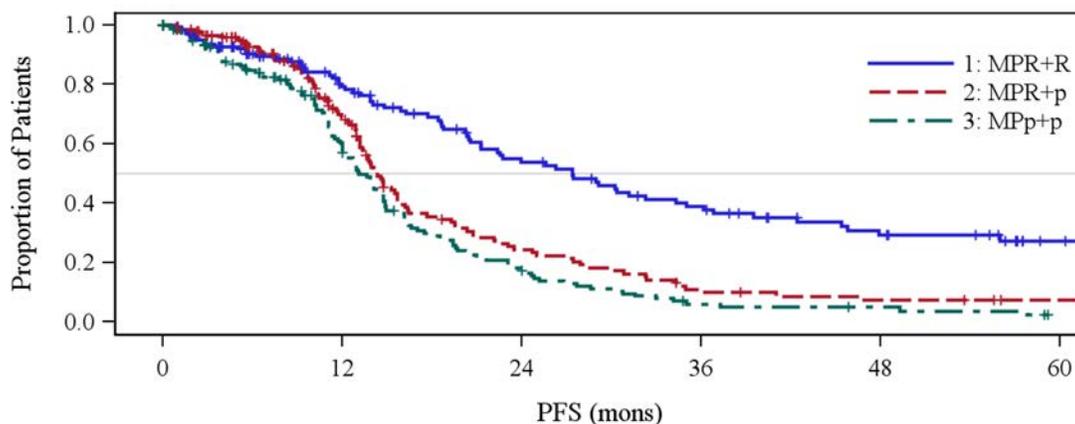
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<b>Name of Finished Product:</b> Revlimid®	Volume: Page:	
<b>Name of Active Ingredient:</b> Lenalidomide (CC-5013)		
<p>preplanned interim analyses.</p> <p>Two interim analyses were planned based on the primary endpoint of PFS, one at approximately 50% information (148 events from all three arms) and one at approximately 70% information (207 events from all three arms), ie, when 50% and 70%, respectively, of the total events required for the final analysis (296 events from all three arms) had been reached.</p> <p>For the preplanned first and second interim analyses, an independent CAC reviewed the myeloma response data to assess responses for each subject and the date of PD, and to determine that the prespecified number of events (disease progression or death) had been reached before the performance of each analysis. The number of events was calculated based on the CAC response assessments and the FDA guidance for cancer trial endpoints (Guidance for Industry – Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007).</p> <p>This CSR summarizes the following efficacy data.</p> <ul style="list-style-type: none"> <li>• Blinded CAC-assessed response and date of PD results using data up to the date of unblinding (11 May 2010) are presented. This study report summarizes the final PFS analysis based on the CAC review. The CAC did not review data collected after the date of unblinding (11 May 2010).</li> <li>• Analyses based on investigator assessments using data up to the 30 Apr 2013 data cutoff date (eg, PFS, myeloma response rate, subsequent antimyeloma therapies, PFS2, OS) are presented.</li> </ul>		
<p><b>SUMMARY – CONCLUSIONS</b></p> <p><b>EFFICACY RESULTS:</b></p> <p>In this clinical study report, efficacy analyses based on investigator assessments are presented using data up to the 30 Apr 2013 data cutoff date, which was approximately 3 years after study unblinding and in-line with ongoing OS data sweeps (at least every 4 months). These analyses are the main focus of this study report.</p> <p>The body of the study report summarizes the final, primary PFS analysis based on the CAC review (11 May 2010 data cutoff date). The observed HR of 0.388 (95% CI = 0.274-0.550) with log-rank test p-value &lt; 0.001 indicates a 61% reduction in the risk of PD or death for Arm MPR+R compared to Arm MPp+p. These results are consistent with the primary analysis based on investigator assessments after almost 3 additional years of study conduct (30 Apr 2013 data cutoff date).</p> <p>The remainder of the efficacy data presented in this summary is based on the investigator assessments as of the 30 Apr 2013 data cutoff date.</p> <p><u>Progression Free Survival (Primary Efficacy Endpoint)</u></p> <p>Progression-free survival counted progressive disease (PD) and death as events. In the primary comparison, PFS time was significantly longer in Arm MPR+R than in Arm MPp+p. The observed HR of 0.371 (95% CI = 0.274-0.503) with log-rank test p-value &lt; 0.001 indicates a 63% reduction in the risk of PD or death for Arm MPR+R compared to Arm MPp+p. A lower percentage of subjects in Arm MPR+R had progressed or died during the treatment period than in Arm MPp+p (46.1% versus 78.6%, respectively). The improvement in median PFS time between Arms MPR+R (27.4 months) and MPp+p (13.1 months) was 14.3 months. The 4-year event-free rate estimate was 29% in Arm MPR+R compared with 5% in Arm MPp+p.</p> <p>Progression-free survival time was also significantly prolonged in Arm MPR+R compared to Arm MPR+p. The observed HR of 0.474 (95% CI = 0.347-0.647) with log-rank test p-value &lt; 0.001 represents a 53% reduction in the risk of PD or death for Arm MPR+R as compared to Arm MPR+p. In Arm MPR+p, 66.0% of subjects had progressed or died, and the median PFS time was 14.3 months. The 4-year PFS event-free rate estimate for Arm MPR+p was 7%.</p> <p>A lower percentage of subjects in Arm MPR+p experienced disease progression during the treatment period than</p>		

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those in Arm MPp+p (66.0% versus 78.6%, respectively). The observed HR of 0.776 (95% CI = 0.595-1.012) indicates a 22% reduction in the risk of PD or death for Arm MPR+p compared to Arm MPp+p. Median PFS time was 14.3 months in Arm MPR+p, and was 13.1 months in Arm MPp+p.

The Kaplan-Meier estimate curves started to separate in favor of Arm MPR+R over Arm MPp+p after approximately 5 months of follow-up, and over Arm MPR+p after approximately 9 months. The separation of the curves widened as follow-up continued. A Kaplan-Meier plot of PFS for Arms MPR+R, MPR+p, and MPp+p (ITT population) is presented below.

**Kaplan-Meier Estimate of Progression-free Survival (Based on Investigator Assessment of Myeloma Response) for Arms MPR+R, MPR+p, and MPp+p Using the Unstratified Test (ITT Population)**



	MPR+R vs MPR+p			MPR+R vs MPp+p			MPR+p vs MPp+p				
	Events: MPR+R=70, MPR+p=101			Events: MPR+R=70, MPp+p=121			Events: MPR+p=101, MPp+p=121				
	Logrank p-value=< 0.001 (2-sided)			Logrank p-value=< 0.001 (2-sided)			Logrank p-value=0.059 (2-sided)				
	HR (95% CI) 0.474 (0.347, 0.647)			HR (95% CI) 0.371 (0.274, 0.503)			HR (95% CI) 0.776 (0.595, 1.012)				
1	152	107	81	65	49	40	33	25	20	18	6
2	153	118	77	36	24	17	9	7	6	5	3
3	154	115	75	35	20	13	6	5	4	3	0

CI = confidence interval; HR = hazard ratio; ITT = intent to treat; M = melphalan; mons = months; p = placebo; P = prednisone; PFS = progression-free survival; R = lenalidomide.

Notes: The HR is based on a proportional hazards model comparing the hazards functions associated with the treatment groups.

The p-value is based on unstratified log-rank test of Kaplan-Meier curve differences between the treatment groups.

Data cutoff = 30 Apr 2013

Analysis of PFS based on the EMA guidelines on Haematologic Malignancies described in Appendix 2 to the Guideline on the Evaluation of Anticancer Medicinal Products in Man was consistent with the results based on the primary definition of PFS, showing highly significant differences between the treatment arms in favor of Arm MPR+R. The observed HR of 0.433 (95% CI = 0.332-0.565) with log rank test p-value < 0.001 indicates a 57% reduction in the risk of PD or death for Arm MPR+R compared to Arm MPp+p. Median PFS time was 30.3 months in Arm MPR+R, and was 13.9 months in Arm MPp+p. At 4 years after randomization, an estimated 37% of subjects in Arm MPR+R remained event-free compared with 11% of the subjects in Arm MPp+p.

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Landmark Analysis of Progression Free Survival (Preplanned Analysis)

A landmark analysis of PFS time calculated from the start of the maintenance therapy period instead of from the randomization date was performed to further isolate the contribution of lenalidomide maintenance therapy to PFS. Only Arms MPR+R and MPR+p were compared in this analysis because the induction treatment was identical for these 2 arms. Continuation of lenalidomide in the maintenance period maintained and deepened the response benefit achieved during induction for a longer period of time yielding a significantly longer median PFS time in Arm MPR+R. An observed HR of 0.394 (95% CI = 0.275-0.564) with log-rank p-value < 0.001 indicates a 61% reduction in the risk of PD or death for Arm MPR+R compared to Arm MPR+p.

Time to Progression (Secondary Efficacy Endpoint – Sensitivity Analysis for PFS)

Analysis of TTP for Arms MPR+R and MPp+p for the ITT population was consistent with the results based on the primary definition of PFS, showing notable differences for the overall treatment period between the treatment arms in favor of Arm MPR+R. An observed HR of 0.325 (95% CI = 0.235-0.451) indicates a 68% reduction in the risk of disease progression for Arm MPR+R compared to Arm MPp+p. In addition, the observed HR of 0.404 (95% CI = 0.290-0.563) with log-rank test p < 0.001 indicated a 60% reduction in the risk of disease progression for Arm MPR+R compared to Arm MPR+p.

Time to Treatment Failure (Preplanned Sensitivity Analysis for PFS)

Analysis of time to treatment failure (TTF) for Arms MPR+R and MPp+p for the ITT population was consistent with the results based on the primary definition of PFS, showing notable differences between the treatment arms in favor of Arm MPR+R. Disease progression, death, discontinuation, and receiving second-line AMT were counted as events in the TTF analysis.

The observed HR of 0.591 (95% CI = 0.466-0.750) with log-rank test p < 0.001 indicates a 41% reduction in the risk of PD/death/ discontinuation/receipt of other AMT for subjects treated with MPR+R compared with those treated with MPp+p. In addition, the observed HR of 0.680 (95% CI = 0.537-0.862) with log-rank test p = 0.001 indicates a 32% reduction in the risk of PD/death/ discontinuation/receipt of other AMT for subjects treated with MPR+R compared with those treated with MPR+p.

Response Rate (Secondary Efficacy Endpoint)

The addition of lenalidomide to MP induction therapy (Arms MPR+R and MPR+p) was associated with notably higher response rates (78.9% and 75.8%, respectively) compared to 54.5% for MP alone (Arm MPp+p) (p<0.001). For the primary comparison, the overall response (comparison of the dichotomized response [CR + PR]) was 78.9% (120/152 subjects) in Arm MPR+R compared to 54.5% (84/154 subjects) in Arm MPp+p (p < 0.001, Fisher’s exact test). The odds of achieving at least a PR were 3.1 times greater for subjects treated with MPR+R than for subjects treated with MPp+p. The overall response rate based on investigator assessment was 75.8% (116/153 subjects) in Arm MPR+p compared to 54.5% (84/154 subjects) in Arm MPp+p (p < 0.001; Fisher’s exact test). The odds of achieving at least a PR were 2.6 times greater for subjects treated with MPR+p than for subjects treated with MPp+p.

While the overall response rates were similar between Arm MPR+R (78.9%) and Arm MPR+p (75.8%), the proportion of subjects achieving CR during the treatment period was higher in Arm MPR+R (19.7%; 30/152) than in Arm MPR+p (11.1%; 17/153). The difference in CR was achieved during the maintenance therapy period when 14 subjects in Arm MPR+R achieved CR, compared to only 3 subjects in Arm MPR+p.

Time to First Response (Secondary Efficacy Endpoint)

Adding lenalidomide during induction therapy (Arms MPR+R and MPR+p) was associated with notably shorter time to response during the treatment period among the subjects who responded (CR + PR). For the primary comparison, median time to first response was 2.8 months for the 120 responders in Arm MPR+R compared to

<b>Name of Sponsor/Company:</b> Celgene Corporation	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Revlimid®	Volume: Page:	
<b>Name of Active Ingredient:</b> Lenalidomide (CC-5013)		

3.7 months for the 84 responders in Arm MPp+p (p = 0.014; Wilcoxon rank sum test)

In addition, the median time to first response was also notably shorter for the 116 responders in Arm MPR+p (2.7 months) than in Arm MPp+p (p < 0.001; Wilcoxon rank sum test).

Duration of Response (Secondary Efficacy Endpoint)

Among the responders (defined as subjects who achieved at least a PR), the median duration of response was notably longer in subjects treated with MPR+R compared with those treated with MPp+p (p < 0.001, log-rank test; HR = 0.370; 95% CI = 0.259-0.529). Based on the KM estimates, more than half (55%) of the responders in Arm MPR+R had responses lasting at least 2 years compared to 16% of subjects in Arm MPp+p. After 3 years, the estimates for a 3-year duration of response were 38% of subjects in Arm MPR+R and 7% of subjects in Arm MPp+p.

Among the responders, the duration of response was also longer in subjects treated with MPR+R compared with those treated with MPR+p (p < 0.001, log-rank test; HR = 0.433; 95% CI = 0.307-0.612). Among the responders, the duration of response was similar between Arm MPR+p (12.4 months) and Arm MPp+p (12.0 months) (p = 0.344, log-rank test; HR = 0.857; 95% CI = 0.622-1.181).

Time to Next Antimyeloma Therapy (Secondary Efficacy Endpoint)

The time to the next AMT was defined as the time from randomization to the start of another AMT, which also included subjects who received open-label lenalidomide (ie, planned dose of 25 mg lenalidomide daily on Days 1 to 21 of a 28-day cycle).

The time to the next AMT was longer for subjects treated with lenalidomide during maintenance (Arm MPR+R) compared with those treated with MPp+p (p < 0.001, log-rank test; HR = 0.413; 95% CI = 0.312-0.547) or MPR+p (p < 0.001, log-rank test; HR = 0.495; 95% CI = 0.373-0.656). At 3 and 4 years after randomization, an estimated 44% and 38% of subjects, respectively, in Arm MPR+R had not received second-line AMT compared with 11% and 9% in Arm MPp+p, and 18% and 13% in Arm MPR+p.

Subsequent Therapy (Post Hoc Analysis)

Overall, a lower proportion of all subjects in Arm MPR+R (55.9%; 85/152) received any second-line AMT compared with Arms MPR+p (78.4%; 120/153) and MPp+p (83.8%; 129/154).

Considering only subjects who received second-line AMT, a lower proportion in Arm MPR+R (28.2%) received lenalidomide, compared with Arms MPR+p (57.5%) and MPp+p (72.1%). In contrast, a higher proportion of subjects received bortezomib in Arm MPR+R (49.4%) compared with Arms MPR+p (27.5%) and MPp+p (20.9%). For subjects who received second-line therapies other than lenalidomide or bortezomib, the proportions of subjects who received other therapies as second-line AMT generally were similar among the 3 treatment arms.

Time From Second-line Antimyeloma Therapy to Third-line Antimyeloma Therapies (Post Hoc Analysis)

The times from second-line AMT to third-line AMT were comparable across all 3 treatment arms, regardless of whether lenalidomide was used in induction and / or maintenance during first-line treatment. Median times from second-line AMT to third-line AMT were 12.6 months for Arm MPR+R, 16.2 months for Arm MPR+p, and 14.8 months for Arm MPp+p, with overlapping CIs.

The times from second-line AMT to third-line AMT for subjects who received non-lenalidomide as second-line therapy were also comparable between Arms MPR+R and MPp+p (HR = 0.839 [95% CI = 0.524-1.342]), indicating that lenalidomide as part of first-line AMT does not negatively impact non-lenalidomide second-line AMTs. This was further emphasized when the efficacy of a consistent (and different class of) second line therapy was analysed, ie, in subjects who received bortezomib, wherein the times from second-line AMT to third-line AMT were also comparable between Arms MPR+R and MPp+p (HR = 0.797 [95% CI = 0.459-1.383]).

Progression-free Survival After Next-line Therapy (PFS2) (Ad Hoc Analysis)

<b>Name of Sponsor/Company:</b> Celgene Corporation	Individual Study Table Referring to Part of the Dossier  Volume:  Page:	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Revlimid®		
<b>Name of Active Ingredient:</b> Lenalidomide (CC-5013)		

The PFS2 analysis showed a notably prolonged PFS2 time in Arm MPR+R compared to Arm MPp+p. As of the 30 Apr 2013 data cutoff date, 63.8% (97/152) of subjects in Arm MPR+R had PFS2 events compared to 78.6% (121/154) of subjects in Arm MPp+p. The observed HR of 0.701 (95% CI = 0.536-0.916) with log-rank test p-value = 0.009 indicates a 30% reduction in the risk of death or having to the start third-line AMT for Arm MPR+R compared to Arm MPp+p, and translates into a 10.9 month improvement in median PFS2 from 28.8 months to 39.7 months.

Overall Survival (Secondary Efficacy Endpoint)

As of the most recent data cutoff (30 Apr 2013), the median follow-up time for all subjects who took study drug is 62.5 months, with 53.4% (245 events in 459 subjects) of death events.

In the primary comparison between Arm MPR+R and Arm MPp+p, the observed HR was 0.948 (95% CI = 0.696-1.292), favoring Arm MPR+R. The median OS is 55.9 months for Arm MPR+R and 53.9 months for Arm MPp+p and the estimated 5-year OS rate was 47% for Arm MPR+R and 44% for Arm MPp+p.

Quality of Life

QoL assessment was performed using the EORTC generic 30-item, oncology-specific QLQ C30 instrument and the 20-item, MM-specific QLQ MY20 module. The questionnaires were to be completed at baseline, at the beginning of every third treatment cycle, and at treatment discontinuation (for any reason). Six QoL domains were selected for analysis a priori based on the perceived clinical relevance of each scale in this trial (eg, EORTC QLQ-C30: Global Health Status, Physical Functioning, Pain, and Fatigue; EORTC QLQ-MY20: Disease Symptoms and Side Effects of Treatment).

Domains for disease symptoms, pain, fatigue, physical functioning, and global health were generally notably improved at every visit compared to baseline. Mean values for the side effects of treatment generally remained comparable to baseline levels throughout treatment.

Considering the above-mentioned 6 domains of QoL, generally no differences over time were detected between the treatment groups.

The results of the analyses of the 6 domains suggest that QoL is maintained while subjects are progression free but, upon PD, QoL deteriorates (fewer data are available for subjects in Arm MPR+R, consistent with the markedly prolonged PFS/delay in PD in this arm). Assessing respective pairs of best on-study versus PD evaluation, a statistically significant (p < 0.001) difference was determined for all QoL domains. This statistically significant difference is made clinically meaningful by the parallel statistically significant increase in median PFS of 14.3 months in the comparison of MPR+R versus MPp+p.

Karnofsky Performance Status

There were no clinically meaningful differences between all 3 treatment arms in the mean or median changes from baseline of Karnofsky performance status scores during the treatment period.

**SAFETY RESULTS:**

Dosing Information

Induction Therapy Period: The median treatment duration was consistent among the 3 treatment arms: 253.0, 257.5, and 252.0 days in Arms MPR+R, MPR+p, and MPp+p, respectively. The median cumulative dose of lenalidomide/placebo was 1470.0 mg in Arm MPR+R and 1517.5 mg in Arm MPR+p; the median cumulative dose of placebo (Arm MPp+p) was 1850.0 mg. The median relative dose intensity was 0.86, 0.81, and 0.97, respectively. When lenalidomide was added as a third drug to the standard MP regimen in the induction therapy period, treatment tolerability of the MPR+R regimen was reduced for the typically more fragile subjects > 75 years compared with subjects ≤ 75 years. This reduced tolerability in subjects > 75 years led to a higher frequency of

<b>Name of Sponsor/Company:</b> Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Revlimid®		
<b>Name of Active Ingredient:</b> Lenalidomide (CC-5013)		

dose reductions, and reduced relative dose intensity for melphalan and lenalidomide, compared with the stratum of subjects ≤ 75 years.

**Maintenance Therapy Period:** The median treatment duration was 576.5 days in Arm MPR+R (including maintenance treatment after study unblinding) compared with 194.5 days in Arm MPR+p and 219.0 days in Arm MPp+p. The median cumulative dose of lenalidomide (Arm MPR+R) was 3146.3 mg; the median cumulative dose of placebo maintenance was 1325.0 mg in Arm MPR+p and 1670.0 mg in Arm MPp+p. The median relative dose intensity was 0.88, 0.97, and 1.00, respectively.

**Adverse Events - Summary**

The tables below summarize AEs during the induction therapy period and maintenance therapy period, respectively.

**Overview of Treatment-emergent Adverse Events During the Induction Therapy Period (Safety Population)**

	<b>MPR+R (N = 150) n (%)</b>	<b>MPR+p (N = 152) n (%)</b>	<b>MPp+p (N = 153) n (%)</b>
<b>Subjects With ≥ 1:</b>			
AE	148 (98.7)	150 (98.7)	152 (99.3)
Grade 3 or 4 AE	132 (88.0)	124 (81.6)	90 (58.8)
Grade 5 AE	7 (4.7)	5 (3.3)	5 (3.3)
SAE	54 (36.0)	56 (36.8)	42 (27.5)
AE Leading to Discontinuation of Lenalidomide/Placebo	19 (12.7)	22 (14.5)	10 (6.5)

AE = adverse event; M = melphalan; p = placebo; P = prednisone; R = lenalidomide; SAE = serious adverse event.

**Overview of Adverse Events During the Maintenance Therapy Period (Safety Population)**

	<b>MPR+R (N = 88) n (%)</b>	<b>MPR+p (N = 94) n (%)</b>	<b>MPp+p (N = 102) n (%)</b>
<b>Subjects With ≥ 1:</b>			
AE <sup>a</sup>	79 (89.8)	73 (77.7)	85 (83.3)
Grade 3 or 4 AE <sup>a</sup>	55 (62.5)	25 (26.6)	34 (33.3)
Grade 5 AE	3 (3.4)	3 (3.2)	2 (2.0)
SAE	33 (37.5)	15 (16.0)	24 (23.5)
AE Leading to Discontinuation of Lenalidomide/Placebo	20 (22.7)	4 (4.3)	4 (3.9)

AE = adverse event; M = melphalan; p = placebo; P = prednisone; R = lenalidomide; SAE = serious adverse event.

<sup>a</sup> Includes all AEs that had a start date on or after the date of the first dose in the maintenance therapy period or that worsened in intensity during the maintenance therapy period.

**Common Adverse Events**

**Induction Therapy Period:** The most frequent AEs (> 50% of subjects) reported for the combined lenalidomide-containing arms (MPR+R plus MPR+p) and Arm MPp+p were the hematologic AEs of neutropenia, anemia, and thrombocytopenia; these AEs were reported with a higher frequency in the lenalidomide-containing arms compared with Arm MPp+p. The most frequent nonhematologic AEs (> 20% of subjects) reported for both the lenalidomide-containing arms combined and Arm MPp+p were fatigue, constipation, nausea, bone pain, and diarrhea.

**Maintenance Therapy Period:** The most frequently reported (≥ 10%) hematologic AEs (new or worsening in

<b>Name of Sponsor/Company:</b> Celgene Corporation	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Revlimid®	Volume:	
<b>Name of Active Ingredient:</b> Lenalidomide (CC-5013)	Page:	

intensity) were anemia, thrombocytopenia, and neutropenia, all of which were reported for a higher proportion of subjects in Arm MPR+R versus Arms MPR+p and MPP+p. The most frequently reported (> 10%) nonhematologic AE in all 3 treatment arms was bone pain.

Drug-related Adverse Events

Induction Therapy Period: A greater percentage of subjects in the combined lenalidomide-containing arms (Arm MPR+R plus Arm MPR+p) reported drug-related AEs (95.0%), drug-related Grade 3 or 4 AEs (78.5%), and drug-related SAEs (22.5%), compared with subjects in Arm MPP+p (83.0%, 42.5%, and 5.2%, respectively). The most frequently reported drug-related AEs for both the lenalidomide-containing arms and Arm MPP+p were the hematologic AEs of neutropenia, thrombocytopenia, anemia, and leukopenia.

Maintenance Therapy Period: A greater percentage of subjects in Arm MPR+R reported drug-related AEs (new or worsening intensity) (65.9%) and drug-related Grade 3 or 4 AEs (35.2%) compared with subjects who received placebo as maintenance therapy in either Arm MPR+p (41.5% and 9.6%, respectively) or Arm MPP+p (35.3% and 5.9%, respectively). Drug-related SAEs were reported at a similar frequency in each of the 3 treatment arms (4.5% in Arm MPR+R, 5.3% in Arm MPR+p, and 2.9% in Arm MPP+p). The AEs related to lenalidomide/placebo that were reported more frequently in Arm MPR+R than in Arm MPP+p were the cytopenias, fatigue, and diarrhea.

Grade 3/4 Adverse Events

Induction Therapy Period: The most frequent Grade 3 or 4 AEs (> 10% of subjects) reported for both the lenalidomide-containing arms and Arm MPP+p were the hematologic AEs of neutropenia, thrombocytopenia, anemia, and leukopenia. The frequencies of nonhematologic Grade 3 or 4 AEs were low and similar between the lenalidomide-containing arms and Arm MPP+p. An increased frequency of Grade 3 or 4 AEs (overall, hematologic, infections, and general disorders) in the stratum of subjects > 75 years was observed compared with the stratum of subjects ≤ 75 years.

Maintenance Therapy Period: Grade 3 or 4 AEs (new or worsening intensity) were reported for a greater percentage of subjects in Arm MPR+R (62.5%) compared with subjects who received placebo as maintenance therapy (Arms MPR+p and MPP+p; 26.6% and 33.3%, respectively). The frequency of hematologic Grade 3 or 4 AEs was higher in Arm MPR+R than in Arms MPR+p and MPP+p. The frequencies of nonhematologic Grade 3 or 4 AEs were low in each of the 3 treatment arms, with the frequency higher in Arm MPR+R than in Arms MPR+p and MPP+p.

Long-term Tolerability with Prolonged Exposure: Overall, as assessed by onset time of Grade 3 or 4 AEs in subjects in Arm MPR+R with treatment duration > 2 years, lenalidomide as single-agent maintenance therapy was well tolerated with long-term tolerability observed through 24 months. Compared with later intervals, the frequencies of Grade 3 or 4 AEs with onset during the first 12 months of treatment were higher, which largely represents the induction therapy period during the first 9 months. In particular, the frequencies of Grade 3 or 4 hematologic AEs of neutropenia, thrombocytopenia, leukopenia, and anemia with onset during the 0-6 months and 6-12 months periods were highest, and decreased considerably after 12 months. Onset of febrile neutropenia (8.3%) was reported only during the first 6 months of treatment. Likewise, Grade 3 or 4 fatigue decreased after the first 6 months. No other notable trends were observed regarding the onset of Grade 3 or 4 AEs over time. Most subjects in Arm MPR+R with treatment duration > 2 years were ≤ 75 years old (85.4%).

Deaths

As of the 30 Apr 2013 cutoff, 244 subjects have died in the study. Of the 244 deaths, 17 occurred during the induction therapy period, 4 occurred during the maintenance therapy period, and 223 occurred during posttreatment (open-label extension phase or follow-up). Most deaths were due to disease progression.

Induction Therapy Period: Of the 17 deaths during the induction therapy period, 11 deaths occurred in subjects randomized to the 2 lenalidomide treatments (7 in Arm MPR+R and 4 in Arm MPR+p) and 6 deaths occurred in

<b>Name of Sponsor/Company:</b> Celgene Corporation	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Revlimid®	Volume:	
<b>Name of Active Ingredient:</b> Lenalidomide (CC-5013)	Page:	

subjects randomized to Arm MPp+p. For 7 subjects, the investigator suspected the Grade 5 AEs associated with the deaths to be related to lenalidomide/placebo: cardiogenic shock, infection and septic shock, pulmonary embolism (1 subject each) and pneumonia (2 subjects) in Arms MPR+R and MPR+p; and lower respiratory tract infection and cardiogenic shock in Arm MPp+p (1 subject each). Of the 17 subjects who died during the induction therapy period, 10 subjects were in the > 75-year stratum and 7 subjects were in the ≤ 75-year stratum.

Maintenance Therapy Period: None of the Grade 5 AEs associated with the 4 deaths reported during the maintenance therapy period (2 in Arm MPR+R and 1 each in Arms MPR+p and MPp+p) was suspected to be related to lenalidomide/placebo.

Serious Adverse Events

Induction Therapy Period: The percentage of subjects who had SAEs was higher in the lenalidomide-containing arms (Arms MPR+R plus MPR+p) than in Arm MPp+p (36.4% versus 27.5%, respectively). The frequencies of individual SAEs were low, with the following being most commonly reported across all 3 study arms: pneumonia, anemia, pyrexia, febrile neutropenia, and neutropenia. Reduced tolerability was observed for subjects > 75 years in the induction therapy period, as evidenced by an increased frequency of SAEs compared with subjects ≤ 75 years.

Maintenance Therapy Period: The frequencies of individual SAEs reported for all 3 treatment arms were very limited.

Adverse Events Leading to Permanent Discontinuation

Induction Therapy Period: Adverse events leading to discontinuation of lenalidomide or placebo were reported for a greater percentage of subjects who received lenalidomide (12.7% and 14.5% in Arms MPR+R and MPR+p, respectively) compared with those who received placebo (6.5% in Arm MPp+p). Thrombocytopenia and neutropenia were the most commonly reported AEs leading to discontinuation of lenalidomide/placebo across the treatment arms. The reduced tolerability in subjects > 75 years during the induction therapy period led to a higher frequency of treatment discontinuations due to AEs compared with the stratum of subjects ≤ 75 years.

Maintenance Therapy Period: Adverse events leading to discontinuation of lenalidomide or placebo were reported for a greater percentage of subjects who received lenalidomide during the maintenance therapy period (Arm MPR+R, 22.7%) compared with those who received placebo (Arm MPR+p, 4.3%; Arm MPp+p, 3.9%). Acute myeloid leukemia (AML), diarrhea, and neutropenia were the most commonly reported AEs leading to discontinuation of lenalidomide/placebo in Arm MPR+R.

Adverse Events Leading to Dose Interruption/Reduction

Induction Therapy Period: The frequencies of AEs leading to lenalidomide/placebo dose interruptions or reductions were higher in the lenalidomide-containing arms compared with Arm MPp+p. In general, neutropenia, thrombocytopenia, anemia, and rash were reported as AEs leading to dose interruption or reduction of lenalidomide/ placebo in higher percentages of subjects in Arms MPR+R and MPR+p compared with Arm MPp+p.

Maintenance Therapy Period: Adverse events leading to dose interruption or reduction of lenalidomide/placebo were reported for a greater percentage of subjects who received lenalidomide during the maintenance therapy period (Arm MPR+R) compared with the subjects who received placebo (Arm MPR+p and Arm MPp+p). In general, neutropenia, anemia, thrombocytopenia, leukopenia, granulocytopenia, diarrhea, fatigue, and rash were reported as AEs leading to dose interruption or reduction of lenalidomide/placebo in higher percentages of subjects in Arm MPR+R compared with Arms MPR+p or MPp+p.

Selected Adverse Events

The selected AEs identified and described in the study consider the known or potential safety risks of lenalidomide, and also include those for which pro-active pharmacovigilance is in place. These are events of

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<b>Name of Sponsor/Company:</b> Celgene Corporation	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Revlimid®	Volume: Page:	
<b>Name of Active Ingredient:</b> Lenalidomide (CC-5013)		

regulatory interest, including events for which monitoring has been requested by a regulatory authority.

In the induction and maintenance therapy periods, thrombocytopenia occurred more frequently in Arms MPR+R and MPR+p compared with Arm MPp+p. For Grade 3 or 4 thrombocytopenia, the frequency was slightly higher in Arm MPR+p (41.4%) than in Arm MPR+R (39.3%).

Although neutropenias occurred in more subjects in Arms MPR+R and MPR+p than Arm MPp+p, overall infections occurred with similar frequencies across all 3 treatment arms.

During the induction and maintenance therapy periods, rash and related terms were reported more often in Arms MPR+R (20.7%) and MPR+p (28.9%) compared with MPp+p (9.8%), with very few SAEs reported in subjects. Overall, few cases in the severe cutaneous reactions category or of urticaria were reported. All cases in the lenalidomide-containing arms (Arms MPR+R and MPR+p) were either nonserious or had associated confounding factors. There were no cases of Stevens-Johnson Syndrome or toxic epidermal necrolysis reported in this study.

Renal failure events occurred in 18 (12.0%) subjects in Arm MPR+R, 12 (7.9%) subjects in Arm MPR+p, and 26 (17.0%) subjects in Arm MPp+p during the induction and maintenance therapy periods. There is no apparent safety signal for renal failure events in this study. Renal failure may be associated with disease status in this study.

Events associated with hepatic disorders occurred in 16 (10.7%) subjects in Arm MPR+R, 22 (14.5%) subjects in Arm MPR+p, and 14 (9.2%) subjects in Arm MPp+p during the combined induction and maintenance therapy periods. The most frequently reported individual event was blood alkaline phosphatase increased, reported in 4.7%, 7.2%, and 3.3% of subjects in the respective treatment arms. All other individual events were reported in less than 2% of the subjects overall in the study.

SAEs of venous thromboembolic events (VTE) occurred in 3 (2.0%) subjects in Arm MPR+R, 9 (5.9%) subjects in Arm MPR+p, and no subjects in Arm MPp+p. All subjects who had a SAE of VTE had risk factors for VTE, which included erythropoiesis-stimulating agent (ESA) use, prior VTE, cardiac disease, infection, respiratory disease, and past history of cerebrovascular accident (CVA).

SAEs of cardiac arrhythmias occurred in 1 (0.7%) subject in Arm MPR+p, and no subjects in Arms MPR+R and MPp+p. SAEs of atrial fibrillation occurred in 1 (0.7%) subject in Arm MPR+R, 3 (2.0%) subjects in Arm MPR+p, and 5 (3.3%) subjects in Arm MPp+p. Atrial fibrillation occurred more frequently in Arm MPp+p (all events, grade 3/4 events, and SAEs). SAEs of cardiac failure occurred in 6 (4.0%) subjects in Arm MPR+R, 2 (1.3%) subjects in Arm MPR+p, and 2 (1.3%) subjects in Arm MPp+p. Three subjects had SAEs of myocardial infarction (1 in Arm MPR+R and 2 in Arm MPR+p); none of these events resulted in death.

Peripheral neuropathy occurred more frequently in subjects in the lenalidomide-containing arms (16.0% in Arm MPR+R and 15.1% in Arm MPR+p) compared with Arm MPp+p (8.5%) during the induction and maintenance therapy periods. Of these events, 2 were Grade 3/4 events (neuralgia in 1 subject in Arm MPR+R, and peripheral neuropathy in 1 subject in Arm MPp+p), and 1 event (peripheral neuropathy in Arm MPp+p) was a SAE.

Overall, 2 subjects (both in Arm MPR+R) experienced SAEs of hypersensitivity or angioedema. One SAE of hypersensitivity was reportedly due to Neupogen®, and 1 SAE of angioedema (face edema) was suspected to be related to lenalidomide, which was confounded by the fact that the subject was also taking ciprofloxacin at the time the event occurred.

One nonserious Grade 3/4 event of tumor lysis syndrome was reported in Arm MPR+p during the maintenance therapy period.

Second Primary Malignancies

The frequency of subjects with invasive SPMs was higher in Arm MPR+p (11.2%) than in Arm MPR+R (9.3%). The frequency of subjects with invasive SPMs was higher in combined lenalidomide-containing arms

<b>Name of Sponsor/Company:</b> Celgene Corporation	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Revlimid®	Volume: Page:	
<b>Name of Active Ingredient:</b> Lenalidomide (CC-5013)		
<p>(Arms MPR+R plus MPR+p) compared with Arm MPP+p (10.3% versus 3.9%, respectively). Of those with invasive SPMs, 16 of the 18 subjects with hematologic SPMs, including AML, myelodysplastic syndromes (MDS), and other hematologic malignancies, were in the lenalidomide-containing arms (Arms MPR+R [9 subjects] and MPR+p [7 subjects]), while 2 subjects (AML and MDS [1 subject each]) were in Arm MPP+p. Of the 37 subjects who experienced an invasive SPM, 9 remain alive (8 in the lenalidomide-containing arms and 1 in Arm MPP+p), while 28 have died (23 in the lenalidomide-containing arms and 5 in Arm MPP+p).</p> <p><u>Open-label Extension Phase</u></p> <p>Approximately one-third of the subjects entered the open-label extension phase, receiving lenalidomide (with or without dexamethasone) as second line AMT. Of the 154 subjects in the open-label extension phase, 74 subjects (21 from Arm MPR+R and 53 from Arm MPR+p) had previously received lenalidomide during the treatment phase, and 80 subjects from Arm MPP+p received lenalidomide for the first time. In general, the overall frequencies of AEs were similar in the 3 arms; the most commonly reported AEs and Grade 3 or 4 AEs in all arms were neutropenia, anemia, thrombocytopenia, leukopenia, and fatigue. There was no evidence of any additional toxicity in those subjects who had previously received lenalidomide in Arms MPR+R and MPR+p, as the overall frequencies of Grade 3 or 4 AEs and SAEs were lower in those arms compared with Arm MPP+p.</p> <p><u>Clinical Laboratory Assessments</u></p> <p>Shifts in hematologic laboratory values were consistent with the reporting of hematologic AEs across all 3 treatment arms during the induction therapy period and the maintenance therapy period. There were few clinically meaningful shifts from baseline in chemistry laboratory values and were consistent across all 3 treatment arms during the induction therapy period and the maintenance therapy period.</p> <p><u>Vital Signs and Electrocardiograms</u></p> <p>There were few clinically meaningful changes from baseline in vital sign measurements or ECGs observed across all 3 treatment arms in this study.</p> <p><b>CONCLUSION:</b></p> <p>The results of this study demonstrate the favorable benefit-risk profile of the continued use of lenalidomide, initially in combination with melphalan and prednisone and subsequently as single agent maintenance therapy, in subjects with NDMM who are 65 years of age or older. Disease control is lost significantly earlier when treatment is discontinued and no maintenance is administered as exemplified by the comparison between treatment arms MPR+R and MPR+p. The availability of multiple active therapies, including experimental drugs, is having a positive impact on long-term outcome for patients with multiple myeloma as exemplified by the unexpected median OS of 54 months (versus 36 months expected at the inception of the protocol) for subjects randomized to the MP control arm. By examining PFS after next-line therapy, it can be concluded that lenalidomide maintenance does not impact negatively on efficacy of second-line AMTs and that the sequence lenalidomide followed by a second-line therapy is beneficial over the alternative treatment sequence. The safety profile of lenalidomide in this study was consistent with the known safety profile of lenalidomide and the increased frequency of invasive SPMs does not seem to outweigh the overall treatment benefit of the MPR+R regimen. Careful selection of patients older than 75 years, along with vigilant monitoring and dose adjustment, is suggested by the findings in subjects over the age of 75 years.</p> <p><b>Date of the report:</b> 30 Oct 2013</p>		