

CELGENE PROPRIETARY INFORMATION

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product: Revlimid® Capsules	Volume:	
Name of Active Ingredient: Lenalidomide (CC-5013)	Page:	
<p>dose of dexamethasone was 20 mg daily for 4 days every 4 weeks. Subjects who could not tolerate these doses were discontinued from the study unless they had achieved a plateau phase of response to therapy. Subjects who achieved a plateau phase of response to therapy continued to adhere to the schedule of study assessments until disease progression occurred even though one or both of the study drugs had been discontinued.</p> <p>The primary efficacy endpoint was TTP, calculated as the time from randomization to the first occurrence of disease progression as determined by a detailed review of all the myeloma response assessment data using the Bladé criteria (Bladé, 1998). If disease progression was based on increasing M-paraprotein levels, then the Bladé criteria required that the increasing M-paraprotein level be documented on two consecutive occasions at least 1 week apart. Disease progression based on bone marrow findings, worsening lytic bone disease, progressively enlarging extramedullary plasmacytomas, or hypercalcemia did not require a second confirmatory measurement. TTP based on the investigators' assessment of response was performed as a sensitivity analysis. Two additional supportive analyses, progression-free survival (PFS) and time to treatment failure (TTF), were conducted to confirm the robustness of the results of the primary endpoint TTP. Progression-free survival was calculated as the time from randomization to documented progression or death due to any cause on study or within 2 months of the last adequate assessment, whichever occurred first. Except for the manner in which deaths were counted in the analysis, the definition PFS was identical to the TTP. Time to treatment failure was defined as the time from randomization to treatment failure.</p> <p>The secondary efficacy endpoints were overall survival (OS); the myeloma response rate; the time to the first symptomatic skeletal-related event (SRE) (not actually analyzed due to limited data); and the time to the first worsening in the Eastern Cooperative Oncology Group (ECOG) performance status. Also, a post hoc analysis was performed for determining duration of response. The safety endpoints were treatment-emergent adverse events and laboratory measures, which are graded according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC), Version 2.0; electrocardiograms (ECG); vital signs; and physical examinations.</p> <p>An interim analysis was included in the study plan and was to be performed after 50% of the progressions required for full power for the comparison of TTP over both treatment groups had occurred (i.e., when approximately 111 subjects over both treatment arms total had progressed). The interim analysis was intended to determine if the study should be stopped for superiority, futility, or unfavorable toxicity. At the time of this interim analysis, the predetermined stopping criteria for superiority in the primary efficacy endpoint, TTP, had been surpassed, with $p < 0.001$ in favor of the lenalidomide/dexamethasone treatment group. The data also demonstrated that lenalidomide/dexamethasone was well tolerated, with an acceptable safety profile. After the interim analysis results were reviewed by the Independent Data Monitoring Committee (IDMC) on 28 Feb 2005, the investigators' assessments of disease progression were confirmed in an independent review by an external panel of myeloma experts who were blinded to the subjects' treatment assignments. The results of the external panel's review confirmed the significant differences that were observed in the interim analysis. Based on the results of the preplanned interim analysis, which surpassed the prespecified O'Brien-Fleming boundary for superior efficacy in favor of the lenalidomide/dexamethasone treatment arm, the decision was made to unblind all subjects remaining in the treatment phase of the study.</p> <p>Unblinding was initiated on 07 Jun 2005 and the primary analyses were based on this data cutoff date. Analyses including all the data up to the extended follow-up cutoff date (23 Jul 2008) were primarily for the survival update, but analyses for other efficacy and safety endpoints were performed as well. As of 23 Jul 2008, 6 patients were still ongoing in Canada.</p>		
<p>Number of patients (planned and analyzed): Planned: 302 subjects, randomized in a 1:1 ratio to 1 of the 2 treatment groups Enrolled: 353 subjects Analyzed: 353 subjects – 177 in the lenalidomide/dexamethasone group and 176 in the placebo/dexamethasone group</p>		
<p>Diagnosis and main criteria for inclusion: Prior or current diagnosis of Durie-Salmon stage II or III multiple myeloma and considered to have disease progression after at least 2 cycles of antimyeloma treatment or to have relapsed with progressive disease after treatment; measurable levels of myeloma paraprotein (M-paraprotein) in serum (≥ 0.5 g/dL) or urine (≥ 0.2 g excreted in a 24-hour collection sample); and an ECOG performance status of 0, 1, or 2.</p>		
<p>Test product, dose and mode of administration, batch number: Lenalidomide was supplied by Celgene as 25-mg or 5-mg (for dosage reductions) capsules. The lenalidomide capsules were supplied in 28-day blister packs; each blister pack contained 21 capsules of lenalidomide (for administration on Days 1-21 of each cycle) and 7 matching placebo capsules (for</p>		

CELGENE PROPRIETARY INFORMATION

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product: Revlimid® Capsules	Volume:	
Name of Active Ingredient: Lenalidomide (CC-5013)	Page:	
<p>administration on Days 22-28 of each cycle). The double-blind lenalidomide capsules packaged in blister cards were from the following batch/lot numbers: 0033U, 0264U, 0067W, 0068W for the 25-mg dosage; and 0151W, 0180U, 0380W, 0104X for the 5-mg dosage.</p> <p>The open-label lenalidomide supply used after unblinding were packaged in 21-count bottles in either 25-mg or 5-mg dosage. The open-label lenalidomide was taken from the following batch numbers: 0216X, 424532, 425075, and 432877 for the 25-mg lenalidomide capsules; and 424499, 430488, and 433461 for the 5-mg lenalidomide capsules.</p> <p>The dexamethasone tablets for the combination therapy were obtained commercially by the subjects using prescriptions provided by the investigators.</p>		
<p>Duration of treatment: Treatment continued until disease progression or until the subject withdrew from the study for another reason.</p>		
<p>Reference therapy, dose and mode of administration, batch number: Placebo capsules were identical in appearance to the 25- and 5-mg lenalidomide capsules and contained the inactive ingredients of the lenalidomide formulation. The placebo capsules were supplied by Celgene in 28-day blister packs that were identical in appearance to the lenalidomide blister packs; each blister pack of placebo contained 28 placebo capsules (for administration on Days 1 to 28 of the 28-day cycle). The double-blind placebo capsules packaged in blister cards were from the following batch numbers: 0179U and 0373U for the matching 25-mg capsules; and 0181U and 0374U for the matching 5-mg capsules.</p> <p>The dexamethasone tablets for the combination therapy were obtained commercially by the subjects using prescriptions provided by the investigators.</p>		
<p>Criteria for evaluation:</p> <p>Efficacy: <u>Primary.</u> TTP based on reviewer’s assessment; TTP based on the investigators’ assessment was analyzed as a sensitivity analysis; PFS and TTF were also analyzed as additional supportive analyses. <u>Secondary.</u> OS, myeloma response rate, and time to first worsening of ECOG performance status. An additional post hoc analysis was also performed for duration of response.</p> <p>Safety: Incidence of adverse events and change from baseline in clinical laboratory tests, ECGs, and vital signs.</p>		

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

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Time to Progression

The primary efficacy endpoint is TTP based on the reviewer’s assessment. A total of 68.2% (120/176) of the subjects in the placebo/dexamethasone group, compared with 41.2% (73/177) of subjects in the lenalidomide/dexamethasone group, had progressed as of the 07 Jun 2005 data cutoff date (see Table below). The median TTP was 60.1 weeks (13.9 months) in the lenalidomide/ dexamethasone group and 20.1 weeks (4.6 months) in the placebo/dexamethasone group.

Summary of Time to Progression (Based on Reviewer’s Assessment) Up to Unblinding (07 Jun 2005) (ITT Population)

	Statistic	Lenalidomide/Dexamethasone	Placebo/Dexamethasone
TTP	N	177	176
Progressed	n (%)	73 (41.2)	120 (68.2)
Censored	n (%)	104 (58.8)	56 (31.8)
Overall TTP (weeks)	Median	60.1	20.1
	[95% CI] [a]	[41.1, 80.0]	[16.1, 21.1]
	Mean	36.0	17.5
	SD	27.53	16.42
	Min, Max	0.1, 103.3	0.1, 79.0
Hazard Rate Ratio	HR [95% CI] [b]	0.285 [0.210, 0.386]	
Log-rank Test	p-value [c]	< 0.001	

CI = confidence interval; HR = hazard ratio; ITT = intent to treat; max = maximum; min = minimum; SD = standard deviation; TTP = time to progression.

Notes: The median is based on Kaplan-Meier estimate and the mean is the univariate mean without adjusting for censoring.

[a] 95% confidence intervals about the median overall time to progression.

[b] Based on a proportional hazards model comparing the hazard functions associated with the treatment groups (lenalidomide/dexamethasone : placebo/dexamethasone).

[c] The p-value is based on an unstratified log rank test of survival curve differences between the treatment groups.

The TTP was significantly longer in the lenalidomide/dexamethasone group than in the placebo/dexamethasone group (p < 0.001, two-tailed unstratified log rank test of survival curve difference between treatment groups). Based on the hazard ratio (0.285), subjects in the placebo/dexamethasone group were 3.5 times as likely to progress as those in the lenalidomide/dexamethasone group at any time during the treatment phase of the study. The results of the stratified log-rank test confirmed those of the unstratified analysis (primary analysis).

Subgroup analysis of TTP showed that lenalidomide/dexamethasone treatment was significantly more effective than placebo/dexamethasone treatment in all the subgroups analyzed (p < 0.001) including: male and female subjects; subjects ≤ 65 years and those > 65 years; subjects with a baseline serum β₂-microglobulin level of ≤ 2.5 mg/L and in those with a baseline level of > 2.5 mg/L (i.e., in those with a high tumor burden); subjects who had been previously treated with HDT and SCT and those who had not; subjects who had 1 prior antimyeloma therapy and those who had 2 or more prior antimyeloma therapies; and subjects who had prior treatment with thalidomide or Velcade® (bortezomib). The robustness of the TTP results based on the reviewer’s assessment was supported by analyses of TTP based on the investigators’ assessment, PFS and TTF.

Overall Survival

As of the 07 Jun 2005 data cutoff date, 37 (20.9%) of the 177 subjects in the lenalidomide/dexamethasone group and 60 (34.1%) of the 176 subjects in the placebo/dexamethasone group had died (see next Table).

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

Summary of Overall Survival Up to Unblinding (07 Jun 2005) (ITT Population)

	Statistic	Lenalidomide/Dexamethasone	Placebo/Dexamethasone
Overall Survival	N	177	176
Died	n (%)	37 (20.9)	60 (34.1)
Censored	n (%)	140 (79.1)	116 (65.9)
Overall survival time since randomization (weeks)	Median	NE	103.7
	[95% CI] [a]	NE	[82.6, NE]
	Mean	65.6	55.5
	SD	23.29	25.09
	Min, Max	1.1, 108.6	0.0, 109.6
Hazard Rate Ratio	HR [95% CI] [b]	0.499 [0.330, 0.752]	
Log-rank Test	p-value [c]	< 0.001	
Wilcoxon Test	p-value [d]	0.001	
Pepe-Fleming Test	p-value [e]	0.004	

CI = confidence interval; HR = hazard ratio; ITT = intent to treat; max, maximum; min, minimum; NE = not estimable; SD = standard deviation.

Notes: The median is based on Kaplan-Meier estimate and the mean is the univariate mean without adjusting for censoring.

- [a] 95% confidence intervals about the median survival time.
- [b] Based on a proportional hazards model comparing the hazard functions associated with the treatment groups (lenalidomide/dexamethasone : placebo/dexamethasone).
- [c] The p-value is based on an unstratified log rank test of survival curve differences between the treatment groups.
- [d] The p-value is based on an unstratified Wilcoxon test of survival curve differences between the treatment groups.
- [e] Using the Pepe-Fleming test (Pepe, 1989).

Median OS had not yet been reached in the lenalidomide/dexamethasone group, and in the placebo/dexamethasone group, it was 103.7 weeks (24.0 months). Overall survival was significantly different between the 2 treatment groups utilizing the log rank (p < 0.001), Wilcoxon (p = 0.001), and Pepe-Fleming (p = 0.004) tests. Based on the hazard ratio of 0.499 (assuming proportional hazard ratio over time), the subjects in the placebo/dexamethasone group were 2.0 times as likely to die at any time as those in the lenalidomide/dexamethasone group.

Results of analysis of other secondary efficacy endpoints (i.e., myeloma response rate and time to first worsening of ECOG performance status) and a post hoc analysis for duration of response demonstrate significant differences supporting the effectiveness of the lenalidomide/dexamethasone treatment compared with placebo/dexamethasone treatment.

SAFETY RESULTS:

Adverse Events

All subjects reported at least 1 adverse event during the study. Thirteen subjects in each treatment group died ≤ 30 days of the last dose of study drug and most of these deaths were related to the disease (i.e., disease progression, disease progression not otherwise specified [NOS], multiple myeloma). A higher percentage of subjects in the lenalidomide/dexamethasone group compared with the placebo/dexamethasone group had at least 1 serious adverse event (54.8% versus 50.3%); at least 1 adverse event leading to study drug discontinuation (26.0% versus 18.9%); at least 1 adverse event leading to study dose reduction or interruption (76.3% versus 56.6%); at least 1 drug-related serious adverse event (30.5% versus 17.7%); or at least 1 grade 4 adverse event (27.7% versus 20.6%).

Common adverse events (reported by ≥ 10% of subjects in either treatment group) were generally reported with higher frequencies in the lenalidomide/dexamethasone group than in the placebo/dexamethasone group. Neutropenia, constipation, anemia NOS, rash NOS, thrombocytopenia, tremor, pneumonia NOS, hypokalemia, deep vein thrombosis (DVT), and hypocalcemia were notably reported more frequently in the lenalidomide/dexamethasone group.

CELGENE PROPRIETARY INFORMATION

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

Neutropenia and thrombocytopenia were the primary reasons for dose reductions or interruptions in the lenalidomide/dexamethasone group (31.6% and 11.9%, respectively), but the frequency of discontinuations of the study drug in this treatment group due to these adverse events was low ($\leq 2.8\%$). Most cases of neutropenia and thrombocytopenia were assessed by the investigator as drug-related and few cases ($\leq 2.3\%$) in the lenalidomide/dexamethasone were serious. Grade 4 neutropenia and thrombocytopenia were reported at low frequencies ($\leq 5.6\%$) in the lenalidomide/dexamethasone group.

Gastrointestinal toxicities including diarrhea NOS, constipation, and abdominal pain NOS were reported more frequently in the lenalidomide/dexamethasone group than in the placebo/dexamethasone group. The proportion of subjects who reported nausea, dyspepsia, and vomiting NOS was comparable between the treatment groups. No grade 4 diarrhea, constipation, nausea, or vomiting NOS was reported in either treatment group.

DVT and PE were reported more frequently by subjects in the lenalidomide/ dexamethasone group (13.6% and 3.4%, respectively) compared with those in the placebo/dexamethasone group (3.4% and 0.6%, respectively). The majority of the incidences of DVT and PE were grade 3/4 in both treatment groups.

Neuropathy NOS and peripheral neuropathy NOS was reported at higher frequencies in the lenalidomide/dexamethasone group; peripheral sensory neuropathy was reported at comparable frequencies in both treatment groups. No grade 4 peripheral sensory neuropathy, peripheral neuropathy NOS, or neuropathy NOS was reported in either treatment group.

Rash NOS was reported in twice as many subjects in the lenalidomide/dexamethasone group compared with those in the placebo/dexamethasone group (29.9% versus 14.3%).

Cardiac disorders (of interest due to the advanced age of the study population) of any kind were reported more frequently in the lenalidomide/dexamethasone group than in the placebo/dexamethasone group (19.8% versus 8.0%). The frequencies of individual cardiac-related adverse events were generally low in both treatment groups. The cardiac disorder with the highest incidence was atrial fibrillation, which occurred in 6.2% of the lenalidomide/dexamethasone-treated subjects versus 0.6% of the placebo/dexamethasone-treated subjects. Of the 11 subjects in the lenalidomide/dexamethasone group who reported atrial fibrillation, 8 cases were considered to have a suspected relationship to study drug.

The proportion of subjects who reported upper respiratory tract infection NOS, pneumonia NOS, sinusitis NOS, oral candidiasis, urinary tract infection NOS, and herpes simplex in the lenalidomide/dexamethasone group was higher than those in the placebo/dexamethasone group. Herpes zoster was reported by 7 (4%) subjects each in the lenalidomide/dexamethasone and placebo/dexamethasone groups, with 3 (1.7%) cases in each treatment group having a suspected relationship to study drug. Four (2.3%) subjects in the lenalidomide/dexamethasone group and 3 (1.7%) subjects in the placebo/dexamethasone group reported grade 4 pneumonia NOS.

Overall, the addition of lenalidomide to dexamethasone had a favorable safety profile; the adverse events were easily monitored and managed clinically.

Clinical Laboratory, ECG, and Vital Signs Assessments

A higher percentage of subjects in the lenalidomide/dexamethasone group compared with the placebo/dexamethasone group had shifts from baseline values of grade 0, 1, or 2 to a worst postbaseline value of grade 3 in absolute neutrophil count (ANC) (45.5% versus 3.0%) and WBC (28.3% versus 1.8%) based on central laboratory assessments.

A higher percentage of subjects in the lenalidomide/dexamethasone group compared with the placebo/dexamethasone group had shifts from baseline values of grade 0, 1, or 2 to a worst postbaseline value of grade 3 in phosphorus (14.1% versus 9.3%). Conversely, more subjects in the placebo/dexamethasone group compared with the lenalidomide/dexamethasone had shifts in grade 3 glucose (12.3% versus 5.3%) and grade 4 uric acid (7.6% versus 1.2%). Other than these, no clinically notable differences were observed between the treatment groups in the percentages of subjects who had shifts in the serum chemistry parameters. There was no evidence of a proportional increase in cases of clinically notable values (grade 3 or 4 values) with increasing exposure to the study drug.

Few shifts from baseline were seen in any value for any urinalysis parameter. For TSH, most subjects had normal values at baseline and the worst postbaseline values remained within the normal range. The proportion of subjects who had a worsening in TSH during treatment was low and comparable between the treatment groups.

Little variation was observed in vital signs, ECGs, or weight in either treatment group during the study; abnormalities were observed in low and comparable proportions of subjects in each treatment group.

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Revlimid® Capsules		
Name of Active Ingredient: Lenalidomide (CC-5013)		
CONCLUSION: Overall, the results of this study showed that the extended use of lenalidomide in combination with dexamethasone demonstrated a highly favorable benefit-to-risk ratio for multiple myeloma subjects who have received at least 1 prior antimyeloma therapy. Date of the report: 09 Dec 2008		

CELGENE PROPRIETARY INFORMATION