2. SYNOPSIS

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

Title of Study: A multicenter, randomized, double-blind, placebo-controlled, 3-arm study of the efficacy and safety of 2 doses of lenalidomide versus placebo in red blood cell (RBC) transfusion-dependent subjects with low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion (del) 5q[31] cytogenetic abnormality.

Coordinating Principal Investigator:

Investigators: A list of the investigators and their institutional affiliations is provided in Appendix 16.1.4.

Study center(s): 38 sites

Publications (reference): Not applicable

Studied period (years): Date first patient enrolled: 08 Jul 2005 Date last patient completed: 14 Jun 2010	Phase of development: 3

Objectives:

Primary:

To compare the efficacy of 2 doses (10 mg and 5 mg) of lenalidomide to that of placebo in subjects with red blood cell (RBC) transfusion-dependent low- or intermediate-1-risk IPSS MDS associated with a deletion (del) 5q[31] cytogenetic abnormality.

Secondary:

To compare the safety of 2 doses of lenalidomide (10 mg and 5 mg) to that of placebo in subjects with RBC transfusion-dependent low- or intermediate-1-risk IPSS MDS associated with a del 5q[31] cytogenetic abnormality.

Methodology:

This multicenter, randomized, double-blind, placebo-controlled, 3-arm study of 2 doses of oral lenalidomide versus placebo administered to RBC transfusion-dependent adult subjects with low- or intermediate-1-risk IPSS MDS associated with a del 5q[31] cytogenetic abnormality was conducted in three phases: a prerandomization phase, a double-blind treatment phase, and an open-label extension phase.

Prereandomization phase: Potential protocol-eligible subjects were to enter the pre-randomization phase after signing informed consent and were evaluated for the inclusion and exclusion criteria for enrollment in the double-blind treatment phase of this study. The pre-randomization phase lasted for up to 56 days (8 weeks). Subjects meeting all inclusion and exclusion criteria were randomized in a 1:1:1 ratio by a validated interactive voice response system (IVRS) to receive one of three regimens: lenalidomide 10 mg once PO daily on Days 1–21 every 28 days, lenalidomide 5 mg once PO daily, or placebo. Randomization was stratified according to karyotype of the MDS clone (IPSS karyotype score of 0 versus score of > 0; ie, isolated del 5q[31] abnormality versus del 5q[31] abnormality plus at least one additional cytogenetic abnormality).

Double-blind treatment phase: The double-blind treatment phase was to start (Day 1) within 3 days of randomization, and could continue for up to 52 weeks (until Day 365 of the double-blind treatment phase). On Day 1, all subjects began treatment with 5 mg lenalidomide, 10 mg lenalidomide, or placebo. Study visits were to

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occur every 28 days (whether or not study drug had been interrupted for dose-limiting toxicity [DLT]), and serial measurements of safety and efficacy were to be performed. The dose of lenalidomide or placebo was to be reduced if DLTs occurred, and CBCs were to be obtained weekly following the development of dose-limiting neutropenia or thrombocytopenia. The use of granulocytic growth factors were strongly encouraged for subjects who developed febrile neutropenia or those who experienced ≥ grade 3 neutropenia (including those subjects who had grade 3 neutropenia at baseline).

Subjects who had evidence of at least a minor erythroid response after 16 weeks of treatment phase participation were able to continue therapy in the double-blind treatment phase for up to 52 weeks (Day 365 of the double-blind treatment phase) unless there was disease progression or erythroid relapse. Subjects who did not have evidence of at least a minor erythroid response after 16 weeks of double-blind treatment phase participation were to be discontinued from the double-blind treatment phase for lack of therapeutic efficacy, and unblinded. Subjects discontinued from the double-blind treatment phase of the study for disease progression were not eligible for inclusion in the open-label extension phase. Subjects who had an erythroid relapse following the achievement of at least a minor erythroid response were discontinued from the double-blind treatment phase for lack of therapeutic efficacy and their assigned treatment arm was unblinded.

Subjects who completed the total duration of 52 weeks in the double-blind treatment phase without disease progression or erythroid relapse were unblinded after Week 52 and entered the open-label extension phase at their current dose of lenalidomide.

Open-label extension phase: Subjects were to begin treatment in the open-label extension phase within 28 days of either completing or early discontinuation from the double-blind treatment phase. Study visits occurred every 28 days and serial measurements of safety and efficacy were performed. The dose of lenalidomide was reduced if DLTs occurred.

Subjects were permitted to continue lenalidomide therapy in the open-label extension phase for up to 156 weeks of total study participation unless the following occurred: 1) at least a minor erythroid response was not achieved within 16 weeks of open-label extension phase treatment; 2) disease progression developed, or 3) the RBC transfusion requirement returned to baseline in the absence of hypothyroidism in female subjects, or hypothyroidism and/or hypogonadism in male subjects.

Subjects who did not achieve at least a minor erythroid response within 16 weeks of open-label extension phase treatment, or who developed an erythroid relapse without low TSH (all subjects) or testosterone (male subjects only) levels following the achievement of a minor or major erythroid response, were treated as follows: 1) subjects who started the open-label extension phase at the 10 mg dose level were discontinued from the study for lack of therapeutic efficacy; 2) subjects who started the open-label extension phase at the 5-mg dose level and who previously required a lenalidomide dose reduction were discontinued from the study for lack of therapeutic efficacy; 3) subjects who previously had tolerated lenalidomide at the 5-mg dose level without a dose reduction were permitted to escalate the dose of lenalidomide to 10 mg once daily on Days 1–21 every 28 days. Subjects who developed a decreasing blood hemoglobin (Hgb) level during a period of RBC transfusion independence were permitted to remain in the open-label extension phase until their RBC transfusion requirement returned to baseline (erythroid relapse).

Subjects who discontinued the study for any reason were to be followed every 4 months (directly via telephone or information obtained from their treating physician) for survival and/or to collect any events of progression to AML.

Number of patients (planned and analyzed):

Enrollment for the study was expanded from 162 subjects to 205 in order to achieve the prespecified 135 evaluable subjects.

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Diagnosis and main criteria for inclusion:

RBC transfusion-dependent adult subjects with low- or intermediate-1-risk IPSS MDS associated with a del 5q[31] cytogenetic abnormality (subjects with MDS clones that have a del 5q[31] cytogenetic abnormality with additional cytogenetic abnormalities remain eligible for enrollment into this study).

Test product, dose and mode of administration, batch number:

Celgene Corporation supplied lenalidomide 5 mg capsules and placebo capsules in blister packs during the double-blind treatment phase. The placebo capsules were identical in appearance to the 5 mg lenalidomide capsule. For the open-label extension phase, Celgene supplied lenalidomide 5 mg capsules in bottles. A list of the batch numbers is provided in Appendix 16.1.6.

Duration of treatment:

Subjects could receive up to 156 weeks of total study participation unless the following occurred: 1) at least a minor erythroid response was not achieved within 16 weeks of Open-Label Extension Phase treatment; 2) disease progression developed; or 3) the RBC transfusion requirement returned to baseline in the absence of hypothyroidism in female subjects or hypothyroidism and hypogonadism in male subjects.

Reference therapy, dose and mode of administration, batch number: Not applicable

Criteria for evaluation:

Efficacy: RBC-transfusion independence (for ≥ 182 days and ≥ 56 days); hemoglobin, neutrophil, and platelet counts; bone marrow biopsy/aspirate; cytogenetic evaluations of hematopoietic cells; overall survival; progression to AML; and Health Related Quality of Life

Safety: Adverse events, concomitant medications, clinical laboratory evaluations, vital signs, ECG, and pregnancy testing.

Statistical methods:

The primary comparisons of interest were the response rates of each of the active treatment groups to placebo during the double-blind treatment phase. A step-wise modified Bonferroni procedure was used to control the experiment-wide error rate. The Mantel–Haenszel procedure blocking by karyotype (IPSS karyotype score of 0 versus greater than 0) was used to compare the response rates for 10 mg versus placebo and 5 mg versus placebo. The Mantel–Haenszel procedure was also used to compare the secondary response measures: erythroid, cytogenetic, and bone marrow response together with the number of subjects with ongoing transfusion independence at one year following initiation of treatment. The Kaplan–Meier procedure was used to characterize the duration of response. Analyses of variance was used to analyze the changes in blood Hgb concentrations, platelet counts, and absolute neutrophil counts from baseline, and the changes in the components and total of the FACT-An HRQoL assessment, and the frequency with which transfusions were given. In these analyses, the average number of transfusions given over 56-day intervals prior to randomization were compared to the averages over 56-day intervals during the double-blind treatment phase.

Subgroup analyses to compare response rates were performed for:

The factor used for stratification:

- IPSS karyotype score: 0 versus > 0

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Additional prespecified subgroup analyses:

- Baseline serum or plasma erythropoietin levels: ≤ 500 mIU/mL versus > 500 mIU/mL
- Age group: <=65 versus >65
- Baseline FAB category
- Gender
- Years since MDS diagnosis: <=2.0 versus >2.0
- IPSS risk category (central reviewed): Low, Int-1, Int-2 and High
- AML progression: yes, no
- Dose reduction/interruption: yes, no

Multivariate analyses were performed to identify the prognostic variables for AML-free survival (AML or death, whichever occurs first, will be counted as the event), AML progression and overall survival. A univariate Cox proportional hazards model was used to assess the impact of the individual prognostic variables. After the potentially significant prognostic variables have been identified, a multivariate Cox proportional hazards model was used to simultaneously determine the impacts of the most important prognostic variables.

Cox proportional hazards modelling is a multivariate technique that considers the event rate in the study group and controls for varying lengths of follow-up for individual subjects. In the analysis of overall survival, each prognostic variable was first considered separately to capture its univariate relationship with the survival. A p-value <0.15 was used to select the potentially significant prognostic variables. A Cox model was then used to evaluate the effects of all of these potentially significant prognostic variables simultaneously (e.g., the risk of death associated with one variable is considered in the context of all other variables). Risk factors that had the least significant relationship with death were sequentially removed from the model using a backward elimination approach. The fit of the model was tested after the elimination of each risk factor until all remaining variables had a p-value < 0.15, which is a customary threshold in post hoc exploratory analysis. The variable selection was completed when no more variables could be eliminated from the model. The Cox model based on these selected variables was used to determine the most important prognostic variables that were statistically significant at a level of 0.05. The same statistical approach was used to analyze AML progression.

The following baseline characteristics, considered to be the prognostic variables for the survival (ref), were evaluated: age, duration of MDS prior to study entry, baseline RBC transfusion burden, cytogenetic complexity, bone marrow blast count, number of cytopenias, baseline platelet count, absolute neutrophil count, hemoglobin level, baseline EPO level, ferritin level and WPSS risk score. Transfusion burden was defined as the number of RBC units transfused during the 8 weeks immediately prior to study entry. Cytogenetic complexity was evaluated by comparing subjects with an isolated 5q deletion with those with either an intermediate or complex karyotype (i.e., del(5q) + 1 and del(5q) + > 2. Number of cytopenias was evaluated by comparing subjects with one cytopenia versus those with more than one cytopenia. WPSS risk score was used to select the subjects in the low or intermediate risk group versus those in the high or very high risk group. Age, duration of MDS prior to study entry, RBC transfusion burden, blast count, platelet count, neutrophil count, hemoglobin level, EPO level and ferritin level were considered as the continuous variables. For these analyses, an additional factor referred to as the 182+ days RBC transfusion independence was used as a time-dependent variable in the model.

Response rates and the frequency of transfusions were determined for each arm of the open-label extension phase. Pre-randomization values were used as the baseline in these analyses. For subjects entering from the placebo arm, additional analyses were performed to compare results to values obtained during the last 112 days of the double-blind treatment period. Those subjects who failed to respond on 5 mg, but who responded on 10 mg, were identified. Descriptive analyses were performed to summarize other variables.

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

As shown in this randomized phase 3 trial, lenalidomide was effective in achieving durable transfusion independence in transfusion dependent subjects with lower risk MDS (IPSS low or INT-1) associated with del(5q) with or without additional cytogenetic abnormalities. Specifically:

- Lenalidomide at both 5 mg and 10 mg was superior to placebo in achieving the primary endpoint of the study, transfusion independence for 182+ days; a significantly higher proportion of subjects achieved transfusion independence in the 10 mg (56%) and 5 mg (42.6%) lenalidomide treatment groups compared to placebo (5.9%) The results were similar for both the MITT and ITT analyses.
- The transfusion independence attained with lenalidomide treatment was seen across all of the subgroups analyzed including baseline cytogenetics (isolated del(5q) vs. 1 or more cytogenetic abnormalities), EPO levels > 500, FAB classification, IPSS and WPSS risk groups.
- Transfusion independence responses to lenalidomide were durable with median duration of transfusion independence response for the lenalidomide-treated group expected to exceed 2 years. The onset of transfusion independence in response to lenalidomide treatment is rapid and likely to begin within the first 2 cycles of treatment
- The effect of treatment with lenalidomide on hemoglobin was robust with major erythroid responses in subjects who achieved transfusion independence and median changes in Hgb levels between 5 and 6 g/dL.

In addition to achieving transfusion independence, lenalidomide was effective in eliminating the malignant clone as demonstrated by cytogenetic responses and in achieving bone marrow remission. Specifically,

- Lenalidomide treatment produced major and minor cytogenetic responses in the 10 mg (42.5%) and 5 mg dose (21.6%) treatment group compared with placebo (0%).
- Overall, there were no significant differences in the proportion of cytogenetic responders between the del(5q) subgroups (isolated vs. more than 1 cytogenetic abnormality) in either of the lenalidomide treatment groups.
- Lenalidomide-induced cytogenetic response is associated with achievement of durable RBC-transfusion independence. However, the achievement of transfusion independence is not dependent upon complete elimination of the malignant clone since a proportion of subjects achieved transfusion independence in the absence of a cytogenetic response.
- Lenalidomide produced a 10-17% bone marrow remission (complete + partial remissions). During the double-blind phase, approximately 50% of subjects in the study achieved stable bone marrow disease and a small fraction (4-6%) exhibited bone marrow progression.

The achievement of transfusion independence in lenalidomide treated patients was associated with an improvement in quality of life as evidenced by the following:

- There were statistically significant differences in the FACT-An total score at Week 12 between both lenalidomide treatment groups and placebo. Treatment differences for the TOI-Anemia and the TOI-Fatigue trended toward significance in favor of lenalidomide treatment.
- Criterion cut points for minimal clinically meaningful improvement were met and sustained through Week 48 for all three primary endpoint scales in the 10 mg lenalidomide group. Mean changes from baseline for these three scales also met MCID criteria in the 5 mg lenalidomide group but were sustained only through Week 36.
- Clinically important improvements in FACT-An scores throughout the study were most robustly and consistently noted among subjects who either started and maintained a 10 mg dose or who began a 10 mg dose but switched to 5 mg dosing.

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Overall, based on a median follow up of 3 years, there was no evidence to suggest that treatment with lenalidomide was associated with an increase in the rate of progression to AML or negatively affected overall survival compared with placebo whether based on the Intent to treat or the "As Treated" analyses. Specifically,

- From the ITT analysis 31% of subjects progressed to AML in the placebo treatment group compared with 23% in the 5 mg and 22% in the 10 mg treatment groups. The 2 year cumulative incidence was 20.7%. During the first 16 weeks of the study 3% of placebo subjects progressed to AML compared with 2.9% in the 5 mg and 0% in the 10 mg lenalidomide treatment groups.
- When using the "As treated" analysis, 36.4% of placebo patients who never received lenalidomide treatment (n=11) progressed to AML compared 23.2 % in the 5 mg and 21.7% in the 10 mg treatment groups. Overall median time to AML has not yet been reached for the lenalidomide treatment groups.
- Based on a multivariate analysis assessing the influence of prognostic factors on progression to AML, subjects who achieved the primary end point of 26-week transfusion independence response had a lower cumulative incidence of progression to AML than those who did not respond with a 2-year cumulative incidence of 12.6% compared to 38.5%. Furthermore, achieving a cytogenetic response may reduce the risk of progression to AML with a cumulative 2-year incidence of 14.7% compared with 26.6% for non-responders.
- Overall, a similar proportion of lenalidomide-treated subjects across all treatment groups had died over the course of the study regardless of initial or subsequent treatment assignments whereas the proportion of deaths among subjects who did not receive lenalidomide was larger (92 of 194 [47.4%] subjects vs. 9 of 11 [81.8%].
- Based on a multivariate analysis assessing the influence of prognostic factors on overall survival, subjects who achieved transfusion independence had a better OS than non responding subjects. Achieving RBC transfusion independence correlated with longer survival compared with non-response (34.9% and 36.8% deaths among 182+ days and 56+ days responders vs. 53.4% and 54.2% deaths among non-responders). Analysis using the Cox Proportional Hazard Model showed that achieving transfusion independence was associated with a significant reduction in the risk of death (HR=0.53; 95% CI 0.31, 0.90; p=0.019).Based
- Similarly, achieving a cytogenetic response to lenalidomide was associated with prolonged overall survival compared with non-response.

With respect to dose, the composite information indicates that overall, 10 mg results in consistently higher proportions of subjects achieving transfusion independence and cytogenetic responses compared with 5 mg including across all subgroups analyzed.

- For transfusion independence (182+ days) and cytogenetic response (complete and partial) 10 mg was associated with higher proportions of subjects achieving these endpoints (56.1% and 42.5% respectively) compared with the 5 mg treatment group (42.6% and 21.6% respectively).
- Subgroup analysis of transfusion independence response by baseline disease characteristics revealed that 10 mg lenalidomide was more effective than 5 mg in subjects with EPO levels > 500 mIU/mL (76.2% vs. 33.3%) compared with those with EPO levels ≤ 500 mIU/mL (42.9% vs. 53.8%). In addition, the 10 mg dose was associated with consistently higher responses across the other subgroups including subjects with an isolated del(5q) cytogenetic abnormality than in subjects with complex del(5q) plus 1 or more additional cytogenetic abnormalities, in subjects with a lower IPSS Risk score and when analyzed by WPSS risk score across all categories. Examination of subgroups (including age, gender, FAB classification, IPSS risk category, years from diagnosis, baseline EPO levels, prior use of ESA, baseline cytogenetics and baseline platelets) using the Forest plot demonstrates a significant trend in favor of the 10 mg dose for the majority of the subgroups analyzed.
- A proportion (28.6%) of subjects who failed to respond to 5 mg lenalidomide during the double-blind phase achieved transfusion independence when switched to 10 mg in the open-label phase. producing responses in

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subjects with a more resistant form of the disease.

Overall, data support the use of 10 mg lenalidomide as a starting dose; treatment should be discontinued for subjects who have not achieved a response within 4 cycles of treatment.

SAFETY RESULTS:

Overall in this study, lenalidomide, administered at a dose of 10 mg on Days 1-21 or 5 mg on Days 1-28 of repeated 28 day cycles, demonstrated a safety profile that is consistent with the known safety profile of lenalidomide. Adverse events were easily monitored and were managed clinically. No new safety concerns were identified.

- Subjects in the 10-mg group tended to stay on study longer (presumably due to erythroid response). Approximately 40% of subjects in the 10-mg group received treatment for at least 52 weeks (median 50.3 weeks), compared with approximately 20% of subjects in the 5-mg group (median 18.0 weeks).
- While more subjects experienced AEs in the lenalidomide groups, the dropout rate due to AEs in the lenalidomide groups was relatively low overall.
- Most adverse events tended to occur early during therapy with lenalidomide, generally occurring most frequently during the first 2 cycles.
- Analysis of the long-term safety data in patients receiving lenalidomide was generally similar to that observed during the first 16 weeks, suggesting that there was no delayed or cumulative toxicity.
- Grade 3/4 neutropenia and thrombocytopenia were the most common AEs associated with the administration of lenalidomide. However, discontinuation from the study due to neutropenia and thrombocytopenia occurred infrequently, suggesting that these AEs can be managed through dose reductions or interruptions and with the use of appropriate supportive care.
- There were 101 deaths overall during the study (with comparable distribution between the placebo group and the lenalidomide groups). Of those, 10 deaths occurred within 30 days of the subject's last dose (4 in the placebo group, 2 in the 5-mg group, and 4 in the 10-mg group).
- Overall, for the entire study period (DB and OL), comparable percentages of subjects progressed to AML (31.3% in the placebo group, 23.2% in the 5-mg group, and 21.7% in the 10 mg group.
- The percentage of subjects with hemorrhagic events during the DB phase was similar between the placebo and 5 mg groups, and slightly higher in the 10-mg group. Most hemorrhagic events reported were cutaneous in nature, grade 1 or 2 in severity, and non-serious. Although lenalidomide treated subjects had a higher incidence of thrombocytopenia than placebo-treated subjects, there did not appear to be a correlation between low platelet count and bleeding events.
- The VTEs of DVT and PE occurred more frequently in the lenalidomide-treated subjects vs. the placebo subjects. The frequency of DVT and PE events did not appear to be dose dependent. The majority of DVTs and PEs occurred during the first 2 cycles of lenalidomide treatment. Approximately half of the subjects with DVT or PE had a pre-existing medical condition or risk factor associated with these events. Most DVT and PE events were serious and considered by the investigator to be related to study drug. Three subjects discontinued due to DVT or PE.
- Neuropathy occurred more frequently in the lenalidomide-treated groups, but the incidence did not differ between the 5 mg and 10 mg dosing regimens. The majority of neuropathy AEs occurred after the first 4 cycles of treatment. Overall, the incidence of neuropathy was low, all instances were non-serious, and no event led to discontinuation of study drug.
- The overall incidence of cardiac AEs was similar between lenalidomide-treated subjects and placebo subjects. There was no difference in the incidence of these AEs between subjects administered the 5 mg vs. 10 mg

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dosing regimens. Most of the subjects who experienced events of myocardial infarction and congestive heart failure had pre-existing risk factors. These events did not tend to occur early during lenalidomide therapy.

- Infections occurred more frequently in the lenalidomide-treated groups. The most commonly reported events were nasal or respiratory infections and onset was most frequently observed during the first 16 weeks of treatment. The majority of AEs were non-serious and less than Grade 1 or 2 in severity, and few led to study drug discontinuation.
- The rates of pruritus and rash reported in this study are consistent with the known profile of lenalidomide. Most of the pruritus and rash AEs occurred during the first 16 weeks. There were no reports of severe cutaneous reactions, and no instances of Stevens-Johnson syndrome or toxic epidermal necrolysis. Most of the events were Grade 1 or 2 in severity, all were non-serious, and a minority led to dose interruption, dose reduction, or study drug withdrawal.
- The percentages of subjects who had shifts in hematology laboratory values from baseline values of grade 0, 1, or 2 to a worst postbaseline value of grade 3 or 4 were similar between the lenalidomide groups and higher than those for the placebo group. The majority of the shifts observed in lenalidomide-treated subjects occurred in WBC, ANC, and platelets.
- The percentages of subjects who had shifts in serum chemistry laboratory values from baseline values of grade 0, 1, or 2 to a worst postbaseline value of grade 3 or 4 were low (< 7%) and similar between the lenalidomide groups and the placebo group. The majority of shifts were in only 1 subject each, and were to grade 3.

Overall, the safety profiles from the first 16 weeks of the DB phase, the full DB phase, the OL phase, and across the entire study, were consistent with one another, and with the known safety profile of lenalidomide. These results demonstrate that no new safety signals or cumulative toxicity emerged with longer-term treatment (maximum potential total of 3 years [156 weeks]) of study participation.

CONCLUSION:

The treatment of patients with IPSS low and intermediate -1 MDS is a challenge. While 90% of patients are anemic at diagnosis and managing the anemia is the primary treatment goal, there are no effective therapies for the majority of patients other than to administer red blood cell (RBC) transfusions with it is numerous risks (Dunbar, 2001; Greenberg 1997) Although bone marrow transplantation (BMT) can cure IPSS low and intermediate -1 MDS, given the older age and co-morbidities in patients with MDS the significant morbidity and mortality associated with BMT does not allow intensive treatment in the majority of patients. There is a need for effective alternative therapies.

MDS-004, a phase 3 study, was designed to compare 2 dosing regimens of lenalidomide to placebo in the treatment of transfusion dependent patients with low or Int-1 MDS associated with del (5q) with or without other cytogenetic abnormalities. The results of this phase 3, double-blind, placebo-controlled study demonstrate that lenalidomide is a safe and effective treatment for achieving RBC transfusion independence in subjects with low- or intermediate-1-risk IPSS MDS associated with a del 5 (q31-33) cytogenetic abnormality when administered at doses of either 5 mg daily for 28 days of a 28-day cycle, or 10 mg daily for 21 days of a 28-day cycle. The study design for this trial provided for patients, who had not achieved a hematologic response at week 16, to cross-over, based on very impressive, and clinically relevant results of lenalidomide in patients with 5qdel MDS. The population included in the study was representative of low and intermediate 1 risk MDS and included patients with both isolated del 5q as well as subjects with at least 1 additional chromosomal abnormality (23.7% of the mITT population). All subjects were transfusion dependent (median RBC transfusion requirements = 6 units/8 weeks) with most with duration of MDS of more than 2 years (median =2.6 years). Indicative of the severity of the anemia of the study population, between 30-40% of subjects across the treatment groups had hemochromatosis and

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over 75% had either failed an ESA or had epo levels > 500.

Lenalidomide at both 5 mg and 10 mg was superior to placebo in achieving transfusion independence for 182+ days; this was achieved in 56% of the 10 mg treatment group, 42.6% in the 5mg lenalidomide treatment group compared to 5.9% in the placebo group ($p<0.001$). Similar results were obtained in the ITT population and across all of the subgroups analyzed underscoring the robustness of these results. The transfusion independence attained with lenalidomide was durable with a median duration in excess of 2 years. The onset of transfusion independence was rapid and likely to begin within the first 2 cycles of treatment with 95% of patients achieving a response by the completion of 3 cycles of treatment. Furthermore, the effect of lenalidomide treatment on hemoglobin was robust with median increases in Hgb levels between 5 and 6 g/dL in subjects who achieved transfusion independence.

Treatment with lenalidomide was also associated with cytogenetic responses including complete and partial remissions. Specifically, lenalidomide treatment produced major and minor cytogenetic responses in the 10 mg (42.5%) and 5 mg dose (21.6%) treatment group compared with placebo (0%). Overall, there were no significant differences in the proportion of cytogenetic responders between the del(5q) subgroups (isolated vs. more than 1 cytogenetic abnormality) in either of the lenalidomide treatment groups. Of note, patients who achieved a cytogenetic response were more likely to achieve transfusion independence compared to those who did not have a cytogenetic response. However, the achievement of transfusion independence is not dependent upon complete elimination of the malignant clone since a proportion of subjects achieved transfusion independence in the absence of a cytogenetic response. In addition, between 10-17% of subjects also achieved bone marrow remission (complete + partial remissions). Approximately 50% of subjects in the study achieved stable bone marrow disease and while a small fraction (4-6%) exhibited bone marrow progression.

With respect to dose, the composite information indicates that overall, the 10 mg treatment group consistently had higher proportions of subjects achieving transfusion independence and cytogenetic responses compared with 5 mg. This trend was also observed across all subgroups analyzed including those with baseline EPO levels > 500 mIU/mL (76.2% vs. 33.3%). In addition, a proportion (28.6%) of subjects who failed to respond to 5 mg lenalidomide during the double-blind phase achieved transfusion independence when switched to 10 mg in the open-label phase demonstrating responses in subjects with a more resistant form of the disease.

Overall, the HRQoL results (ITT population) demonstrated that lenalidomide produced clinically meaningful improvements within 24 weeks of treatment that were sustained among subjects continuing through 48 weeks of therapy. There was a trend for greater improvement in the 10 mg group compared with the 5-mg group.

Overall, based on a median follow up of 3 years, there was no evidence to suggest treatment with lenalidomide led to an increase in the rate of progression to AML or negatively affected overall survival. In the ITT population, 31% of placebo subjects progressed to AML compared with 23% in the 5 mg and 22% in the 10 mg treatment groups. There were also no differences in the rate of progression during the first 16 weeks (prior to possible cross-over) of the study between the placebo (3%), 5 mg (2.9%) and the 10 mg (0%) lenalidomide treatment groups. Similarly, there was no increase in the rate of progression to AML in the lenalidomide treatment groups, when using the "As treated" analysis comparing placebo patients who never received lenalidomide treatment (36.4%) with the 5 mg (23.2%) and 10 mg (21.7%) treatment groups. Subjects who achieved the primary end point of 26-week transfusion independence had a lower 2 year cumulative incidence of progression to AML (12.6%) compared with those who did not respond (38.5%). Furthermore, achieving a cytogenetic response also appeared to reduce the risk of progression to AML with a cumulative 2-year incidence of 14.7% compared with 26.6% for non-responders. The median time to AML has not yet been reached for the lenalidomide treatment groups.

With respect to overall survival, there were no differences across the randomized treatment groups (ITT), although these results are confounded by the cross over design. However, there was no evidence to suggest an increase risk of death in patients exposed to lenalidomide in either the ITT or "As treated" analyses. Achieving a cytogenetic response was associated with prolonged overall survival compared with non-response. Based on a multivariate analysis assessing the influence of baseline prognostic factors (with transfusion independence for 182+ days and

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cytogenetic response as a time dependent covariates) on AML-free and OS, transfusion independence for 182+ days was associated with a reduced risk of death (HR= 0.43; 95% CI 0.25, 0.71) and with a reduced risk of AML progression or death (HR = 0.47; 95% CI, 0.28, 0.77).

Lenalidomide, administered at a dose of 10 mg on Days 1-21 or 5 mg on Days 1-28 of repeated 28 day cycles, demonstrated a safety profile that is consistent with the known safety profile of lenalidomide. The most frequently reported TEAEs were hematologic (thrombocytopenia, neutropenia), GI (nausea/diarrhea) and skin (rash). Most adverse events tended to occur early during therapy with lenalidomide, generally during the first 2 cycles. As expected, rates of neutropenia were higher in both the 10 mg (75.4%) and the 5 mg (76.8%) treatment groups compared to placebo (17.9%). Infections occurred more frequently in the lenalidomide-treated groups, although the most commonly reported infectious events were non serious and included nasal or respiratory infections; SAEs of febrile neutropenia and pneumonia were reported in < 3% of lenalidomide treated subjects. Despite the higher proportion of patients experiencing thrombocytopenia in the 10 mg (44.9%) and 5 mg (42%) treatment groups compared to placebo (3%), the percentage of subjects with hemorrhagic events during the DB phase was similar between the placebo and 5 mg groups, and slightly higher in the 10-mg group. Most hemorrhagic events reported were cutaneous in nature, grade 1 or 2 in severity, and non-serious. Neutropenia and thrombocytopenia were also the most common Grade 3/4 AEs associated with the administration of lenalidomide. However, SAEs of infection or bleeding occurred infrequently (< 3%) and few lenalidomide treated subjects discontinued (< 3%) from the entire study (double blind + open label) due to neutropenia or thrombocytopenia, indicating these AEs can be managed through dose reductions or interruptions and with the use of appropriate supportive care.

The VTEs of DVT and PE occurred more frequently in the lenalidomide-treated subjects vs. the placebo subjects. The frequency of DVT and PE events did not appear to be dose dependent. The majority of DVTs and PEs occurred during the first 2 cycles of lenalidomide treatment and approximately half of the subjects who had DVT or PE had a pre-existing medical condition or risk factor associated with these events. Three percent (4/141) of lenalidomide treated subjects discontinued due to DVT or PE.

Of note, the adverse event profile (including the frequency of neutropenia/thrombocytopenia) for the 10-mg lenalidomide dose was similar to that of the 5-mg dose when considering that a higher percentage of subjects in 10-mg group had at least one AE leading to dose reduction or interruption compared with the 5-mg group, although a lower percentage of subjects actually discontinued due to AEs. The use of G CSF was comparable between the 5-mg and the 10-mg lenalidomide groups.

As a reflection of efficacy as well as the tolerability, subjects in the 10-mg group tended to stay on study longer. Approximately 40% of subjects in the 10-mg group received treatment for at least 52 weeks (median 50.3 weeks), compared with approximately 20% of subjects in the 5-mg group (median 18.0 weeks). Analysis of the long-term safety data in patients receiving lenalidomide was generally similar to that observed during the first 16 weeks, suggesting that there was no delayed or cumulative toxicity.

There were 101 deaths overall during the study (with comparable distribution between the placebo group and the lenalidomide groups). Of those, 10 deaths occurred within 30 days of the subject's last dose (4 in the placebo group, 2 in the 5-mg group, and 4 in the 10-mg group).

Overall, the safety profiles from the first 16 weeks of the DB phase, the full DB phase, the OL phase, and across the entire study, were consistent with one another, and with the known safety profile of lenalidomide. These results demonstrate that no new safety signals or cumulative toxicity emerged with longer-term treatment (maximum potential total of 3 years [156 weeks]) of study participation.

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In conclusion, the results of this Phase 3, double-blind, placebo-controlled study demonstrate the following:

- Lenalidomide is a safe and effective treatment for subjects who have low- or intermediate-1-risk IPSS MDS associated with a del 5 (q31-33) cytogenetic abnormality with or without other cytogenetic abnormalities, and they are consistent with the data from prior studies.
- Hematological improvement, manifested clinically as RBC-transfusion independence, is supported objectively by sustained elevations and improvements in Hgb values, and cytogenetic normalization.
- RBC transfusion independence was durable and associated with a reduced risk of progression to AML or death.
- 10 mg treatment was consistently associated with a higher proportion of patients achieving transfusion independence and cytogenetic response
- No new or unexpected safety signals were seen during treatment with lenalidomide. The safety profile of lenalidomide was consistent with the safety profile observed in previous clinical studies ;
- No significant difference in safety or tolerability of 10mg compared to 5 mg;
- Patients should be started at 10 mg with subsequent dose reductions as required.
- Treatment should be stopped if there is no evidence of a hematological response after 4 cycles of treatment.

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